ORIGINAL ARTICLE

Effects of bone mineral density of the lumbar spine and prevalent vertebral fractures on the risk of immobility

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Abstract

Summary To clarify the contribution of osteoporosis to future immobilization, a prospective observational study was carried out on Japanese postmenopausal women. The prevalence of low bone mineral density (BMD) and vertebral fracture were independent risks for future immobilization.

Introduction Immobilization by hip fracture requires more medical care and higher costs. Osteoporosis increases the risk of hip fracture, but there is little data linking osteoporosis and immobilization in postmenopausal Japanese women.

Methods The study participants consisted of postmenopausal ambulatory volunteers. Baseline information such as BMD, prevalent fractures, comorbidities, pain in the body, and variables were obtained from 1993, and time course of occurrence of immobilization was observed until 2008.

Results A total of 1,312 participants were enrolled and were observed for a total of 6.7 ± 4.1 years. A total of 75 subjects suffered immobilization. In multivariate analysis to calculate the Cox's hazard ratio of baseline parameters for immobilization, four independent variables were observed:

age (hazard ratio, 1.52 [95% CI, 1.29 to 1.80], $p=0.000$), pain in the body (2.54 [1.42 to 4.89, $p=0.001$]), low BMD (1.83 [1.10 to 3.13, $p=0.020$]), and dementia (3.58 [91.80 to 6.76, $p=0.001$]). The hazard ratio of prevalent vertebral fracture was 1.98 (1.20 to 3.30, $p=0.007$) instead of low BMD of above model.

Conclusion These results indicate that low BMD and prevalent vertebral fracture pose an independent risk for future immobilization in postmenopausal Japanese women.

Keywords Dementia · Immobilization · Osteoporosis · Vertebral fracture

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Introduction

Japan is known as a rapidly aging society. In fact, the total number of households with persons aged 65 or older shot up from 8.5 million in 1980 to 18.5 million in 2005. Due to significant changes in family composition in Japan after industrial success, approximately half of the 18.5 million households are maintained by elderly people who live alone or as elderly pair and potentially need care [1]. In addition, a total of approximately 60 billion dollars were required for the public health care system in 2007 [2], the cost of care for patients with fractures accounted for around 13% (8 billion dollars) [3], and the overall cost of treating fractures was the third highest expense [4]. With Japan's first generation of baby boomers entering their 60s, a significant increase in the number of elderly households and drastically higher costs for their care are expected in the near future. Globally, the demand for medical care and social services for elderly people is increasing, while medical resources are apparently becoming scarcer, especially in Japan and the USA [5]. Seeking possible strategies and solutions to these

issues, communities in each country should take prompt action by grasping and analyzing the current status of elderly patient care.

In conclusion, osteoporosis—a systemic skeletal disease characterized by deteriorated bone strength [6]—is considered a national issue in our aging society because it increases susceptibility to bone fractures, which impair quality of life (QOL) and decrease the mobility of affected patients [7, 8]. Special care is required by osteoporotic patients, especially those with hip fractures. In addition, it is reported that vertebral fractures are a risk factor increasing mortality in the Caucasian [9–12] and Asian populations [13]. However, there are no available data to show whether low bone mineral density (BMD), prevalent fractures, or incident vertebral fractures pose a risk of future immobility. For this reason, we have attempted to investigate the risk and frequency of immobilization in this prospective observational study among postmenopausal ambulatory Japanese women.

Methods

Subject selection and follow-up

This prospective observational study began April 1, 1993 in Nagano prefecture, Japan. Study participants were postmenopausal ambulatory volunteers over 50 years of age who were recruited from patients visiting Research Institute and Practice for Involutional Diseases and were selected by two practitioners (MS and YS). Exclusion criteria included critical illness and irregular clinical visits. Patients with metabolic bone diseases such as primary hyperparathyroidism, hyperthyroidism, osteomalacia, and malabsorption syndrome; steroid users; and those with severe renal failure were also excluded from the study. The period of follow-up for each participant was calculated as the time from inclusion in the study to the occurrence of immobilization, exit from study, or end of study (April 30, 2008). Whenever a participant did not show up, an attempt was made to contact the participant, by telephone or letter, and recommend a visit to the clinic. Participant immobility and survival were also confirmed through inquiries. When we lost contact with subjects who moved to relatives' homes mainly due to loss of independence in their daily life, follow-up was terminated upon confirmation they had moved. Other missing cases were patients referred to other hospitals for various reasons. The follow-up periods for those cases were terminated upon the date of referral. Follow-up for participants who died during the observation was terminated when the date of death was confirmed by death certificate. Subjects bed-bound in their homes and receiving familial care or institutionalized in nursing homes were defined as immobile,

and their follow-up was terminated on the date they were bed-bound or institutionalized.

Baseline data collection

As a baseline examination, anthropometrical indices such as body weight, body height, and body mass index (BMI, kg/m^2) were measured. An interview was carried out to determine smoking and alcohol drinking habits. When subjects visited practitioners due to pain in the body during locomotion, the exact site of pain was identified as knee, leg, hip, or dorsal lesion. The effect of baseline pain in the body on immobilization was analyzed for different types of pain and general pain. Lumbar osteoarthrosis was diagnosed based on the Kellgren–Lawrence score (K–L score) [14], and rheumatoid arthritis was diagnosed based on criteria proposed by the American Rheumatism Association [15]. The other histories of comorbidities including diabetes mellitus, hypertension, dyslipidemia, dementia, malignancies, and cardio- and cerebro-vascular events were investigated. When subjects indicated some comorbidity, the diagnosis of that comorbidity was made by the proper diagnostic measures reported previously [13].

Measurements of bone mineral density and biochemical indices

Axial bone mineral density at lumbar spine (LBMD) was measured by dual-energy X-ray absorptiometry (DXA) using a Lunar DPX-L or DPX-IQ (Lunar Corporation, Madison, WI, USA). The inter-assay variance of LBMD in our laboratory was $0.5\pm0.5\%$ (CV ± SD) [16]. To detect machine drift, a quality assurance test was carried out with every measurement.

Non-fasting serum, plasma and urine samples were collected at the time of enrollment as baseline data. Biochemical examinations such as serum levels of calcium, phosphate, Al-P activity, total protein, total cholesterol, triglycerides, HbA1c, glucose, and creatinine were measured immediately after centrifugation using an auto-analyzer.

Diagnosis of osteoporosis and treatment

The diagnosis of osteoporosis was made in accordance with the diagnostic criteria for osteoporosis (year 2000 version) proposed by the Japanese Society for Bone and Mineral Research [17], in which osteoporosis is diagnosed as the presence of fragility fractures in any bone lesion in those with less BMD than 80% (−1.63SD) of the young adult mean (YAM). Osteoporosis is also diagnosed when the LBMD is less than 70% (−2.45SD) of the YAM even in those without prevalent fragility fractures. In those diagnosed as having osteoporosis, bone resorption inhibitors

(bisphosphonate, estrogen, or selective estrogen receptor modulator), 1-alpha-OH vitamin D_3, or vitamin K_2 were administered if they desired such treatment. The specific treatment each subject received was selected according to subject preference and with our assistance. Some of these patients did not want to receive any osteoporotic drugs, for various reasons, and some patients exhibited very low compliance to the therapeutic regimen prescribed. Therefore, the subjects were categorized into three groups in accordance with treatment status: no treatment, bisphosphonate or estrogen, and vitamin groups.

Definition of prevalent and incident fracture

We investigated the presence of prevalent and incident fractures of vertebral and long bones (fractures of the hip, distal end of radius, surgical neck of humerus or other long bone). Vertebral fractures were diagnosed by a semiquantitative visual method reported by Genant et al. [18] that was adapted to the present study in accordance with the method reported previously [19, 20]. The vertebral X-ray films were taken every 1 to 2 years interval, and the additional X-ray films were also taken when the participants complained the clinical symptoms suspicious for vertebral fractures. The presence of prevalent long bone fractures was determined through interviews with participants, on the basis of medical records, or by X-ray film confirmation.

Assessment of mobility

Mobility was defined in accordance with the subject's locomotive ability. Subjects bed-bound at home (lying in bed all day) or institutionalized in nursing homes (lying in bed or using a wheelchair for locomotion), were defined as immobile. Subjects who moved to relatives' homes, another type of dependency, were defined as missing cases because the reasons for moving were expected to be complicated, and immobility was not the only reason for moving.

Ethical considerations

The ethical committee of the Research Institute and Practice for Involutional Diseases reviewed the protocol of the present study. Detailed written informed consent was also obtained from all subjects.

Statistical analysis

In the descriptive analysis of baseline characteristics, the numerical data are expressed as mean±SD. To clarify the relationship between subjects with or without immobility and baseline characteristics, the age-adjusted Cox's proportional hazard model was used to estimate the association and time dependency between immobility and baseline data. Here, we estimated the age-adjusted hazard ratios with 95% confidence intervals as study variables. Second, in multivariate Cox's regression analysis, we used the backward variable selection method. The exclusion criterion was a p value of less than 0.1. All p values presented were taken from the two-side test and considered significant when less than 0.05. All analyses were performed using JMP software, version 5.1.2 (SAS Institute Inc., Carly, NC, USA).

Results

Demography of the subjects

A total of 1,405 postmenopausal women met the inclusion criteria. Among them, 93 subjects refused to participate in the present study, and the remaining 1,312 subjects were enrolled in the study. The mean and SD of age was 65.1± 9.2 years old, and the follow-up period was 6.7±4.1 years with the longest observation time being 15 years. The numerical and categorical data at baseline are listed in Tables 1 and 2, respectively. In contrast to data reported for the Caucasian population, subjects with smoking or alcohol habits were markedly fewer. Factors affecting locomotion ability included prevalent fractures (24.2% of subjects) and pain in the body at joints, legs, or dorsal lesion (63.1% of subjects). Categorized baseline data were summarized in Table 2. A total of 525 (40.0%) osteoporotic patients were treated with anti-resorptive drugs (bisphosphonates and selective estrogen receptor modulator or estrogen), and the remaining 787 (60.0%) participants were followed without drug intervention for osteoporosis.

Outcomes during observation

Follow-up for 746 of the 1,312 cases (56.9%) continued until the end of the study on April 30, 2008. The remaining

Table 1 Baseline characteristics (numerical data)

item	Mean ± SD (n)
Age (years)	65.1±9.2 (1312)
Years since menopause (years)	15.9±9.8 (1259)
Body mass index (kg/m^2)	22.5±3.2 (1312)
Lumbar bone mineral density (g/cm^2)	0.91±0.20 (1311)
Total protein (g/dl)	7.3±0.6 (1292)
Calcium (mg/dl)	9.2±0.4 (1293)
Phosphate (mg/dl)	3.5±0.5 (1293)

The table shows numerical baseline data obtained at the time of registration.

Table 2 Baseline characteristics (categorical data)

Item	Prevalence number (%)
Pain category	
No pain	484 (36.9)
Back pain	450 (34.3)
Other site	378 (28.8)
BMD category[a]	
Normal	427 (32.5)
Osteopenia	310 (23.6)
Osteoporosis	575 (43.8)
Pre-existing fracture	
No fracture	994 (75.8)
Vertebral fracture	269 (20.5)
Colles fracture	29 (2.2)
Hip fracture	12 (0.9)
Other site fracture	29 (2.2)
History of comorbidities	
Lumbar osteoarthritis K–L score 3-5[b]	274 (20.9)
Knee osteoarthritis	327 (24.9)
Hip osteoarthritis	40 (3.1)
Reumatoid Arthritis[c]	58 (4.4)
Diabetes Mellitus	74 (5.7)
Dyslipidemia	506 (38.7)
Hypertension	583 (44.6)
Cardio- or cellebro-vascular event	133 (10.2)
Dementia	55 (4.2)
Malignancy	105 (8.0)

The table summarizes categorized baseline data. Items without footnotes indicated were diagnosed by criterion described in the text [13].

BMD bone mineral density, *K–L score* Kellgren–Lawrence score

[a] Diagnosed based on criteria proposed by the Japanese Society for Bone and Mineral Research [17]

[b] Diagnosed by Kellgren–Lawrence grade criteria [14]

[c] Rheumatoid arthritis was diagnosed based on criteria proposed by the American College of Rheumatology [15]

466 cases (35.5%) dropped out of the study. A total of 75 cases met the definition of immobilization in the present study (5.7%, 8.6 per 1,000 person-years). Twenty-five subjects moved from their own house to a relative's house. Some lost a degree of independence but not enough to meet the definition of immobilization. Furthermore, the causes of moving were not simply due to disability but also economical reason or dementia.

Table 3 summarizes incident fractures observed during the observation period. The most frequent type of incident fracture was vertebral fractures, including both morpho-metrical and clinical fractures.

Table 4 presents the age-adjusted hazard ratio of baseline or incident parameter in the event of immobilization. As

shown in Table 4, hazard ratios of age, pain in the body, fracture (prevalent), BMD, diabetes, and dementia indicate a *p* value of less than 0.1. In contrast to expectations, the odds ratio for immobilization of incident fracture did not reach a significant level.

Additionally, we also conducted variable selection for these significant factors. The presence of osteoporosis and prevalent fractures showed a very high correlation: the presence of fractures was 40.9% (235 cases out of 575) in subjects with osteoporosis and 4.6% (34 cases out of 737) in those without osteoporosis. In our two-model analysis, the type-1 model included the presence of osteoporosis, and the type-2 model included the presence of fractures. Table 5 shows the multivariate hazards ratio by Cox's regression analysis of risks for immobility adjusted for age, presence of pain, osteoporosis, and dementia. Table 6 shows the multivariate hazards ratios of prevalent fractures, instead of presence of osteoporosis, in the type-1 model. Each factor posed a significant independent risk for immobility in postmenopausal Japanese women.

Discussion

The primary aim of the present study was to clarify whether osteoporosis poses a future risk for immobilization. The Cox's hazard model demonstrated that osteoporosis and prevalent vertebral fractures are associated with immobilization after adjustment of confounding factors. Osteoporosis is a known disease that raises susceptibility to future fractures and hip or vertebral fractures resulting in decreased QOL [21–23] or disability after hip fractures [24–27]. In the present study, 451 incident fractures were observed during the observation period among 1,312 participants. Although prevalent fractures were a significant risk factor, incident fractures were not. These results suggested that fractures that occurred early and existed for a long time affected mobility more than the ones that occurred after entering the study. However, these results did not indicate less importance of incident fractures in terms of

Table 3 Type and number of incident fractures

Type of fracture	Number of participants	Percent
Vertebrae	368	81.6
Distal end of radius	39	8.6
Hip	14	3.1
Other site	29	6.4
Vertebral and other site fracture	1	0.2

Recognition of incident fractures in vertebrae was made on vertebral X-ray film taken at 1- to 2-year intervals [18]. Fractures in other sites were confirmed on X-ray film or by interview.

Table 4 Age-adjusted hazard ratio of baseline or incidental parameter vs immobile event (Cox's hazard model)

Item	HR	95%CI		p
Age/5	1.71	1.48	1.98	0.000
BMI	1.00	0.92	1.01	0.896
Lumbago, yes/no	1.56	0.98	2.48	0.062
Pain in all sites (bodily pain), yes/no	2.32	1.30	4.45	0.003
Prevalent fracture, yes/no	2.12	1.28	3.54	0.004
Incident all site fracture, yes/no	1.08	0.63	1.89	0.789
Prevalent or incident all site fracture, yes/no	2.12	1.13	4.30	0.018
Prevalent vertebral fracture, yes/no	2.20	1.31	3.69	0.003
BMD category osteoporosis/normal+osteopenia	1.69	1.02	2.89	0.043
Lumbar osteoarthritis K–L score 3–5/1–2	1.05	0.60	1.96	0.857
Knee osteoarthritis, yes/no	0.89	0.51	1.47	0.651
Hip osteoarthritis, yes/no	2.35	0.71	5.71	0.144
Rheumatoid arthritis, yes/no	1.83	0.55	4.49	0.284
Diabetes, yes/no	0.38	0.11	1.00	0.050
Dyslipidemia, yes/no	0.72	0.42	1.20	0.209
Hypertension, yes/no	0.94	0.57	1.56	0.804
Cardio-cerevo-vascular event	1.51	0.81	2.66	0.184
Dementia, yes/no	2.60	1.31	4.88	0.007
Malignancy event, yes/no	1.05	0.40	2.27	0.911
Anti-resorptive treatment for osteoporosis, yes/no	0.69	0.42	1.10	0.121

HR and CI were calculated by Cox's proportional hazards model. The hazard ratios of the baseline data listed in the Table 4 were adjusted by age.

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *BMD* bone mineral density, *K–L score* Kellgren–Lawrence score

occurrence of immobilization. It may be simply due to lack of statistical power.

We have been focusing on the occurrence of immobilization in postmenopausal Japanese women but not on quality of life or activities of daily living (ADL) scores, which can estimate the subject's status of activity quantitatively. The QOL or ADL score may not be enough to clearly understand the subject's activity directly. On the other hand, the immobilization defined in the study may be recognized more easily in practice to assess the subject's activity than the QOL or ADL score. This is why we evaluated the subject's morbidity by housebound or institutionalized condition.

In the present study, we evaluated the effect of multiple factors potentially affecting locomotion or mobility, such as

bone and joint diseases, vascular diseases, and dementia. In addition to locomotion-related diseases, comorbidities of common diseases in the elderly, such as hypertension, dyslipidemia, diabetes, and past history of malignancies were also evaluated in the participants. Those baseline evaluations may enable assessment of the effects of the total condition on immobility in the elderly. As shown in Table 6, pain in the body and dementia are independent risks for immobility, and these findings appear reasonable. We did not evaluate the causes of pain and the degree of pain because the causal factors for some kinds of pain could not be analyzed, and the assessment of degree of pain is thought to vary subjectively. Since most pain may be due to bone and joint degenerative diseases, such as osteoarthrosis in vertebrae or leg joints and osteoporosis, our findings were within expectations. While individual site of pain did

Table 5 Multivariate Cox's regression analysis: risk of immobile event adjusted for age, prevalence of body pain, osteoporosis, and dementia

Item	HR	95%CI		p
Age, 5 years up	1.52	1.29	1.80	0.000
Pain in the body, yes/no	2.54	1.42	4.89	0.001
BMD category, osteoporosis/normal + osteopenia	1.83	1.10	3.13	0.020
Dementia, yes/no	3.58	1.80	6.76	0.001

HR and CI were calculated by Cox's proportional hazards model. Bodily pain was summarized as pain at any site.

HR hazard ratio, *CI* confidence interval, *BMD* bone mineral density

Table 6 Multivariate Cox's regression analysis: risk of immobile event adjusted for age, prevalence of body pain, vertebral fracture, and dementia

Item	HR	95%CI		p
Age, 5 years up	1.50	1.27	1.78	0.000
Pain in the body, yes/no	2.38	1.33	4.61	0.003
Prevalent vertebral fracture, yes/no	1.98	1.20	3.30	0.007
Dementia, yes/no	3.30	1.67	6.18	0.001

Prevalent vertebral fractures were composed of a clinical and morphometrical fracture. Morphometrical fractures were diagnosed by a semi-quantitative method on vertebral X-ray film [18].

not pose a significant risk of immobilization, overall pain in the body did pose a significant risk of immobilization. Three possible explanations may account for the findings. The first possible explanation is that the accumulation of pain from various sites may be a risk, and the second reason is that degree of pain is important but not the pain location. The third reason is that the number of sites of pain did not have a significant statistical power when the pain in the body was divided into each site of pain. Further clarification may be required. Since previous reports also indicated that subjects with dementia were prone to a significantly greater risk of decline in daily activities [28], the present result in terms of the relation between dementia and immobilization was good agreement. The other comobidities did not show any significant relation to immobilization. The patients with nervous diseases were also expected to have immobilization. However, the numbers of patient with nervous systems were very small, and the statistical power may not be enough.

The effect of osteoporotic treatment by bone resorption inhibitors on future immobilization was not significant in this study group. It has been reported that alendronate, calcitonin, and teriparatide treatments were known to decrease low back pain [29–31]. Furthermore, estrogen and bisphosphonate treatments were known modalities for preventing incident fractures. Thus, it is possible that the treatment of osteoporosis is a factor that reduces the likelihood of immobilization. However, the present results did not show a significant reduction in the risk of future immobilization in subjects who receive osteoporotic treatment. This is because osteoporotic treatment may reduce the risk of immobilization caused by osteoporotic fractures, but the causal factors for immobilization in the present study include not only osteoporosis but also osteoarthrosis and dementia. Therefore, the effect of osteoporotic treatment on immobilization should be evaluated in osteoporotic patients by drug comparative trial.

In conclusion, age, pain in the body, osteoporosis, and dementia are independent risk factors for future immobilization among Japanese postmenopausal women.

Conflicts of interest None.

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