The FRAX® (Fracture Risk Assessment Tool) was developed to estimate the 10-year probability of fractures in individual patients by the World Health Organization (WHO) in 2008 based on 11 risk factors identified from worldwide data in ten cohorts. FRAX is a convenient tool to easily identify a person at high risk for fractures, and therefore has been incorporated into the criteria for initiation of pharmacological treatment in the present guidelines (see "Criteria for initiation of pharmacological treatment").

Prevention

Primary prevention of osteoporosis

The most important measure for primary prevention of osteoporosis is education appropriate to each age group: in early life to acquire as high a peak bone mass (PBM) as possible, to maintain acquired PBM through exercise thereafter, and to minimize its decrease after menopause.

A study on the age-specific distribution of bone mass in Japanese women revealed that PBM is achieved at 18 years of age [7]. Thus, before age 18 is the most effective time for physicians to encourage young people to increase PBM to its maximal level. Guidance on maintenance of adequate weight, active intake of calcium, and weight-bearing exercise is effective.

For middle-aged and older persons, guidance on maintenance of adequate weight, aerobic exercises especially walking, and weight-bearing exercise is effective. Smoking cessation and limiting alcohol intake to less than 3 units/day (1 unit=8–10 g ethanol) is likely to decrease the fracture risk.

Prevention of falls

Most proximal femoral fractures in elderly people occur because of a fall. Risk factors for proximal femoral fractures are a past history of falls and the number of falls, and fall-related factors including generalized weakness, paralysis, muscular weakness, use of sleep-inducing drugs, and decreased vision.

Approaches to prevent falls include (1) exercise interventions (e.g., training to increase strength of muscle, balance, walking ability, and flexibility); (2) non-exercise interventions (e.g., instruction about medication, diet, and environment, along with education and guidance for behavior modification); and (3) multifactorial intervention (e.g., in addition to 1 and 2, an individualized approach based on the physical and mental functioning, environment, and medical assessment of a patient).

In elderly people, vitamin D deficiency increases the risk of falls, and administration of vitamin D can reduce the frequency of falls.

Wearing a hip protector is effective for the prevention of proximal femoral fractures; especially in high-risk groups in elderly care facilities.

Osteoporosis screening

Osteoporosis screening is spreading as a part of the Elderly Health Services (currently as a project under the Health Promotion Law) in Japan, and is performed every 5 years in women from 40 to 70 years old. The screening rate (the percentage of women who underwent osteoporosis screening against the entire target female population) was 4.6 % in 2005.

Osteoporosis screening for people of middle and older age is aimed at early detection of asymptomatic osteoporotic patients and persons at risk of osteoporosis to prevent future fractures. Persons at risk of osteoporosis should be given guidance on diet and exercises, and asymptomatic patients should be targets for early intervention (secondary prevention).

In screening, persons should be classified as either "Complete examination required", "Guidance required", or "No apparent abnormality" based on the results of the medical interview and bone mass measurement (Fig. 7) [8]. The criteria for requiring a complete examination is a bone mass of less than 80 % of YAM; this is different from the diagnostic criteria for osteoporosis (i.e., when BMD is less than 70 % of YAM in the absence of fragility fracture). In addition, bone mass measurement at the calcaneus (including QUS), which is not used to diagnose osteoporosis, is also permitted in the screening. The reason for these differences is that screening should identify the persons requiring the full diagnostic assessment for osteoporosis.

FRAX® will become suitable for osteoporosis screening after the cutoff values for fracture probability are established for complete examination and for guidance.

Treatment

Criteria for initiation of pharmacological treatment

The goals of osteoporosis treatment are prevention of fracture as a complication and maintenance of good skeletal health. Important strategies to reduce the fracture risk in osteoporotic patients are treatment with a bone resorption inhibitor or bone formation stimulant and guidance to establish a lifestyle that leads to maintenance and enhancement of bone strength and to avoid risk factors for fractures, such as a fall, that are independent of a decrease in bone strength.

The risk factors for fracture include low BMD, factors that contribute to a decrease in BMD, and deterioration of bone matrix, including lifestyle-related diseases. A prevalent fragility fracture is the most important among all these

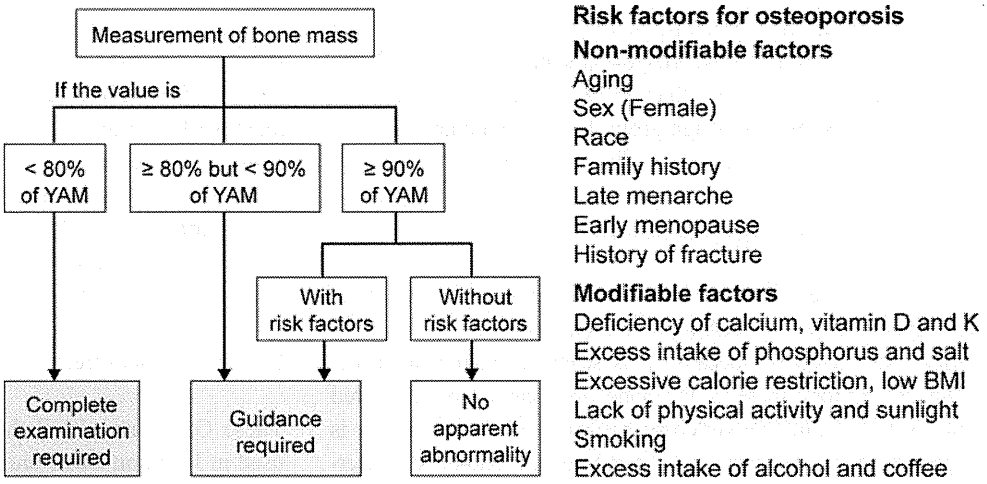


Fig. 7 Criteria for osteoporosis screening. Risk factors for osteoporosis: non-modifiable factors: aging, sex (female), race, family history, late menarche, early menopause, and history of fracture. Modifiable factors: deficiency of calcium, vitamin D, and K; excess intake of phosphorus and salt; excessive calorie restriction; low BMI; lack of physical activity and sunlight; smoking; and excess intake of alcohol and coffee Orimo [8]

factors with the exception of low BMD. Family history of proximal femoral fractures significantly increases the fracture risk even in persons without a fragility fracture who have a "low bone mass" based on their BMD.

Based on this new knowledge about risk factors and the consideration about using FRAX® (see "Risk factors for fracture"), the criteria for initiating pharmacological treatment to prevent fragility fracture was established as shown in Fig. 8. In these criteria, FRAX® is used to consider whether or not to initiate pharmacological treatment in persons without a fragility fracture who have a low bone mass. This is because persons with a fracture risk comparable to patients with osteoporosis possibly could be included in this group and need other measures to assess the magnitude of the fracture risk other than low BMD. Considering that the 10-year probability of major osteoporotic fractures in the patients receiving pharmacological treatment was observed around 15 % in Japanese clinical settings, we adopted 15 % as a treatment threshold for the persons with low bone mass. In the guidelines, FRAX® is not used in the first-line screening to determine the persons who need further examination such as bone densitometry. As stated earlier, the

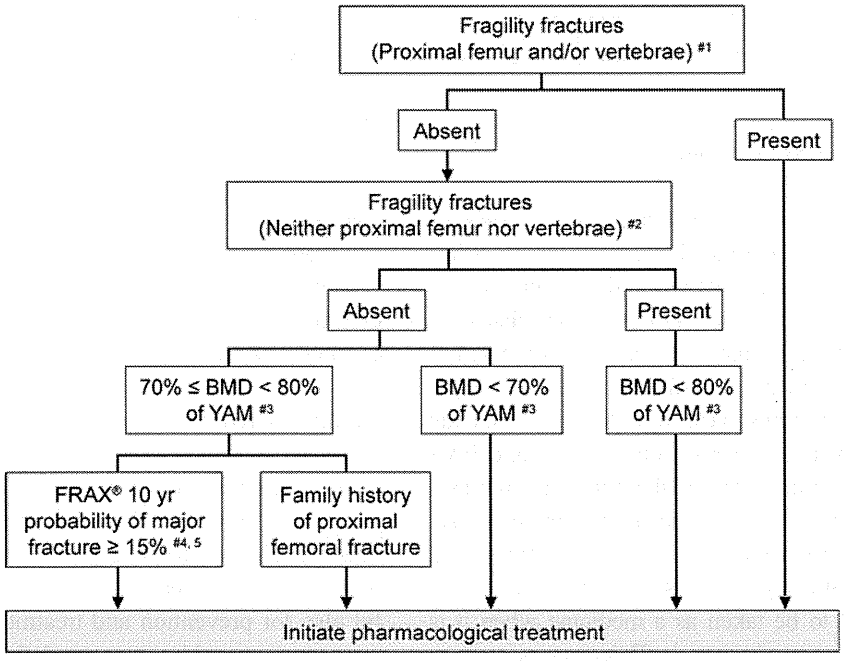


Fig. 8 Criteria for initiation of pharmacological treatment. #1: this means proximal femoral fracture and/or vertebral fracture caused by slight external force after menopause in women and after age 50 in men. #2: this means distal forearm, proximal humerus, pelvis, lower leg and/or rib fracture caused by slight external force after menopause in women and after age 50 in men. #3: revision of additional T-scores is under consideration for some measurement sites. #4: this should be applied in persons <75 years. Additionally, a lower cutoff value does not include all young persons in and around their 50s for whom pharmacological treatment is recommended based on the present diagnostic criteria. #5: as these criteria refer to primary osteoporosis, they should not be applied to persons whose FRAX® risk factors are "glucocorticoid", "rheumatoid arthritis", or "secondary osteoporosis". That is, these criteria should be applied only in persons who answer "No" to each of these items

cutoff value for the screening in Japan is being studied. The cutoff value of a 15 % 10-year probability is used for women and men younger than 75 years old, because almost all of the persons of this age group have a value above 15 % and thus its power as a cutoff value is too weak.

Evaluation of response to treatment

The optimal method for bone mass measurement to evaluate the therapeutic effect is DXA at the lumbar vertebrae on the anteroposterior direction, because it is sensitive enough to detect changes in bone mass. If the bone mass cannot be measured precisely at the lumbar vertebrae, measurement at the total hip is recommended. The timing of measurement should be determined based on the least significant change of each method.

The efficacy of drugs with significant effects on bone metabolism can be evaluated by measuring bone metabolic markers. It is beneficial to measure bone resorption markers at 3 to 6 months after the initiation of treatment and bone formation markers every 6 to 12 months. Attention should be paid to the minimum significant change of each marker.

Plain radiography is useful for detection of incident vertebral fractures after the initiation of treatment. CT, MRI, and bone scintigraphy are sometimes required for confirmation of minor fractures, incomplete fractures, and unapparent fractures, and for differentiation from other clinical conditions including tumors.

QOL assessment using the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) is useful also for evaluation of therapeutic effects.

Basic treatments (non-pharmacological treatment)

A daily intake of calcium (700 to 800 mg) is recommended to optimize the effect of pharmacological treatment. It has been reported that calcium derivatives and calcium supplements may increase the risk of cardiovascular diseases. However, dietary intake of the same amount of calcium has not been shown to increase cardiovascular risk. Moreover, those adverse findings were reported from outside Japan, where calcium intake, serum lipid levels, and BMI are different from those in Japan. At this time, calcium as a medicine or supplement should not exceed 500 mg per dose.

Vitamin D (recommended daily intake, 10 to 20 μg) and vitamin K (250 to 300 μg) are also essential, and they should be prescribed to be taken as a medicine when it is difficult for the patient to obtain a sufficient amount from dietary sources. Hyperhomocysteinemia due to vitamin deficiency (vitamins B_6, B_{12}, and folic acid) involved in homocysteine metabolism has been shown to be a BMD-independent risk factor for fracture. It is recommended to warn patients not to consume excessive amounts of phosphorus, salt content, caffeine, and alcohol.

It has been demonstrated that high-impact activities, resistance exercises, back muscle exercises, stretching exercises, aerobic exercises, walking, and balance training can increase BMD and prevent vertebral fractures and falls in patients with osteoporosis.

In terms of pain relief, few data from randomized controlled trials are available about the effects of various physical therapies, nerve blocks, and surgeries; however, the efficacy of some drugs has been demonstrated.

Pharmacological treatment

These Guidelines detail the effect of each therapeutic agent used in Japan on BMD and the risk of vertebral fracture, non-vertebral fracture, and proximal femoral fracture, based on evidence from Japan and abroad. Each recommendation is also graded (Table 1). In regard to some therapeutic agents, the effect on QOL is also described. Table 2 shows the prescription drugs covered by the public health insurance in Japan.

For the selection of therapeutic agents, the full range of drug-related information must be considered: the efficacy of each medicine on BMD, fracture risk, QOL including pain, bone metabolic markers, risk of fall, as well as safety, including effects other than those on bone metabolism per se and adverse effects. Further, the patient's clinical state must be considered.

The systematic review published by MacLean and colleagues indicated that bisphosphonates (alendronate and risedronate) are a first-line agent for patients at high risk of vertebral, non-vertebral, or proximal femoral fracture [9]. Parathyroid hormone derivatives are first-line agents for patients at high risk of vertebral or non-vertebral fracture. Selective estrogen receptor modulators (SERMs) are first-line agents for patients at high risk of vertebral fracture. Minodronic acid, a bisphosphonate developed in Japan, is expected to be used for the high-risk group for vertebral fracture. Eldecalcitol, an active vitamin D_3 derivative developed in Japan, is expected to be used for the high-risk group for vertebral or non-vertebral fracture. However, more data are required for these new agents.

Estrogen derivatives

A postmenopausal decrease in bone mass is caused by estrogen deficiency. Therefore, estrogen replacement has been considered to be an effective treatment option for osteoporosis since early times. Estrogen replacement is useful also for prevention and treatment of other diseases and symptoms caused by estrogen deficiency. Administration of estrogen to young amenorrheic women or relatively young postmenopausal women can prevent osteoporosis. Estrogen is also useful for treatment of osteoporosis in women with climacteric symptoms in relatively early stage of postmenopause. Conjugated estrogen, estradiol, and estriol are the approved estrogen derivatives in Japan.

Table 1 Grading of recommendation of therapeutic agents for osteoporosis in Japan

Therapeutic agent		BMD	Vertebral fracture	Non-vertebral fracture	Proximal femoral fracture
Calcium	Calcium L-aspartate hydrate	C	C	C	C
	Dibasic calcium phosphate hydrate	C	C	C	C
Estrogen	Estriol	C	C	C	C
	Conjugated estrogens[a]	A	A	A	A
	Estradiol	A	C	C	C
Active vitamin D_3	Alfacalcidol	B	B	B	C
	Calcitriol	B	B	B	C
	Eldecalcitol	A	A	B	C
Vitamin K_2	Menatetrenone	B	B	B	C
Bisphosphonate	Etidronate disodium	A	B	C	C
	Alendronate sodium hydrate	A	A	A	A
	Sodium risedronate hydrate	A	A	A	A
	Minodronic acid hydrate	A	A	C	C
SERM	Raloxifene hydrochloride	A	A	B	C
	Bazedoxifene acetate	A	A	B	C
Calcitonin[b]	Elcatonin	B	B	C	C
	Calcitonin (Salmon)	B	B	C	C
PTH	Teriparatide (genetical recombination)	A	A	A	C
Other drugs	Ipriflavone	C	C	C	C
	Nandrolone decanoate	C	C	C	C

A strongly recommended to use, *B* recommended to use, *C* not enough evidence to recommend use, *D* recommended not to use

[a] Administration of conjugated estrogen for osteoporosis is not covered by the public health insurance in Japan

[b] Calcitonin has an analgesic effect, and reduces pain due to osteoporosis (grade A)

Table 2 Prescriptions of anti-osteoporotic agents covered by the public health insurance in Japan (as of September 2011)

Generic name	Launched	Prescription for osteoporosis
Calcium L-aspartate hydrate	1968	1.2 mg/day, p.o.
Dibasic calcium phosphate hydrate	1985	3 g/day, p.o.
Estriol	1969	1 mg/day, p.o.
Conjugated estrogens	1999	Not covered by the public insurance
Estradiol	2008	1 mg/day, p.o.
Alfacalcidol [a]	1981	0.5 or 1 μg/day, p.o. (adult)
Calcitriol	1986	0.5 μg/day, p.o.
Eldecalcitol[a]	2011	0.75 or 0.5 μg/day, p.o.
Menatetrenone[a]	1995	45 mg/day, p.o.
Etidronate disodium	1990	200 or 400 mg/day, p.o. (intermittent)
Alendronate sodium hydrate	2001	5 mg/day or 35 mg/w, p.o.
Sodium risedronate hydrate	2002	2.5 mg/day or 17.5 mg/w, p.o.
Minodronic acid hydrate [a]	2009	1 mg/day or 50 mg/4w, p.o.
Raloxifene hydrochloride	2004	60 mg/day, p.o.
Bazedoxifene acetate	2010	20 mg/day, p.o.
Elcatonin[a]	1982	20 IU/w, i.m.
Calcitonin (Salmon)	1990	20 IU/w, i.m.
Teriparatide (genetical recombination)	2010	24 μg/day, s.c. (up to 24 months)
Ipriflavone	1988	200 mg/day, p.o.
Nandrolone decanoate	1984	25 or 50 mg/3 w, i.m.

Teriparatide acetate, a new drug developed in Japan, came to market in November 2011. Prescription is 56.5 μg/w, s.c., up to 72 weeks

[a] Agents developed in Japan

Although conjugated estrogen increases BMD and prevents vertebral, non-vertebral, and proximal femoral fracture, it is not covered by the public health insurance in Japan for the treatment of osteoporosis.

Estradiol increases BMD, but there is little evidence that it prevents fractures.

There is almost no evidence about the effects of estriol.

Alfacalcidol and calcitriol (active vitamin D_3 derivatives)

Alfacalcidol and calcitriol are active vitamin D_3 derivatives. Alfacalcidol, developed in Japan, is a prodrug requiring hydroxylation in the liver for activation. Because these derivatives were approved for the treatment of osteoporosis in 1983 and 1989, respectively, there is insufficient large clinical trial data. However, several reports suggested these agents maintain lumbar BMD at a significantly higher level as compared to placebo, or reduce the risk of vertebral and non-vertebral fractures (not statistically significant; Fig. 9a) [10].

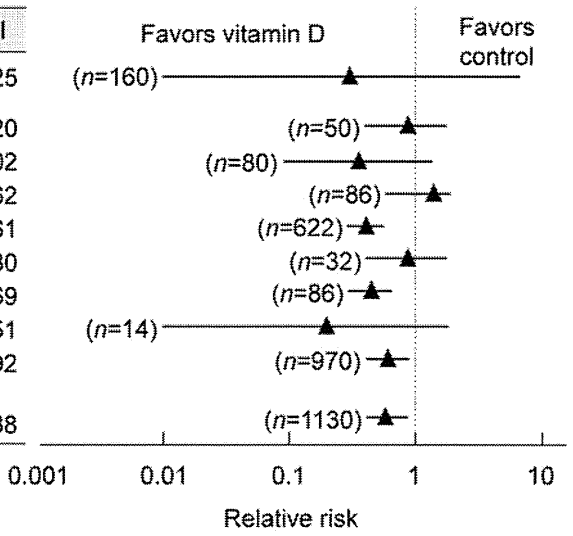
It has been reported also that vitamin D deficiency causes atrophy of the type II muscle fibers, and that vitamin D supplementation improves trunk imbalance. Active vitamin D_3 derivatives (alfacalcidol and calcitriol) reduce falls among the elderly (Fig. 9b) [11]. These active vitamin D_3 derivatives have been confirmed to be safe, even for long-term use, and they are recommended for the elderly (see "Combination therapy" for combination with bisphosphonate).

Eldecalcitol (active vitamin D_3 derivative)

Although the conventional active vitamin D_3 derivatives have been reported to be effective for preventing fractures, they have not been shown to increase BMD significantly. Various vitamin D_3 derivatives have been investigated; of these eldecalcitol was developed in Japan. Eldecalcitol showed superior efficacy to alfacalcidol to increase BMD (Fig. 10a) [12], while its effect on calcium absorption was nearly unchanged. Eldecalcitol may exert its actions by

a

	Source (Year)	RR	95% CI
Standard Vit. D	Baeksgaard L (1998)	0.33	0.10–1.25
Hydroxylated Vit. D	◇Gallagher JC (1990)	0.90	0.82–1.20
	◆Orimo H (1994)	0.37	0.55–2.02
	◇Ott SM (1989)	1.46	0.59–3.62
	◇Tilyard MW (1992)	0.43	0.31–0.61
	◆Geusens P (1986)	0.88	0.43–1.80
	◇Orimo H (1987)	0.46	0.31–0.69
	◆Caniggia A (1984)	0.20	0.01–3.51
	Pooled hydroxylated Vit. D	0.64	0.44–0.92
Pooled estimate		0.63	0.45–0.88



b

Source (Year)	Vitamin D	OR	95% CI
Pfeifer M (2000)	Natural type	0.47	0.20–1.10
Bischoff-Ferrari HA (2003)	Natural type	0.68	0.30–1.54
Gallagher JC (2001)	Active type	0.53	0.32–0.88
Dukas L (2004)	Active type	0.69	0.41–1.16
Graafmans WC (1996)	Natural type	0.91	0.59–1.40
Pooled (Uncorrected)		0.69	0.53–0.88

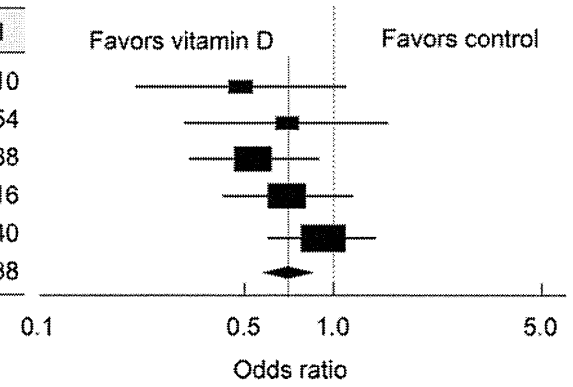


Fig. 9 Meta-analyses on the efficacy of vitamin D. **a** Relative risk for vertebral fractures after treatment with vitamin D. *RR* relative risk, *CI* confidence interval. *Open rhombus* indicates using calcitriol and *closed rhombus* using alfacalcidol. Adapted from Papadimitropoulos [10] (Copyright© 2002 The Endocrine Society). **b** Compared risk of falling between vitamin D-treated group and control group. *OR* odds ratio, *CI* confidence interval. Adapted from Bischoff-Ferrari [11] (Copyright© 2004 American Medical Association)

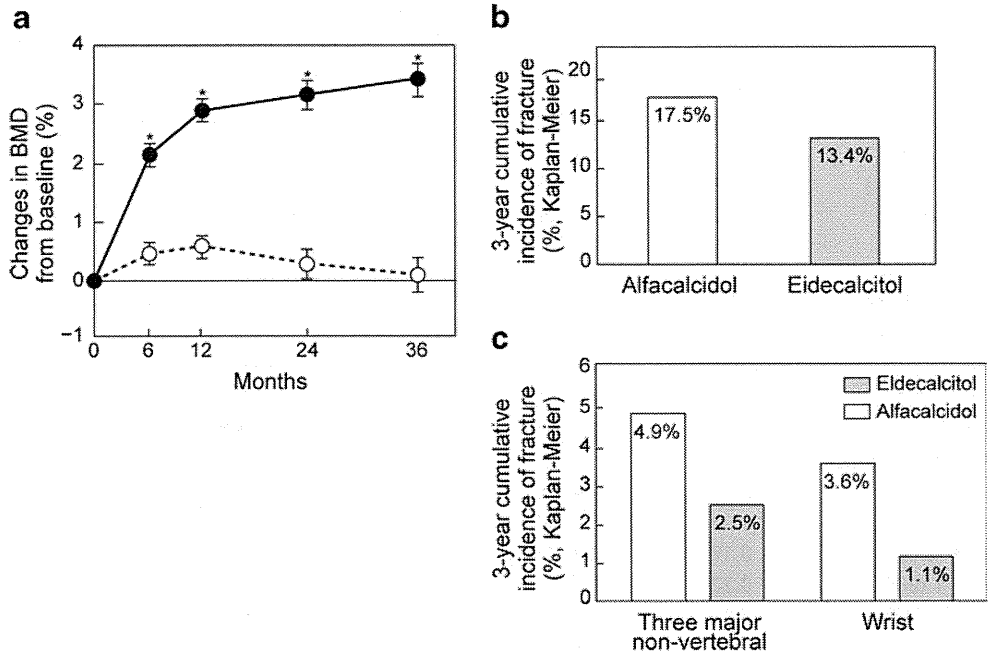


Fig. 10 Effect of eldecalcitol compared with alfacalcidol. **a** Change in lumbar BMD. Data are mean ± SE, *$p<0.001$ vs alfacalcidol group by Student t test (Matsumoto [12] (Copyright© 2011 Elsevier)). **b** Incidence of vertebral fracture. Hazard ratio (*HR*) is 0.74 and 95 % confidence interval (*CI*) is 0.56–0.97. Data from Matsumoto [12] (Copyright© 2011 Elsevier). **c** Incidence of non-vertebral fractures. HR for three major non-vertebral fractures is 0.52 and 95 % CI is 0.29–0.93, $p=0.031$. Three major non-vertebral sites mean humerus, wrist, and hip, i.e., the three sites of major non-vertebral fractures recognized as osteoporotic fractures in FRAX®. HR for wrist fractures is 0.29 and 95 % CI is 0.11–0.77, $p=0.005$. Data from Matsumoto [12] (Copyright© 2011 Elsevier) and the website of Pharmaceuticals and Medical Devices Agency (in Japanese)

promoting calcium absorption from the small intestine, similar to the conventional active vitamin D_3 derivatives, and prevent bone resorption by inhibiting osteoclastic function.

In a comparative study of eldecalcitol and alfacalcidol, the incidence of vertebral fractures was found to be significantly lower in the eldecalcitol group (Fig. 10b) [12]. While there was no significant difference in the overall incidence of non-vertebral fractures between the eldecalcitol and alfacalcidol groups, there was a trend towards a greater decrease in the incidence of non-vertebral fractures at the three major sites (humerus, wrist, and hip) in the eldecalcitol group than in the alfacalcidol group (Fig. 10c) [12]. Of note, the incidence of wrist fractures was significantly reduced in the eldecalcitol group.

Clinical trials of eldecalcitol have been conducted in patients over a wide range of age and severity, and this agent can be used across the entire spectrum of patients with osteoporosis.

Menatetrenone (vitamin K_2 derivative)

In elderly women and patients with osteoporosis being treated with a bisphosphonate, insufficient intake of vitamin K is a BMD-independent risk factor for fractures. Menatetrenone, a vitamin K_2 derivative, promotes carboxylation of osteocalcin, and thereby it reduces the serum level of ucOC, an index of vitamin K deficiency.

Menatetrenone slightly increases lumbar BMD and reduces vertebral and non-vertebral fractures (Fig. 11) [13]. Menatetrenone is considered to exert its fracture-reducing effect via a mechanism of action other than increasing BMD.

Etidronate (bisphosphonate)

Notably, for etidronate, a first-generation bisphosphonate, there is a small margin between its serum level for the onset of its inhibitory actions on bone resorption and the serum level for its inhibitory effects on bone formation. Close attention must be paid to its narrow safety range. Thus, a cyclical intermittent treatment strategy (200 to 400 mg/day once daily for 2 weeks, followed by a rest period of 10 to 12 weeks) is essential.

Because etidronate reduces bone resorption, it is effective particularly for high-turnover osteoporosis, and it maintains bone mass even in low-turnover osteoporosis. Etidronate reduces blood and urine levels of bone metabolic markers. Etidronate reduces incident vertebral fractures in patients who have vertebral fractures. There is no clear evidence about whether or not etidronate reduces non-vertebral fractures.

Alendronate (bisphosphonate)

Alendronate, a second-generation bisphosphonate, has a very wide safety range. Its inhibitory effect on bone resorption is exerted at a much smaller dose than the dose for its inhibitory effect on bone formation (approximately 1/6,000).

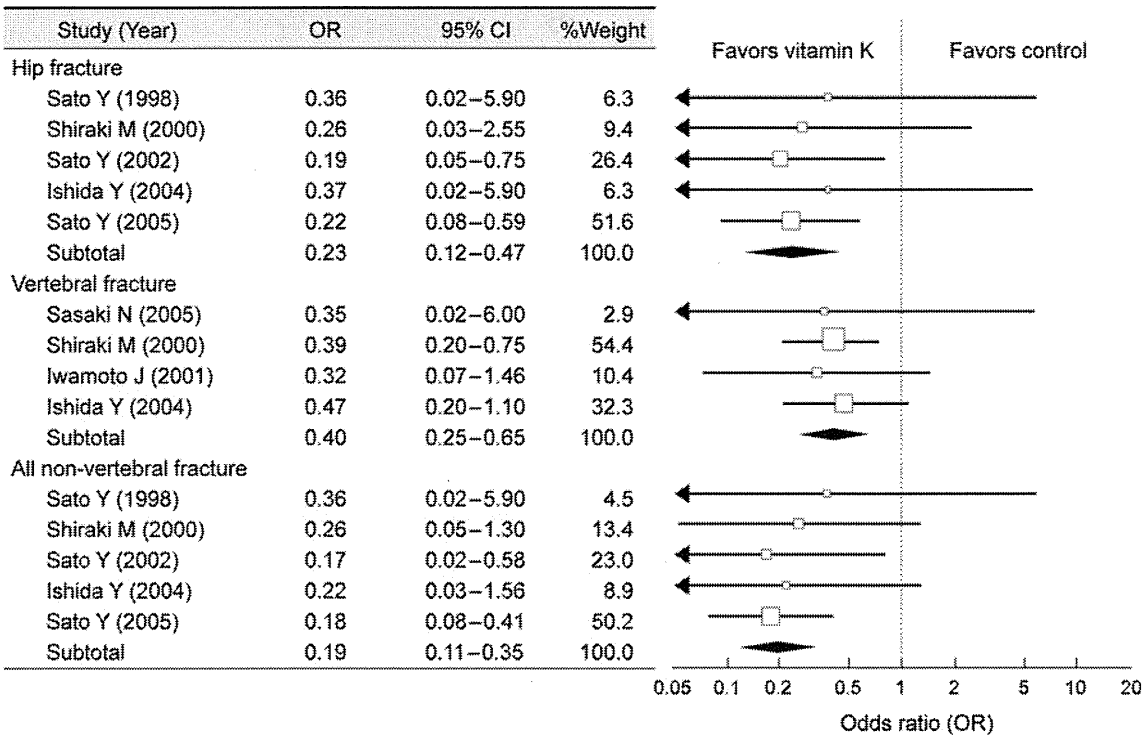


Fig. 11 Meta-analysis on the efficacy of menatetrenone on fractures. *OR* odds ratio, *CI* confidence interval (Cockayne [13] (Copyright© 2006 American Medical Association))

Many clinical trials and meta-analyses have shown that alendronate increases BMD, reduces fractures at the vertebra/non-vertebra, proximal femur, and distal end of the forearm; and improves the bone metabolic marker profile. Alendronate has been reported to reduce vertebral fracture and increase lumbar BMD also in men with osteoporosis.

In terms of QOL, a decrease in the duration of bed rest for low back pain, a decrease in the days of activity restriction, and improvement of arthralgia and pain-related QOL scores after treatment with alendronate have been reported (see "Combination therapy" for the combination with active vitamin D_3 derivatives).

A once-weekly dose of alendronate (35 mg), compared to a daily dose of alendronate (5 mg) was shown to have a similar effect on lumbar BMD and urinary levels of type I collagen cross-linked N-telopeptides (NTX); the incidence of adverse reactions and drug discontinuation was lower in the once-weekly group.

Risedronate (bisphosphonate)

Risedronate, a third-generation bisphosphonate, has a strong inhibitory effect on bone resorption.

Many clinical trials and meta-analyses have shown that risedronate increases BMD and reduces fractures at the vertebra/non-vertebra and proximal femur in postmenopausal women. Risedronate was reported to increase lumbar BMD also in men with osteoporosis. Large-scale clinical trials in North America, Europe, and Australia have shown preventive effects with risedronate against incident vertebral fracture from the first year of treatment. In Japan, it was reported that risedronate improved scores for body pain, vitality, and social functioning in QOL assessment using the SF-36 scale.

Once-weekly risedronate (35 mg), compared to daily risedronate (5 mg), was shown to increase BMD at the femoral neck and trochanter to the same degree in a study in the USA. In a Japanese clinical trial, once-weekly risedronate (17.5 mg), compared to daily risedronate (2.5 mg), increased lumbar BMD to the same degree at 48 weeks.

Minodronic acid (bisphosphonate)

Minodronic acid is the only domestically developed bisphosphonate for osteoporosis, and the only bisphosphonate which has been investigated for its inhibitory effect on fracture in Japanese patients at doses approved in Japan. Minodronic acid has the strongest inhibitory effect on bone resorption among the bisphosphonates currently available in Japan.

The efficacy of minodronic acid on BMD at the lumbar spine and total hip is equivalent to alendronate (Fig. 12a) [14]. In addition, minodronic acid significantly increased BMD in patients who had a poor response to other bisphosphonates.

Minodronic acid reduced vertebral fracture risk by 59 % in Japanese patients with osteoporosis (Fig. 12b) [15], and no

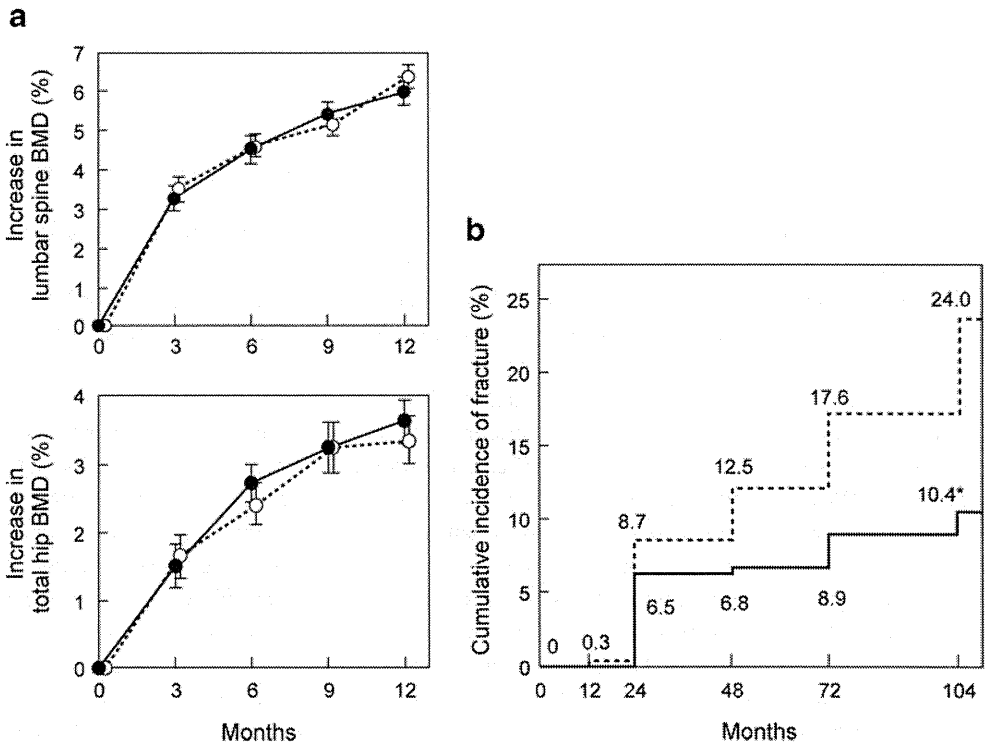


Fig. 12 Effect of minodronic acid on BMD and vertebral fracture. **a** Percent change in lumbar spine and total hip BMD. *Solid line* is minodronic acid 1 mg (n=134) and *broken line* is alendronate 5 mg (n=135). Data are mean ± SE (Hagino [14] (Copyright© 2009 Elsevier)). **b** Incidence of vertebral fracture. *Solid line* is minodronic acid (n=339) and *broken line* is placebo (n=328). Relative risk is 0.411 (95 % confidence interval 0.267–0.634) by Cox regression model. *p<0.0001 by log-rank test between the groups (Matsumoto [15] (Copyright© 2009 Springer Science + Business Media BV))

difference was observed in the effect between patients above and below 75 years of age. No clinical trial to determine the effect of minodronic acid on non-vertebral fracture or proximal femoral fracture has been conducted. The results of the ongoing Japanese Osteoporosis Intervention Trial (JOINT)-04 initiated in 2011 by the Adequate Treatment of Osteoporosis (A-TOP) Research Group (see "Combination therapy") are greatly anticipated to answer these questions. Minodronic acid is available for daily use (1 mg) and once every 4 weeks (50 mg).

Raloxifene (SERM)

Raloxifene, a selective estrogen receptor modulator, binds to the estrogen receptor (ER) with an affinity equivalent to estrogen and induces a conformational change at the helix 12 in the C-terminal part of ER; this conformational change produced by raloxifene is different from that produced by estrogen. Thus, raloxifene has a tissue-selective pharmacological action: it shows estrogen-like effects on bone, but not on the breast or uterus.

The Multiple Outcomes of Raloxifene Evaluation, a large-scale randomized controlled trial with 7,705 patients in 25 countries, demonstrated that raloxifene increased BMD and reduced incident vertebral fractures, regardless of the presence or absence of prevalent vertebral fractures and even in subjects with low bone mass (osteopenia). Additionally, raloxifene significantly reduced the incidence of non-vertebral fractures in patients with severe vertebral fractures. In Japan, a 3-year post-marketing surveillance demonstrated that the overall incidence of clinical fractures was as low as 1.2 %.

Many observational studies from Japan and abroad demonstrated the effect of raloxifene on QOL, including pain relief. A meta-analysis revealed that raloxifene decreases the overall mortality by 10 %.

Venous thromboembolism is one of the clinically important adverse events of SERMs. The incidence of venous thromboembolism in patients treated with raloxifene is 0.2 %, stated in the drug package insert, based on the results of a 3-year post-marketing surveillance conducted in 7,557 Japanese patients.

Bazedoxifene (SERM)

Bazedoxifene, a SERM, has an estrogen-like action selectively on bone metabolism and lipid metabolism, but not on the breast or uterus.

An international multi-center clinical trial demonstrated that bazedoxifene increases BMD and reduces vertebral fractures, similar to raloxifene. Although no overall reduction on non-vertebral fractures was observed with bazedoxifene, the incidence of non-vertebral fracture in postmenopausal women at a higher risk of fracture was significantly reduced by bazedoxifene as compared to placebo and raloxifene. Additionally, the higher the FRAX® score, the more effectively bazedoxifene reduced osteoporotic fractures. Bazedoxifene was also reported to improve the profile of bone metabolic markers. The effect of bazedoxifene on proximal femoral fracture has not been studied yet.

A significant decrease in the incidence of vertebral fractures and the safety of the drug were consistently observed during the 5-year treatment with bazedoxifene.

Calcitonin derivatives

Calcitonin is a bone resorption inhibitor acting directly on osteoclasts and pre-osteoclasts to control their functions. Calcitonin also relieves pain via the central serotoninergic system, and therefore its derivatives may be the first choice to obtain pain relief and improves QOL in the early phase after the occurrence of osteoporotic fractures or in patients with postural distortion associated with vertebral fractures.

There are some reports on the effect of calcitonin derivatives on BMD and vertebral fracture (Fig. 13a) [16], but none on non-vertebral or proximal femoral fractures.

Some randomized clinical trials and systematic reviews revealed significant reductions in the severity of pain associated with ADLs 1 to 4 weeks after calcitonin was started (Fig. 13b) [17]. In terms of QOL, improvement in SF-36 scores, pain relief, and improved ADLs, and an enhanced effect of rehabilitation in patients who had a total hip replacement after proximal femoral fracture was reported.

Outside of Japan, intra-nasal formulations of calcitonin derivatives are used primarily, and a preventive effect on fractures and beneficial effect on pain was observed. However, the increased risk of cancer was reported from the European Medical Association (EMA) in patients treated with calcitonin and intra-nasal calcitonin was withdrawn from the European market.

Although antibodies might be produced after injection of calcitonin derivatives, they do not influence the effect of calcitonin and are not involved in the side effects of calcitonin derivatives. Therefore, patient monitoring is not needed.

Teriparatide (recombinant human parathyroid hormone)

Unlike bone-resorption inhibitors, intermittent administration of teriparatide (a recombinant form) as a daily subcutaneous injection specifically increases serum P1NP, a bone formation marker, indicating promotion of bone remodeling followed by the formation of bone tissue.

Teriparatide, given as a daily subcutaneous injection, is recommended in patients at high risk of fractures such as patients who have had a fracture(s) while being treated with a bisphosphonate or SERM, elderly patients with multiple vertebral fractures or proximal femoral fractures, or patients with significantly reduced BMD. The combination of teriparatide with an oral bisphosphonate is not recommended.

Teriparatide increases BMD at the lumbar vertebrae and proximal femur, and reduces vertebral and non-vertebral fracture. The incidence of a radial fracture is reduced with teriparatide, while the apparent BMD of the radius is slightly decreased in association with the formation of new bone matrix, and the external diameter of the radius is increased. A meta-analysis revealed that teriparatide reduces low back pain.

Teriparatide (a recombinant form) approved in Japan is self-injected daily at home, after instruction by physicians or nurses. The total dosing period is limited to 24 months. After 24 months of treatment with teriparatide, adequate treatment with a bone-resorption inhibitor is recommended to maintain the bone strength.

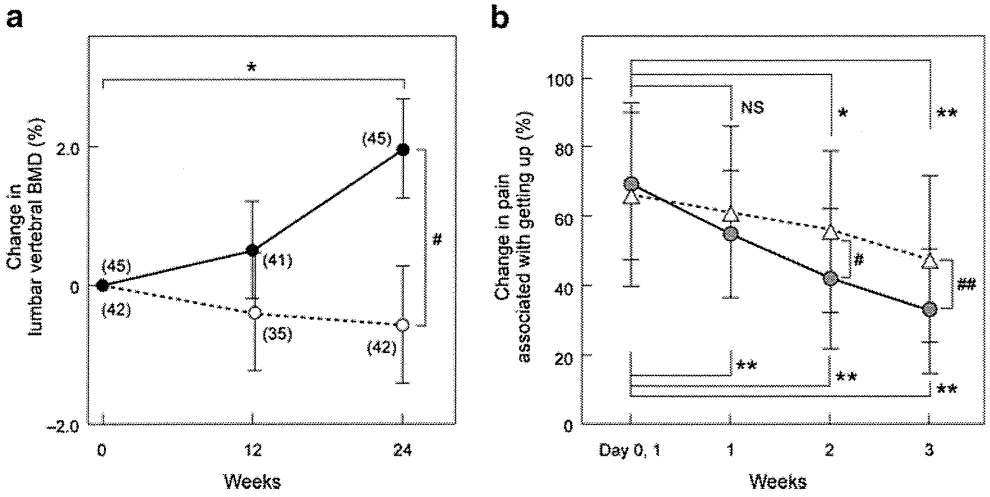


Fig. 13 Effect of elcatonin on BMD and pain associated with vertebral fracture. **a** Percent change in lumbar spine BMD. *Solid line* is elcatonin (20 units per week) with 0.6 g calcium lactate and *broken line* is control (calcium lactate only). Data are mean ± SE. Numerals in parentheses denote number of patients. Comparison within groups: Student's paired *t*-test, #$p<0.05$; between groups: Student's unpaired *t*-test, *$p<0.05$. Orimo H [16] (Copyright© 1996 Springer Science + Business Media BV). **b** Percent change in pain associated with getting up evaluated with visual analog scale (*VAS*). *Solid line* is elcatonin (20 units per week, $n=44$) and *broken line* is control (untreated, $n=42$). Two-way repeated-measures ANOVA, *$p<0.05$, **$p<0.01$, *NS* not significant. Mann–Whitney *U* test, #$p<0.05$, ##$p<0.01$ (Nakano [17])

Combination therapy

Osteoporosis is a multifactorial disease, thus combination therapy with agents with different mechanisms of action is considered reasonable. However, the efficacy of combination therapy lacks evidence at this time.

The Adequate Treatment of Osteoporosis (A-TOP) Research Group was authorized in the year 2000 by the Japan Society of Osteoporosis and assisted by the Public Health Research Foundation to obtain clinical evidence regarding osteoporosis treatment. It conducted a clinical trial comparing monotherapy with alendronate, a new bisphosphonate at the time, and combination therapy with alendronate and alfacalcidol, an active vitamin D_3 derivative developed in Japan (Japanese Osteoporosis Intervention Trial: JOINT-02). The incidence of vertebral fracture was significantly reduced in the combination therapy group during the first 6 months of treatment, and in both subgroups of patients with multiple vertebral fractures and grade 3 vertebral fractures by semiquantitative assessment during the 2-year treatment period (Fig. 14) [18]. The incidence of non-vertebral fracture (weight-bearing bones) was also significantly reduced in the combination therapy group. Based on these results, combination therapy with alendronate and an active vitamin D_3 derivative is recommended for the prevention of incident vertebral and non-vertebral fracture in patients at a high risk of fracture.

Secondary osteoporosis

Osteoporosis secondary to other diseases

Secondary osteoporosis is defined as decreased BMD and deteriorated bone quality (pathologic state specific to osteoporosis) having one or more causes in addition to genetic factors, lifestyle, menopause, and aging. Secondary osteoporosis that is caused by a disease, such as hyperparathyroidism, can be improved by treating the underlying disease.

Hyperparathyroidism can be classified into either primary hyperparathyroidism, a disorder of the parathyroid itself, or secondary hyperparathyroidism, a pathological state secondary to other disorders, such as chronic kidney disease or vitamin D deficiency/depletion. In both types of hyperparathyroidism, excessively secreted parathyroid hormone promotes bone turnover and consequently decreases the BMD, resulting in an increased fracture risk. However, the therapeutic strategies employed for each type are entirely different. Primary hyperparathyroidism is treated mainly by parathyroidectomy, and there is no evidence regarding pharmacologic treatment. Secondary hyperparathyroidism improves with treatment of its underlying disease. Hyperparathyroidism secondary to CKD should be treated in accordance with the Japanese Evidence-based Practice Guideline for the Treatment of CKD.

In rheumatoid arthritis, bone resorption increases and BMD decreases because of several factors, including activation of inflammatory cytokines, immobility, and use of glucocorticoids. Consequently, the fracture risk increases. Infliximab, an anti-TNF agent used to treat rheumatoid arthritis, increases BMD in patients with osteoporosis secondary to rheumatoid arthritis. Among the useful therapeutic medications for osteoporosis, bisphosphonates reduce fracture risk.

Osteoporosis secondary to lifestyle-related diseases

In recent years, it was demonstrated that bone metabolism is influenced by some atherosclerosis-inducing disorders such as diabetes mellitus, dyslipidemia, hypertension, and chronic kidney disease. In particular, osteoporosis caused by diabetes mellitus or CKD is established as "osteoporosis secondary to

Factors		*n*	HR	95% CI	*p* value
All randomized		2016	0.89	0.64–1.25	0.51
Age (years)	<75	805	0.87	0.47–1.63	0.67
	75≤ <80	662	1.19	0.67–2.13	0.54
	80≤	549	0.66	0.38–1.16	0.15
25(OH)vitamin D (ng/mL)	<20	435	1.02	0.47–2.24	0.96
	20≤	1426	0.84	0.57–1.23	0.36
Number of prevalent vertebral fracture	0	805	1.73	0.85–3.55	0.13
	1	626	1.28	0.66–2.47	0.46
	2≤	585	0.51	0.32–0.84	0.01
Maximum grade of prevalent vertebral fracture	0	805	1.74	0.85–3.55	0.13
	1	391	1.04	0.33–3.21	0.96
	2	395	0.89	0.46–1.71	0.72
	3	425	0.55	0.38–0.94	0.03

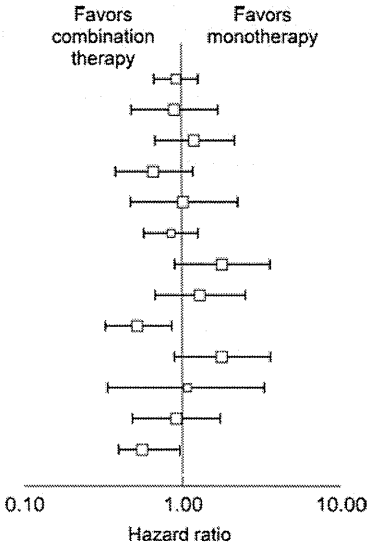


Fig. 14 Efficacy of combination therapy with alendronate and active vitamin D_3 on vertebral fracture. *HR* hazard ratio of incident vertebral fracture, *CI* confidence interval (Orimo [18] (Copyright© 2011 Informa Plc.))

lifestyle-related diseases", bringing it special attention within secondary osteoporosis. A vigorous assessment for osteoporosis is recommended in patients with these diseases.

Osteoporosis secondary to lifestyle-related diseases is mainly associated with deterioration in bone quality, whereas BMD is relatively well-preserved in most cases. Therefore, therapeutic intervention in patients with diabetes mellitus or CKD should be started as soon as "decreased bone mass" is identified, in accordance with the diagnostic criteria of osteoporosis.

The main cause of deterioration in bone quality in these patients is thought to be altered cross-links among the collagen molecules in bone tissue (nonphysiological collagen cross-links, i.e., advanced glycation endproducts) due to an increase in oxidative stress and acceleration of glycation.

While the therapeutic modality has not been established yet, the benefit of alendronate, risedronate, raloxifene, and parathyroid hormone derivatives has been reported in large clinical trials. Pentosidine is likely to be a marker for bone quality and is expected to be an index of the fracture risk.

Treatment-related osteoporosis

Glucocorticoid agents and sex hormone lowering therapy are important causes of treatment-related osteoporosis.

Systemically administrated glucocorticoid decreases bone mass and increases fracture risk, thus 50 % of patients under long-term treatment with glucocorticoids suffer from osteoporosis. In general, patients taking glucocorticoids at doses of 5 mg (prednisolone equivalent) or more per day for 3 months or more should be assessed for bone mass and the need for osteoporosis treatment. Moreover, it is recommended to start treatment at higher BMD values than those used in the criteria for treatment of primary osteoporosis. In Japan, a revision of the 2004 "Guidelines on the management and treatment of corticosteroid-induced osteoporosis" is being developed.

Even though guidelines currently recommend bisphosphonates for the treatment of glucocorticoid-induced osteoporosis, generally they are not recommended for women intending to become pregnant. Although teriparatide is expected to increase bone mass, it is indicated only for "osteoporosis with a high risk of fractures".

Endocrine therapy (sex hormone lowering therapy) for breast cancer and prostate cancer decreases BMD. Bisphosphonates can improve BMD in these patients, but there is no evidence yet about its ability to reduce fracture risk.

Conflicts of interest None.

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J Bone Miner Metab (2013) 31:1–15
DOI 10.1007/s00774-012-0392-y

SPECIAL REPORT

Guidelines for the use of bone metabolic markers in the diagnosis and treatment of osteoporosis (2012 edition)

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Received: 17 June 2012 / Accepted: 11 September 2012 / Published online: 10 November 2012

Abstract Recently the clinical application of bone metabolic markers has achieved significant progress and the measurements of these indices give us a better understanding of the pathogenesis of osteoporosis. Bone metabolic markers were adapted to select drug treatment for osteoporosis and to evaluate drug efficacy. Therefore, the proper application and assessment of bone metabolic markers in clinical practice is very important. To achieve these aims, the committee on the guidelines for the use of biochemical markers of bone turnover in osteoporosis authorized by the Japan Osteoporosis Society has summarized recent progress in bone markers and proposed the proper utilization of bone markers. Although the use of bone metabolic markers now has an important role in the daily management of osteoporosis, their use in Japan is still insufficient because of insurance coverage limitations. Since the Japan Osteoporosis Society first created the 2001 guidelines, new bone metabolic markers have been

For the Committee on the Guidelines for the Use of Biochemical Markers of Bone Turnover in Osteoporosis, Japan Osteoporosis Society Committee Organization.

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introduced into clinical practice. The availability of new osteoporosis treatments that promote bone formation has changed the clinical application of bone metabolic markers in current practice. Therefore, revisions to the current clinical practice are needed which led to the proposal to create these new 2012 guidelines.

Keywords Guideline · Bone metabolic marker · Osteoporosis

Introduction

Current definition and concepts in osteoporosis

Since osteoporotic fractures and the associated medical costs are a serious concern in an aging society, considerable effort has been made to prevent fractures [1]. In 2000, at the National Institutes of Health (NIH) consensus conference in the United States, osteoporosis was defined as 'a skeletal disorder in a person who already has compromised bone strength, thus increasing the risk of bone fracture' [2]. Bone strength is determined by integrating bone mass and bone quality. The measurement of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) is extraordinarily important for the diagnosis and monitoring of osteoporosis [3]. BMD measurements are widely used to diagnose osteoporosis in accordance with diagnostic criteria around the world [4]. Since low BMD is known to be an independent risk factor for future fractures, BMD measurement has been adapted as a predictive factor for fractures in the calculation of the 10-year fracture probability in the WHO fracture risk assessment tool (FRAX®) [5]. However, in terms of the judgment on the treatment efficacy on an individual level, the clinical significance of BMD measurement is still controversial [6].

Bone quality, which is another constitutional factor of bone strength, is characterized by the following components—bone microarchitecture, bone turnover rate, microdamage accumulation, degree of calcification, and properties of bone matrix proteins including collagen and other bone-specific proteins [7, 8]. Among them, bone turnover rate and the properties of bone matrix proteins can be assessed at every clinical site by the measurement of bone metabolic markers and bone matrix markers [9] in serum and urine. Recently the clinical application of bone metabolic markers has achieved significant progress and the measurements of these indices give us a better understanding of the pathogenesis of osteoporosis. Furthermore, some of the bone metabolic markers predict future fracture risk. The bone metabolic markers were adapted to select drug treatment for osteoporosis and to evaluate drug efficacy. Therefore, the proper application and assessment of bone metabolic markers in clinical practice is very important. To achieve these aims, the committee on the guidelines for the use of biochemical markers of bone turnover in osteoporosis authorized by the Japan Osteoporosis Society has summarized recent progress in bone markers and proposed the proper utilization of bone markers.

If the progression of osteoporosis is prevented with effective treatment, quality of life (QOL) will be maintained in osteoporosis patients, and the costs of medical care for fractures are thought to be reduced. Therefore, early diagnosis of osteoporosis, effective treatment in patients who already have osteoporosis, more accurate treatment monitoring, and evaluation of fracture risk are important. Currently, bone morphological parameters based on bone biopsy are evaluated to meet these requirements. The findings can serve as markers to ascertain bone dynamics, including degree and rate of bone calcification, extent and degree of bone resorption, and degree and rate of bone formation. In addition, bone biopsy is an essential means to evaluate bone architecture. However, bone biopsy is an invasive test and is therefore not performed repeatedly in general clinical settings. Moreover, the results only reflect localized bone changes at the bone tissue sample site and may be unsuitable for evaluation of systemic bone changes.

Recently, quantification of BMD as the main method to diagnose osteoporosis and measurement accuracy has dramatically improved. However, essential clinical parameters of osteoporosis include more dynamic markers such as bone metabolic markers. Bone metabolism undergoes daily dynamic changes, and even with the same BMD, the metabolic state differs and the pathologic significance also differs. Therefore, to use BMD measurement as a dynamic marker, one must wait for an observation period of 6 months to 1 year before remeasurement, whereas bone metabolic markers accurately reflect the state of bone metabolism at the point in time of the measurement.

Bone metabolic markers can also be used as a guide to selecting pharmacotherapy. When there is doubt about choosing a drug, the use of bone metabolic markers can enable a more appropriate selection. Furthermore, to evaluate the effects of drug therapy on disease improvement, assessing the state of bone metabolism at the time of diagnosis is recommended whenever possible (Fig. 1). However, if a decision is made to select treatment with little influence on bone metabolism, then measuring bone metabolic markers to monitor drug treatment effects has little clinical significance.

Since the mechanism of bone remodeling has come to be better understood, novel bone metabolic assays to measure the products of collagen metabolism have also been developed. These measurements are now available in

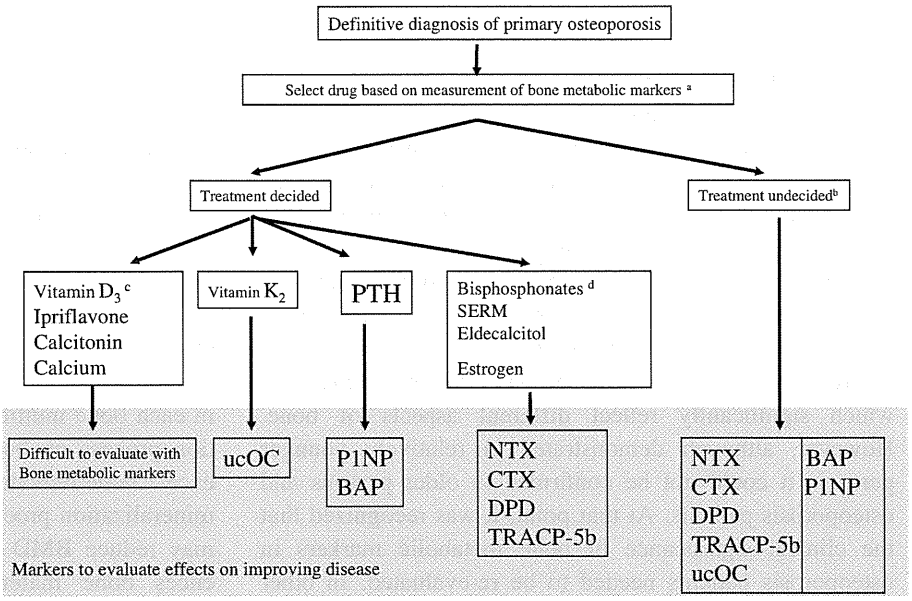

Fig. 1 Measurement of bone turnover markers in drug treatment of osteoporosis. This figure is taken from page 28 of the 2011 Osteoporosis Prevention and Treatment Guidelines (in Japanese). *a* In patients taking bisphosphonates, measure after stopping drug for at least 6 months, and in patients taking other osteoporosis drugs, measure after stopping drug for at least 1 month. *b* Measure one type each of a resorption marker and formation marker. *c* Excluding eldecalcitol. *d* In patients expected to be on long-term bisphosphonate therapy, measure bone resorption markers and BAP or P1NP

addition to those with a high sensitivity and specificity for the enzyme activity of osteoblasts and osteoclasts. Thus, bone metabolic markers have attained a position as a tool to clinically evaluate bone turnover. Other than bone metabolic markers, there are no other means to clinically evaluate bone turnover. Bone metabolic markers have become indispensable clinical test parameters in the management of osteoporosis and their use continues to expand. Guidelines for the use of bone metabolic markers in osteoporosis (2012 edition) are a revision of the 2004 edition [10] and subsequent new National Health Insurance (NHI) coverage of bone metabolic markers.

Changes in the diagnosis and treatment of osteoporosis

Together with significant changes in the disease concept of osteoporosis, new technology continues to be incorporated into clinical diagnosis and treatment of osteoporosis. With the introduction of DXA to measure BMD, more precise diagnostic criteria have been established [11]. The measurement of bone metabolic markers, approved by NHI in routine clinical practice in the field of osteoporosis, has allowed (1) estimation of bone turnover state at the time of measurement, (2) prediction of the rate of BMD change in near future, (3) assessment of the effect of drug treatment, and (4) evaluation of bone quality [10].

In addition, with the introduction into clinical practice of various bone antiresorptive drugs which can prevent fractures based on scientific evidence, the incidence of fractures due to osteoporosis has decreased according to epidemiologic studies [12].

In the future, with the goal of ideal treatment to increase bone mass, the risk of fracture or osteoporosis will be evaluated from the bone loss to decide whether to initiate drug treatment, and strategies will be sought to maintain or increase QOL in osteoporosis and assess fracture risk in lifestyle-related diseases. In other words, there will be relentless efforts towards establishing a comprehensive system to manage osteoporosis.

Change in views about the significance of measuring bone metabolic markers

The significance of measuring bone metabolic markers was originally considered important as a surrogate marker for BMD change rates, but now its significance as a means to evaluate bone quality [13] and to assess the future risk of fracture has been emphasized [14–16]. In addition, because the newly available antiresorptive drugs markedly inhibit bone metabolic markers, the measurement of bone metabolic markers is a useful means to assess drug efficacy [17, 18].

Although the use of bone metabolic markers now has an important role in the daily management of osteoporosis, their use in Japan is still insufficient because of insurance coverage limitations [19]. Since the Japan Osteoporosis Society first created the 2001 guidelines, new bone metabolic markers have been introduced into clinical practice. The availability of new osteoporosis treatments that promote bone formation has changed the clinical application of bone metabolic markers in current practice. Therefore, the necessity to revise the current clinical practice led to the proposal to create these new 2012 guidelines.

Changes in guidelines

If we look back at the process of creating the guidelines to date, from the 2001 edition [20] to the 2002 edition [21], there was a strong awareness of the relationship between bone metabolic markers and changes in BMD which was reflected in their actual use. On the other hand, in the 2004 guidelines [10], there was a marked shift regarding what is described below. Based on the terms 'bone resorption markers' and 'bone formation markers' it was conceived that changes in BMD might be determined by changes in the ratio of these two types of bone metabolic markers, which significantly reflect different aspects of bone. However, although demonstrated in relatively younger persons, it could not be confirmed in older persons and osteoporosis patients. At that point, it was recognized that the clinical significance of bone metabolic markers in osteoporosis patients needed to be re-evaluated. In other words, measurements of BMD and bone metabolic markers in osteoporosis management (each related to bone strength) were a means of observing two different aspects of bone. As stated by the NIH consensus conference [2], these two factors are also independent bone strength parameters. Conversely, the phenomenon of a discrepancy between changes in BMD and bone turnover with drug treatment is characteristic of the clinical picture of osteoporosis.

The fundamentals of clinical significance of bone metabolic markers

Since proper treatment of osteoporosis may be expected to reduce osteoporosis-related medical cost, the early diagnosis of osteoporosis and the precise understanding of bone dynamism in osteoporosis are important in terms of fracture prevention. Bone formation and resorption play a key role in maintaining bone mass volume and bone quality. Bone mineral content or density is increased by bone formation process regulated by osteoblasts, and decreased by bone resorption process regulated by osteoclasts. These two different cell activities are coupled and balanced by cross-talk between these two cellular processes in normal conditions. A few decades ago, bone morphometrical analysis of bone specimens was the only method to evaluate bone dynamism. Measured BMD is a powerful predictor of future fracture; however, the evaluation of individual values of BMD obtained during close observation of a patient, remains considerably controversial [6, 22]. Furthermore, areal densitometrical analysis gives us limited information about bone strength; in fact, this index does not provide bone material composition and structural design [23]. Therefore, the BMD value is not a complete surrogate to estimate bone strength. In addition to the areal mineral density, we need to know the cellular mechanisms responsible for bone modeling and remodeling which are mediated by osteoblasts and osteoclasts [24].

Bone modeling and remodeling change the size of bone and internal architecture by the deposition or removal of bone from the surface of bones. Bone strength therefore depends highly on the bone remodeling activity in reverse U-shape [7]. Bone remodeling activity also affects bone mineral apposition rate. Bone mineral accumulation consists of two metabolic processes—firstly primary calcification occurs mediated by osteoblasts followed by secondary calcification induced by non-cellular processes in each bone multicellular unit. Since this entire calcification process on bone takes approximately 3 months, the excess bone remodeling speed interferes with the complete mineralization process and the subsequent bone resorption may reduce BMD [24]. Bone remodeling strongly influences bone material properties including nature and amount of collagen as well as other bone-specific proteins such as bone sialoprotein, osteopontin or osteocalcin. Among them, the role of collagen metabolism and osteocalcin on bone strength has been well documented. Collagen cross-linking is a major post-translational modification and plays an important role in the biological and biochemical features of bone [25]. The proposed determinants of bone strength at the material level are the degree of mineralization of basic structure units, microdamage accumulation, and collagen cross-link formation; these are regulated by cellular activities and tissue turnover [23]. There are two types of collagen cross-link formation—one is enzymatic and the other is non-enzymatic one. Enzymatic cross-links are formed by lysyl hydroxylase- and lysyl oxidase-mediated processes [26]. On the other hand, non-enzymatic cross-links are produced by time-dependent glycation processes such as advanced glycation end-products. Impaired enzymatic cross-links and/or an increase in non-enzymatic cross-links in bone collagen are both determinants of impaired bone mechanical properties in aging, osteoporosis and diabetes mellitus [25]. The enzymatic synthesis of collagen cross-linkings is highly regulated by $1,25(OH)_2$ vitamin D_3 through expression of lysyl hydroxylase and lysyl oxidase. Therefore, vitamin D deficiency in bone may deteriorate bone strength [27]. In addition to vitamin D deficiency, homocysteine has been reported to be a negative regulator of enzymatic collagen cross-links via a reduction in gene expression and enzymatic activity of lysyl oxidase [28, 29]. Furthermore, recent progress in the risk analysis for fracture has revealed that mild elevation of plasma homocysteine is an independent predictor for future fracture [30, 31].

Osteocalcin is a bone-specific protein produced by osteoblasts. Osteocalcin receives subsequent post-translational modification on Glu residues to γ-carboxy glutamic

acid (Gla) in its molecule by vitamin K-dependent carboxylase. Secreted Gla containing osteocalcin binds to hydroxyapatite crystals in bone and bound Gla osteocalcin may be stabilized by hydroxyapatite crystals [32]. Since γ-carboxylation of osteocalcin depends highly on vitamin K nutrition, vitamin K deficiency produces under-carboxylated osteocalcin (ucOC), which has less ability to bind hydroxyapatite. Therefore, the serum level of ucOC is a sensitive marker for vitamin K deficiency in bone [33]. Although the exact mechanism is still obscure, many reports indicated that ucOC is an independent predictor for osteoporotic fracture [34, 35].

Basic principles in guideline development

These guidelines are proposed based on the following three basic principles:

- To provide a conceptual introduction about the significance of measuring bone metabolic markers in patients with osteoporosis;
- To revise the 2004 guidelines with a focus on bone metabolic markers for which assay methods have changed since creation of the 2004 guidelines, or which are newly covered by insurance; and to propose reference values as specific numerical values; and
- The proposed reference values are equally applicable to all Japanese persons.

Osteoporosis and bone metabolic marker assay methods

Deoxypyridinoline (DPD), a hydroxypyridinium cross-link, is formed during the extracellular maturation of fibrillar collagen and is released during mature collagen degradation. Measured values of DPD are not affected by the degradation of collagen after being newly synthesized, are not influenced by meals, and are thus highly specific for bone tissue. In urine, DPD is present as a free form (about 40 %) and a peptide-bound form (about 60 %) [9]. A highly sensitive immunoassay to measure type I collagen cross-linked telopeptide has been developed. Assay kits for both urinary type I collagen cross-linked N-telopeptide (uNTX) and type I collagen cross-linked C-telopeptide (uCTX) are commercially available [9]. The free form of DPD and collagen telopeptides containing NTX and CTX cross-linked sites have now been confirmed as useful clinical parameters to evaluate bone resorption, and simple immunoassays have been available since the 1990s (Table 1).

In Japan, clinical trials have been conducted in patients with osteoporosis, bone and calcium metabolic disorders, and metastatic bone disease; much clinical data have been accumulated on type I collagen cross-linked peptides and related measurements using immunoassays. As a result, in December 1999, the use of DPD and NTX as bone metabolic markers for osteoporosis was first approved for reimbursement by health insurance plans in Japan. These measurements are performed using the Osteolinks® DPD and Osteomark® NTx kits [10]. Both are enzyme-linked immunosorbent assay (ELISA) kits using urine samples. Four years later (2003), NHI also started to cover the measurement of urinary CTX (uCTX) using FRELISA® β CrossLaps® [36].

Thus, the measurement of urinary free DPD and telopeptide is becoming widespread in clinical practice. NTX and CTX can also be measured in blood. Measurements of serum NTX (sNTX) using the Osteomark® NTx serum kit, and blood (serum/plasma) CTX (sCTX) using the FRELISA® β CrossLaps® N kit was approved in 2003 [10]. In addition, bone tartrate-resistant acid phosphatase-5b (TRACP-5b), an isozyme of the osteoclast enzyme tartrate-resistant acid phosphatase, can be measured in blood (serum/plasma) using Osteolinks® TRAP-5b, which was approved in 2008 [37].

Bone formation markers are substances directly or indirectly produced by osteoblasts at each stage of osteoblast differentiation. They reflect various aspects of osteoblast function and bone formation, and most are measured in the blood. One of these, alkaline phosphatase (ALP), is an enzyme that plays an important role in osteoid formation and mineralization. The serum pool of total ALP consists of several isozymes from various tissues, including the liver, bone, intestine, spleen, kidneys, and placenta. In adults with normal liver function, about 50 % of total ALP activity in serum is from the liver, and 50 % is from bone [9]. Immunoassay of bone alkaline phosphatase (BAP) is widely performed for disorders of abnormal bone metabolism; the assay is similar to that used to measure bone formation markers. BAP immunoassays for abnormal bone metabolism including osteoporosis can be used clinically [38] using two assay kits— Osteolinks® BAP [enzyme immunoassay (EIA)] [10] and Access Ostase® [chemiluminescence enzyme immunoassay (CLEIA)] [38]. Type I procollagen-N-propeptide (P1NP), which is a metabolic product released when type I collagen (synthesized and secreted by osteoblasts) is cleaved by peptidase, can also be measured. Measurement using the Procollagen Intact P1NP kit was approved in 2010 [39].

Osteocalcin is well known as a bone-specific non-collagen protein secreted from osteoblasts. Insufficient γ-carboxylation and the glutamic acid type of osteocalcin, which is a bone matrix marker, is called ucOC and can be measured. Measurement using the Picolumi® ucOC kit was approved in 2007 [33].

Table 1 Bone turnover markers used in the diagnosis and treatment of osteoporosis

Marker	Abbreviation	Sample	Assay method	Comments
Bone formation markers				
Osteocalcin	OC	Serum	IRMA·ECLIA	IRMA: intact OC: not approved
				ECLIA: N-Mid OC: not approved
Bone alkaline phosphatase	BAP	Serum	EIA·CLEIA	
Type 1 procollagen-N-propeptide	P1NP[a]	Serum	RIA·ECLIA	RIA (intact P1NP)
				ECLIA (total P1NP): not approved
Bone resorption markers				
Pyridinoline	PYD	Urine	HPLC	Not approved
Deoxypyridinoline	DPD	Urine	HPLC·EIA·CLEIA	HPLC: not approved
Type 1 collagen cross-linked N-telopeptide	NTX	Serum/urine	EIA·CLEIA	CLEIA (urine): not approved
Type 1 collagen cross-linked C-telopeptide	CTX	Serum/plasma/urine	EIA·ECLIA	ECLIA (serum): not approved/in development
Tartrate-resistant acid phosphatase 5b	TRACP-5b	Serum/plasma	EIA	
Bone matrix-related markers				
Undercarboxylated osteocalcin	ucOC	Serum	ECLIA	
Pentosidine[a]	–	Plasma/urine	HPLC·EIA	HPLC: not approved
				EIA: not approved for the evaluation of bone/in development, but it is applied to evaluate renal function
Homocysteine[a]	HCY	Plasma/urine	HPLC·enzymatic·CLIA	HPLC·enzymatic·CLIA: not approved
				Applied to diagnose homocystinuria

Enzymatic: compatible with general purpose autoanalyzers widely used for clinical laboratory tests

Homocysteine: denotes total homocysteine (protein-bound form + free oxidized form + free reduced form). By HPLC, covered by National Health Insurance (homocystinuria, folate/vitamin B_{12} deficiency): National Health Insurance points 320

IRMA immunoradiometric assay, *ECLIA* electrochemiluminescent immunoassay, *EIA* enzyme immunoassay, *CLEIA* chemiluminescent enzyme immunoassay, *RIA* radio immunoassay, *HPLC* high-performance liquid chromatography, *CLIA* chemiluminescent immunoassay

[a] A promising bone quality marker if evidence for bone mass loss and bone fracture risk is further accumulated

Thus, various bone metabolic markers can be measured in osteoporosis management; however, there are some restrictions on their use for measurements under health insurance coverage in Japan. In osteoporosis, the primary purpose of measuring bone metabolic markers is to evaluate the state of bone metabolism in patients clinically diagnosed with osteoporosis in order to select drug treatment and assess treatment effects. Bone resorption markers, which reflect this state, are approved for measurement when starting treatment and once within 6 months after starting treatment to evaluate treatment effects.

Evaluation by measurement of bone metabolic markers

Now that fractures due to osteoporosis may be predicted, three types of evaluations are necessary in osteoporosis management. The first evaluation that should be performed is to assess the risk of bone fracture in each individual patient. Based on this, a decision is made whether to initiate drug therapy. The second evaluation is to select the most appropriate drug, and the third is the evaluation of treatment effects.

Evaluation of fracture risk should include BMD, history of previous fracture, bone metabolic markers, age, and the risk of falling. FRAX® is also used as a standard to evaluate fracture risk and determine the need for drug therapy. Bone metabolic marker values are useful as parameters to assess fracture risk [40]. In selecting drug therapy, evaluation of nutritional disorders and evaluation of bone turnover are important factors. In particular, evaluation of the therapeutic effect of bone antiresorptive drugs, changes in BMD and bone metabolic markers, the occurrence of new fractures, and changes in QOL are important factors to assess treatment effects. At each stage of osteoporosis treatment, measurement of bone metabolic markers provides an important basis for evaluation. Measurement of BMD is also important, but the measurement methods are limited and various (non-uniform) measurement sites and methods are also a major drawback. In contrast, values of bone metabolic markers can easily be obtained at any institution. Bone metabolic markers, as compared to BMD, fractures, and QOL, show earlier changes and, characteristically, the degree of change may be remarkable. Furthermore, an early decrease in bone resorption marker values during treatment reflects a reduction in long-term fracture risk [41, 42].

In other words, appropriate evaluation of changes in bone metabolic markers at the earliest stage provides a basis for deciding whether to continue treatment. Increased BMD alone has recently been shown to under-estimate the reduction in fracture risk with bone antiresorptive therapy [43]. Even in a setting where BMD can be measured, the measurement of bone metabolic markers has been established as an essential tool to supplement BMD measurement. However, when assessing treatment effects, bone metabolic markers are significant for both bone antiresorptive and bone formation-promoting parathyroid hormone (PTH) drugs, particularly teriparatide (daily subcutaneous injection). Measured values of bone metabolic markers, irrespective of BMD and history of previous fracture, are an independent predictor of new fractures [40]. This serves as a basis for using bone antiresorptive drugs with higher antiresorptive effects in patients with elevated values. Bone metabolic markers show relatively large changes in response to treatment with bone antiresorptive drugs. Showing patients the changes in these values may increase treatment compliance; this is also an advantage of using bone metabolic markers [44].

Appropriate use of bone metabolic markers in the diagnosis and treatment of osteoporosis

Specimen collection and handling

Bone metabolic marker values in individual patients are known to have diurnal variations [9]. Therefore, early morning fasting urine and blood samples are recommended. However, TRACP-5b, BAP, P1NP and ucOC levels are not affected by food intake, so collection of fasting samples is not necessary. For measurement of urinary DPD, uNTX, and uCTX, values should be corrected for creatinine using early morning first- or second-voided urine samples [9].

When measuring bone metabolic markers to evaluate bone metabolism for the purpose of initiating drug therapy, if other drugs that affect bone and calcium metabolism are discontinued for at least 1 month previously, they will have little influence on bone metabolic marker values. However, the effects of bisphosphonates may last for at least 3 months. For patients who are already on drug therapy, bone metabolism should be assessed while the current medication is being continued.

When repeated measurements are performed on the same patient, some bone metabolic markers may have intra-day or inter-day variations. Therefore, samples should be collected and handled consistently (i.e., same time of day).

Recently, a high prevalence of chronic kidney disease (CKD) has been increasingly recognized in elderly patients, particularly women [45], in whom osteoporosis often co-exists. Among various bone metabolic markers in serum, some markers accumulate in serum due to impairment of urinary excretion by renal dysfunction, while others do not (Table 2) [46]. Since urinary bone metabolic

Table 2 Influence of renal function on bone turnover markers

Marker	Effect of renal dysfunction
Bone formation markers	
OC	(+)
BAP	(−)
P1NP	(−)
Bone resorption markers	
PYD	(+)
DPD	(+)
NTX	(+)
CTX	(+)
TRACP-5b	(−)
Bone matrix-related marker	
ucOC	(+)

Decreased renal function: ≥Stage 3 CKD: (+) is affected by the marker, (−) is not affected by the marker

OC osteocalcin, *BAP* bone alkaline phosphatase, *P1NP* Type 1 procollagen-N-propeptide, *PYD* pyridinoline, *DPD* deoxypyridinoline, *NTX* Type 1 collagen cross-linked N-telopeptide, *CTX* Type 1 collagen cross-linked C-telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *ucOC* undercarboxylated osteocalcin

markers are excreted into urine by the kidney, they should be affected by renal dysfunction. Moreover, urinary levels of bone metabolic markers are corrected for urinary creatinine. Age-related decline in activities of daily living and in muscle mass can also decrease serum creatinine levels and thus urinary creatinine excretion [47]. Therefore, when bone metabolic state is estimated using the marker dependent on renal function, one should be careful to interpret the data taking into account the possible apparent effect of renal dysfunction, independent of bone metabolic state. Moreover, long-term treatment is usually required in the clinical practice of osteoporosis, and these age-related issues should be kept in mind when interpreting the values.

Therefore, the measurement of bone metabolic markers independent of renal dysfunction allows one to assess the bone metabolic state precisely without being affected by age-related issues which may result in false interpretation.

Reference values and abnormal values [42, 48–52]

In osteoporosis, the degree of bone formation and resorption, as evaluated by bone metabolic markers which reflect the underlying condition, may not be in agreement. In many cases, the degree of bone resorption is more prominent than the degree of bone formation. Therefore, prior to treatment of patients with a definitive osteoporosis diagnosis, the status of bone metabolism can be more clearly ascertained by simultaneous measurement of both bone formation and resorption markers. Reference values for bone metabolic markers are within the range of mean ±1.96 SD of the values established in healthy premenopausal women (Table 3). When bone metabolic marker values are high (exceeding reference values stratified by gender and menopause), metastatic bone tumors, other bone metabolism disorders, or calcium metabolism abnormalities may be present which warrant further examination (Table 4).

Evaluation of bone loss and fracture risk using bone metabolic markers

An increase in systemic bone turnover reflected by high bone metabolic marker values is associated with future bone loss independent of bone mass and other osteoporosis risk factors. This does not apply, however, when the high values are due to increases in localized bone resorption due to fracture or arthritis. Values of bone formation markers above the upper reference range limits, and values of bone resorption markers >1.0 SD above the mean in healthy premenopausal women, indicate a high future risk of bone loss [9, 10]. However, in osteoporosis patients who already have a reduction in bone mass, bone metabolic marker values have not been shown to be predictive of future bone mass changes [9].

In a prospective epidemiologic study, high bone metabolic marker values were reported to be related to an increase in fracture risk (vertebral and femoral neck fractures) associated with osteoporosis. In cases where bone resorption markers show values above the upper reference range limits (>1.96 SD above the mean in healthy premenopausal women), a high future fracture risk has also been reported [53]; however, sufficient consensus has not been achieved to date.

Selection of drug treatment using bone metabolic markers

Bone metabolic markers, particularly measured values of the bone resorption markers DPD, NTX, CTX, and TRACP-5b, serve as a basis for selecting drug therapy. Drugs with bone antiresorptive effects, including bisphosphonates, selective estrogen receptor modulators (SERMs), estrogen, and activated vitamin D_3 (particularly, eldecalcitol) are recommended for patients with elevated values above the upper reference range limits. However, drug selection should be based on a comprehensive assessment, including BMD, history of previous fractures, bone metabolic marker values, patient background factors, symp-

Table 3 Bone turnover marker reference values and established conditions

Type of marker (assay method)	Reference values	Established conditions (women)
Bone formation markers		
BAP (CLEIA)[a]	2.9–14.5 μg/L	Premenopausal
BAP (EIA)[b]	7.9–29.0 U/L	30–44 years
P1NP[c]	17.1–64.7 μg/L	30–44 years
Bone resorption markers		
DPD[b]	2.8–7.6 nmol/mmol Cr	30–44 years
sNTX[b]	7.5–16.5 nmol BCE/L	40–44 years
uNTX[b]	9.3–54.3 nmol BCE/mmol Cr	30–44 years
sCTX[c]	0.100–0.653 ng/mL	30–44 years
uCTX[b]	40.3–301.4 μg/mmol Cr	30–44 years
TRACP-5b[a]	120–420 mU/dL	Young adult mean (YAM 30–44 years)
Bone matrix marker		
ucOC[a]	3.94 ng/mL (not established as reference value)	Upper limit in women ≤44 years
	4.5 ng/mL	Cut-off value for the determination of vitamin K insufficiency (more frequent use in clinical setting)
	5.5 ng/mL	Cut-off value for the risk of fracture

Reference values of bone metabolic markers are within the range of the mean ± 1.96 SD, as established in healthy premenopausal women

Established condition shows the age range for which data was collected

BAP bone alkaline phosphatase, *BCE* bone collagen equivalents, *CLEIA* chemiluminescent enzyme immunoassay, *EIA* enzyme immunoassay, *P1NP* Type 1 procollagen-N-propeptide, *DPD* deoxypyridinoline, *sNTX* and *uNTX* serum and urinary (respectively) Type 1 collagen cross-linked N-telopeptide, *sCTX* and *uCTX* serum and urinary (respectively) Type 1 collagen cross-linked C-telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *ucOC* under-carboxylated osteocalcin

[a] Described in kit manufacturer's package insert or manufacturer's in-house data

[b] Described in 2004 guidelines

[c] Article being prepared for submission

Table 4 Bone turnover marker values to consider prompt search for serious bone disease such as metastatic bone tumors or bone/calcium metabolic disorders other than osteoporosis

Type of marker (assay method/sample)	Men	Premenopausal women	Postmenopausal women	Units
Bone formation markers				
BAP (CLEIA)[a]	>20.9	>14.5	>22.6	μg/L
BAP (EIA)[b]	>44.0	>29.0	>75.7	U/L
P1NP[c]	>66.8	>64.7	>79.1	μg/L
Bone resorption markers				
DPD[b]	>5.6	>7.6	>13.1	nmol/mmol Cr
sNTX[b]	>17.7	>16.5	>24.0	nmol BCE/L
uNTX[b]	>66.2	>54.3	>89.0	nmol BCE/mmol Cr
sCTX[c]	>0.845	>0.653	>1.030	ng/mL
uCTX[a]	>299.0	>301.4	>508.5	μg/mmol Cr
TRACP-5b[a]	>590	>420	>760	mU/dL

As a bone metabolic marker in metastatic bone tumors, there is a type I collagen-C-telopeptide (1CTP) assay

With elevated values of bone metabolic markers (≥mean ± 1.96 SD), bone diseases such as metastatic bone tumors, or bone/calcium metabolic disorders such as hyperparathyroidism or hyperthyroidism, should be suspected

Be careful of differences in cut-off values among facilities

BAP bone alkaline phosphatase, *CLEIA* chemiluminescent enzyme immunoassay, *EIA* enzyme immunoassay, *P1NP* Type 1 procollagen-N-propeptide, *DPD* deoxypyridinoline, *sNTX* and *uNTX* serum and urinary (respectively) Type 1 collagen cross-linked N-telopeptide, *sCTX* and *uCTX* serum and urinary (respectively) Type 1 collagen cross-linked C-telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *Cr* creatinine, *BCE* bone collagen equivalent

[a] Partially revised from the kit manufacturer's package insert or manufacturer's in-house data

[b] Described in the 2004 guidelines

[c] Described in manufacturer's in-house data and article in preparation for submission