has tried to reduce medical costs by separating care provided in rehabilitation hospitals from care provided in acute care hospitals and by changing the reimbursement system. Medical costs in Japan have been paid on a fee-for-service basis, which can contribute to longer LOS. A fixed payment system that has more recently been utilized in Japan, called the "diagnosis procedure combination" (DPC), was introduced in acute care special functioning hospitals in 2003 in order to limit costs and LOS [7]. The average LOS of hip fracture was reduced to 45 days in 2006 [8]. The DPC payment system is similar to the Diagnostic Related Groups (DRGs) instituted in the U.S. in 1983 for the purpose of reducing costs from over-utilization of health services [9].

The use of the DPC payment system; however, may not be cost-effective in Japan. Kawabuchi et al. reported that the cost of treatment was lower if patients received their post-hip fracture rehabilitation in the same hospital where they received surgery than those patients who received care at linked rehabilitation hospitals after leaving the acute care setting. Yet, the ambulatory ability at discharge was comparable [10]. The DPC payment system reduced the average LOS, but did not change inpatient expenditures and it did increase outpatient expenditures [11].

The indirect costs of hip fracture due to the loss of production from the patients' family members who participated in the care of the patient were not insignificant [12]; however, these indirect costs have not been reported in the literature. Kawabuchi et al. [10] reported total direct costs of institutional care without adjusting for patients' factors, and costs of elder' care services or indirect costs from the loss of production from the patients' spouse or family members who participated in the care of the patient in Japan were not known.

We reported that shorter LOS in the hospital where patients received surgery was associated with higher mortality rates after discharge from hip fracture surgery in Japan [13]. In this paper, we compared costs during the initial hospitalization, estimated costs of care after discharge and compared total costs in the three hospitals. The objective of this study was to compare the patients' health outcomes and costs of health care services for patients with hip fracture surgery among three hospitals with different care systems in Japan, after adjusting for patients' factors.

2. Materials and methods

This is a retrospective comparative study of three hospitals in Japan (bed size ranged from 200 to 700). One hospital was a university hospital in the mid-western area of Japan, which used the DPC payment system (hospital A). The second hospital was a private general community hospital in Western Island in Japan, and had linked transitional care hospitals (hospital B). The third hospital was a private general community hospital in Tokyo. This hospital did not have a linked rehabilitation hospital and primarily took care of patients until they could be safely discharged to home. Medical records of study patients were reviewed and a questionnaire was sent to patients and/or their family members. Approvals were obtained from the Institutional Review Board from a university in the U.S. and the hospitals in Japan.

2.1. Participants

Inclusion criteria were patients who were 65 years or older who experienced hip fracture for the first time and who were admitted to one of the study hospitals for surgery during the study period, August 2005 to September 2007. Exclusion criteria included patients who had been admitted to the hospital before the hip fracture for another diagnosis, patients who could not walk with or without assistance before hip fracture, patients who had hip fractures caused by cancer metastasis, and patients who had more than one fracture at the same time.

2.2. Collection of data

Hospitals provided access to medical records of patients who had hip fracture surgery during the study period. Japanese law allows researchers to review patients' records without patients' consent for the purpose of research and if any hospitals' employees collaborate with the study [14]. During the medical records review, patients were selected according to the above inclusion and exclusion criteria. One patient in hospital A died during the hospital stay and was excluded. Variables that were collected from the medical records were patients' demographics, treatments and outcomes during hospitalization. Patients' demographics included age, gender, family members, comorbidities, ambulatory ability before hip fracture, and location of residence before hip fracture. Treatment variables included the dates of admission and discharge, dates and types of surgery, types of anesthesia, the initial dates of rehabilitation after surgery, and the hours (duration) of rehabilitation services experienced (physical therapy and occupational therapy). The outcomes during the hospitalization included complications, discharge destination (own home, rehabilitation or transitional care hospital, another acute care hospital, nursing home, other), and ambulatory ability at discharge.

A letter was sent from a co-investigator (an employee of the hospital) at each hospital to the study patients who met the study inclusion criteria. The informed consent included a brief description of the study and instructions on how to complete and return the voluntary and confidential survey. Patients and/or their family members were asked to sign the consent form, complete and return the questionnaire if they agreed to participate in this study.

2.3. Measurement and estimation

The LOS was calculated as the dates of discharge minus the dates of admission at the study hospitals. The number of days patients stayed at another unit for the treatment of comorbidities or complications or rehabilitation care unit (if they stayed) were included as well as the orthopedic care unit. Follow-up days were defined as the days from surgery to death, or to when the questionnaire was answered if the patient was alive.

Ambulatory ability was determined from the medical records and the questionnaire with a 6-level scale (1 = walk independently without use of equipment, 2 = walk with a cane, 3 = walk with a walking frame or cart, 4 = need

people's assistance, 5 = use wheel chair, 6 = confined to bed). Comorbidities were defined as the conditions that patients had before hip fracture surgery. Main comorbidities included: anemia, cancer, dementia, diabetes mellitus, hypertension, ischemic heart disease, arthritis, and osteoporosis. Each comorbidity was collected using a 3 level score (0 = never had, 1 = used to have but currently does not have, and 2 = currently has). The total numbers of comorbidities were calculated as a comorbidity score. Complications were defined as conditions that occurred during or after hip fracture surgery. Complications included: anemia, urinary tract infection, delirium/dementia, deep vein thrombosis, respiratory disorders, cardiovascular disorders, neurological disorders, infection or necrosis and others. The total number of these complications was calculated.

In Japan, costs and charges are one in the same. Hospitals are paid based on an insurance payment system using points. One point is basically regarded as 10 yen (\) (8.6 cents: calculated as 1 dollar = 116 yen) although there is a small variance that is dependent upon the price in the local areas. The costs included basic hospitalization fee (personnel expenses and miscellaneous fee), surgery, procedure, medication, medical administration, consultation, examination, rehabilitation, and X-ray. Basic hospitalization fees vary according to the local areas in Japan. In this study, data were collected from hospitals in different geographical areas. Therefore, "additional local payments" were subtracted from the costs in hospital B and C, which were located in bigger cities than hospital A. One patient in hospital B had a LOS of 233 days but the total hospitalization cost was not available, and this patient was excluded from the cost estimation.

The cost of subsequent hospitalization for rehabilitation was calculated according to the LOS. The hospitals used for subsequent hospitalization were included as other acute care hospitals, rehabilitation or transitional care hospitals, cardiovascular specialty hospitals, or clinics that had beds. These hospitals did not include nursing homes although some nursing homes do provide rehabilitative care. Information on types of hospitals that were used after discharge and LOS were collected from study hospitals records and/or patients' survey.

Types of insurance payments per day per patient in basic hospitalization fees in Japan were decided as an average LOS and took into consideration the patient/nurse ratio. Basic hospitalization fees were calculated according to the payment types in each hospital and how many days they stayed. Many of the rehabilitation or transitional care hospitals (24%) used the same payment types as acute care hospitals (basic payment type no. 1), such as hospital B and C, 22% of hospitals used "rehabilitation units for recovery," 5% were clinic that had beds, and 49% of the hospitals' payment systems were unknown. The hospitals whose payment systems were not known were calculated as the average of basic payment no.1 and no. 2. In basic payment system no. 1, insurance payments per day per patient were \$171 (\19,830) during the initial 14 days, \$151 (\17,470) for next 16 days, and \$134 (\15,550) from 31st day and later. In basic payment no. 2, insurance payments per day per patients were \$146 (\16,970) during the initial 14 days, \$126 (\14,610) for the next 16 days, and \$109 (\12,690) from 31st day and later. In the "rehabilitation unit for recovery," insurance payments per day per patient were \$145 (\16,800). Insurance payments per day per patient for clinic stays were \$69 (\8010). This basic hospitalization payment; however, does not include rehabilitation, medication, procedure, medical administration, consultation, examination or X-rays. Fifty-three patients in this study were discharged to hospitals or clinics but information was available on 41 patients (77.3%). The costs for the remaining patients in these rehabilitation hospitals were not added to the total costs. Therefore, the estimation of costs in this study would be substantially lower than the actual costs and should be regarded as minimal costs.

The study patients were asked the following questions: where they lived at three months after their surgery and where they are living currently, if they used elder's insurance introduced in 2000 in Japan, if they used elder's care services for home care visits, day services and short stays, and how many days they used this care after discharge from the hospital. In this study, the approximate costs were calculated by days used, times the average insurance payment per day. Insurance payments in one prefecture in Japan [15] were used for cost estimation. Home visit rehabilitation costs were \$43 (\5000), day services costs were \$11 (\1300), and short stay costs were \$47 (\5450) per day (averaged for levels of care 1 and 2 and added rehabilitation fee). The survey also asked if anyone in the patients' family took a leave of absence from work in order to take care of the patients and if so, they were asked their approximate salary loss. Costs of outpatient visits and readmissions were considered to be very low and these costs were not included in this study.

2.4. Analyses

The SPSS version 15.0 for Windows was used to analyze the data. Pearson's chi-square tests or Fisher's exact tests were used to compare the categories/ratios of variables, such as gender and place of residence. Continuous variables, such as age and days of care service use, were compared by *t*-tests between two groups and by one-way analysis of variance among three groups. Ordinal measures were compared using Mann–Whitney *U* tests between two groups and by Kruskal–Wallis test among three groups: comorbidity score, complications and ambulatory ability. Pearson's correlation coefficients were used for the relationship of two continuous variables, and Spearman's correlation coefficients were used for two ordinal variables, or for one continuous and one ordinal variable.

The comparison of outcomes and costs among the three hospitals after adjusting for patients' factors were tested by multivariate analyses. Independent variables that have empirical evidence or a theoretical basis to be related to dependent variables were selected as covariates. Ambulatory ability was categorized into 2 levels ("able to walk independently = 6 level ambulatory ability scale 1–3" or "not able to walk independently = 4–6") and logistic regression was used. The Cox Proportional Hazards model was used for outcome variables of survival. The costs data were

Table 1
Comparison among three hospitals ($N = 149$).

	A ($n=21$)	B ($n=56$)	C ($n=72$)	P-value
Average age, (S.D.)	77.9 (9.1)	83.2 (6.9)	82.9 (7.7)	.017
Female, n (%)	15 (71.4)	47 (83.9)	56 (77.8)	.445
Walk without equipment before fracture, n (%)	13 (61.9)	28 (50.0)	36 (50.0)	.536
Length of hospital stay, days (S.D.)	28.5 (11.6)	45.3 (27.7)	46.9 (18.7)	.003
Median (range)	28 (7–59)	41 (24–233)	47.5 (13–111)	
Initial hospitalization costs ($)				
Mean	14,790	13,925	17,435	<.001
Median	15,823	12,992	17,160	
Walk independently with or without equipment at discharge, n (%)	14 (66.6)	51 (91.1)	51 (70.9)	.060
Discharge place, n (%)				
Home	7 (33.3)	21 (37.5)	55 (76.4)	
Nursing home/group home	0 (0.0)	7 (12.5)	6 (8.3)	<.001
Acute care hospital	5 (23.8)	3 (5.4)	0 (0.0)	
Rehabilitation hospital	9 (42.9)	25 (44.6)	11 (15.3)	

	A ($n=19$)	B ($n=56$)	C ($n=69$)	
Residence at 3 months, n (%)				
Home	11 (57.9)	31 (55.4)	50 (72.5)	
Nursing home/group home	2 (10.5)	15 (26.8)	11 (15.9)	.077
Acute care hospital	6 (31.6)	8 (14.3)	8 (11.6)	
Rehabilitation hospital	0 (0.0)	2 (3.6)	0 (0.0)	

	A ($n=18$)	B ($n=49$)	C ($n=65$)	
Current residence, n (%)				
Home	16 (88.9)	30 (61.2)	49 (75.4)	
Nursing home/group home	2 (11.1)	13 (26.5)	15 (23.1)	.109
Acute care hospital	0 (0.0)	4 (8.2)	1 (1.5)	
Rehabilitation hospital	0 (0.0)	2 (4.1)	0 (0.0)	
Walk independently with or without equipment currently, n (%)	14/18 (77.8)	34/50 (68.0)	37/64 (57.8)	.135
Currently alive, n (%)	19/21 (90.5)	50/56 (89.3)	66/72 (91.7)	.900

Calculated as 1 dollar = 116 yen.

right skewed and were transformed into natural logarithm, and then linear regressions were used.

3. Results

Two hundred eleven patients met the inclusion criteria and each received a copy of the questionnaire. One hundred forty-nine patients completed the questionnaire (response rate was 70.6%). The average age was 82.3 years old (S.D. 7.8, range 65–102) and 79.2% ($n = 118$) were female. The average follow-up days was 435 days (S.D. 210, range 46–843) and the mortality rate was 9.4% ($n = 14$). The response rate was significantly greater for patients who lived with any family members before fracture ($P = .031$). There were no significant differences in response rates by other patients' characteristics [13].

Table 1 summarizes the comparison of patients' characteristics, outcomes, and hospitalization costs among the three hospitals. The average age ($f = 4.2$, $P = .017$), comorbidity scores ($z = 42.9$, $df = 2$, $P < .001$), and number of complications ($z = 6.6$, $df = 2$, $P = .036$) were significantly lower in hospital A than hospitals B and C. More patients in hospital C were living in their home prior to hip fracture than the other two hospitals ($\chi^2 = 7.2$, $df = 2$, $P = .028$). There were no differences in gender, ambulatory ability before fracture and follow-up days among hospitals.

There were no differences in the types of surgery, but there was a difference in types of anesthesia ($\chi^2 = 98.6$, $df = 2$, $P < .001$). Initial dates of rehabilitation after surgery were significantly earlier in hospital B than hospital A ($f = 16.30$, $P < .001$). The total hours of rehabilitation during hospitalization ($f = 15.5$, $P < .001$) and LOS ($f = 6.1$, $P = .003$) were significantly shorter in hospital A than hospitals B and C. Hospitalization costs were significantly higher in hospital C than others ($f = 9.5$, $P < .001$). There was no statistical difference in ambulatory ability at discharge among three hospitals, but more than 90% of patients were able to walk independently at discharge from hospital B. Most patients from hospital C (76.4%) were discharged to their home, and patients in hospital A were more likely to be discharged to another acute care hospital than other hospitals ($\chi^2 = 41.0$, $df = 6$, $P < .001$). There were no statistical differences in the places patients lived at three months after surgery or currently, but a relatively high percentage of patients (31.6%) in hospital A were still staying in another acute care hospital (Table 1).

3.1. Comparison of outcomes

There was no significant difference in mortality after discharge among the three hospitals after adjusting for age, gender, living own home before fracture, ambulatory ability before fracture and comorbidity score. There was no significant difference at alpha level of .05, but more patients in hospital B tended to survive than others. More patients in hospital B were currently able to walk independently than others after adjusting for patients' factors and follow-up days (odds ratio = 4.410, $P = .040$).

Table 2
Comparison of hospitalization cost among three hospitals.

	B	S.E.	Exp(B) (95%CI)	P-value
Hospital A	−0.19	0.06	0.83 (0.74–0.93)	.001
Hospital B	−0.18	0.07	0.83 (0.73–0.96)	.009
Age	0.00	0.00	1.00 (0.99–1.00)	.776
Comorbidity	0.01	0.00	1.01 (1.00–1.02)	.104
Lived home before fracture	0.14	0.06	1.15 (1.03–1.29)	.013
General anesthesia	−0.02	0.06	0.99 (0.87–1.11)	.803
Partial hip replacement	0.37	0.04	1.45 (1.34–1.57)	<.001
Total hip replacement	0.18	0.16	1.20 (0.88–1.64)	.257

Linear regression: Dependent variable: log(hospitalization cost), adjusted R^2 = 0.519, exp(B) = exponential(B), CI = confidence interval.

3.2. Comparison of costs

The variables of hospital, age, comorbidity score, living at home before fracture, types of anesthesia and surgery were entered into linear regression whose outcome variable was log hospitalization cost. As a result, both hospitals A (exponential $B = 0.83$, $P = .001$) and B (exponential $B = 0.83$, $P = .009$) had 83% of the costs compared to hospital C (Table 2).

Table 3 summarizes the estimated costs including care after discharge. Although the average LOS of the patients who received surgery at hospital C was the longest, the total days of institutional care was the shortest. There was no statistical difference in total hospitalization costs (initial and subsequent) among patients who had surgery at the three hospitals. There were no statistical differences whether family took a leave, in approximate days of leave or in salary loss. There were no statistical differences in the use of the elder's insurance, care services, or the total estimated costs for these care services. The estimated total direct and indirect costs were the highest for patients who received surgery at hospital A (Table 3).

Table 4
Distribution of cost (%).

Costs	A	B	C	Total
Initial hospital	68.7	70.6	87.7	78.6
Subsequent hospital	21.8	26.1	7.23	16.2
Family's salary loss	0.32	0.03	1.06	0.57
Elder's care services	9.17	3.18	4.03	4.47

Table 5
Comparison of total cost among three hospitals.

	B	S.E.	Exp(B) (95%CI)	P-value
Hospital A	0.07	0.12	1.07 (0.85–1.35)	.566
Hospital B	0.07	0.09	1.07 (0.89–1.29)	.455
Age	0.01	0.00	1.01 (1.00–1.02)	.138
Lived home before fracture	0.24	0.09	1.27 (1.05–1.53)	.014
Comorbidity	0.00	0.01	1.00 (0.98–1.01)	.565
Ambulatory ability before fracture	0.07	0.03	1.07 (1.01–1.14)	.033
General anesthesia	<0.001	0.10	1.00 (0.82–1.22)	.999
Partial hip replacement	0.37	0.07	1.45 (1.28–1.66)	<.001
Total hip replacement	0.49	0.26	1.64 (0.97–2.76)	.064
Follow-up days	<0.001	<0.001	1.00 (1.00–1.00)	.737

Liner regression: Dependent variable: log(total cost), adjusted R^2 = 0.208 "Follow-up days" is days from surgery until death or follow up. Exp(B) = exponential(B), CI = confidence interval.

Table 4 demonstrates the distribution of costs. Hospitals A and B reduced the costs of their hospitals but they increased subsequent hospitalization costs. Overall, 95% of the costs accounted for institutional care (initial and subsequent hospitalizations). There were no significant differences in total costs among the three hospitals after adjusting for patients' factors and follow-up days (Table 5). Coefficients (B) were positive for both hospitals A and B, which means that total costs were higher rather than lower than hospital C.

Table 3
Estimated costs of hip fracture.

	A (n = 7)	B (n = 26)	C (n = 8)	Total (N = 41)	P-value
Days subsequent hospitalization, mean (S.D.)	109.6 (67.7)	79.1 (102.3)	89.6 (61.0)	86.3 (89.5)	.731
Estimated subsequent hospital cost ($), mean (S.D.)	14,064 (8,040)	10,897 (14,150)	12,930 (8,420)	11,834 (12,203)	.806
	A (n = 21)	B (n = 56)	C (n = 72)	Total (N = 149)	
Total days of institutional care, mean (S.D.)	65.0 (65.4)	82.0 (83.7)	56.9 (36.9)	67.5 (63.0)	.080
	A (n = 21)	B (n = 55)	C (n = 72)	Total (N = 148)	
Total hospitalization cost ($), mean (S.D.)	19,478 (9,536)	19,077 (11,709)	18,871 (6,819)	19,034 (9,233)	.965
	A (n = 18)	B (n = 35)	C (n = 60)	Total (N = 113)	
Family's salary loss ($), mean (S.D.)	81.4 (241)	8.1 (33.6)	252.5 (1071)	149.6 (792)	.325
Use of elder's insurance, n (%)	14/21 (66.7)	41/53 (77.4)	55/71 (77.5)	110/145 (75.9)	.567
	A (n = 20)	B (n = 38)	C (n = 62)	Total (N = 120)	
Total estimated cost of care services ($), mean (S.D.)	2,073 (3,502)	908 (2,174)	931 (2,109)	1,114 (2,428)	.154
	A (n = 21)	B (n = 55)	C (n = 72)	Total (N = 148)	
Total cost of hospitalization, care services and family's salary loss ($), mean (S.D.)	21,522 (9,671)	19,710 (11,865)	19,883 (7,439)	20,051 (9,542)	.748

Calculated as 1 dollar = 116 yen.

4. Discussion

This study estimated direct and indirect costs after hip fracture surgery and compared these costs among the three hospitals that had different care systems in Japan. The LOS and hospitalization costs were the highest in patients who had surgery at hospital C, which took care of patients until they recovered, but the total LOS and costs including subsequent hospitalization were the lowest. These results agreed with Kawabuchi et al.'s study in Japan [10]. This study also estimated costs of elder's care services and family's salary loss. There was no difference in the total costs including care after discharge among the three hospitals. The use of the DPC payment system or linked rehabilitation hospital reduced the costs of the initial hospitals stays, but did not reduce the total costs including care after discharge. Early transfer to a rehabilitation center may ultimately be a method for cost-shifting to the rehabilitation center. Even after initial hospitalization, hip fracture patients continued to generate significant costs throughout the one-year period after discharge [16].

Hospital A used the DPC payment system and had significantly shorter LOS, but more patients were discharged to another acute care hospital and more patients were still in acute care hospitals at three months than the other hospitals. Patients in hospital A may have been discharged too early when they still needed acute care and they may not have received continuous acute care. It would have taken more days for them to recover than the total number of days they stayed at hospital A, even though patients in hospital A were younger and had fewer comorbidities and complications than patients in the other hospitals. Fourteen patients were discharged to another acute or rehabilitation hospital after discharge from hospital A, but only half of the patients' information about how many days they stayed in another hospital was available and added to the costs. It should have actually cost more than the estimation used in this study. Therefore, care is not cost-effective in patients who received surgery in hospital A, where patients were transferred to another hospital early.

Hospital B had relatively better outcomes than other hospitals: lower mortality rates and higher current ambulatory ability. Hospital B started rehabilitation earlier than other hospitals after surgery and most of the patients were able to walk independently at discharge although this number decreased at the time of investigation. Therefore, cost-effective care should have been provided in this hospital. Early rehabilitation after surgery such as in hospital B rather than just early discharge in hospital A might be necessary to be considered as cost-effective. On the other hand, the total LOS including subsequent rehabilitation hospital days was the longest in hospital B. Therefore, even though cost-effective care is provided in hospital B, the total care including care after discharge may not be cost-effective. More cost-effective care would have been provided if patients had received continuous care in hospital B rather than in linked rehabilitation hospitals.

There was no significant difference in whether family members took a leave in order to take care of patients with the days and salary loss among the three hospitals. Patients may have stayed in any institution until they recovered and the family's burden of care may not be different among hospitals. Indirect costs may also be of minor importance as most studies on hip fracture occurrence only include patients aged 65 years or older [16], and caregivers are likely already retired as well.

There were no significant differences in the use of days of elders' care services and estimated costs among the three hospitals because of the large variance. However, patients in hospital A tended to use more services and the total costs were the highest although patients in hospital A were younger and relatively healthier before fracture. Even though the LOS in acute care hospitals was reduced, the costs of care services may increase.

The Japanese healthcare system is strictly regulated by the government and combines private services with mandatory health insurance. Hospitals must operate as not-for-profit entities by law. All physicians in Japan are paid the same fee for each service or procedure [17]. Therefore, medical expenditures are relatively lower than other countries. Total expenditure on health per capita in Japan in 2005 was 2474 (in International dollars), compared to 6347 in the U.S., 2598 in United Kingdom, and 3071 in Belgium [18].

In the U.S., although the share of hospital expenditures declined, combined inpatient hospital and skilled nursing facility/home health care spending accounted for almost the same proportion of total Medicare spending before acute care hospital prospective payment system was implemented [19]. The increase in the number of patients remaining in nursing homes one year after the fracture suggests that the overall quality of care may have deteriorated [9]. In Belgium, the total mean cost of the initial hospitalization (29 day LOS) was $9534 for the hip fracture patients. The total direct costs during the year after discharge averaged $13,470. The largest costs were attributable to nursing home or rehabilitation center stays (62%), hospitalizations (16%), and home physical therapy services (14%)[20]. Although the hospitalization cost was lower than Japan, the cost of care after discharge was greater than the hospitalization cost in Belgium. There is no evidence that reducing LOS reduces total costs across developed countries [16]. Even though the cost of nursing home care is lower than hospital care, if patients stay in nursing homes longer, it may ultimately cost more. In the acute care hospitals, patients receive more effective care, including treatment of comorbidity and complication, not only orthopedic rehabilitation. The costs would be higher, but patients would be able to go home earlier.

In this study, we demonstrated that shorter LOS dose not reduce total costs, including care after discharge, but on the contrary, it may increase overall costs. This study retrospectively collected data and estimated direct and indirect cost data from hospital records where patients had surgery or from patients/family reports. Data may not have been accurately reported. There were some missing data. This study estimated costs of care after discharge as just days they used and applied an average of the costs. Data were collected from three different functioning hospitals in different areas in Japan. There might be confounders that could not be identified and adjusted, such as quality of care and the social backgrounds. The costs are based on best

estimates utilizing standard costs for hospital. Data were collected from only three hospitals in Japan. In addition, the low costs of health services in Japan may limit generalizability with other healthcare systems in determining cost effectiveness. Examining the effect of shorter LOS on total costs, including care after discharge, in a larger prospective study will be necessary.

5. Conclusions

There was no clear advantage of reducing the initial hospitals' LOS in terms of reducing total costs of care, including after discharge. On the contrary, more time may be required for patients to completely recover from their injury, and costs were higher if they were transferred to another rehabilitation hospital. Reducing the LOS and costs in the initial hospitals could be just a method of cost-shifting to subsequent hospitals or elders' care services and is unlikely to bring cost-savings in Japan. Future prospective larger studies are warranted.

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ORIGINAL ARTICLE

Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: a randomized placebo-controlled double-blind study

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Abstract
Summary A randomized placebo-controlled trial was conducted to examine the effect of daily oral 1 mg minodronate on vertebral fractures in 704 postmenopausal women with established osteoporosis for 24 months. Minodronate treatment reduced vertebral fractures by 59% without serious adverse events. Minodronate is a safe and effective bisphosphonate for osteoporosis treatment.
Introduction Minodronate increases bone mineral density (BMD) in postmenopausal osteoporotic patients. However, its efficacy in reducing osteoporotic fractures has not been tested.
Methods To examine anti-fracture efficacy and safety of daily oral minodronate in postmenopausal women with established osteoporosis, a randomized, double-blind, placebo-controlled trial was conducted in 704 postmenopausal women (55 to 80 years) with one to five vertebral fractures and low BMD. Subjects were randomly assigned to receive daily oral 1 mg minodronate (n=359) or placebo (n=345) for 24 months, with daily supplements of 600 mg calcium and 200 IU vitamin D_3.
Results Daily 1 mg minodronate for 24 months reduced the risk of vertebral fractures by 59% (95% CI, 36.6–73.3%). Furthermore, when fractures during the first 6 months were

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eliminated, the risk of vertebral fractures from 6 to 24 months was reduced by 74% in minodronate-treated group. Minodronate treatment also reduced height loss. Bone turnover markers were suppressed by about 50% after 6 months of minodronate treatment and remained suppressed thereafter. The overall safety profile including gastrointestinal safety was similar between the two groups. *Conclusions* Daily oral minodronate is safe, well-tolerated, and is effective in reducing vertebral fracture risk in postmenopausal women with established osteoporosis.

Keywords Bisphosphonate · Bone turnover markers · Fracture prevention · Height loss · Minodronate

Introduction

More than one fourth of women in their 70s suffer from at least one osteoporotic vertebral fracture [1, 2]. Incidence of new fractures rises with increasing number of preexisting fractures [3], and not only morbidity but also mortality rate rises with increasing number of fractures [4, 5]. Thus, osteoporosis has become a significant socioeconomic burden in aged societies.

Bisphosphonates have been shown to have potent antifracture efficacy by inhibiting bone resorption, with a reduction in bone turnover and an increase in bone mineral density (BMD). Minodronate (ONO-5920/YM529) is a nitrogen-containing bisphosphonate with potent inhibitory effect on bone resorption [6]. Previous in vitro and in vivo preclinical studies demonstrated that minodronate is about ten times as potent as alendronate in inhibiting bone resorption [7]. A randomized placebo-controlled double-blind trial revealed that daily oral administration of 0.5, 1.0, and 1.5 mg minodronate to Japanese women with postmenopausal osteoporosis for 9 months caused an increase in lumbar BMD by 4.9%, 5.7%, and 5.2%, respectively, compared with the placebo group [8]. Because the incidence of adverse gastrointestinal events did not increase in a dose-dependent manner (0%, 12.6%, 6.3%, and 11.1% by placebo, 0.5, 1.0, and 1.5 mg minodronate treatment, respectively), minodronate was shown to be well tolerated with excellent effect in increasing BMD. In addition, a head-to-head comparison of the effects of daily oral 1 mg minodronate with 5 mg alendronate revealed that the effect of 12-month treatment with 1 mg minodronate on lumbar and total hip BMD was similar to those of 5 mg alendronate and that minodronate was generally well tolerated with similar safety profiles to alendronate (Hagino et al., submitted for publication). These data suggest that minodronate can become a new treatment choice as a potent bisphosphonate for patients with established osteoporosis. However, its efficacy in reducing osteoporotic fractures has not been evaluated. The present phase III clinical trial was conducted to examine the effect of daily oral 1 mg minodronate on the prevention of vertebral fractures in Japanese women with postmenopausal osteoporosis.

Materials and methods

Patient enrollment

We studied postmenopausal women aged 55 to 80 with one to five fragility fractures between the vertebrae T4 and L4 and BMD below 80% (*T* score −1.7 at the lumbar spine) of the young adult mean (YAM) [9]. Data for the YAM and *T* score values were obtained from the reference data in 3,218 Japanese healthy women with 20 to 44 years of age [10].

Subjects were excluded if they had disorders such as primary hyperparathyroidism, Cushing's syndrome, premature menopause due to hypothalamic, pituitary or gonadal insufficiency, poorly controlled diabetes mellitus (HbA1c over 8.0%), or other causes of secondary osteoporosis, or if they had any radiographic finding that might affect the assessment of vertebral fractures and used hard or semi-hard corset in spine part. Subjects with peptic ulcer were excluded. Subjects were excluded if they had taken bisphosphonates at any time. Subjects were also excluded if they had taken glucocorticoids, calcitonin, vitamin K, active vitamin D compounds, or hormone replacement therapy within the previous 2 months, had serum calcium (Ca) levels above 10.6 mg/dL (2.7 mmol/L) or below 8.0 mg/dl (2.0 mmol/L), had serum creatinine levels above 1.5 mg/dL (133 μmol/L), or had clinically significant hepatic disorders.

This study was conducted in accordance with consideration for the protection of patients, as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects gave written informed consent before undergoing any examination or study procedure, which was conducted in compliance with Good Clinical Practice.

Study design

This study was a randomized, double-blind, placebo-controlled, multicenter study at 98 sites in Japan. Subjects who met all the entry criteria were enrolled and sequentially assigned an allocation number independent of study site. Subjects were randomized to take 1 mg minodronate (Astellas Pharma, Tokyo, Japan) or placebo once a day and were treated for 24 months. Randomization was performed by a computerized system. Subjects were instructed to take their tablet on rising and 30 min before food with plain water. All

subjects received daily calcium (600 mg) and vitamin D (200 IU) supplementation once a day after the evening meal. Adherence with the study treatment was assessed with the use of medication diaries and counts of residual medication supplies.

Study outcomes

The primary endpoint of the study was the cumulative proportion of patients with new morphometric vertebral fractures at 24 months of treatment with the study medication. Secondary endpoints included length of the period to the occurrence of new vertebral fractures, the risk of patients and length of the period to the occurrence of clinical fractures, changes in height, and relative changes in bone turnover markers.

Assessment of vertebral fractures Lateral radiographs of the thoracic and lumbar spine were taken at the screening visit to determine the presence of prevalent fractures. Subjects were enrolled based on a visual assessment of prevalent fractures in T4 to L4. All the radiologic specifications and the levels of vertebra at the thoracic sand lumbar spine were standardized throughout the study sites. The assessment of prevalent fractures was made if the ratio of anterior or middle vertebral body height to the posterior vertebral body height was less than 0.8 [11]. Quantitative and semiquantitative techniques [12, 13] were used to identify incident vertebral fractures for the purposes of the efficacy determination. Lateral radiographs of the spine were performed at 6, 12, 18, and 24 months for the assessment of incident fractures. An incident of new vertebral fracture was diagnosed if the anterior, posterior, or middle vertebral height had decreased by at least 15% and by 4 mm in a vertebra that was normal at baseline, or semiquantitatively as a progress in grades [11]. Morphological diagnosis of fractures was made by quantitative and semiquantitative assessment of two evaluators who were blinded to the sequence of films at two independent central reading facilities at Tottori University, Yonago, Japan by Hagino, H. and at the University of Occupational and Environmental Health, Fukuoka, Japan by Nakamura, T., with adjudication by a third investigator (Nakano,T. at Tamana Central Hospital, Kumamoto, Japan) in the event of discrepant results.

Assessment of non-vertebral fractures All non-vertebral fractures were identified symptomatically as clinical fractures, and only non-traumatic fractures assessed by investigators were reported. Suspected clinical fractures at six non-vertebral sites (humerus, radius/ulna, subclavia, pelvis, femur, and tibia/fibula) were adjudicated radiographically, and only radiographically confirmed fractures were listed.

Assessment of bone turnover Serum and urine samples were collected at baseline, 6, 12, 18, and 24 months for measurement of bone turnover markers, including urinary total deoxypyridinoline (DPD) measured by high-performance liquid chromatography (SRL, Tokyo, Japan) [14] after acid hydrolysis, urinary type I collagen *N*-telopeptide (NTX; Osteomark, Ostex International, Seattle, WA, USA), serum bone-specific alkaline phosphatase (BALP; Osteolinks "BAP", Quidel, San Diego, CA, USA), serum osteocalcin (BGP-IRMA Mitsubishi; Mitsubishi Kagaku Iatron, Tokyo, Japan), and serum 25-hydroxyvitamin D (25 (OH)D; 125I RIA Kit, DiaSorin Inc., Saluggia, Italy). Study subjects were asked to visit study sites during the morning, but it was not mandatory to visit in the fasting state.

Assessment of adverse events All subjects were questioned about adverse events (AEs) of treatment at each visit, and all adverse events reported were analyzed regardless of the investigators' assessments of causality. The Medical Dictionary for Regulatory Activities (MedDRA, Version 8.1J) was used to categorize reported adverse events.

Statistical analysis All the data analyses were performed by statisticians from Ono under the supervision and confirmation of data analyses by one of the authors (Ohashi, Y.).

The intention-to-treat (ITT) population comprised all patients who received at least one dose of study medication and who attended at least one follow-up visit for any observation of efficacies. The ITT population was used for all fracture and height analyses. Safety analyses population comprised all patients who received at least one dose of study medication in either treatment group. A per-protocol (PP) approach was used as a primary approach to analyze the bone turnover markers because they can change rapidly by protocol violations, interruption of study therapy, or concurrent illness. The PP approach excluded protocol violators who took less than 75% study drug, who took prohibited medications during the course of the trial, or who violated the protocol in a significant manner as specified in the data analysis plan, and patients who took study drug for less than 12 months. This population included all patients in the ITT population, except those with a protocol deviation deemed to have a significant impact on the efficacy variables, i.e., major deviations regarding the inclusion/exclusion criteria, patients with insufficient compliance (<75% of the study medication), documentation of forbidden concomitant medication that could bias the fracture results, and patients lacking an assessable baseline and follow-up for X-ray assessments for less than 12 months.

The risk of patients with new morphometric vertebral fractures at 24 months, as the primary endpoint, was

analyzed by testing the superiority of minodronate group to the placebo group by the time-to-event curves (Kaplan–Meier method), the event being the first new incident vertebral fracture. The primary hypothesis was tested using an ITT analysis that was modified to include all subjects randomized, who had taken at least one dose of study drug, and attended at least one follow-up visit. A Cox regression model was used to estimate the relative risk of vertebral fracture and its 95% confidence interval in minodronate group and placebo group. Log-rank test was used to determine the superiority of the minodronate group to the placebo group. The power calculation was based on the predictive risk of vertebral fracture. For the study to achieve a power of 90% to detect the superiority, a sample size of 290 subjects per group was required. To allow for subject withdrawals, the intention was to enroll 640 to 650 subjects. Differences were considered to be statistically significant if the p value was less than 0.05.

Group mean and standard error (SE) were given for the percent changes from baseline in bone turnover markers and changes from baseline in height and were used to assess the significance of changes within two groups. T test was used to determine whether minodronate group was significantly different from the placebo group. The comparability between minodronate and placebo groups for demographic information was assessed with Wilcoxon's rank-sum test or Fisher's exact test. Differences in proportions of patients with AEs were analyzed using Fisher's exact test. The treatment groups were also compared for the proportion of patients with gastrointestinal AEs using Fisher's exact test. Statistical analyses were performed using Statistical Analysis Systems (SAS Institute, Cary, NC, USA). All protocol violators were identified before database lock of the study.

Results

Patient disposition

A total of 1,083 subjects were screened at 98 study sites in Japan (Fig. 1). A total of 704 subjects were randomized to take either minodronate (359 subjects) or placebo (345 subjects). Five patients in the minodronate group and three patients in the placebo group were excluded from the safety analysis population for reasons of not receiving the study medication or withdrawal of informed consent. Among the safety analysis population, a total of 161 had been treated with either 20 IU/week calcitonin (154 subjects) or estrogen (seven subjects) before the washout period. None of the study subjects were given glucocorticoid treatment before enrollment. The proportion of the subjects in the ITT analysis (95.5% and 95.9% in minodronate and placebo groups, respectively) and PP analysis (75.5 and 76.2% in minodronate and placebo groups, respectively) was similar between the two groups.

Baseline characteristics of the subjects

The baseline demographics of subjects were well balanced between the two groups (Table 1). The number of vertebral fractures at baseline was not significantly different, and the number of subjects with one, two, and three or more vertebral fractures was similar between the two groups. There was no significant difference in lumbar BMD, serum 25(OH)D, and the levels of bone turnover markers at the baseline between the two groups.

Vertebral fractures

After 24 months of treatment, there was a statistically significant reduction in the risk of vertebral fractures in the minodronate group compared with the placebo group ($p<0.0001$, log-rank test; Fig. 2). The Kaplan–Meier estimates of risk after 24 months of treatment were 10.4% in the minodronate group and 24.0% in the placebo group of the ITT population. Relative risk of vertebral fractures by minodronate treatment was 0.411 (95% confidence interval [CI], 0.267–0.634), and relative risk reduction rate in cumulative fracture incidence by minodronate treatment was 59%. Among patients in the PP population who completed the 2-year study ($n=253$ in the minodronate group and $n=239$ in then placebo group), the incidence of vertebral fractures was 9.9% in the minodronate group and 21.3% in the placebo group. These numbers were very similar to those observed in the ITT population.

A large number of fractures occurred during the first 6 months in both groups (20 and 27 in minodronate and placebo groups, respectively), and the decrease in vertebral fracture risk by minodronate treatment was more pronounced after the initial 6 months until the end of the study period (Table 2). When the incidence of vertebral fractures during the first 6 months was compared between subgroups with one prevalent fracture and two or more fractures, the incidence of vertebral fractures during the first 6 months was five (3.5%) in minodronate group and six (4.3%) in placebo group among patients with one prevalent fracture. In contrast, vertebral fracture incidence during the first 6 months was 15 (9.0%) in the minodronate group and 21 (12.3%) in the placebo group among patients with two or more prevalent fractures. Thus, majority of the fractures during the early study period came from patients with two or more prevalent fractures.

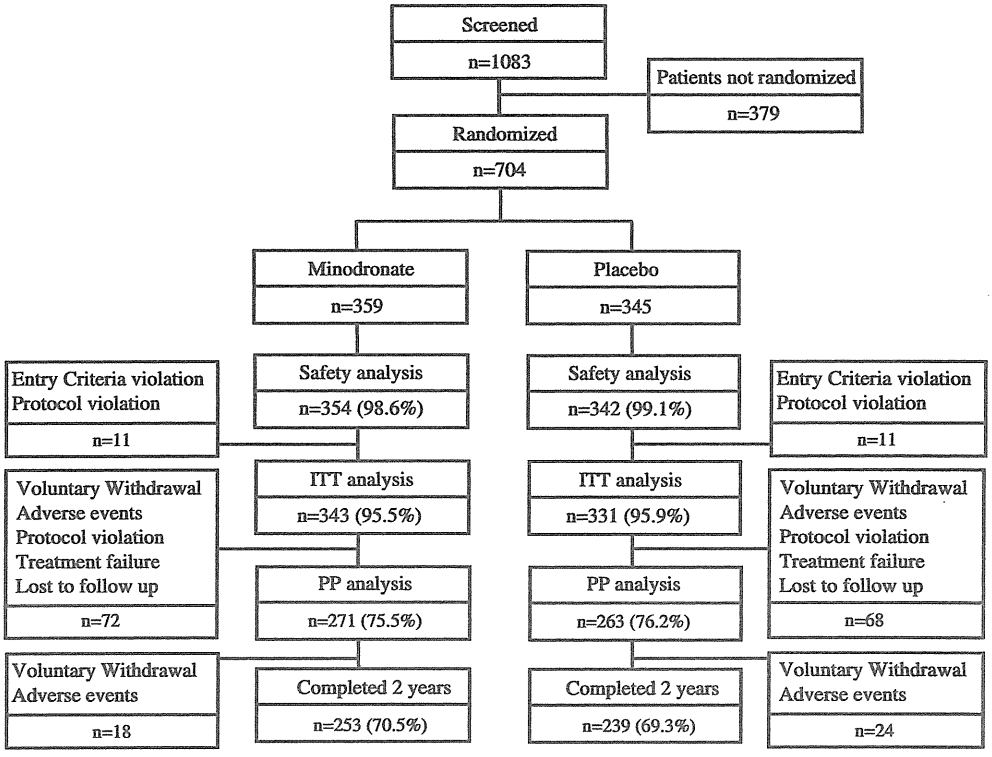

Fig. 1 Enrollment and outcomes. A total of 1,083 subjects were screened, and 704 subjects were randomized to take either minodronate (359 subjects) or placebo (345 subjects)

Height loss

In order to examine whether the effect of minodronate on vertebral fracture prevention was related to the stature of patients, height of studied subjects was assessed at 12 and 24 months using stature meter equipped at each study site. At 12 months, a mean stature loss in the minodronate group (1.2 mm) was already significantly less than that in the placebo group (3.4 mm; $p<0.05$) (Fig. 3a). After 24 months of treatment, a mean stature loss of 6.8 mm was observed in the placebo group, which was significantly larger than that in the minodronate group (3.7 mm, $p<0.01$; Fig. 3a). There was no significant height loss in those patients without fracture, and in those patients who did not fracture, no significant effect of minodronate treatment on the height was observed (Fig. 3b).

Non-vertebral fractures

Non-vertebral fractures that occurred during the trial were picked up from the report of clinical fractures and confirmed by radiographs. Because the number of subjects in each group was small and the study period was short, no significant difference was observed between the groups

Table 1 Demographics and baseline characteristics of subjects

Characteristic	Minodronate (n=343)	Placebo (n=331)
Age (years)	71.4 [6.0]	71.7 [5.6]
Height (cm)	147.6 [5.9]	147.0 [5.9]
Body mass index (kg/m^2)	23.4 [3.1]	23.5 [3.3]
Time since menopause (years)	21.3 [7.2]	22.2 [6.8]
Number of prevalent vertebral fractures	2.0 [1.2]	2.1 [1.2]
With one fracture [n (%)]	161 (46.9)	147 (44.4)
With two fractures [n (%)]	88 (25.7)	80 (24.2)
With three or more fractures [n (%)]	94 (27.4)	104 (31.4)
Lumbar BMD T score	−2.95 [0.77]	−2.95 [0.77]
Serum 25(OH)D (ng/mL)	25.0 [6.0]	25.4 [6.2]
Serum BALP (U/L)	33.0 [11.8]	33.4 [13.0]
Serum osteocalcin (ng/mL)	9.1 [2.8]	9.2 [3.1]
Urine total DPD (pmol/μmol Cr)	8.8 [3.6]	8.9 [3.1]
Urine NTX (nmol BCE/mmol Cr)	50.2 [24.0]	50.9 [21.9]

Data are means [SD] for the indicated number of subjects in each group.

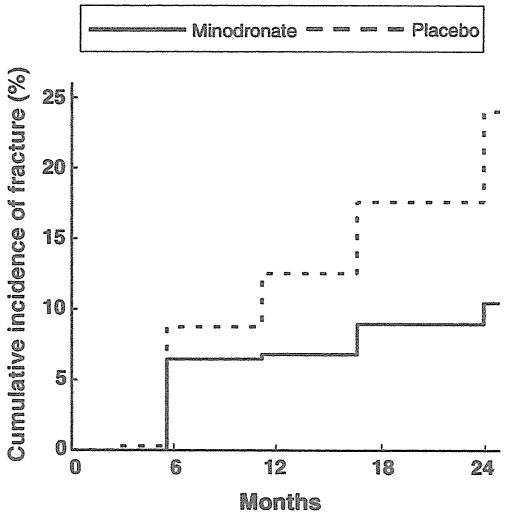

Fig. 2 Kaplan–Meier estimates of the effect of daily oral 1 mg minodronate for 24 months on the risk of vertebral fractures in osteoporotic subjects. Cumulative incidence of vertebral fractures from the start of the study. Minodronate treatment reduced relative risk of vertebral fractures by 59%

with daily 1 mg minodronate and placebo in the incidence of non-vertebral fractures at the major six sites (radius/ulna, humerus, femur, tibia/fibula, subclavia, and pelvis) after 24 months of treatment (2.7% in the minodronate and 3.5% in the placebo group).

Bone turnover markers

Bone turnover markers decreased significantly in the minodronate group, compared with in the placebo group ($p<0.0001$). Mean percent changes in bone resorption markers, urinary DPD and NTX, at 6 months were −42.4% and −49.5%, respectively, in the minodronate group, compared with −4.0% and −7.9%, respectively, in the placebo group. Bone resorption markers remained almost constant thereafter until 24 months of treatment, when the reduction in urinary DPD and NTX in the minodronate group was −37.1% and −56.7%, respectively (Fig. 4a, b). Bone formation markers, BALP and osteocalcin, also decreased at 6 months by −46.2% and −45.5%, respectively, in the minodronate group, compared with −14.1% and −16.3%, respectively, in the placebo group. Bone formation markers also remained almost constant until 24 months of treatment, and reduction in BALP and osteocalcin from baseline was −51.7% and −50.9% in the minodronate group, respectively (Fig. 4c, d).

Adverse events

The overall incidence of AEs was similar in both groups, as was the incidence of gastrointestinal AEs, drug-related AEs, and serious AEs (Table 3). The most common gastrointestinal tract AEs were constipation, gastric discomfort, and diarrhea. Among serious AEs, more patients in minodronate group reported infections/infestations and cardiac disorders. Infections included two pneumonia patients in both minodronate and placebo groups, and all the other infections were reported in only one patient in either group. Cardiac disorders included three patients in minodronate and two patients in placebo group with ischemic heart diseases, and one patient each with cardiac insufficiency and sinus arrhythmia in minodronate group. None of them reported atrial fibrillation. The proportion of subjects who discontinued the study due to AEs was also similar between the two groups. Complaints related to digestive system were the most common AEs associated with withdrawal from the study (Table 3).

Discussion

The present study demonstrated that daily oral administration of 1 mg minodronate for 24 months reduced the risk of new vertebral fractures by 59% compared with that in the placebo group. The effect of minodronate on vertebral fracture was observed within 12 months, and there was also a significant decrease in height loss at 12 months. The overall safety profile including gastrointestinal safety was similar between the two groups.

Table 2 Cumulative incidence of vertebral fractures

Months	Minodronate			Placebo			Log-rank test
	n	Number of patients (%)	Cumulative incidence (%)	*n*	Number of patients (%)	Cumulative incidence (%)	
0	339	0 (0.0)	0.0	328	0 (0.0)	0.0	$P<0.0001$
6	310	20 (6.5)	6.5	308	27 (8.7)	8.7	
12	274	1 (0.4)	6.8	265	11 (4.2)	12.5	
18	261	6 (2.3)	8.9	242	14 (5.8)	17.6	
24	246	4 (1.6)	10.4	219	17 (7.8)	24.0	

Data was analyzed by actuarial method.

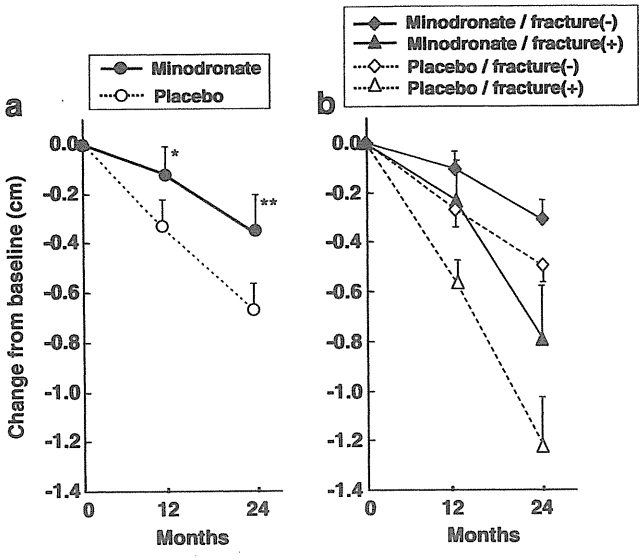

Fig. 3 Effect of daily oral 1 mg minodronate for 24 months on height changes of osteoporotic patients. a Minodronate treatment significantly reduced height reduction at both 12 months (*$p<0.05$) and 24 months (**$p<0.01$). b Height changes in minodronate-treated patients with (*closed triangle*, $n=27$) or without (*closed diamond*, $n=242$) vertebral fracture, and placebo-treated patients with (*open triangle*, $n=61$) or without vertebral fracture (*open diamond*, $n=200$) are shown. Data are means±SE

In the present study, a large number of vertebral fractures occurred during the first 6 months in both groups (20 and 27 in minodronate and placebo groups, respectively). In our previous study, to compare the effect of minodronate on lumbar BMD and bone markers with that of alendronate (Hagino et al., submitted for publication), bone resorption markers were suppressed within 1 month, and lumbar BMD was significantly increased after 3 months of minodronate treatment. It should be noted that the assessment of vertebral fractures at baseline was performed within 2 months before the start of study drug administration. Therefore, a part of vertebral fractures identified after 6 months of drug administration might have occurred before drug administration was started. Although the exact reason why a large number of vertebral fractures occurred during the early period in both groups remains unclear, minodronate showed a marked anti-fracture efficacy from 6 to 24 months of treatment (Table 2).

In contrast to the robust inhibitory effect on vertebral fractures, the present study did not show a significant effect of minodronate in reducing non-vertebral fractures. This is a major limitation of the present study. Because the study was aimed to examine the ability of minodronate to reduce the risk of vertebral fractures, the study did not have enough power in terms of the number of study subjects and the length of study period to examine the effect of minodronate on non-vertebral fractures. Thus, although the study included patients with established osteoporosis having at least one prevalent vertebral fracture, the number of non-vertebral fractures developed in long bones during the 24-month study period was too small to draw any conclusions.

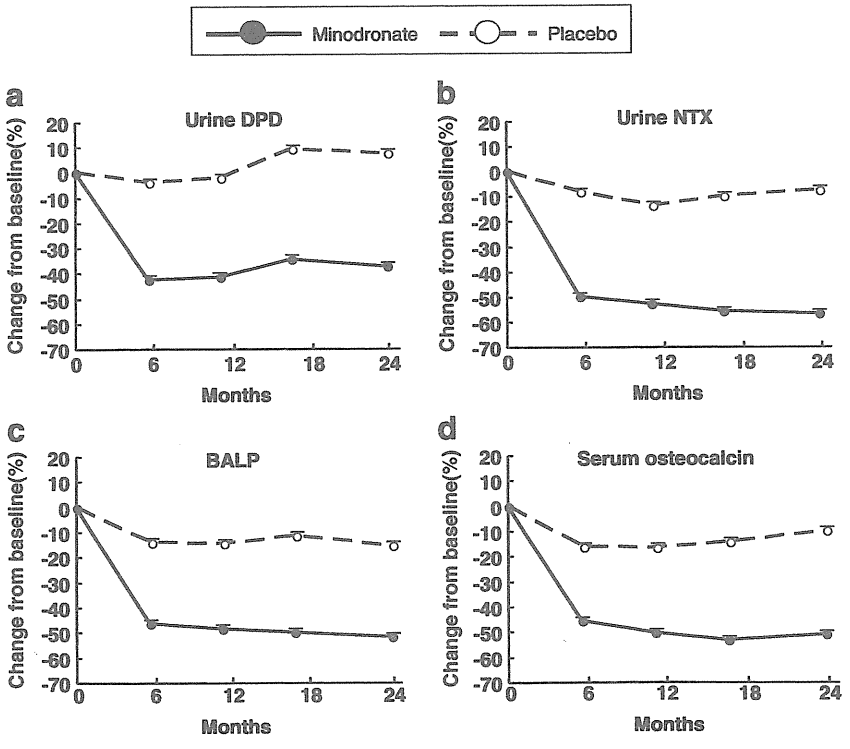

Fig. 4 Effect of daily oral 1 mg minodronate for 24 months on the changes in bone turnover markers in osteoporotic patients. Data are means±SE

Table 3 Summary of adverse events

	Minodoronate, *n* (%)	Placebo, *n* (%)
No. of patients	354	342
Any AE	334 (94.4)	327 (95.6)
Gastrointestinal AE	173 (48.9)	155 (45.3)
"Drug-related" AE[a]	57 (16.1)	54 (15.8)
Serious AE[b]	49 (13.8)	65 (19.0)
Injury, poisoning and procedural complications	10 (2.8)	13 (3.8)
Musculoskeletal and connective tissue disorders	8 (2.3)	9 (2.6)
Gastrointestinal disorders	7 (2.0)	9 (2.6)
Nervous system disorders	4 (1.1)	10 (2.9)
Infections and infestations	7 (2.0)	3 (0.9)
Eye disorders	1 (0.3)	8 (2.3)
Respiratory, thoracic and mediastinal disorders	3 (0.8)	5 (1.5)
Cardiac disorders	5 (1.4)	2 (0.6)
Neoplasms benign, malignant and unspecified	2 (0.6)	4 (1.2)
Discontinued due to AE	55 (15.5)	47 (13.7)
Discontinued due to gastrointestinal AE	17 (4.8)	13 (3.8)
Discontinued due to "drug-related" AE	17 (4.8)	14 (4.1)

Data are number of patients
AE adverse event
[a] AEs reported as drug-related by the investigators are listed as "drug-related"
[b] Serious AEs with more than two patients in either treatment group are listed

With regard to the safety profile of minodronate, no significant difference was observed between the minodronate and placebo groups in any AEs including drug-related or serious AEs. Although the most common AEs were gastrointestinal AEs, the incidence of gastrointestinal AEs, as well as those that caused discontinuation from the study, was very similar between the minodronate and placebo groups. These results suggest that minodronate does not cause any serious disturbance in osteoporotic patients, and daily administration of minodronate can be well-tolerated in patients with osteoporosis.

Minodronate exhibits very similar antiresorptive potency to zoledronic acid in pre-clinical studies [7], and intermittent oral administration of ibandronate [15] as well as yearly intravenous administration of zoledronic acid [16] demonstrated potent anti-fracture efficacy. Therefore, further studies are warranted to examine the effect of intermittent oral and intravenous minodronate on vertebral and non-vertebral fractures in osteoporotic patients.

In conclusion, daily oral minodronate is safe, well-tolerated, and is effective in reducing vertebral fracture risk in postmenopausal women with established osteoporosis. Because the dose of minodronate in reducing fracture incidence was low, further studies are warranted to evaluate the efficacy of intermittent administration of higher doses of minodronate on osteporotic fractures.

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高齢者の転倒の現状と問題点

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Key Words
・転倒
・骨折
・大腿骨近位部骨折

Points

・加齢に伴って骨は脆弱となり，強度が低下するため高齢者ほど転倒をすると骨折に至る危険性が高い．
・わが国では地域在宅高齢者の年間転倒発生率が10～25%で，施設入所者は在宅高齢者よりも転倒発生率が高く10～50%程度である．
・性別では女性のほうが男性よりも転倒発生率が高い．
・転倒者のおよそ54～70%が外傷を受け，6～12%が骨折に至り，その1/4で大腿骨近位部骨折が発生している．
・大腿骨近位部骨折の92%と橈骨遠位端骨折の96%は転倒が原因で発生している．

はじめに

高齢者人口の増加に伴って，転倒とそれによる骨折患者数が急増している．加齢に伴って骨は脆弱となり，強度が低下するため高齢者ほど転倒をすると骨折に至る危険性が高い．また年齢とともに筋肉量の減少（サルコペニア）が進むため転倒発生率も上昇すると同時に，皮下脂肪が減少しクッション作用が低下することも易骨折性を高める．骨折は疼痛と運動器機能障害をもたらし，高齢者では生活機能の制限が生じ，QOLを引き下げる．

最近では，著しい骨粗鬆症化を背景に有する超高齢者が増加し，きわめて軽微な外傷での骨折，いわゆる脆弱性骨折（fragility fracture）に至る症例が増えている．さらに外傷の既往がないのに骨盤部や大腿骨近位部に骨折を発症している場合も多く，このような骨折はinsufficiency fracture（脆弱性骨折）とよばれ，日常生活動作（activities of daily living：ADL）のなかで転倒をくり返した結果発症した可能性がある．

転倒は骨折のみでなく，頭部外傷や脊髄損傷も引き起こす．わが国における頸髄損傷の年齢分布には，若年者と高齢者の2つのピークがある[1]．若年者ではスポーツや交通事故が原因となるが，高齢者では脊柱管狭窄を背景に有する例での転倒がその原因となる．さらに，「不慮の事故」は高齢者死因の第5位であるが，そのうち「転倒・転落」は「不慮の窒息」（29.4%）についで第2位（19.3%）となっている[2]．本稿では，高齢者の転倒の現状とその結果としての骨折について概説する．

高齢者の転倒

1）転倒の発生率

わが国では地域在宅高齢者の年間転倒発生率が10～25%である[2]．施設入所者では報告によって差があるものの，在宅高齢者よりも転倒発生率が高く10～50%程度である．性別では女性のほうが男性よりも転倒発生率が高い．年齢では74歳以下の前期高齢者と75歳以上の後期高齢者を比較すると，転倒の発生率は後者で有意に高く，高齢になるほど発生率は急上昇する．また北欧や米

国の在宅高齢者では30～40％が転倒し，日本人と比較して2倍程度転倒頻度が高い[3]．この理由は不明であるが，転倒率が低いことが，日本人で四肢骨折発生率が低い理由のひとつとなっている．

転倒の発生場所は，施設入所者では病室内が半数以上を占め最も多いのに対して，一般住民に対する調査結果では一般道路・歩道が半数を占める[4]．また，転倒の時刻は施設入所者で午前6時～7時がピークで，ついで午後5時～6時が多く，食事およびトイレへ行くために活動性があがる時間帯に集中すると報告されている[5]．一般住民では午前10時～11時と午後2時～5時の，外出機会が多い時間帯に転倒の頻度も高い[4]．このように，施設入所者と在宅老人では，転倒の場所や時刻が異なるため，それに応じた対応が必要となる．

2）転倒の危険因子

転倒の危険因子は身体機能の低下に起因する内的因子と，居住環境などに起因する外的因子とに分けられる．内的因子には，不整脈，心不全，起立性低血圧，前庭・迷路機能障害，パーキンソン病，片麻痺，変形性関節症，関節リウマチ，視力低下，認知症などの疾患があげられる．認知症高齢者の転倒頻度は一般高齢者よりも約3倍（1.1～6.4倍）高い[6][7]．骨折発生率も認知症を有しない高齢者と比較して2～3倍高値である[8][9]．なかでも徘徊する例では大腿骨近位部骨折発生のリスクが6.9倍に上昇することが知られている[9]．また，降圧薬，鎮痛薬，向精神薬などの薬物も転倒のリスクを高める．

外的因子には滑りやすい床，めくりあがったじゅうたん，廊下の障害物，電気製品のコード，暗い廊下や階段，玄関の大きい段差，階段や風呂の手すりの不備といった住宅環境があげられる．また，和服やロングドレスの着用，ぞうり，スリッパの使用なども転倒リスクを高める外的因子である．

転倒により発生する骨折

1）転倒と骨折

わが国での高齢者の転倒による外傷の頻度は54～70％程度と報告されている．このうち骨折に至る症例は6～12％程度で，その1/4程度が大腿骨近位部骨折であると報告されている[2][10]．転倒が骨折発生に至る割合に関して，75歳以上の336例（在宅）を1年間追跡した調査では，108例（32％）が1回以上転倒し，このうち24％で重度の外傷が生じ，6％で骨折が発生した[11]．そして全体の1％（4例）に大腿骨近位部骨折が発生したと報告している．一般に，高齢となり骨粗鬆化に伴って骨脆弱化が進行するほど，転倒して骨折に至るリスクも高まる．

骨折した患者を対象に，転倒によって骨折がおこったかどうかを聞き取り調査した結果では，大腿骨近位部骨折のうちの92％，橈骨遠位部骨折（前腕骨骨折）では96％の症例で転倒が骨折発生の原因となっていた（表①）[12]．

表① 転倒が原因とする非脊椎骨折の割合

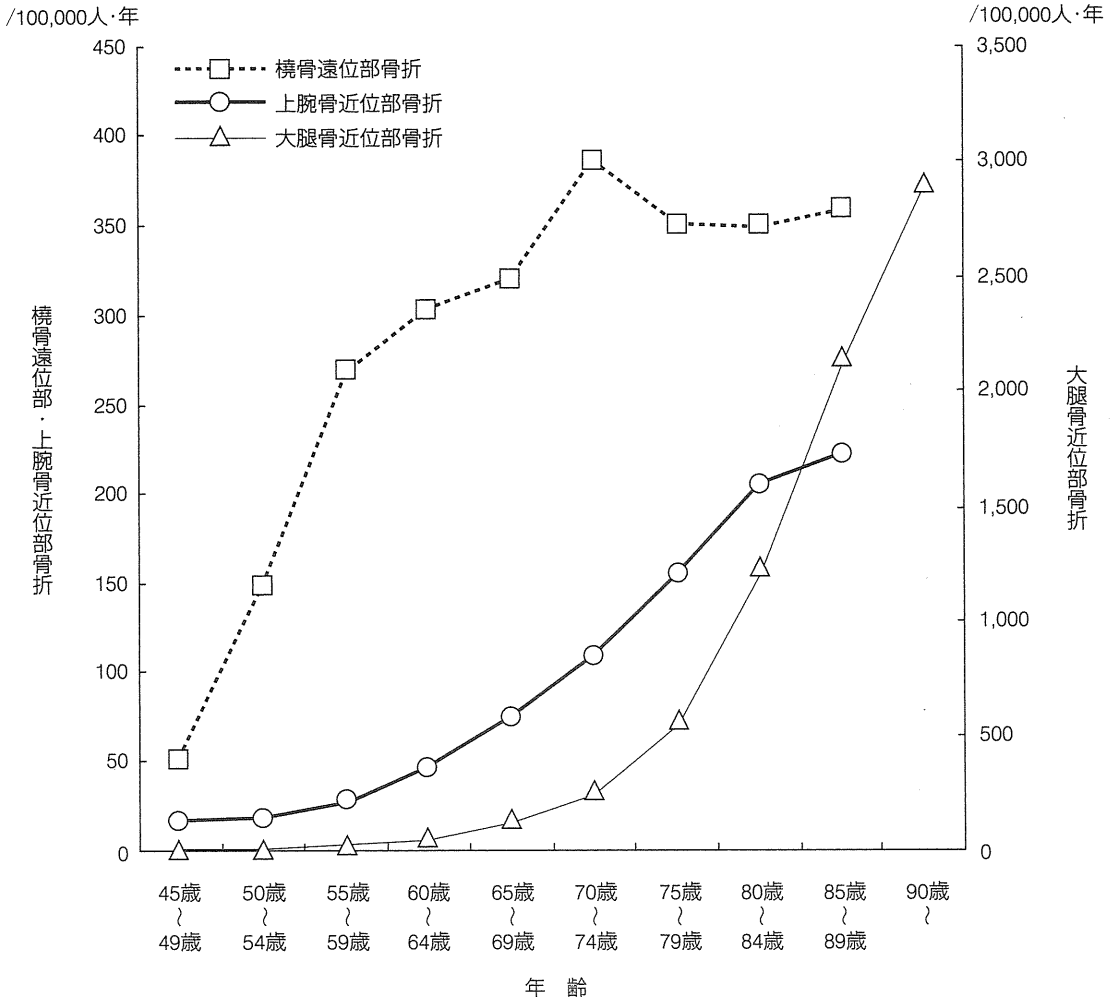
骨折型	転倒の結果の割合（％）
手関節	96
上腕骨	95
肘	95
大腿骨近位部	92
膝蓋骨	89
足関節	88
足部/足趾	82
骨盤	80
顔面	77
手部/指	68
脛骨/腓骨	65
肋骨	59

最近骨折を生じた高齢女性への調査結果
（Cummings SR *et al*, 1994[12]より引用）

2）骨折発生率

a．脊椎骨折

転倒後に背部痛を主訴として受診する症例と，はっきりとした外傷がない症例とがあり，なかには症状を伴わない症例もみられる．症状を有する骨折を「臨床骨折」とよび，無症状の骨折と区別している．「無症状」といっても，背部のだるさや，軽度の痛みを有していたが，患者自身が骨折を起こしたことを自覚していない場合もある．臨床症状を有して診断される脊椎骨折は全体の1/3程度であると考えられ[13]，そのほかは患者自身が骨折を自覚しないあいだに脊椎変形が進行して，徐々に腰痛を生じる．したがって，四肢骨折のように発生時期を特定することが困難なため，これまでおもに有病率が検討されてきた．わが国での有病率は60歳代で7.6～14％，70



図❶ 四肢骨折の年齢階級別発生率（女性）
数値は人口10万人あたりの年間発生数．大腿骨近位部骨折は70歳代後半から発生率が高くなり，指数関数的に上昇する．これに対して橈骨遠位部骨折は50歳代から発生率が上昇し，80歳以上ではその増加が少ない．

（Hagino H, 1999[18]，Hagino H, 2008[20]より改変引用）

歳代で37～45％と報告されている[14)~16)]．

発生率についての報告は少なく，広島での前向き研究のみであり，それによると日本人の脊椎骨折の発生率は加齢とともに上昇し，女性では70歳代で人口10万人あたり年間約4,000人，80歳代で年間約8,400人に達する[17)]．

b．四肢・骨盤骨折

上肢骨折のうち橈骨遠位部骨折は50歳代から発生率が上昇し，80歳以上ではその増加が少ないという特徴がある（図❶）[18)]．上腕骨近位端骨折は80歳以上で発生率が上昇する．これは転倒時に手をついて防御できるかどうかの違いによると考えられ，前期高齢者では転倒時に反射的に手をついて橈骨遠位部骨折を生じるのに対して，後期高齢者では転倒時に手での防御ができずに大腿骨近位部や肩関節を直接受傷して，大腿骨近位部骨折や上腕骨近位部骨折を発症する．

下肢骨折のうち最も患者数が多く，また生活機能やQOLに大きな影響をもたらすのが大腿骨近位部骨折である．大腿骨近位部骨折の患者数は80歳代が最多で，全体の約半分を占めるが，発生率は70歳代後半から指数関数的に上昇し，85歳以上では年間人口10万人あたり2,000人以上に達する（図❶）[19)20)]．大腿骨は近位部とともに遠位部骨折も老人に多発する骨折で，80歳以降に発生率が増加する．

骨盤骨折も骨粗鬆症に関連した骨折で，加齢とともに

発生率が高くなる[21]．骨盤では恥骨，仙骨が insufficiency fracture の好発部位で，X 線像で骨折線が不明であっても，体動時の疼痛や叩打痛がみられたら，骨折を疑う必要がある．

おわりに

わが国における，現在の年齢別骨折発生率と将来推計人口にもとづいて予測した大腿骨近位部骨折の新規発生数は，現在年間約 16 万例と推計され，高齢者人口の増加に伴い，2030 年には年間 26〜30 万人に達すると思われる．しかも 30 年後には 90 歳以上の患者が最も多くなり，全患者数の半分近くを占めることとなる．骨折予防には転倒の防止が重要な役割を果たすため，多職種による総合的な対策が求められる．

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薬物療法各論　主な骨粗鬆症治療薬の特徴，有用性，長期使用による有害事象
ビスホスホネート製剤

リセドロネート

萩野　浩

Risedronate

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Abstract

Risedronate is effective and approved for the treatment of osteoporosis in Japan. Risedronate decreases strongly bone resorption and turnover via a potent inhibitory action on osteoclasts. Risedronate was shown to significantly decrease the risk of nonvertebral fractures including hip fractures as well as vertebral fractures in placebo-controlled, 3-year clinical trials in postmenopausal women with osteoporosis. The efficacy of risedronate elucidated by recent clinical studies was reviewed.

Key words: risedronate, osteoporosis, nonvertebral fracture, hip fracture

はじめに

ビスホスホネート製剤(BP)の一つであるリセドロネートは代表的な骨吸収抑制剤で，破骨細胞による骨吸収を強力に抑制して，骨強度と骨質の改善効果をもたらす．BPの骨吸収抑制能はその側鎖の違いによって100-10,000倍の差がみられ，第3世代のBPであるリセドロネートは骨吸収抑制作用が強く，石灰化抑制作用に対する骨吸収抑制効果は，第1世代のエチドロネートの10,000倍程度である[1]．

リセドロネートは2002年に我が国で骨粗鬆症治療薬として認可され，2.5mg/日の早朝空腹時投与が行われている．更に，2007年から17.5mg錠が認可され，週に1回の服薬による治療も可能となった．米国では1日1回5mg，週に1回35mg，月に2回(連日)75mg，月に1回150mgといった4種類の服用方法が認可されている．これらの種々の治療方法が可能となったのは，プラセボに比較して有意な骨折防止が示された臨床試験結果が得られ，その投与方法と同等の骨量増加効果がそれぞれの投与方法でも示されたからである．

本稿ではリセドロネートの骨量増加効果と骨折防止効果に関するこれまでの臨床成績を示し，本剤の特徴について概説する．

1. 骨量増加効果に関する臨床試験結果

骨粗鬆症治療の目的は脆弱性骨折の防止であるため，骨量増加効果が証明されても，治療薬としての有効性が示されたことにはならない．しかしながら，骨量増加は骨折防止効果と相関することが知られているため，異なる投与方法の開発に当たり，骨量増加が骨折防止効果を認めた治療と同等であることを示して，新たな投与法の有効性が確認されるに至っている．

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