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Risk factors for falls in a longitudinal population-based cohort study of Japanese men and women: The ROAD Study

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ABSTRACT

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). A total of 452 men and 896 women were analyzed in the present study (mean age, 63.9 years). A questionnaire was used to assess the number of falls during the 3-year follow-up. Grip strength, 6-m walking time, and chair stand time were measured at baseline. Knee osteoarthritis (OA) and lumbar spondylosis were defined as Kellgren Lawrence = 2, 3 or 4. Vertebral fracture (VFx) was assessed with the Japanese Society of Bone and Mineral Research criteria. Osteoporosis was defined by bone mineral density using dual energy X-ray absorptiometry based on World Health Organization criteria. Knee and lower back pain were estimated by an interview. During a 3-year follow-up, 79 (17.4%) men and 216 (24.1%) women reported at least one fall, and 54 (11.9%) men and 111 (12.4%) women reported multiple falls. Knee pain was a risk factor for multiple falls in women, but not in men. VFx tended to be associated with multiple falls in women, but not in men. A longer 6-m walking time was a risk factor for multiple falls in women, whereas a longer chair stand time was a risk factor for multiple falls in men. We found gender differences in risk factors for falls.

Introduction

Falls are one of the main causes of injury, disability, and death among the elderly [1,2]. In Japan, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, falls and fractures are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living [3]. However, few population-based studies have been performed on the incidence of falls based on sex and age. Furthermore, in terms of factors associated with falls, muscle strength, balance, vision, functional capacities, and cognitive impairment are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures [4,5]. However, the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues because they cause chronic pain and disability [6,7]. The prevalence rates of radiographic knee OA and LS are 54.6% and 70.2%, respectively, in persons aged 40 years and older in Japan, which indicates that 25,300,000 and 37,900,000 persons aged 40 years and older are estimated to experience radiographic knee OA and LS, respectively [10]. The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require support with activities of daily living [3], but there have been few studies of the association between falls and OA [11,12]. In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain [13], but its correlation with the radiographic severity of knee OA is not as strong as expected [8]. In fact, in a study in Japan, approximately 20% of persons without knee OA had knee pain, and 30% of persons with severe knee OA had no knee pain [8]. Thus, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA [8]. Our previous study showed that knee pain is significantly associated with falls in women [14], but that study used a cross-sectional design; thus, a causal relationship remains unclear. Regarding LS, to the best of our knowledge, no population-based studies have been performed

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regarding its association with falls except for our previous cross-sectional study [14], which showed that LS is not significantly associated with falls. In addition, among fractures due to osteoporosis (OP), vertebral fracture (VFx) is the most likely to lead to marked public health problems. VFx is reportedly associated with functional impairment [15], back pain, kyphosis [16,17], esophageal reflux [18], depressive mood [19], respiratory dysfunctions [20], and mortality [21]. However, whether VFx is an independent risk factor for the incidence of falls remains unclear.

Measuring walking speed is a simple way to assess health and function in older adults [22,23]. Walking speed has been found to be associated with falls in a few studies [4,24–26], although most studies were limited by a small sample size, a cross-sectional design [24,25], or evaluation of a single sex [4,26]. In addition, although walking abnormalities indicative by a slower walking speed are significantly associated with bone and joint diseases such as knee OA, LS, and their associated pain [14], no longitudinal studies have been performed to determine the associations of falls with bone and joint diseases and walking abnormalities at the same time. Furthermore, measuring the chair stand time is also reported to be a simple and established method to assess health and function in the elderly [27,28], but to the best of our knowledge, no longitudinal studies have been performed to determine the associations of falls with chair stand time.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls [12], indicating that single and multiple falls may have different backgrounds. Thus, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with the incidence of single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods

Participants

The ROAD study is a nationwide, prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OP and OA are the representative bone and joint diseases, respectively). ROAD consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [8–10,29]; a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.6 years) who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [30]. The participation rate was 75.6%. Participants in mountainous and coastal regions were also recruited from the resident registration lists, and the participation rates in these two areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Assessment of falls

Three years after the baseline data were obtained, we attempted to trace and review all 3,040 participants between 2008 and 2010; they were invited to attend a follow-up interview. All participants were interviewed with regard to falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 3-year follow-up, and if yes, how many falls did you experience"? At baseline, all participants were also interviewed regarding falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience"? According to a previous study on falls [31], a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment

All participants were interviewed by experienced orthopedists regarding knee pain and lower back pain at baseline and were asked the following questions based on previous studies [8,9]: "Have you experienced knee pain on most days in the past month, in addition to now"? and "Have you experienced lower back pain on most days in the past month, in addition to now"? Those who answered "yes" were defined as having pain. Buttock pain and sciatica were not included as lower back pain in the present study.

Radiographic assessment

At baseline, all participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot-map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. VFx was assessed by lateral radiographs of the lumbar spine (L1-L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria [32]. The films were marked up, and morphometric measurements of anterior, middle, and posterior heights on lateral radiography of the thoracic and lumbar spine were made. Wedge appearance was defined as a site at which the anterior height of the vertebra was $\leq$75% of the posterior height. Biconcave appearance occurred if the height of the central part of the vertebra was $\leq$80% of that of the anterior or posterior parts of the vertebra. Crush appearance occurred if the height of the anterior, central, and posterior parts of an axial vertebra were all reduced to $\leq$80% of the normal value (Supplementary Fig. 1). Knee and lumbar spine radiographs were also read without knowledge of the participant's clinical status by a single, experienced orthopedist (S.M.) using the Kellgren Lawrence (KL) radiographic atlas [33] to determine the severity of KL grading. Radiographs were scored as grade 0–4, with higher grades associated with more severe OA. We defined knee OA and LS as KL $\geq$2 in at least one knee and one intervertebral level, respectively. To evaluate the intraobserver variability of KL grading, 100 randomly selected radiographs of the knee and lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopedic surgeons (S.M. and H.O.) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Bone mineral density (BMD) measurement

BMD was measured at the lumbar spine (L2–4) and the proximal femur using dual energy X-ray absorptiometry (DXA) (Hologic

Discovery; Hologic, Waltham, MA, USA) at baseline. For quality control, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations at different regions. The BMD of the phantom was adjusted to 1.032±0.016 g/cm^2 (±1.5%) during all examinations. In addition, the same physician (N.Y.) examined all participants to prevent observer variability. Coefficient of variance (CV) for L2–L4 in the phantom was 0.35%, and CVs for L2–L4, the proximal femur, Ward's triangle, and the trochanter examined in five volunteers were 0.61–0.90, 1.02–2.57, 1.97–5.45, and 1.77–4.17%, respectively [34].

OP was defined based on World Health Organization (WHO) criteria in which OP was diagnosed as T-scores of BMD ≤2.5 standard deviations (SDs) lower than peak bone mass [35]. Mean L2–4 BMD (SD) for young adult men and women measured using the Hologic QDR devices in Japan is reportedly 1.011 g/cm^2 (0.119 g/cm^2) [36]. Mean femoral neck BMD (SD) in Japan is reported to be 0.863 g/cm^2 (0.127 g/cm^2) for young men and 0.787 (0.109) for young women [36]. The present study therefore defined OP using these indices as lumbar spine BMD <0.714 g/cm^2 for both men and women, and as femoral neck BMD <0.546 g/cm^2 for men and <0.515 g/cm^2 for women.

Physical performance

At baseline, anthropometric measurements were taken, including height and weight, and body mass index (BMI) (weight [kg]/height^2 [m^2]) was estimated based on the measured height and weight. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD, Saitama, Japan), and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded. Participants were told to walk from a marked starting line to a 6-m mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of two trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly persons [37]. The time taken for five consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al. [27] and used by other researchers [28]. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "Go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate [27].

Cognition assessment

At baseline, cognition was also evaluated for all participants using a Mini-Mental State Examination, and a cut-off score of <24 was used to select participants with cognitive impairment [38].

Statistical analyses

The differences in age and anthropometric measurements between the responders (those who completed the study) and non-responders (those lost to follow-up or who did not complete the study as described below) and between men and women were examined with a non-paired Student's *t*-test. Differences in physical performance measurements between the responders and non-responders and between men and women were examined with Wilcoxon signed-rank test. Differences in age and anthropometric measurements, among non-fallers, single fallers, and multiple fallers, were examined with one-way analysis of variance. Differences in physical performance measurements among non-fallers, single fallers, and multiple fallers were examined with the Kruskal–Wallis test. The prevalence of bone and joint diseases and cognitive impairment was compared between men and women and among non-fallers, single fallers, and multiple fallers with the chi square test. Multinomial logistic regression analysis after adjusting for age and BMI was used to determine the association of anthropometric measurements, physical performance, bone and joint diseases, and cognitive impairment with single and multiple falls compared with the absence of falls in men and women. Further, to determine an independent association of physical performance with single and multiple falls compared with the absence of falls, we used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory variables. To determine independent risk factors for single and multiple falls, we used multinomial logistic regression analysis with age, BMI, physical performance, bone and joint diseases, and cognitive impairment as explanatory variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1,690 participants in the mountainous and seaside cohorts at baseline in 2006 and 2007, 40 (2.4%) had died by the time of the review 3 years later, 97 (5.7%) did not participate in the follow-up study due to poor health, 16 (0.9%) had moved away, 51 (3.0%) declined the invitation to attend the follow-up study, and 47 (2.8%) did not participate in the follow-up study for other reasons. Among the 1,439 volunteers who did participate in the follow-up study, 68 (4.0%) provided incomplete fall questionnaires. In addition, six (0.4%) provided incomplete pain questionnaires; these were excluded. We also excluded eight (0.5%) participants who had undergone total knee arthroplasty before baseline. An additional nine (1.9%) participants did not perform the 6-m walking time or chair stand time, leaving a total of 1,348 (79.8%) participants (452 men and 896 women) from whom radiographs at baseline and complete fall and pain histories were obtained. The mean followup time was 2.93±0.12 years, ranging from 2.65 to 3.22 years. Table 1 shows characterisctics of responders and non-responders. The responders were significantly younger than the non-responders (63.9 and 70.7 years, respectively). Physical performance measurements were better in responders than non-responders. Prevalence of knee OA, LS and knee pain was lower in responders (47.0, 61.6 and 9.7%,

Table 1
Baseline characteristics of responders and non-responders.

	Overall	Responders	Non-responders
Number of participants	1,690	1,348	342
Female (%)	64.7	66.5	57.9***
Age (years)	65.2±12.0	63.9±11.8	70.7±11.4*
Height (cm)	155.2±9.3	155.6±9.0	153.6±10.1*
Weight (kg)	55.6±10.8	56.1±10.7	53.7±10.8*
BMI (kg/m^2)	23.0±3.4	23.1±3.4	22.7±3.4
Grip strength (kg) (median [IQR])	26.0 [21.0–33.0]	26.0 [21.0–34.0]	24.0 [18.0–30.0]**
6-m walking time (s) (median [IQR])	5.0 [4.0–7.0]	5.0 [4.0–6.0]	7.0 [5.0–9.0]**
Chair stand time (s) (median [IQR])	9.0 [7.0–12.0]	9.0 [7.0–11.0]	12.0 [8.25–15.0]**
Cognitive impairment (%)	4.5	2.8	11.4***
Radiographic knee OA (%)	50.4	47.0	63.8***
Radiographic LS (%)	63.2	61.6	69.1***
Radiographic VFx	10.1	9.7	12.0
Knee pain (%)	24.3	22.2	32.6***
Lower back pain (%)	21.1	20.6	22.9
Previous falls (%)	17.3	16.3	21.0***

Values are mean±SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. responders by non-paired Student's *t*-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

Table 2
Baseline characteristics of participants.

	Men	Women
Number of participants	452	896
Age (years)	64.9 ± 11.7	63.3 ± 11.8*
Height (cm)	164.0 ± 7.0	151.3 ± 6.6*
Weight (kg)	63.3 ± 10.7	52.5 ± 8.7*
BMI (kg/m^2)	23.5 ± 3.2	22.9 ± 3.4*
Grip strength (kg) (median [IQR])	37.0 [32.0–42.5]	23.5 [20.0–23.5]**
6-m walking time (s) (median [IQR])	5.0 [4.0–6.0]	5.0 [4.0–6.0]
Chair stand time (s) (median [IQR])	8.5 [7.0–11.0]	9.0 [7.0–11.0]
Cognitive impairment (%)	3.6	2.4
Radiographic knee OA (%)	37.4	51.9***
Radiographic LS (%)	76.1	54.2
Radiographic VFx	8.9	10.1
Knee pain (%)	15.3	25.7***
Lower back pain (%)	18.8	21.5
Previous falls (%)	13.1	18.0***

Values are mean ± SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. men by non-paired Student's t-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

respectively) than non-responders (63.8, 69.1 and 12.0, respectively). Prevalence of previous falls was significantly lower in responders than non-responders (16.3 and 21.0%, respectively).

Table 2 shows the age, anthropometric measurements, physical performance, and prevalence of cognitive impairment, bone and joint diseases, and previous falls of participants at baseline in men and women. Regarding physical performance, grip strength and chair stand time were significantly better in men (37.0 kg and 8.5 s, respectively) than in women (23.5 kg and 9.0 s, respectively), but the 6-m walking time was not (5.0 s and 5.0 s, respectively). The prevalence of radiographic knee OA and knee pain was significantly higher in women (51.9% and 25.7%, respectively) than in men (37.4% and 15.3%, respectively), whereas that of LS and lower back pain was not different between men and women. The prevalence of previous falls was significantly higher in women than in men (18.0% and 13.1%, respectively).

During the 3-year follow-up, 79 (17.4% [95% confidence interval [CI] 14.3–21.2]) men and 216 (24.1% [95% CI 21.4–27.0]) women reported at least one fall, and 54 (11.9% [95% CI 9.3–15.3]) men and 111 (12.4% [95% CI 10.4–14.7]) women reported multiple falls. The chi square test showed that the incidence of falls was significantly different between men and women ($p=0.0011$). The incidence of single and multiple falls was significantly higher in the mountainous regions (11.5% and 17.4%, respectively) than coastal regions (8.1% and 7.8%, respectively). With increasing age, the incidence of falls increased in women, but the incidence of falls was similar in men in their 60s and 70s (Fig. 1).

Table 3 shows the age, anthropometric measurements, physical performance, and BMD at baseline between non-fallers, single fallers, and multiple fallers. Age and BMI were significantly higher in female fallers than non-fallers, but this was not the case in men. Grip strength was worse in female fallers than non-fallers, but this was not the case in men. The 6-m walking time and chair stand time were longer in both male and female fallers than in non-fallers. LS and neck BMD were significantly lower in female fallers than non-fallers, but this was not the case in men.

We next examined the incidence rate of falls during the 3-year follow-up according to previous falls at baseline in men and women (Supplementary Fig. 2). The incidence rates of multiple falls were 7.9%, 22.7%, and 48.7% in men and 8.8%, 20.4%, and 43.1% in women among non-fallers, single fallers, and multiple fallers, respectively. The incidence rates of single falls were 5.9%, 9.1%, and 0.0% in men and 12.5%, 7.8%, and 8.6% in women among non-fallers, single fallers, and multiple fallers, respectively. The chi square test showed that the incidence of falls during the 3-year follow-up was significantly associated with previous falls at baseline in men and women ($p<0.0001$).

Fig. 2 shows the incidence rate of falls during the 3-year follow-up according to the presence of bone and joint diseases and cognitive impairment. The incidence rates of multiple falls were 16.6% and 9.2% in men and 14.8% and 9.7% in women in those with and without knee OA, respectively. The incidence rates of a single fall were 8.3% and 3.9% in men and 14.2% and 9.1% in women in those with and without knee OA, respectively. The chi square test showed that knee OA at baseline was significantly associated with the incidence rate of falls during the 3-year follow-up in men and women ($p<0.0001$). Regarding knee pain, the incidence rates of multiple falls were 18.8% and 10.7% in men and 18.7% and 10.2% in women in those with and without knee pain, respectively. The incidence rates of a single fall were 8.7% and 5.0% in men and 10.4% and 10.4% in women in those with and without knee OA, respectively. The chi square test showed that knee pain at baseline was significantly associated with the incidence of falls during the 3-year follow-up in men and women ($p<0.0001$). LS and lower back pain were not significantly associated with the incidence of falls in men ($p=0.52$ and 0.77, respectively) or in women ($p=0.45$ and 0.58, respectively). VFx at baseline was significantly associated with the incidence of falls in women (multiple falls 22.2% and 11.3%, single falls 14.4% and 11.4%, in those with and without VFx, respectively, $p=0.005$), but not in men ($p=0.06$). OP defined by L2–4 and femoral neck BMD was not associated with the incidence of falls in men and women. Cognitive impairment

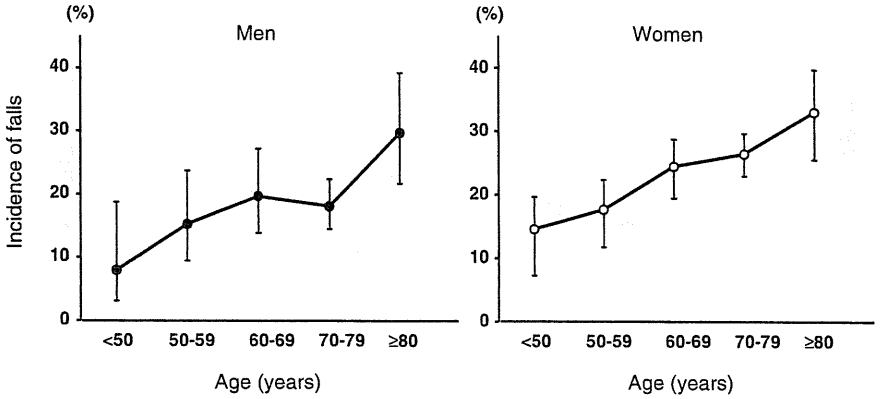

Fig. 1. Incidence rate of falls (error bars represent 95% confidence intervals) by gender and age strata.

Table 3
Comparison of characteristics among non-fallers, single fallers, and multiple fallers in men and women.

	Men				Women			
	Non-fallers	Single fallers	Multiple fallers	p value	Non-fallers	Single fallers	Multiple fallers	p value
Number of participants	373	25	54		680	105	111	
Age (years)	64.4 (11.7)	67.2 (13.2)	67.6 (10.1)	0.10	62.4 (11.6)	66.0 (12.6)	66.7 (11.4)	<0.001
BMI (kg/m^2)	23.4 (3.1)	24.6 (3.9)	23.7 (3.3)	0.16	22.8 (3.5)	22.7 (3.1)	23.8 (3.5)	0.01
Grip strength (kg) (median [IQR])	37.0 [32.0–43.0]	37.0 [30.0–41.5]	35.0 [28.8–40.0]	0.08	24.0 [20.0–27.0]	23.0 [19.5–27.0]	22.0 [18.0–26.0]	0.01
6-m walking time (s) (median [IQR])	4.5 [4.0–6.0]	5.5 [4.6–7.3]	6.2 [5.0–6.6]	<0.0001	5.0 [4.0–6.0]	5.0 [4.0–6.5]	5.5 [4.0–7.5]	<0.0001
Chair stand time (s) (median [IQR])	8.0 [7.0–10.0])	11.0 [9.0–12.0]	10.0 [8.0–13.0]	<0.0001	9.0 [7.0–11.0]	9.0 [8.0–12.0]	10.0 [8.0–12.25]	0.0001
LS BMD	1.05 (0.20)	1.05 (0.20)	1.05 (0.15)	0.99	0.89 (0.18)	0.85 (0.16)	0.86 (0.17)	0.04
Neck BMD	0.75 (0.13)	0.77 (0.12)	0.75 (0.10)	0.79	0.65 (0.13)	0.61 (0.11)	0.63 (0.11)	0.003

Values are the means (standard deviation), except where indicated.
One-way analysis of variance was used to determine the differences in age, height, weight and BMI among non-fallers, single fallers, and multiple fallers.
Kruskal–Wallis test was used to determine the differences in grip strength, 6-m walking time and chair stand time among non-fallers, single fallers, and multiple fallers.
The chi square test was used to determine the differences in the prevalence of cognitive impairment among non-fallers, single fallers, and multiple fallers.
BMI: body mass index, LS: lumbar spondylosis, BMD: bone mineral density.

was associated with the incidence of falls in men (multiple falls 31.3% and 10.9%, single falls 18.8% and 5.1%, in those with and without cognitive impairment, respectively, $p=0.002$), but not in women ($p=0.19$).

In men, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time, longer chair stand time, and previous falls were risk factors for falls, but grip strength, bone and joint diseases, and cognitive impairment were not

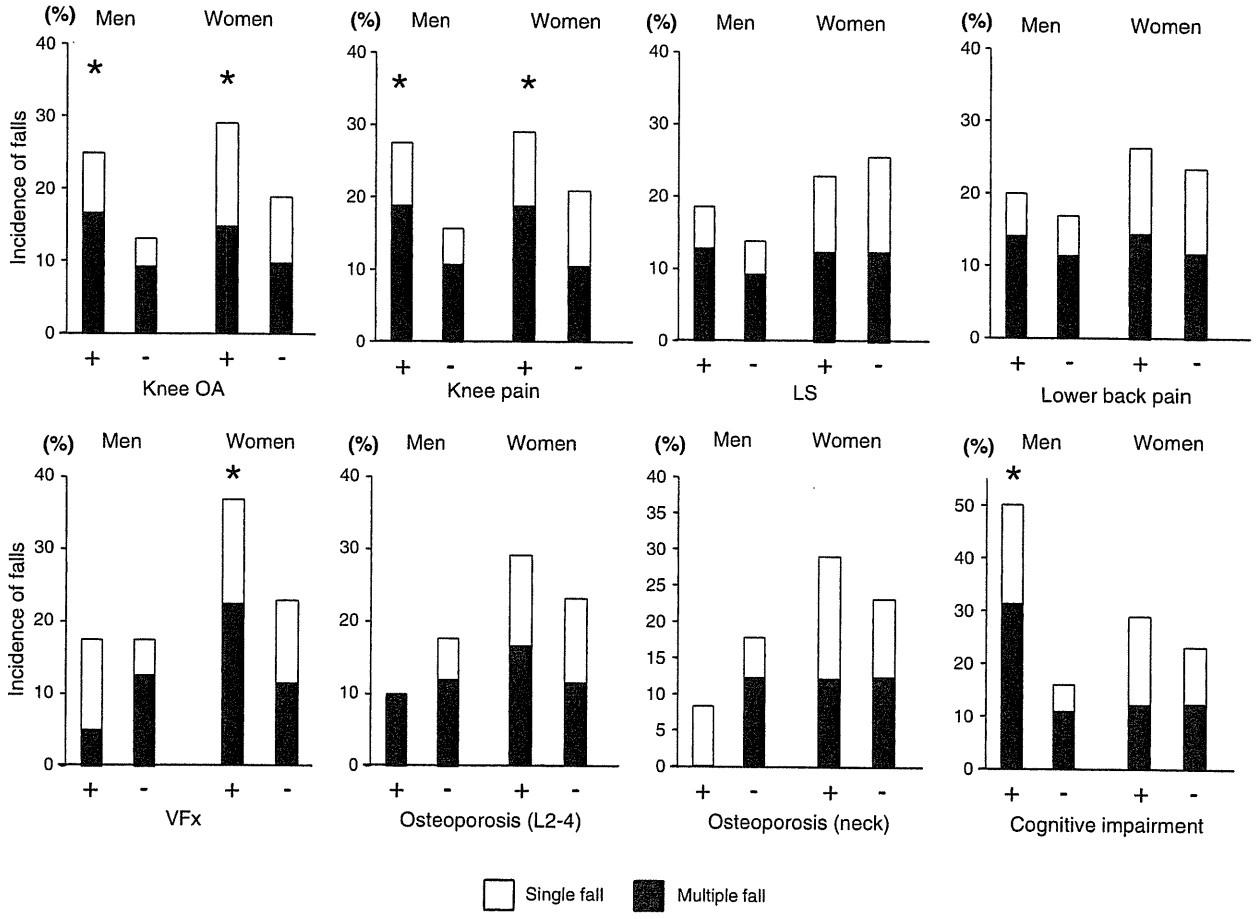

Fig. 2. Incidence of single and multiple falls by bone and joint diseases and cognitive impairment. *$p<0.05$ vs. participants without each disease or pain, respectively, according to the chi square test. OA, osteoarthritis; LS, lumbar spondylosis; VFx, vertebral fracture.

Table 4
Risk factors for single and multiple falls in men.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.90 (0.71–1.14)	0.84 (0.71–0.99)	1.14 (1.01–1.29)	0.88 (0.72–1.08)
6-m walking time (1 s increase)	1.12 (0.98–1.27)	1.13 (1.03–1.26)	1.11 (0.95–1.25)	1.11 (1.01–1.23)
Chair stand time (1 s increase)	1.17 (1.03–1.32)	1.21 (1.11–1.33)	1.15 (1.00–1.32)	1.21 (1.09–1.33)
LS BMD (0.1 mg/cm^2 increase)	1.00 (0.80–1.22)	1.00 (0.86–1.16)	0.92 (0.73–1.15)	0.97 (0.83–1.13)
Neck BMD (0.1 mg/cm^2 increase)	1.10 (0.81–1.47)	0.98 (0.78–1.21)	1.07 (0.73–1.51)	1.01 (0.77–1.30)
Knee OA	2.44 (1.09–5.56)	2.08 (1.18–3.70)	2.07 (0.84–5.21)	1.77 (0.95–3.33)
Knee pain	2.04 (0.72–5.09)	2.05 (0.99–4.00)	1.65 (0.57–4.21)	1.78 (0.85–3.55)
VFx	2.58 (0.82–6.85)	0.40 (0.06–1.36)	2.48 (0.75–7.04)	0.32 (0.05–1.13)
Cognitive impairment	6.19 (1.29–23.1)	4.83 (1.41–15.1)	13.48 (0.98–178.64)	3.17 (0.44–21.99)
Previous falls				
Single fall	–	–	–	3.52 (1.07–9.97)
Multiple falls	1.18 (0.25–4.61)	9.54 (3.15–30.08)	–	12.6 (5.80–27.97)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

(Table 4). Previous falls were significantly associated with the incidence of multiple falls. In women, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time was a risk factor for multiple, but not single falls (Table 5). Chair stand time also tended to be associated with the incidence of single and multiple falls. Regarding bone and joint diseases, knee pain was a risk factor for single and multiple falls. VFx also tended to be associated with multiple falls, but radiographic knee OA was not associated with falls. Cognitive impairment was a risk factor for multiple falls, but not for single falls. A history of previous falls was a risk factor for multiple, but not single falls.

To determine the independent association of each physical performance parameter with the incidence of falls, multinomial logistic regression analysis was performed with age, BMI, 6-m walking time, and chair stand time as explanatory variables. We found that a longer chair stand time was an independent risk factor for multiple falls (OR 1.18, 95% CI 1.06–1.32), but a longer 6-m walking time was not (OR 1.05, 0.93–1.16). In women, a longer 6-m walking time tended to be associated with the incidence of multiple falls (OR 1.09, 95% CI 0.98–1.22), but a longer chair stand time was not (OR 1.01, 95% CI 0.94–1.07). After adjusting for previous falls, the independent association of a longer chair stand time with the incidence of falls remained in men (OR 1.15, 95% CI 1.02–1.30), and the independent association of a longer 6-m walking time with the incidence of falls remained in women (OR 1.12, 95% CI 1.00–1.25). In addition, knee pain and cognitive impairment in women were also significantly associated with falls, and VFx tended to be associated with falls with multinomial logistic regression analysis after adjusting for age and BMI. Thus, to determine the independent association of physical performance, bone and joint diseases, and cognitive impairment, multinomial logistic regression analysis was used with age, BMI, 6-m walking time, knee pain, VFx, and cognitive impairment as explanatory variables. We found that a longer 6-m walking time was an independent risk factor for multiple falls (OR 1.08, 95% CI 1.00–1.18), but the significant association of knee pain, VFx, and cognitive impairment with the incidence of falls disappeared (OR 1.47, 95% CI 0.91–2.35, OR 1.52, 95% CI 0.80–2.81, and OR 1.16, 95% CI 0.35–3.24, respectively).

Discussion

The present study is the first longitudinal population-based cohort study to examine whether physical performance, bone and joint diseases, and cognitive impairment are risk factors for single and multiple falls in men and women. We found gender differences in risk factors for

Table 5
Risk factors for single and multiple falls in women.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.84 (0.70–0.99)	0.81 (0.68–0.95)	0.94 (0.77–1.11)	0.91 (0.75–1.08)
6-m walking time (1 s increase)	1.10 (1.01–1.19)	1.16 (1.08–1.25)	1.04 (0.94–1.14)	1.11 (1.02–1.20)
Chair stand time (1 s increase)	1.07 (1.02–1.12)	1.07 (1.03–1.12)	1.04 (0.99–1.10)	1.04 (0.99–1.09)
LS BMD (0.1 mg/cm^2 increase)	0.88 (0.78–1.00)	0.90 (0.80–1.01)	0.96 (0.83–1.11)	0.92 (0.80–1.06)
Neck BMD (0.1 mg/cm^2 increase)	0.75 (0.63–0.90)	0.85 (0.72–1.01)	0.79 (0.62–1.01)	0.87 (0.69–1.10)
Knee OA	1.79 (1.18–2.78)	1.75 (1.16–2.63)	1.52 (0.94–2.50)	1.12 (0.79–1.82)
Knee pain	1.83 (1.17–2.83)	2.22 (1.44–3.37)	1.62 (1.00–2.60)	1.60 (1.00–2.54)
VFx	1.54 (0.78–2.85)	2.40 (1.35–4.12)	1.15 (0.57–2.20)	1.81 (0.98–3.24)
Cognitive impairment	0.42 (0.02–2.12)	2.12 (0.68–5.60)	0.73 (0.19–2.61)	4.95 (1.50–16.08)
Previous falls				
Single fall	0.55 (0.16–1.74)	1.51 (0.33–5.41)	0.70 (0.30–1.43)	2.48 (1.40–4.28)
Multiple falls	0.86 (0.39–1.81)	8.55 (3.80–19.20)	1.06 (0.35–2.62)	6.93 (3.76–12.72)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

falls. Regarding physical performance, a longer chair stand time was an independent risk factor for falls in men, whereas a longer 6-m walking time was an independent risk factor for falls in women. Knee pain, VFx, and cognitive impairment were associated with falls in women, but not in men.

The present study is a population-based longitudinal study to determine whether bone and joint diseases are risk factors for falls in Japanese men and women. After adjusting for age and BMI, knee pain was a risk factor for falls in women, but not in men. The sex differences regarding the association of knee pain with falls may be partly explained by the weaker quadriceps muscles in women, which is known to be an independent risk factor for falls [16]. Muscle strength is higher in men than in women in all decades [39], which may obscure the association of knee pain with falls. In addition, given the insignificant association of radiographic knee OA with falls, falls may occur due to symptoms such as pain rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain is significantly associated with falls [11]. In other words, falls may be preventable when pain is relieved by medical care, even if patients have radiographic knee OA.

In the present study, LS and lower back pain were not associated with falls, whereas VFx was associated with falls. Lower BMD was not associated with falls in the present study, and thus, radiographic changes but not OP may be associated with falls. Studies of patients with VFx have reported increased kyphosis angles [16,17], which is an independent risk factor for injurious falls [40]. Previous studies [41,42] have demonstrated that people with kyphosis have greater balance abnormalities as assessed by computerized dynamic posturography. Specifically, they reported that women with OP-related kyphosis had greater mediolateral displacement and increased mediolateral velocity compared to controls [42]. In addition, lateral spontaneous sway amplitude has been reported to be the single best predictor of future risk of falls [43]. These observations may partly explain the association between VFx and falls.

In the present study, after adjusting for age and BMI, both a longer 6-m walking time and a longer chair stand time were associated with falls in men and women. A previous study also showed that slower walking speed is a risk factor for falls [44], although men and women were not separately analyzed in the study. To determine the independent association of the 6-m walking time and chair stand time, we further used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory factors, and found that in men, a longer chair stand time was an independent risk factor for multiple falls, but a longer 6-m walking time was not. In women, a longer 6-m walking time was associated with the incidence of multiple falls, whereas a longer chair stand time was not. This indicates that slower walking speed may more strongly affect the risk of falling in women than in men, whereas a longer chair stand time may more strongly affect the risk of falling in men than in women. The walking time and chair stand time can be easily and quickly measured in clinical and research settings without requiring monitoring devices or extensive training. The present study may indicate that walking time is a simple and quick option for measuring the risk of falling, particularly in women, and measuring the chair stand time is a simple and quick option for estimating the risk of falling, particularly in men.

The present study has several limitations. First, our participants lived in the community, and thus, our findings may not apply to elderly persons residing in institutions. Second, we did not include other anatomical locations of weight-bearing OA such as hip OA in the analysis, although this disorder also affects falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women [46], respectively, which is lower than that of KL=3 or 4 knee OA (12.2% and 21.0% in men and women, respectively) in the present study. Thus, it is possible that hip OA would not strongly affect the results of the present study. Third, non-responders were older, had lower physical performance and higher prevalence of knee pain, which were risk factors for falls. This means that the incidence of falls in the present study may have been underestimated. Fourth, the accuracy and reliability of recall of falls over the past 3 years was not assessed in the present study. Previous studies have shown that 13–32% of elderly subjects with confirmed falls did not recall falling over a 12-month period [47], even when excluding subjects with cognitive impairment. Therefore, the incidence of falls may be underestimated, particularly in older subjects and those with cognitive impairment. In addition, individuals are more likely to recall a fall that resulted in injury, which may have influenced the results of this study.

Conclusion

The present longitudinal analysis using a large-scale population from the ROAD study revealed gender differences in risk factors for falls. A longer walking time was a risk factor for falls in women, whereas a longer chair stand time was a risk factor for falls in men. Knee pain and VFx were risk factors for falls in women, but not in men. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of bone and joint diseases and their relationship with falls.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bone.2012.10.020.

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

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SPECIAL REPORT

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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

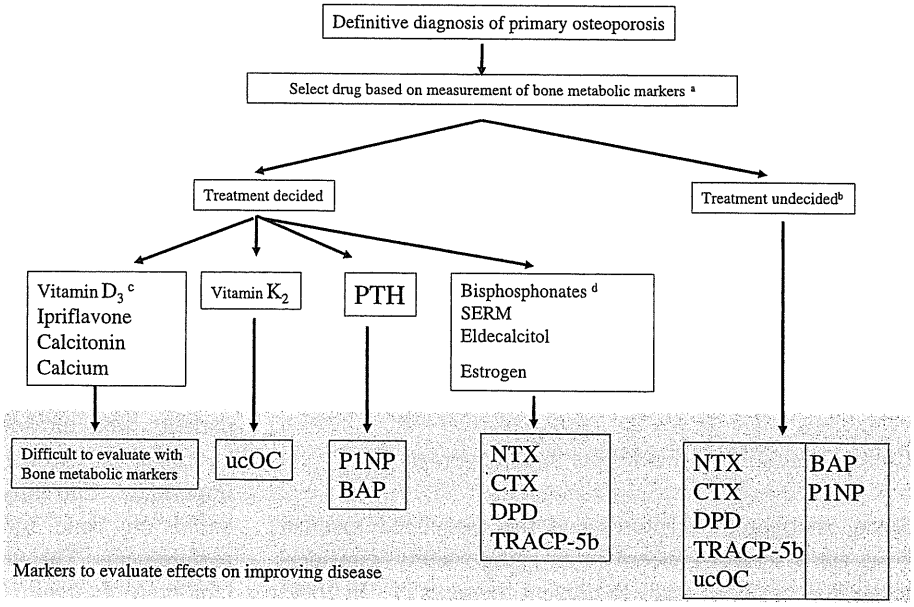

Fig. 1 Measurement of bone turnover markers in drug treatment of osteoporosis. This figure is taken from page 28 of the 2011 Osteoporosis Prevention and Treatment Guidelines (in Japanese). *a* In patients taking bisphosphonates, measure after stopping drug for at least 6 months, and in patients taking 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

toms, complications, drug contraindications, and previous treatment history. The bone matrix marker, ucOC, reflects vitamin K deficiency, so this information is useful when selecting vitamin K_2 drugs and as an adjunct when evaluating their efficacy (Figs. 2, 3).

Evaluation of drug treatment effects in osteoporosis using bone metabolic markers

Combination of evaluable bone metabolic markers and therapeutic drugs

Using only baseline values of bone metabolic markers it is difficult to predict drug treatment effectiveness. Drug treatment effectiveness can be monitored by repeating the measurement at a given interval after the start of treatment to evaluate changes from baseline values. With drug treatment, only significant changes from baseline values in bone metabolic markers indicate that bone metabolism has changed and the treatment has been effective. In individual patients, the effectiveness of bisphosphonates, SERMs, or estrogen treatment can be assessed using DPD, NTX, CTX, TRACP-5b, BAP, or P1NP. The effectiveness of activated vitamin D_3 (particularly, eldecalcitol) can be assessed using NTX or BAP. The effectiveness of PTH drugs (daily subcutaneous injection) is assessed using P1NP. For other drugs, evaluation by measurement of these bone metabolic markers is not easy. In addition, in treatment using bisphosphonates such as alendronate that have amino groups, changes in urinary free DPD, compared to telopeptides, are known to be smaller [9, 15] (Fig. 4).

One criterion for evaluating treatment effectiveness is whether a change has exceeded the minimum significant change (MSC). The MSC is defined as twice the inter-day variation in the morning in premenopausal women (Table 5). Despite measurement at uniform sample collection times, if no significant changes in bone metabolic markers with drug treatment are observed, patient treatment compliance should first be confirmed. The possibility of another underlying disease causing secondary osteoporosis must also be considered (Table 6). With bisphosphonate therapy, it is also important to check that the time interval between drug administration and meals is sufficient so that there are no problems with drug absorption. If there is no problem with treatment compliance, then the

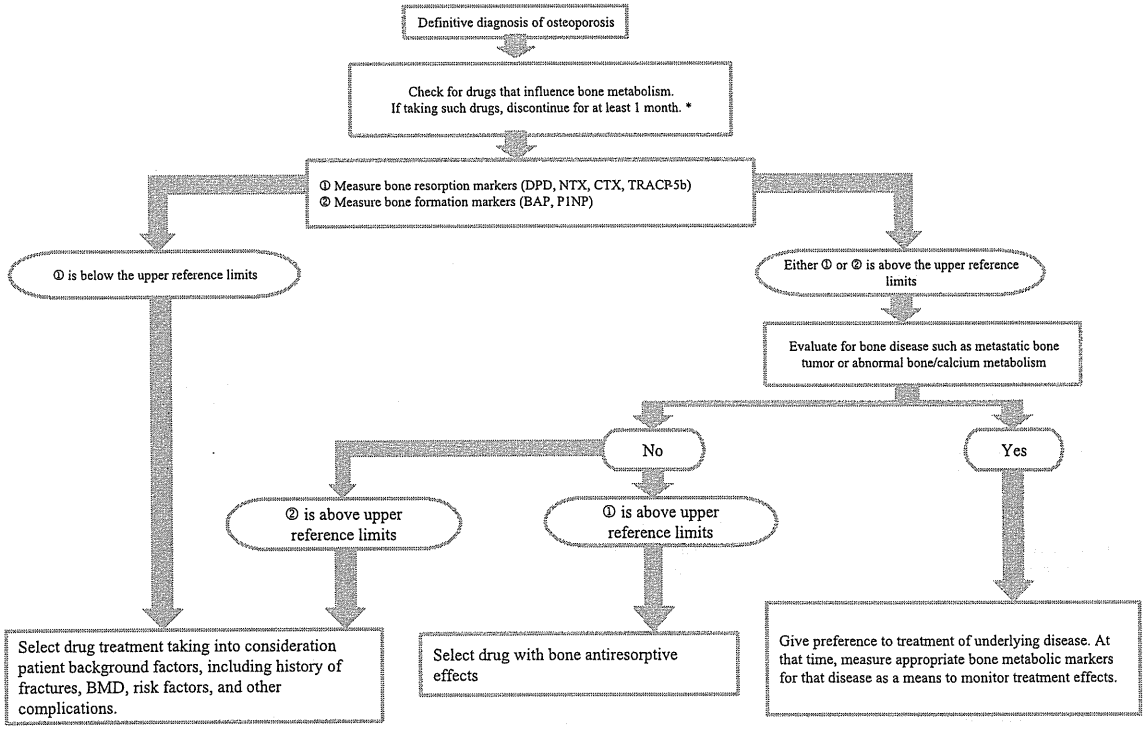

Fig. 2 Measurement of bone resorption markers and bone formation markers when selecting drug treatment for osteoporosis. *Asterisk* for bisphosphonates after stopping for at least 3 months. Bisphosphonates (etidronate disodium, alendronate sodium hydrate, risedronate sodium hydrate, minodronic acid hydrate), SERMs (raloxifene, bazedoxifene), estrogens (estradiol, estriol), calcitonin (elcatonin, salmon calcitonin), and activated vitamin D_3 (eldecalcitol) drugs are known to have bone antiresorptive effects

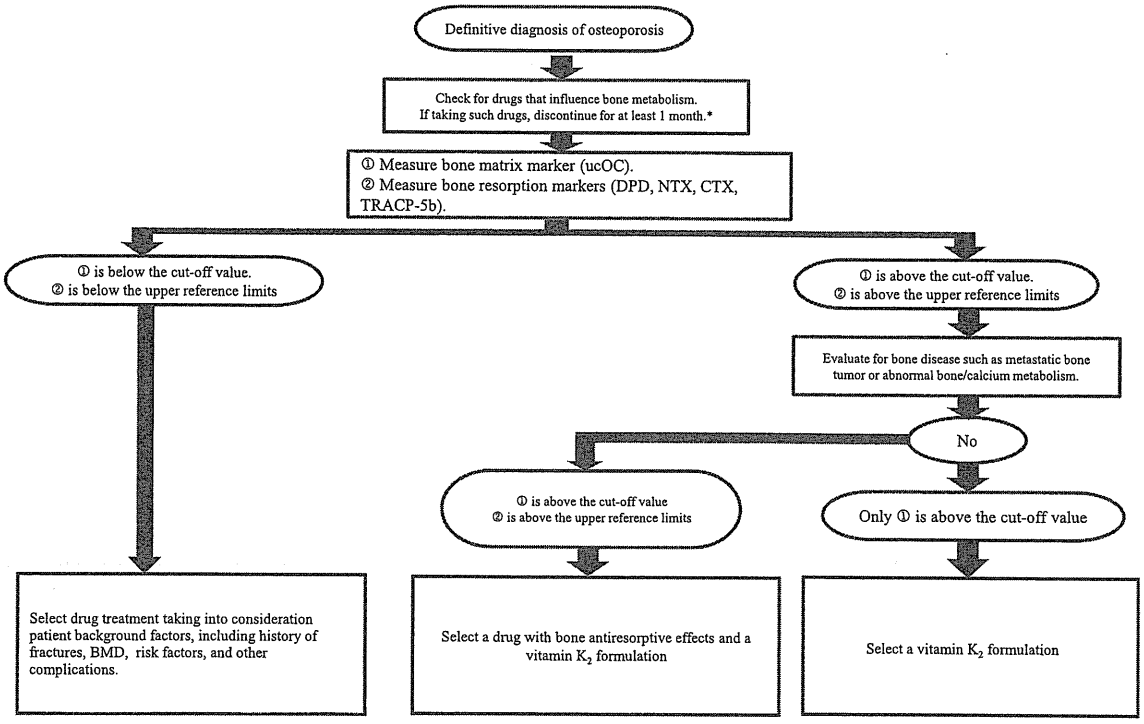

Fig. 3 Measurement of ucOC and bone resorption markers when selecting drug treatment in osteoporosis. *Asterisk* for bisphosphonates after stopping for at least 3 months

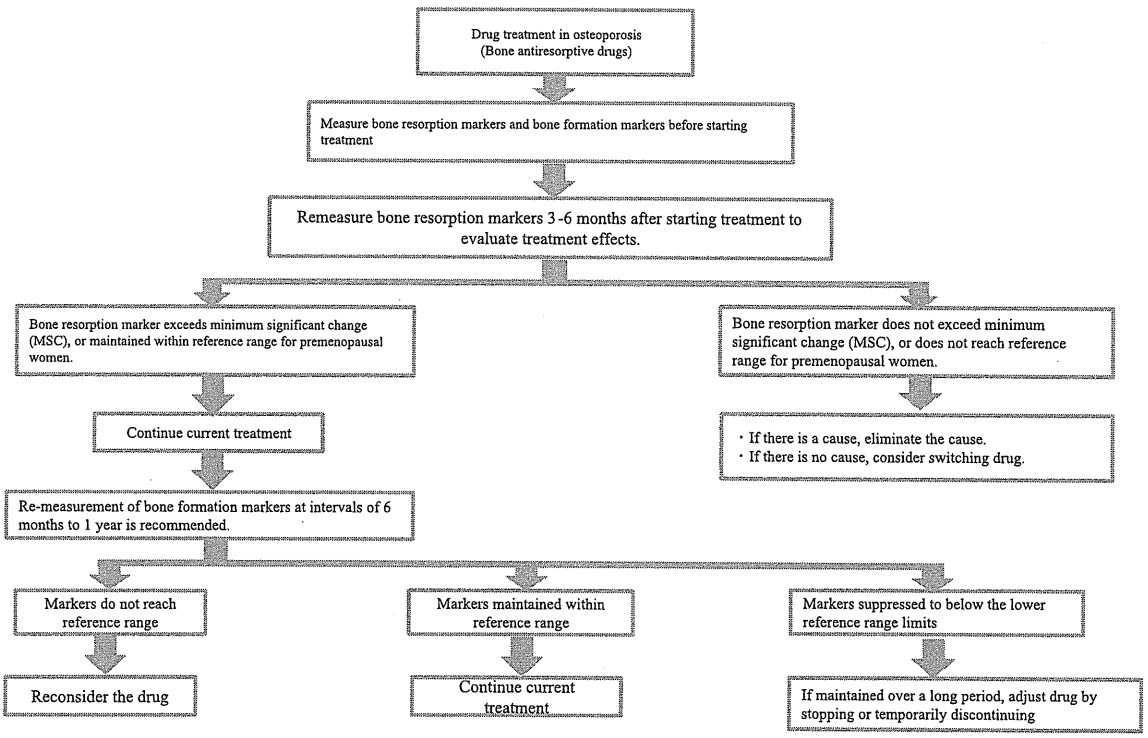

Fig. 4 Evaluation of therapeutic effects of bone antiresorptive drugs using bone resorption markers. Please refer to Table 6

response to drug treatment is inadequate and an increase in dose or switch to another drug is indicated. 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, or P1NP are not readily apparent.