Table 3. Patients who died without surgery (3-year total)

Patients	Nonsurgical deaths (no.)	Living situation at time of fracture: Average age (years)	Living alone	Living with family	Living in facility	Unknown	Neck fracture: No.	Neck fracture: Complications	Trochanteric fracture: No.	Trochanteric fracture: Complications
Men	31	85.5 ± 8.5	3	9	5	14	11	1.9	20	2.8
Women	38	87.5 ± 6.0	4	7	3	24	14	3.2	24	2.6
Unknown	1	87	1							

Table 4. Treatments and surgery (3-year total)

Treatment	Neck fractures (n = 4537) No.	%	Trochanteric fractures (n = 6710) No.	%	Unknown (n = 238) No.
No surgery	288	6.3	291	4.7	19
Surgery	3885	85.6	5485	88.2	194
Ender nail	3	0.1	214	3.4	3
Screw	681	15.0	52	0.8	18
Gamma nail	9	0.2	1269	20.4	15
CHS	201	4.4	3556	57.2	59
Plate	1	0	5	0.1	1
Hemiarthroplasty	1847	40.7	164	2.6	42
Total hip arthroplasty	978	21.6	22	0.4	16
Other	110	2.4	118	1.9	13
Unknown	31	0.7	21	0.3	3
Compound	24	0.5	64	1.0	24
No response	364	8.0	441	7.1	25

CHS, captured hip screw

Table 5. ADL independence before fracture

ADL independence before fracture (scores 1–8)	No.	%
1 Able to go out using public transportation	2667	24.3
2 Can go out to visit neighbors	2928	26.6
3 Can go out with assistance and spend the day out of bed	1997	18.2
4 Rarely goes out; spends the day in bed	1971	17.9
5 Uses a wheelchair and only leaves bed to eat or use the bathroom	700	6.4
6 Can get in and out of a wheelchair with assistance	469	4.3
7 Able to turn over in bed independently	67	0.6
8 Unable to turn over in bed independently	46	0.4
Unknown and other	29	0.3
Total responses	10992	100.0
No response	118	1.1

ADL, activities of daily living

neighbors independently — J2) accounted for 12.7% and 14.1%, respectively, for a total of 26.8%. This represented a decrease of 29.5 percentage points from the preoperative score ($P < 0.01$; continuity adjusted chi-squared test). However, the section for ADL independence 1 year after the initial visit was left blank by 2820 patients (25.7%), suggesting difficulties associated with conducting the prognostic survey (Table 6).

Preoperative complications (3-year period)

Many patients with hip fracture develop complications. Of the 10992 patients treated over the 3-year period, the section for preoperative complications was completed for 10908 patients and left blank for 84 patients. Only 882 patients (8.0%) experienced no complications. The most common complication was hypertension, followed by dementia, neuropathy, and heart disease, in that order.

One-year mortality rate for each surgery (3-year period)

Table 7 shows 1-year mortality rates for the various surgical methods. Mortality rate was highest for plate

fixation (14.3%, 1/7), followed by Ender nailing (14.0%) and Gamma nailing (12.3%). Apart from the "Others" category, the 1-year mortality rate was lowest for the screw method, at 7.7%. The mean postoperative mortality rate was 10.1%.

One-year survival rate for each calendar age (3-year period)

Table 8 shows 1-year survival and mortality rates for each year of age from 65 years and older. The number of hip fracture patients exceeded 300 among these 78–90 years of age. The greatest number of patients was 416, at 85 years of age. The 1-year survival rate for patients in their eighties was higher than 80%, whereas that for patients in their nineties was above 70%, confirming that the 1-year survival rate decreases with age.

Table 6. ADL independence 1 year after surgery/initial visit

ADL independence 1 year after surgery/initial visit	No.	%
1 Able to go out using public transportation	1399	12.7
2 Can go out to visit neighbors	1550	14.1
3 Can go out with assistance and spend the day out of bed	1427	13.4
4 Rarely goes out; spends the day in bed	1080	9.8
5 Uses a wheelchair and only leaves bed to eat or use the bathroom	1000	9.1
6 Can get in and out of a wheelchair with assistance	1034	9.4
7 Able to turn over in bed independently	167	1.5
8 Unable to turn over in bed independently	174	1.6
Unknown and other	341	3.1
Total responses	10992	100.0
No response	2820	25.7

Table 8. One-year survival rate for each year of age

Age (years)	Alive (no.)	Deceased (no.)	Survival rate (%)
65	91	3	96.8
66	117	4	96.7
67	109	4	96.5
68	122	3	97.6
69	144	10	93.5
70	150	8	94.9
71	167	10	94.4
72	189	13	93.6
73	172	20	89.6
74	212	23	90.2
75	234	13	94.7
76	250	26	90.6
77	266	15	94.7
78	325	29	91.8
79	333	31	91.5
80	287	35	89.1
81	323	40	89.0
82	318	49	86.6
83	321	42	88.4
84	355	58	86.0
85	356	60	85.6
86	344	66	83.9
87	338	65	83.9
88	344	58	85.6
89	254	61	80.6
90	265	53	83.3
91	198	56	78.0
92	160	50	76.2
93	111	38	74.5
94	107	22	82.9
95	51	26	66.2
96	50	14	78.1
97	43	11	79.6
98	18	3	85.7
99	36	8	81.8
100	13	7	65.0
101	9	4	69.2
102	0	2	0
103	0	0	0
111	1	0	100.0

Table 7. One-year mortality rate for each surgery method

Method	Alive	Deceased	Unknown	Total count	Mortality rate (%)
Surgery					
Ender nail	108	31	81	220	14.0
Screw	512	58	181	751	7.7
Gamma nail	762	159	372	1293	12.3
CHS	2300	381	1134	3815	10.0
Plate	4	1	2	7	14.3
Artificial head replacement	1302	146	604	2052	7.1
Total hip replacement	670	77	269	1016	7.6
Others	162	17	62	241	7.1
Unknown	322	171	506	999	17.1
Nooperation	509	70	19	598	11.7
Total	6651	1111	3230	10992	10.1 (average)

Table 9. Discharge status and 1-year mortality

Discharge status		Alive	Deceased	Unknown	No response	One-year total
Well	9012	6367	555	1122	968	9012
No change	503	282	87	59	75	503
Deceased	397					
Others	1080	2	72	220	786	1080
Total	10992	6651	714	1401	1829	10595

Table 10. Complications and 1-year mortality

		Alive		Deceased		Unknown	
Complications	Total	No.	%	No.	%	No.	%
No	698	583	83.5	41	5.8	74	10.6
Yes	7794	5700	73.1	1045	13.4	1049	13.4
No response	2500	368	14.7	25	1.0	2107	84.2
Total	10992	6651	67.9	1111	16.8	3230	15.1

Table 11. One-year mortality rate and sex

	1999		2000		2001		Total	
Sex	No.	%	No.	%	No.	%	No.	%
Male	115		127		117		145	
Female	270		220		237		242	
No response	16		6		3		10	
Total	401		353		357		1111	
Total patients (mortality rate)	3656	10.9*	3393	10.4	3943	9.0*	10992	10.1

* $P < 0.01$ (continuity adjusted chi-squared test)

Outcomes at discharge and the 1-year prognosis

The 1-year prognosis was investigated based on discharge status for the 10992 patients treated over the 3-year period. Of the 9012 patients discharged in good health, 503 (4.6%) were discharged with unchanged condition, and 396 (4.4%) were dead at discharge. Of the 9012 patients in good health at discharge 555 (6.2%) were dead, and 87 (17.3%) of 503 patients with an unchanged condition were dead, 1 year postoperatively. Of the 1081 patients whose condition at discharge was unknown or left blank, 72 (6.7%) were dead 1 year postoperatively (Table 9).

Comparison of 1-year survival and mortality in relation to complications

The 1-year mortality rate for the 698 patients without complications was 5.8%, compared to 13.4% for the 7794 patients with complications and 1.0% for the 2500 patients for whom the section on complications was left blank (Table 10).

Comparison of 1-year mortality during 3-year period for men and women

The 1-year mortality rate for each year of age among men was 17.3% for the 664 patients in 1999, 19.7% for the 646 patients in 2000, and 16.2% for the 724 patients in 2001. The 1-year mortality rate for the women was 9.4% for the 2858 patients in 1999, 8.1% for the 2716 patients in 2000, and 7.5% for the 3176 patients in 2001. The mortality rate of both sexes was 10.9% for 3656 patients in 1999, 10.4% in 2000, and 9.0% in 2001. The 1-year mortality rate showed a tendency to decrease year by year. ($P < 0.01$, continuity adjusted chi-squared test) (Table 11).

Discussion

In Japan, the first epidemiological study on hip fracture was conducted in 1987 by Orimo et al.,[2] and about 52300 cases of hip fracture were estimated to occur annually each year in Japan. The JOA then took a leadership role and the Committee has conducted annual epidemiological studies on hip fracture since 1997. Between 1998 and 2000, a total of 110747 hip fractures were reported[3] and about 90000 hip fractures are estimated to occur each year in Japan. To supplement these studies, a hip fracture project was started in 1999 at selected hospitals in Japan in an attempt to clarify the 1-year prognosis following hip fracture. Comparing the JOA study and the fixed-point observation project, the project studied about 10% of the number of patients enrolled in the epidemiological study in 1999 and 2000, and the types, laterality, and causes of femoral neck fracture were comparable.

The mean hospitalization for patients with hip fracture in various countries is reportedly 10 days for the Ullevaal hip screw in Norway, 12 days for the Hansson hook-pin in Norway,[4] 10 days for internal fixation in Sweden, 12 days for arthroplasty in Sweden,[5] 17.8 days in England,[6] 18 days in Austria,[7] 20.6 days in Thailand,[8] 24 days in Denmark,[9] 35 days in Italy,[10] and 23.3 days in the United States.[11] In Japan, the mean length of hospitalization is 83.6 days for pinning, 53.0–58.8 days for hemiarthroplasty,[12,13] 83.9 days for CHS,[14] 2.4 months for the Ender procedure, and 1.9 months for DHS or the Gamma nail.[15] Compared to other countries, the length of hospitalization following surgery for hip fracture is longer in Japan. In other countries, once acute-phase surgery for hip fracture is performed, patients are transferred to institutions specializing in rehabilitation, such as nursing homes. As a result, the duration of stay in the orthopedic department is low. In Japan, many hospitals are capable of handling both acute- and chronic-phase care, including rehabilitation, thus resulting in longer stays in the orthopedic department.

Based on data obtained from the fixed-point observation project, the number of days from surgery to discharge decreased each year, from 52.2 days ($P < 0.01$, t-text) in 1999 ($n = 3365$) to 49.0 days in 2000 ($n = 3127$) and 48.4 days ($P < 0.01$, t-test) in 2001 ($n = 3640$). As for the decrease at the hospitalization period, advances in the treatment method and the expansion of facilities after discharge are suspected.

Zückerman et al. developed the functional recovery score (FRS) as a disease-specific health assessment tool.[16] Using this system, they reported that FRS for patients with hip fracture was 88.1 points before fracture, decreasing by 15.8 points to 72.3 points 1 year later.[17] To assess patient function, we used the assessment criteria established by the Ministry of Health, Labour, and Welfare of Japan.[1] Thus, ADL independence was classified into eight grades, from (1) able to go out freely by utilizing public transportation, to (2) able to visit immediate neighbors independently, and (3) able to go out with assistance and spend the day out of bed to (8) unable to turn over in bed independently. ADL independence was assessed preoperatively and 1 year after the initial visit (within 6 months in some cases). Over the 3-year period, grade 1 and 2 patients accounted for 24.3% and 26.6%, respectively, of the patients preoperatively. Thus, 50.9% of patients were able to walk without assistance, but at 1 year after the initial visit grade 1 and 2 patients accounted for 12.7% and 14.1%, respectively, for a total of 26.8%. This represented a decrease of 24.1 percentage points. Of the various types of functional disabilities experienced by patients with hip fracture, the degree of disability in stair climbing is marked.[18] In the Baltimore Hip Study, among 804 patients with hip fracture who were ≥65 years old, 55.6% required assistance climbing five stairs preoperatively, and 89.9% required assistance with the same task 12 months postoperatively. Many studies have documented decreases in independent walking following hip fracture,[4,7,11,12,14,19] and one found that the ratio of patients requiring assistance walking one block was 42.4% preoperatively and 55.2% at 12 months postoperatively. However, the degree of decrease in independence was lower when compared to stair climbing, and degree of decrease in walking 10 feet remained low, at 9.2 percentage points.[19]

Because many elderly patients with a hip fracture experience complications, mortality rates for these patients are markedly higher than in the general cohort.[20,21] The 1-year mortality rate for hip fracture has decreased over the last few decades, from 21.6%,[22] 24.0%,[23] and 27.0%[9,24] during the 1970s and 1980s, to 16.8%,[19] 18.0%,[25] 20.0%[10,25,26] during the 1990s and 10.9%[11] during the 2000s. In the present study, the 1-year mortality rate for the entire patient population decreased every year over the 3-year period, from 10.9% in 1999 to 10.4% in 2000 and 9.0% in 2001 (3-year average 10.1%; 1111 of the 10992 patients were dead 1 year after the initial visit — $P < 0.01$, continuity adjusted chi-squared test). Compared to other countries, the duration of hospitalization is longer in Japan, but the mortality rate is lower.

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Original article

Effects of unipedal standing balance exercise on the prevention of falls and hip fracture among clinically defined high-risk elderly individuals: a randomized controlled trial

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Abstract
Background. The aim of this study was to assess the effectiveness of the unipedal standing balance exercise for 1 min to prevent falls and hip fractures in high-risk elderly individuals with a randomized controlled trial. This control study was designed as a 6-month intervention trial.
Subjects. Subjects included 553 clinically defined high-risk adults who were living in residences or in the community. They were randomized to an exercise group and a control group.
Methods. Randomization to the subjects was performed by a table of random numbers. A unipedal standing balance exercise with open eyes was performed by standing on each leg for 1 min three times per day. As a rule, subjects of the exercise group stood on one leg without holding onto any support, but unstable subjects were permitted to hold onto a bar during the exercise time. Falls and hip fractures were reported by nurses, physical therapists, or facility staff with a survey sheet every month. This survey sheet was required every month for both groups.
Results. Registered subjects were 553 persons ranging in age from 37 to 102 years (average, 81.6 years of age). Twenty-six subjects dropped out. The number of falls and hip fractures for the 6-month period after the trial for 527 of the 553 subjects for whom related data were available were assessed. The exercise group comprised 315 subjects and the control group included 212 subjects. The cumulative number of falls of the exercise group, with 1 multiple faller omitted, was 118, and the control group recorded 121 falls. A significant intergroup difference was observed. However, the cumulative number of hip fractures was only 1 case in both groups. This difference was not statistically significant.
Conclusions. The unipedal standing balance exercise is effective to prevent falls but was not shown to be statistically significant in the prevention of hip fracture in this study.

Introduction

Injurious falls constitute an important health problem. Changes in the sensory, neurological, and musculoskeletal systems in older adults affect several motor tasks, including postural balance and gait. Various studies have examined the effects of specific exercises on balance in older people with conflicting results.[1,2] Postmenopausal or involutional osteoporosis in elderly people affects the fragility of the proximal femur and may ultimately lead to hip fractures. To prevent hip fracture, there are three methods: (1) prevention of falls,[3,4] (2) treatment of osteoporosis, and (3) hip protectors.[5,6] The unipedal standing exercise is useful for improvement of the proximal femoral bone density and postural balance.[7] To ascertain the effects of unipedal standing training on the prevention of falls and femoral neck

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fracture, the Japanese Orthopaedic Association Osteoporosis Committee conducted a randomized study on individuals clinically defined as high-risk adults, including residents of nursing homes and nursing care facilities and users of outpatient rehabilitation centers.

Subjects

Initially, orthopedic surgery departments at medical schools and universities across Japan were contacted to ask for their recommendations of special nursing homes for the aged and nursing care facilities at which motion exercise training might be accepted and carried out. Subsequently, a questionnaire was mailed to each recommended facility to ask for their participation in the present randomized study. Subjects defined as high-risk adults were residents of special nursing homes for the aged or nursing care facilities who could stand on their own while holding onto a bar, and users of outpatient rehabilitation centers. Dementia patients who had agreement from their family were also enrolled in this study, but severe dementia patients or patients without agreement provided by themselves or family were not enrolled.

Methods

Because the present study was a human trial, the study protocol was reviewed and approved by the Medical Ethics Review Board of Showa University School of Medicine in November 2002. Before participation in this study, all subjects were required to have an institutionally approved informed consent form signed by themselves, family, or the patient's guardians in accordance with the Helsinki Declaration. This form involved agreeing to be randomized to an exercise or a control group. Randomization of the subjects into an exercise group or a control group was performed by the Department of Information Science of our university.

In general, the unipedal standing balance exercise was carried out as follows. With their eyes open, subjects were instructed to stand on their right leg for 1 min and then their left leg for another minute, for a total of 2 min, three times in a day. If a subject was unable to stand on one leg continuously for 1 min and required several breaks, he or she was instructed to stand on either leg until the total duration of one-leg standing reached 1 min. A single set of this one-leg standing balance exercise consisted of standing on the right leg for 1 min and the left leg for 1 min. Each day, subjects performed three sets, one in the morning, one at noon, and one in the afternoon. A control group was observed without exercise in the follow-up period.

The unipedal standing balance exercise was carried out under the guidance of a physical therapist or a similarly qualified individual. The individuals who prescribed and monitored the unipedal standing exercise (or facility staff) were asked to complete a survey sheet every month and mail the survey to the study office (Department of Orthopaedic Surgery in Showa University School of Medicine).

Investigated items

The survey sheet was designed to collect information regarding clinical diagnosis, age, frequency of falls, and fracture site. In addition, the survey sheet also included items that assessed compliance with performance of the exercise as already described. Simultaneously, we ascertained the number of falls over the 6-month period immediately before the study (as indicated by patients' survey responses or ascertained from medical charts). A prospective, randomized, controlled clinical trial with the unipedal standing balance exercise was designed by the Department of Information Science of Show University.

Results

Participating institutions and participants

Before February 2005, survey sheets were received from a total of 32 institutions comprising 24 nursing care facilities, 3 special nursing homes for the aged, and 5 outpatient rehabilitation centers. A total of 553 (142 men and 411 women) subjects were enrolled in the present study. Of these subjects, 397 (94 men and 303 women) were residents of nursing care facilities, 38 (5 men and 33 women) were residents of special nursing homes for the aged, and 118 (43 men and 75 women) were users of outpatient rehabilitation centers.

Age of subjects

Subjects ranged in age from 37 to 102 years. The mean ages of male and female subjects were 77.2 and 83.1 years, respectively. For the exercise and control groups, the mean ages were 81.2 and 82.3 years, respectively. The overall mean age of the subjects was 81.6 ± 9.0 years (mean ± SD). Table 1 shows the age distribution of all subjects.

Medical conditions among subjects

Residents of nursing care facilities and special nursing homes for the aged, and the users of outpatient rehabilitation centers, had various underlying diseases and many patients had multiple diseases and ailments.

Table 2 summarizes the primary underlying diseases of the subjects in the present study.

Unipedal standing balance exercise and fall prevention

Even though grouping was carried out according to the randomized method (table of random numbers), the number of survey sheets received was lower for the control group and the number of falls before the study was higher for the exercise group. Table 3 shows the results at 3 months after the start of the investigation. Subjects ($n = 553$) included 337 individuals who underwent training to stand on one leg with eyes open (training group) and 216 individuals who did not undergo this training (control group). The number of falls over a 3-month period ranged from 0 (training group, $n = 302$; control group, $n = 189$) to 19 (training group, $n = 1$; control group, $n = 0$). Table 4 shows the distribution of the number of falls for the 6-month period after training of the 527 subjects for whom the related data were available. The exercise group comprised 315 subjects and the control group comprised 212 subjects.

Effects on the number of falls

A statistical comparison was conducted on the differences in the number of falls between the exercise and control groups. At 3 months, a total of 79 falls were observed for the training group, whereas 58 falls were recorded for the control group. A Fisher's probability test showed no significant difference between the training group ($n = 337$, 79 falls) and the control group ($n = 216$, 58 falls) ($P = 0.4959$). However, after excluding 1 subject in the training group who had multiple falls, the same test showed a significant difference (training group, $n = 336$, 60 falls; control group, $n = 216$, 58 falls) ($P = 0.0500$). At 6 months after training, 1 subject in the

Table 1. Age distribution

Age (years)	Men ($n = 142$)	Women ($n = 411$)	Total ($n = 553$)
37–39	2	0	2
40–44	0	0	0
45–49	3	0	3
50–54	1	2	3
55–59	6	1	7
60–64	3	9	12
65–69	13	9	22
70–74	11	29	40
75–79	35	66	101
80–84	29	104	133
85–89	22	107	129
90–94	16	74	90
95–99	1	8	9
100–	0	2	2

Table 2. Primary underlying disease of subjects

Underlying disease	Number of subjects
Cerebrovascular disorder	204
Dementia	91
Fracture	71
Spinal disease	66
Cardiovascular disease	38
Motor organ disease	32
Diabetes	16
Respiratory organ disease	7
Neuropsychiatric disorder	7
Others	21
Total	553

Table 3. Exercise training and number of falls at 3 months

			Exercise group		Control group			
Number of falls (a)	Number of subjects	Percent	Number (b)	Cumulative number of falls (a × b)	Number (b′)	Cumulative number of falls (a × b′)	Men	Women
0	488	88.2	300	0	188	0	126	362
1	40	7.2	25	25	15	15	9	31
2	12	2.2	7	14	5	10	2	10
3	5	0.9	1	3	4	12	1	4
4	3	0.5	1	4	2	8	0	3
5	1	0.2	0	0	1	5	0	1
6	1	0.2	1	6	0	0	1	0
8	2	0.4	1	8	1	8	2	0
11	0	0.0	0	0	0	0	0	0
12	0	0.0	0	0	0	0	0	0
13	0	0.0	0	0	0	0	0	0
19	1	0.2	1	19	0	0	0	1
Total	553	100	337	79	216	58	141	412

Table 4. Exercise training and number of falls at 6 months

Number of falls (a)	Subjects	Percent	Exercise group		Control group		Men	Women
			Number (b)	Cumulative number of falls (a × b)	Number (b′)	Cumulative number of falls (a × b′)		
0	408	77.4	247	0	161	0	108	300
1	68	12.9	42	42	26	26	13	55
2	20	3.8	14	28	6	12	5	15
3	20	3.8	8	24	12	36	5	15
4	4	0.8	0	0	4	16	0	4
5	1	0.2	1	5	0	0	0	1
6	0	0.0	0	0	0	0	0	0
7	2	0.4	1	7	1	7	1	1
11	1	0.2	0	0	1	11	0	1
12	1	0.2	1	12	0	0	1	0
13	1	0.2	0	0	1	13	1	0
29	1	0.2	1	29	0	0	0	1
Total	527	100	315	147	212	121	134	393

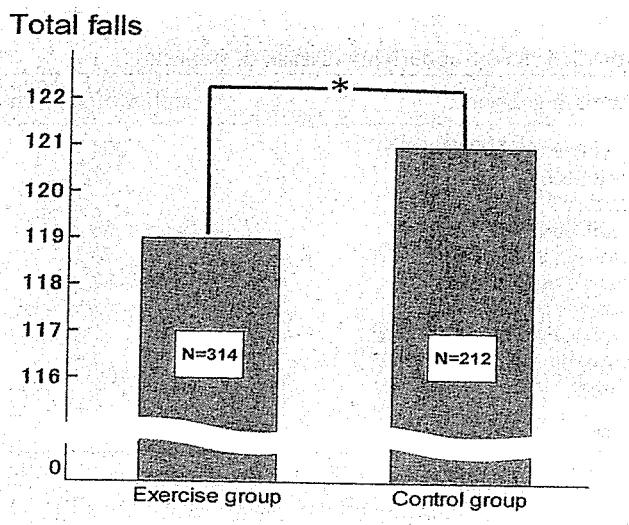

Fig. 1. Relationship of intervention to falls (*Fisher's exact probability test: $*P = 0.0067$; $P < 0.01$)

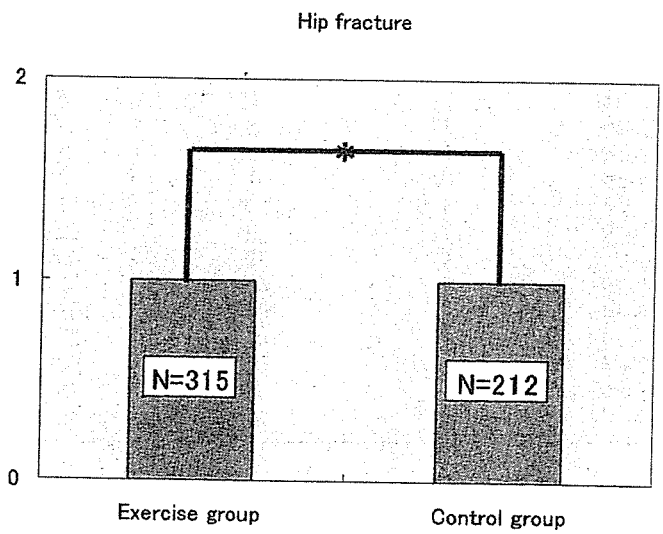

Fig. 2. Relationship of intervention to hip fractures (*Fisher's exact probability test: $P > 0.999$; *NS)

exercise group fell 60 times before the study and a total of 29 times after training; therefore, this subject was excluded from the statistical analysis. A Fisher's exact probability test was used to compare the cumulative number of falls between the exercise and control groups. A significant intergroup difference was observed ($P < 0.01$) (Fig. 1).

At 3 and 6 months after the start of the investigation, individuals who received a longer intervention tended to have lower P values, thus suggesting that the assessment of the effects of the intervention (training to stand on one leg with eyes open) was highly reliable.

Effects of unipedal standing balance exercise on hip fracture

At 1 month after the start of the study, a 61-year-old woman with Recklinghausen's disease in the control group had a femoral neck fracture. At 2 months after the start of the study, an 84-year-old woman with dementia in the exercise group had a femoral neck fracture. This fracture did not occur while the woman was exercising.

The incidence of hip fracture in the exercise group was 0.3% (1/315) whereas the incidence in the control group was 0.5% (1/212). However, this difference was not statistically significant (Fig. 2).

Discussion

The primary causes of hip fracture are osteoporosis of the femoral neck and falls.[8–11] According to an epidemiological study of hip fracture conducted by the Japanese Orthopaedic Association Osteoporosis Committee, a total of 110747 cases of femoral neck fracture were recorded from 1998 to 2000.[12] Of these, 74814 cases (74.0%) were caused by simple falls. Although the prevention of hip fracture using drugs is important,[13–16] these medications are very expensive.[17] From the point of view of cost-to-benefit ratio, a more effective way to prevent hip fracture would be to prevent falls.[3,4,18–20]

The following interventional exercise therapy programs have been demonstrated to be effective for preventing falls: muscle strengthening three times a week, balance training, and walking for 2 months[21]; 1 h muscle strengthening and endurance training three times a week for 6 months[21]; and a group Tai Chi class twice a week with two 15-min sessions of daily individual Tai Chi practice.[22] Although these exercise programs are effective for preventing falls, to remain effective they must be carried out continuously. However, it is difficult to administer an exercise program to elderly residents of nursing homes and nursing care facilities because of the difficulty faced by residents of these facilities in consistently carrying out the exercises. Therefore, it is necessary to design an exercise program that is more convenient for elderly individuals with various diseases who are at a higher risk for falls.

Several studies have reported that standing on one leg for 1 min with eyes open three times a day increases the bone mineral density of the femoral neck region.[23] Furthermore, it has been shown that unipedal standing for 1 min is equivalent to the amount of exercise gained through walking for approximately 53 min.[7]

In the present study, we investigated the effects of unipedal standing for 1 min with the eyes open on the prevention of falls and hip fracture in 553 residents of nursing homes and nursing care facilities. The cumulative number of falls over a 6-month period was 118 for the exercise group ($n = 314$) and 121 for the control group ($n = 212$). A Fisher's exact probability test showed a significant difference ($P = 0.0062$). Accordingly, with statistical significance established at the level of $P < 0.01$, the present exercise program was shown to prevent falls. However, as a single case of hip fracture was observed in each group, we could find no statistically significant intergroup difference for hip fracture incidence.

Conclusions

The results of the present study suggest that standing on one leg for 1 min with the eyes open is effective in preventing falls. Therefore, we believe that facilities should adopt this exercise program to prevent hip fracture among high-risk individuals.

Acknowledgments. We thank the individuals at the 32 facilities for their participation in the present interventional study. This study was supported by a Grant-in-Aid from Japanese Ministry of Health, Labour and Welfare (H12-Choju-033 and H17-Chojyu-002).

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Urinary γ-glutamyltransferase (GGT) as a potential marker of bone resorption

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Abstract

We recently identified γ-glutamyltransferase (GGT) as a novel bone-resorbing factor. The present study was undertaken to determine whether GGT is a marker of bone resorption in two genetic models of hyper- and hypo-function of osteoclasts, as well as in postmenopausal women with accelerated bone resorption, using type I collagen N-telopeptide (NTX) and deoxypyridinoline (DPD) as established biochemical markers. Urinary excretion of GGT, corrected for creatinine, was found to be increased in osteoprotegerin (OPG)-deficient osteoporotic mice as well as in patients with postmenopausal osteoporosis (67–83 years of age); in both cases the urinary level decreased after treatment of patients or mice with alendronate, a selective inhibitor of bone resorption, concomitantly with a reduction in DPD and NTX. Conversely, in osteopetrotic *op/op* mice, urinary GGT increased in parallel with DPD after induction of osteoclasts with M-CSF injection. Constant infusion of parathyroid hormone (PTH) also increased urinary GGT along with DPD. In a survey of 551 postmenopausal women (50–89 years of age) at their regular health checkup, urinary GGT excretion exhibited a high correlation with DPD ($\rho=0.49$, $p<0.0001$). The calculated sensitivity and specificity for diagnosing elevated bone resorption, as determined by a DPD value higher than 7.6 nM/mM Cr, were 61% and 92%, respectively, when a cut-off value of 40 IU/g Cr was assigned for urinary GGT. Since GGT activity can be measured inexpensively in large numbers in a very short time, the measurement of urinary level may provide a convenient and useful method for mass screening to identify those with increased bone turnover and hence at increased risk for bone fracture.

Keywords: Osteoclast; Bone resorption; GGT

Introduction

Osteoporotic fractures are a major cause of morbidity and mortality in the aging population [1]. The annual incidence of hip fractures has been increasing and exceeded one hundred thousand cases in the most recent 2002 survey in Japan. The diagnosis of osteoporosis is made on the basis of bone mineral density (BMD) measurement, as in other countries [9]; however, due to the limited availability of devices for dual X-ray absorptiometry (DXA), the number of those who actually receive medical treatment is estimated to be only 20–30% of the more than 10 million patients with osteoporosis in our country. Thus, it is of utmost importance to develop a noninvasive, simple and inexpensive method to estimate bone fragility and the associated increased risk of fractures.

Although low BMD is the most reliable surrogate for the assessment of fracture risk, other traits, referred to collectively as "bone quality", entailing size, architecture, turnover, damage accumulation and mineralization, contribute to bone strength as well [1,21]. Among these, biochemical markers of bone turnover have been shown to predict the risk of fractures independently of BMD [5,6]. Bone undergoes continuous remodeling, in which bone resorption always precedes formation. Elevated

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osteoclastic bone resorption plays a central role in the pathogenesis of osteoporosis, leading to fragility and fracture [24], with anti-resorptive drugs, represented by bisphosphonates, currently regarded as the first choice of treatment [4]. Recent studies using mouse genetics have identified regulators of osteoclast differentiation and function, among which receptor activator of NF-κB ligand (RANKL) has attracted considerable attention [2]. A humanized monoclonal antibody against RANKL, which has recently been shown to increase BMD by inhibiting bone resorption, is emerging as a new treatment option [14]. The discovery of the extracellular signals that control osteoclastogenesis is much anticipated and expected to provide an attractive target for the development of new diagnostic and therapeutic strategies.

In a search for new bone-resorbing cytokines using a *Xenopus* oocyte expression cloning technique, we have recently identified γ-glutamyltransferase (GGT or γ-GTP) as an osteoclastogenic factor, and demonstrated that recombinant human GGT as well as purified GGT from rat kidney stimulates bone resorption [16]. Further, during the course of our study examining the involvement of GGT in bone and joint diseases characterized by accelerated bone resorption, we unexpectedly found that GGT activity in urine, but not in serum, correlates with bone resorption. The present study was undertaken to determine whether GGT is a potential marker of bone resorption, using genetic mouse models as well as human subjects.

Materials and methods

Reagents

Alendronate sodium hydrate was purchased from Teijin Pharma Ltd. (Osaka, Japan). Human PTH (1–34) and M-CSF were kindly provided by Asahi Kasei Pharma (Tokyo, Japan) and Morinaga Milk Industry (Tokyo, Japan), respectively.

Animal experiments

Osteoprotegerin (OPG)-deficient male mice and BALB/cA mice were purchased from Clea Japan Inc. (Tokyo, Japan), and acclimated under standard laboratory conditions at 24±2°C and 50–60% humidity. The mice were allowed free access to tap water and commercial standard rodent chow (CE-2) containing 1.20% calcium, 1.08% phosphate and 240 IU/100 g vitamin D_3 (Clea Japan Inc., Japan). At the age of 9 weeks, OPG homozygous and heterozygous knockout mice (as control) were treated s.c. with vehicle (saline) or 1 mg/kg BW alendronate 5 times a week for 2 weeks, and urine was collected during the final 24 h. Blood samples were centrifuged to obtain the serum.

Eight-week-old female BALB/cA mice were infused with PTH at a rate of 4.3 pmol/h for 4 days. In brief, human PTH (1–34) was resolved in 2% L-cysteine solution, and loaded into Alzet osmotic minipumps. After equilibrated in saline at 37°C overnight, the pumps were implanted in a subcutaneous space on the back. Urine was collected during the final 24 h for biochemical analysis.

op/+ heterozygous mice were obtained from Jackson Laboratory (Bar Harbor, ME), and fed CE-2 powder chow (Clea Japan Inc., Japan). At the age of 5 weeks, *op/op* homozygous mice were treated i.p. with 5 μg M-CSF twice daily for 3 days, and urine and serum samples were collected before and after M-CSF treatment. Tibiae were removed for micro-CT scanning and tartrate-resistant acid phosphatase (TRAP) staining.

The animal experiments were carried out in accordance with the institutional ethical guidelines for animal care, and the experimental protocols were approved by the animal care committee of NCGG.

Subjects

Blood and spot urine samples were collected at 10:00–12:00 am from 10 patients with postmenopausal osteoporosis (67–83 years of age; average, 76.7), who visited the National Center for Geriatrics and Gerontology Hospital from April 2003 through August 2004, before and after alendronate treatment for measurement of blood GGT as well as urinary GGT and NTX. The diagnosis of osteoporosis was made based on the criteria recommended by the Japanese Society for Bone and Mineral Research [18], i.e., at least one non-traumatic vertebral fracture and a BMD lower than 80% of the young adult mean (YAM) or BMD lower than 70% of YAM without fracture.

Urine samples were also collected from 551 volunteer postmenopausal women (50–89 years of age; average, 66) at their regular health checkup for the measurement of GGT and deoxypyridinoline (DPD). The human studies were approved by the institutional review board, and written informed consent was obtained from all individuals.

Biochemical analysis

GGT activity and creatinine concentrations in the serum and urine were determined by using an autoanalyzer (model AU5232, Olympus) on the day following sample collection after storage at room temperature, since we found that GGT activity in the urine was stable for up to 1 week at room temperature or at 4°C but was lost after freezing at −20°C and subsequent thaw. Intra- and inter-assay variations for GGT were 0.58–1.77% and 0.29–1.78%, respectively. NTX and free DPD concentrations in the urine were measured using Osteomark [7] and Osteolinks-DPD (Sumitomo Seiyaku Biomedical Co., Ltd., Osaka, Japan) assay kits [20], respectively, and the values were corrected for creatinine. Intra- and inter-assay variations were 1.8–4.5% and 4.7–10.8% for NTX, and 1.4–7.4% and 4.2–6.4% for DPD, respectively. Leucine aminopeptidase, alkaline phosphatase, acid phosphatase and *N*-acetyl-β-D-glucosaminidase (NAG) in the urine were determined by using autoanalyzers (model AU5200 and AU600, Olympus).

Urinary GGT, creatinine and free DPD concentrations for the 551 volunteer women were measured by using "γ-GTP C-TestWako" (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and "Determina-L CRE" (Kyowa Medex Co., Ltd., Tokyo, Japan) assay kits, respectively.

For fractionation of GGT activity, urine was collected from 6 healthy volunteers (3 females and 3 males; aged 29–35 years). After centrifugation at 17,000×*g* for 15 min, the supernatant was further centrifuged at 200,000×*g* for 3 h. GGT activity in the pellet and supernatant fractions after each centrifugation was measured using γ-GTP C-TestWako (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Bone analysis

For bone analysis, right tibiae were dissected and stored in 70% ethanol for micro-computed tomography scanning. Left tibiae were fixed in 4% paraformaldehyde, and TRAP staining was performed by a standard technique [17].

Micro-computed tomography scanning was performed on proximal tibias by using a μCT-40 (SCANCO Medical AZ, Bassersdorf, Switzerland) with a resolution of 12 μm, as described previously [8].

Statistical analysis

Data are expressed as the mean±SD. Changes in GGT and DPD or NTX excretion before and after alendronate treatment were analyzed by unpaired or paired Student's *t* test. The relation between GGT and DPD was assessed by Spearman rank order correlation analysis. $P<0.05$ was considered statistically significant.

Results

In order to determine if GGT is involved in bone diseases associated with accelerated bone resorption, we first assessed

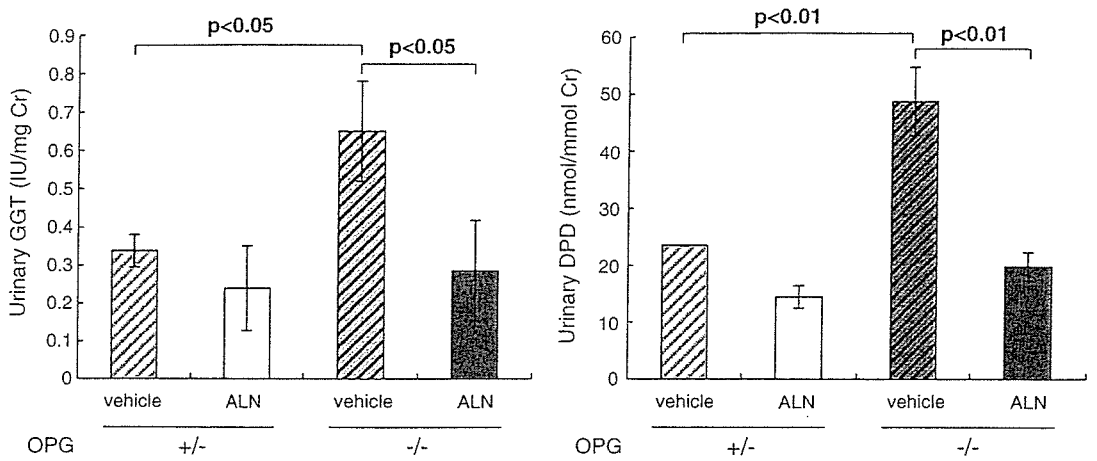

Fig. 1. Reduction in urinary GGT excretion after treatment of OPG-deficient mice with alendronate. Nine-week-old osteoprotegerin (OPG)-deficient male mice were treated s.c. with vehicle (saline) or 1 mg/kg BW alendronate (ALN) 5 times a week for 2 weeks, and urinary excretion of GGT (left) and DPD (right) was then determined. OPG heterozygous knockout mice served as the control. $n=3$ for vehicle groups and $n=7$ for treatment groups.

blood and urinary levels of GGT in a genetic model of osteoporosis, i.e., osteoprotegerin (OPG)-deficient mice [2]. OPG is a decoy receptor of RANKL, an essential cytokine for the formation of osteoclasts, and mice lacking OPG exhibit osteoporosis due to unopposed RANKL signaling and accelerated bone resorption [2]. Serum GGT activity in these mice was very low (less than 4 IU/l), compared with that in humans (normal range being 10–63 IU/l), and did not differ between OPG homozygous and heterozygous knockout mice or after treatment with alendronate, a selective inhibitor of bone resorption (data not shown). In contrast, as shown in Fig. 1, urinary excretion of GGT as well as of DPD was significantly increased in OPG homozygous knockout mice, compared with the levels of the control heterozygous mice. Treatment of OPG-deficient mice with alendronate resulted in a significant reduction in both urinary GGT and DPD excretion to the control levels found in the heterozygous mice. These findings suggest that urinary excretion of GGT, not serum levels, reflects the activity of bone resorption in the body.

Urinary excretion of leucine aminopeptidase (0.048±0.023 in WT vs. 0.065±0.021 U/mg Cr in OPG KO) and alkaline phosphatase (0.032±0.054 in WT vs. 0.021±0.015 IU/mg Cr in

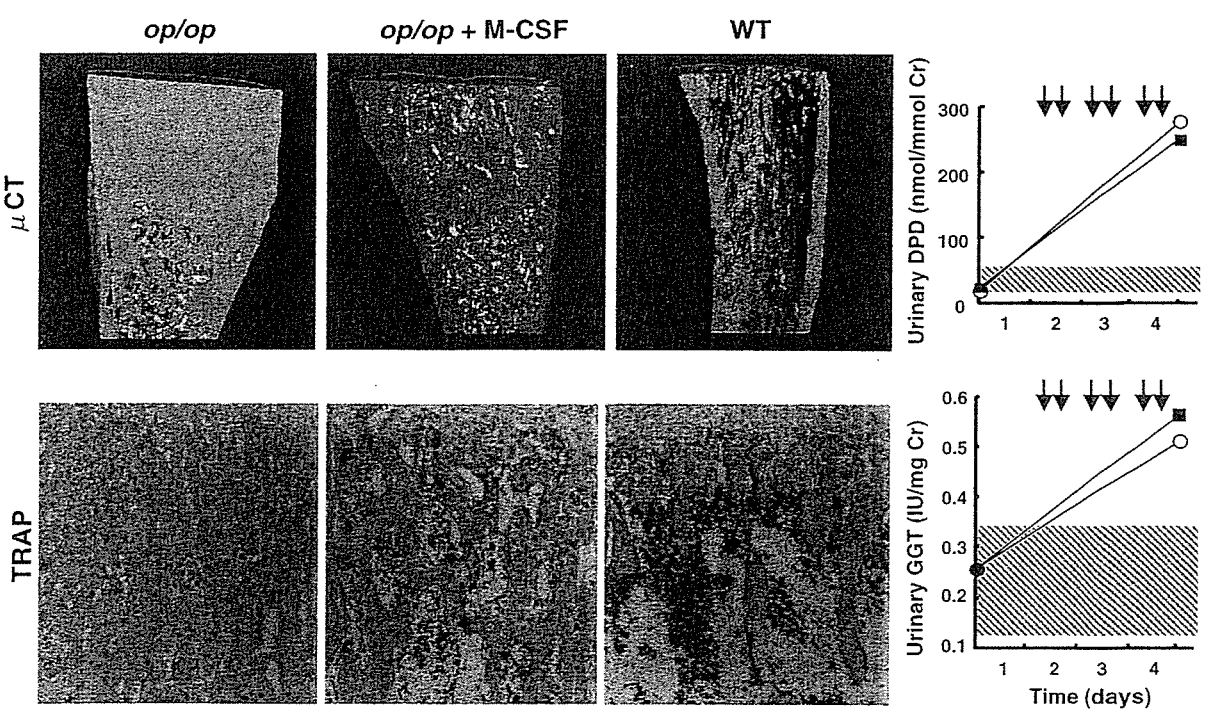

Fig. 2. Increase in urinary GGT excretion after osteoclast induction in *op/op* mice. Six-week-old osteopetrotic *op/op* female mice ($n=2$ each) were treated i.p. with 5 μg M-CSF twice daily for 3 days, and urinary excretion of DPD and GGT was then determined before and after injections. Age- and sex-matched wild-type mice served as the control as shown as the shaded area (mean±SD, $n=10$). Arrows indicate M-CSF injections. Representative micro-CT images and photomicrographs of TRAP staining of the proximal tibia are shown.

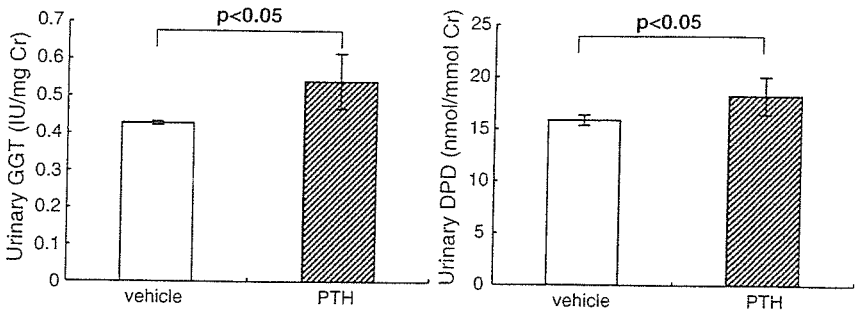

Fig. 3. Increase in urinary GGT excretion after constant PTH infusion. Eight-week-old female BALB/cA mice ($n=3$ each) were subjected to constant infusion of PTH (1–34) at a rate of 4.3 pmol/h for 4 days through Alzet osmotic minipumps, and urinary excretion of DPD and GGT was determined during the final 24 h. Age- and sex-matched mice with constant infusion of vehicle (2% L-cysteine) served as the control. Osteoclast surface and eroded surface per bone surface were markedly increased in the tibial metaphyses and lumbar vertebrae of PTH-infused mice.

OPG KO), enzymes located at the brush border membrane of renal tubules, did not differ significantly between wild-type and OPG knockout mice. Of lysosomal enzymes, urinary excretion of acid phosphatase did not differ (0.0030±0.0011 in WT vs. 0.0026±0.0015 IU/mg Cr in OPG KO), while that of *N*-acetyl-β-D-glucosaminidase (NAG) was significantly increased in OPG KO mice (0.066±0.028 vs. 0.193±0.074 IU/mg Cr, $p<0.01$). Thus, certain enzymes of proximal renal tubular cells including GGT may be excreted during elevated bone resorption.

We also employed a gain-of-function approach with another genetic model, osteopetrotic *op/op* mice, to examine whether urinary GGT excretion increases following the induction of osteoclasts with M-CSF injection. Fig. 2 shows representative micro-CT images (upper panel) and bone sections stained with TRAP activity (lower panel) at the proximal tibia. *op/op* mice at 6 weeks old exhibited typical osteopetrosis with very few osteoclasts, although osteoclasts appeared spontaneously with aging [17]. Administration of M-CSF twice daily for 3 days caused marked increases in bone marrow cavity and TRAP-positive osteoclasts (Fig. 2). Urinary DPD and GGT excretion both increased after M-CSF treatment (Fig. 2, right panel).

Continuous excess of PTH and PTH-related protein is associated with elevated bone resorption, as seen in patients with primary hyperparathyroidism and hypercalcemia of malignancy, respectively. As a model mimicking these conditions, we infused PTH (1–34) to mice constantly through osmotic minipumps. Histological examination on sections of tibial metaphyses and lumbar vertebrae revealed that osteoclast number and eroded surface per bone surface markedly increased following PTH infusion (data not shown). As shown in Fig. 3, constant infusion of PTH also increased urinary excretion of GGT significantly along with DPD. Collectively, our loss- and gain-of-function experiments using genetic and pharmacological models with excessive and deficient osteoclastic bone resorption, respectively, indicate that urinary GGT changes in parallel with DPD and reflects bone resorption activity in the body.

Based on these data, we analyzed urinary excretion of GGT in osteoporotic patients with elevated bone resorption. Urine samples were collected from 10 patients with postmenopausal osteoporosis (67–83 years of age; average, 76.7), before and after alendronate treatment. As shown in Fig. 4, urinary excretion of GGT decreased significantly along with NTX and DPD following treatment with alendronate. Serum GGT concentrations in these patients were within normal limits (10–63 IU/l) and did not change following treatment (data not shown).

In order to gain some insight into the form in which GGT exists in human urine, urine collected from healthy volunteers was fractionated by centrifugation, and the GGT activity in each fraction was determined. As shown in Table 1, when urine was centrifuged at 17,000×*g* (17 K) to remove cells and cell debris,

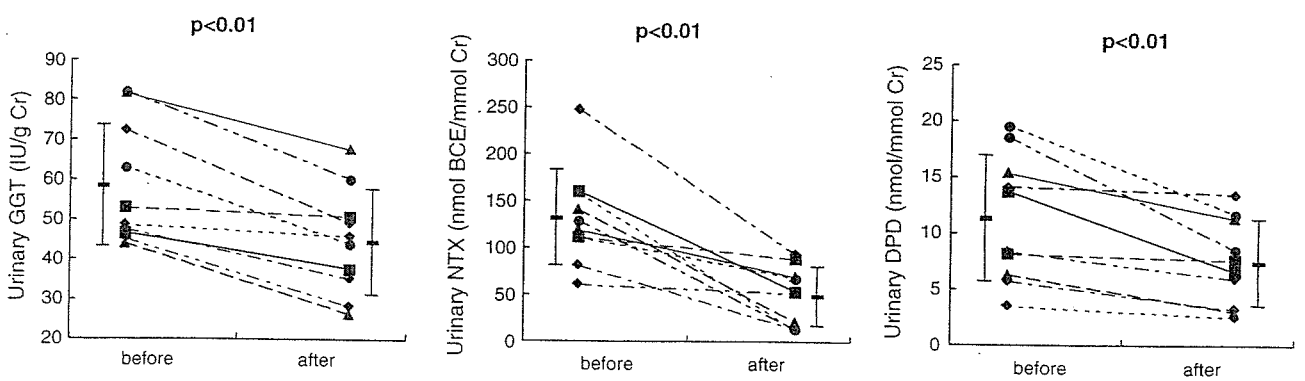

Fig. 4. Reduction in urinary GGT excretion after treatment of postmenopausal osteoporosis with alendronate. In 10 patients with postmenopausal osteoporosis (mean age: 76.7 years old), urinary excretion of GGT (left) decreased concomitantly with a reduction in urinary NTX (middle) and DPD (right) after treatment with alendronate (for 7 months on average). Individual data are shown with the mean±SD.

Table 1
Fractionation of urinary GGT activity

	Male				Female			
Urinary GGT	1	2	3	Mean	1	2	3	Mean
(IU/L)	32.7	37.0	63.6	44.4	45.3	30.8	14.6	30.2
17 K								
S	29.3	34.6	55.7	39.9	43.4	29.9	13.9	29.1
P	3.5	4.6	6.5	4.9	4.3	3.3	1.8	3.1
200 K								
S	6.5	6.3	9.5	7.4	5.0	6.3	3.5	4.9
P	23.7	26.9	47.0	32.5	36.5	28.9	13.3	26.2
% of P	72.5	72.7	73.9	73.2	80.6	93.8	91.1	86.8

Urine was collected from healthy volunteers (3 males and 3 females), and GGT activity in the whole urine was determined (top). After centrifugation at 17,000×*g* (17 K) and 200,000×*g* (200 K), GGT activity was determined in both supernatant (S) and pellet (P) fractions.

more than 90% of the total GGT activity in the urine was recovered in the supernatant fraction. When the 17 K supernatant was further subjected to centrifugation at 200,000×*g* (200 K), 73.2 to 86.8% of the total GGT activity was found in the pellet fraction, suggesting that GGT in human urine does not exist as a soluble form but rather is mostly associated with certain microstructures that sediment at 200 K.

Finally, to determine if urinary GGT can be used for screening individuals with elevated bone resorption in the general population, we assessed the urinary excretion of GGT and DPD in 551 volunteer postmenopausal women (50–89 years of age; average, 66) at their regular health checkup. As shown in Fig. 5A, there was a high correlation between urinary excretion of GGT and DPD in this population ($p<0.0001$). Of these 551 individuals, 113 had increased bone resorption, as judged from DPD values higher than 7.6 nM/mM Cr (17.0±15.0), the cut-off value for diagnosing elevated bone resorption recommended by the Japanese Society for Bone and Mineral Research. These individuals exhibited significantly elevated urinary excretion of GGT (85.7±95.0 IU/g Cr), compared with those that had normal DPD values (GGT: 22.0±12.0 IU/g Cr, DPD: 3.8±1.9 nM/mM Cr; Fig. 5B). When a cut-off value of 40 IU/g Cr was assigned for urinary GGT, the calculated sensitivity and specificity for discriminating those with elevated bone resorption, as determined by a DPD value higher than 7.6 nM/mM Cr, were 61% and 92%, respectively, and 75% and 79% for a GGT cut-off value of 30 IU/g Cr.

Discussion

GGT is an ectopeptidase that catalyzes the transfer of a γ-glutamyl moiety to an acceptor and plays a critical role in glutathione degradation and cysteine metabolism [11,23]. Mice deficient in GGT exhibit growth retardation, cataracts and severe osteoporosis, and die early at 10–18 weeks of age [12]. Osteopenia of GGT-deficient mice is due mainly to impaired bone formation, which is reversible by supplementation with *N*-acetylcysteine, suggesting that GGT plays an important physiological role in regulating bone formation through cysteine metabolism [10]. We have identified GGT as a bone-resorbing factor in the expression cloning of an osteoclastogenic activity contained in murine T lymphoma, which caused marked osteolysis in mice, and demonstrated that recombinant GGT at 100 IU/l, a level often seen in patients with excess alcohol intake or fatty liver, is indeed capable of stimulating osteoclastogenesis in bone marrow cultures [16]. Furthermore, the generation of transgenic mice overproducing GGT has revealed that excess GGT causes osteopenia due to accelerated bone resorption (Hiramatsu et al. manuscript submitted). Taken together, it is suggested that GGT levels should be maintained within a set physiological range and both deficiency and excess can lead to osteoporosis, but by distinct mechanisms, i.e., through suppressed bone formation and elevated bone resorption, respectively. Interestingly, a mutated GGT molecule devoid of enzyme activity is fully active in promoting osteoclast formation (Hiramatsu et al. manuscript submitted), suggesting that the osteoclastogenic function of GGT is dissociated from its enzyme activity, does not involve glutathione or cysteine metabolism, and may represent a novel mode of action as a cytokine.

In the present study, we demonstrate that the urinary excretion of GGT changes in parallel with established biochemical markers of bone resorption, NTX and DPD, and therefore reflects bone resorption activity both in animal models and human subjects. Whereas serum GGT activity derives mainly from the liver, GGT is most abundantly expressed in the proximal tubule of the kidney, where this ectoenzyme is located

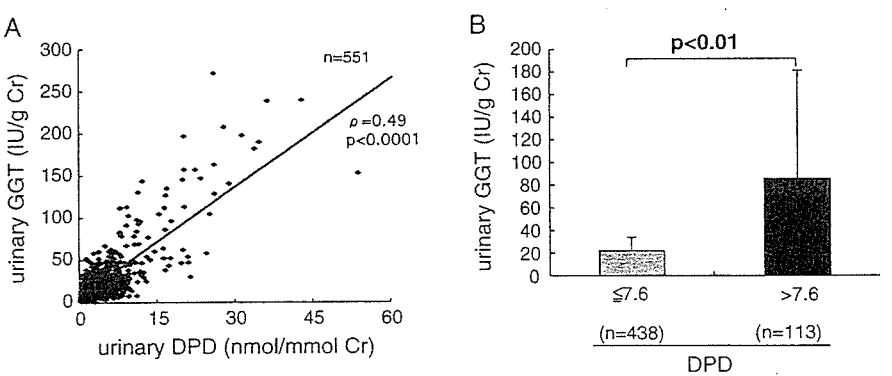

Fig. 5. Correlation between urinary GGT and DPD excretion in postmenopausal women. (A) In 551 postmenopausal women (50–89 years old; mean age, 66), urinary excretion of GGT showed a highly positive correlation with urinary DPD ($p<0.0001$). (B) Of these individuals, 113 showed elevated bone resorption (DPD >7.6 nmol/mmol Cr); and their urinary GGT excretion was increased significantly compared with that of the individuals with lower DPD values ($p<0.01$).

on the apical membrane [23]. Although the exact mechanism underlying GGT excretion in high bone turnover states remains to be determined, increased GGT activity in the urine of humans as well as experimental animals with accelerated bone resorption, without appreciable increase in serum concentrations, prompts us to hypothesize that the GGT anchored to the plasma membrane of renal tubular cells and exposed to the tubular lumen is prone to being shed into the urine in response to some signaling cue from bone turnover. Communication between bone and kidney is known for collagen cross-links; the conversion of peptide bound to free DPD in the kidney has been reported to become more efficient as bone turnover decreases [15].

By fractionation we found that most of the GGT activity in human urine was recovered in the pellet fraction after centrifugation at 200,000×*g*, suggesting that GGT is not excreted in a soluble form but rather in association with certain microstructures. A recent proteomic analysis of exosomes [membrane vesicles that originate as internal vesicles of multivesicular bodies (MVBs)] in the urine identified protein components of MVBs, among which GGT was included [19]. Taken together with our observations, it is tempting to speculate that increased GGT activity in a high bone turnover state is associated with exosomes and the shedding of exosomal GGT from the proximal renal tubules is stimulated in response to some cue from elevated bone resorption [25]. This may provide an explanation for the unexpected observation that unlike serum GGT activity, which is stable after freezing at −20°C and thawing, most of the urinary GGT activity is lost after freezing at −20°C. Alternatively, the possibility that GGT is produced in bone sites undergoing elevated resorption and is excreted in the urine after filtration through the glomerulus cannot be completely ruled out, although it seems unlikely that GGT, with a relatively high molecular weight, is filtered through the glomerulus under physiological conditions. Further studies are required to identify the molecular form(s) of GGT in the urine, and to clarify the specific mechanism(s) by which its excretion is enhanced in diseases with elevated osteoclastic activity.

Osteoporosis is pandemic in industrialized countries, and early diagnosis with timely measures is crucial for mitigating further bone loss and preventing bone fracture [1,13]. The widely used measurement of BMD alone is not sufficient for assessing fracture risk and can miss most of the postmenopausal women who experience fracture [22]. In addition to BMD, several other factors are known to impact the quality of bone, including bone geometry and microstructure, microdamage, and bone turnover, but only biochemical markers of bone turnover are available for use in clinical practice [5]. Measurement of these biochemical markers, however, is time consuming and costly, and a simple and inexpensive method for mass screening is urgently required. Since GGT activity can be measured inexpensively in-house for large numbers of patients in a very short time with little variability, the measurement of the GGT urinary level may provide a highly convenient and useful method for screening individuals who have increased bone turnover and therefore an increased risk for bone fracture. It is to be noted that since urinary GGT activity can be increased in renal dysfunction due to drug intoxication, diabetes and hypertensive nephropathy [3,26,27], the results should be interpreted with caution.

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Recurrence of hypertrophic spinal pachymeningitis

Report of two cases and review of the literature

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✓ Hypertrophic spinal pachymeningitis (HSP) is a comparatively rare disease characterized by hypertrophic inflammation of the dura mater and clinical symptoms that progress from local pain to myelopathy. The authors report two cases of recurrent HSP and review the English- and Japanese-language literature focusing on the recurrence of HSP.

In the first case, a man who presented at 67 years of age with lower-extremity numbness, gait disturbance, and bladder dysfunction experienced two recurrences of HSP during the 11 years of follow up after his initial laminectomy. Both recurrences were successfully treated with laminoplasty and duraplasty. Three years after his last surgical procedure, he was still able to walk with the aid of a walker. In the second case, a man who presented at 62 years of age with lower-extremity numbness and gait disturbance was initially treated successfully with steroid pulse therapy. Approximately 8 months after his initial presentation, his symptoms recurred. He underwent laminoplasty and duraplasty. At the 2.5-year follow-up examination, he had only mild neurological deficits and was still able to walk unaided.

To explore possible causes of recurrence, the authors searched the English- and Japanese-language literature for cases of HSP. Of the 96 cases identified, 11 were recurrent. Data on the presence or absence of inflammatory signs were available for 84 patients. A chi-square analysis revealed a significantly increased rate of recurrence for patients who had at least one positive inflammatory sign before surgery (six [20%] recurrent cases of 30) compared with those who had no positive inflammatory signs before surgery (two [3.7%] recurrent cases of 54) ($p < 0.05$). The authors conclude that HSP recurrence occurs because of active inflammation of the dura before surgery and the influence of chronic inflammation, including residual arachnoiditis.

KEY WORDS • **dura mater** • **disease recurrence** • **hypertrophy** • **arachnoiditis** • **hypertrophic spinal pachymeningitis** • **spinal lesion**

HYPERTROPHIC spinal pachymeningitis is a comparatively rare disease characterized by hypertrophic inflammation of the dura mater and a clinical course that progresses from local pain to myelopathy.[2,4] The cause and natural history of HSP are not well understood. Since it was first reported by Charcot and Joffroy[3] in 1869, few articles related to this disease have been published in the medical literature. Furthermore, the authors of most of these articles limited their focus to a short period after initial treatment and did not include information on recurrence. In the present article we report two cases of recurrent HSP. In addition, we review the English- and Japanese-language literature focusing on the recurrence of HSP.

Abbreviations used in this paper: HSP = hypertrophic spinal pachymeningitis; MR = magnetic resonance.

Case Reports

Case 1

First Examination, Operation, and Outcome. This man with chronic back pain was admitted to our hospital in October 1993 at age 67 years, complaining of lower-extremity numbness, gait disturbance, and bladder dysfunction. The muscle power in his right and left lower extremities were Grades 3/5 and 2/5, respectively. A sensory disturbance of pain and touch was found below T-8. The patient had no fever, and his erythrocyte sedimentation rate was 53 mm/hour. The results of serological tests, including white blood cell count and C-reactive protein level measurement, were within normal ranges. Cerebrospinal fluid values were also within the normal range. Magnetic resonance imaging showed that the spinal cord had been compressed between T-6 and T-7 in the dorsal and ventral portions (Fig. 1). Although epidural abscess or

tumor was suspected, we were unable to establish a definite diagnosis before surgery. A laminectomy was performed at the T6–8 level in December 1993. The dura mater was found to be thickened (~ 3 mm), with marked adhesion of epidural fat. After the dura mater constricting the spinal cord was removed, duraplasty was performed. Microscopic examination of sections of the excised dura revealed the presence of plasma cells and infiltrated lymphocytes (Fig. 2). We considered the findings to be compatible with a diagnosis of HSP. Two months postoperatively, the patient could walk unaided.

Second Examination, Operation, and Outcome. In August 1997, the patient's back pain and bladder dysfunction recurred, and on December 30, numbness of the lower extremities and gait disturbance developed. Two weeks later, MR imaging revealed thickened dura mater compressing the spinal cord at the T3–4 level. On January 29, 1998, laminoplasty and duraplasty were performed. Histological examination of dural sections revealed the same pathological findings as had been previously observed. Within two months of surgery, the patient was able to walk with a cane.

Third Examination, Operation, and Outcome. In February 2000, the patient presented with numbness of the upper extremities, and complained of weakness and numbness of fingers in both hands as well as gait disturbance. Three weeks later, MR imaging revealed thickened dura mater at C-6 to T-1. On May 9, laminoplasty and duraplasty were performed, and the same histopathological findings were noted. Postoperative cervical MR imaging showed cord decompression. Three years later, the patient was still able to walk with the aid of a walker.

Case 2

First Examination and Treatment. This man presented with lower-extremity numbness and gait disturbance in September 2000 at age 62 years. The muscle power in his lower extremities was almost normal, but he had reduced sensation of pain and touch below the T-6 level. Like the patient in Case 1, this patient had no fever, and results of his serological and cerebrospinal fluid tests were within the normal range. Spinal MR imaging revealed hypertrophic dura mater and cord compression at the T1–5 level (Fig. 3). Steroid pulse therapy (9300 mg) was administered. Three weeks later the patient's condition had improved, and another set of MR images showed that the thickened dura had become thinner. By November, the patient was able to walk with a cane.

Second Examination, First Operation, and Outcome. The following May, the patient was admitted to the hospital, again complaining of gait disturbance. Examination revealed that sensation was diminished at the T-6 level. We considered that he might be suffering from recurrence of HSP in the area in which it had been observed in the pretreatment MR images, and on June 12 performed a C6–T5 laminoplasty and duraplasty. We found the dura mater to be approximately 7 mm thick. Histological examination of sections of the thickened dura revealed nonspecific chronic inflammation. At follow up 2.5 years after surgery, the patient had only mild neurological deficit and could walk unaided.

Discussion

Hypertrophic spinal pachymeningitis is a comparatively rare disease. According to Charcot and Joffroy,[3] its clinical progression may be viewed in three stages: in the first stage, patients experience local and radicular pain; in the second stage, signs of nerve root compression are present; and in the third stage, patients suffer from signs and symptoms of spinal cord compression. Elsberg[7] has indicated that HSP should be suspected when a patient with spinal cord compression has radicular pain in three or more nerve root regions. There have been many case reports in which the authors have documented short-term results.[2,5,6]

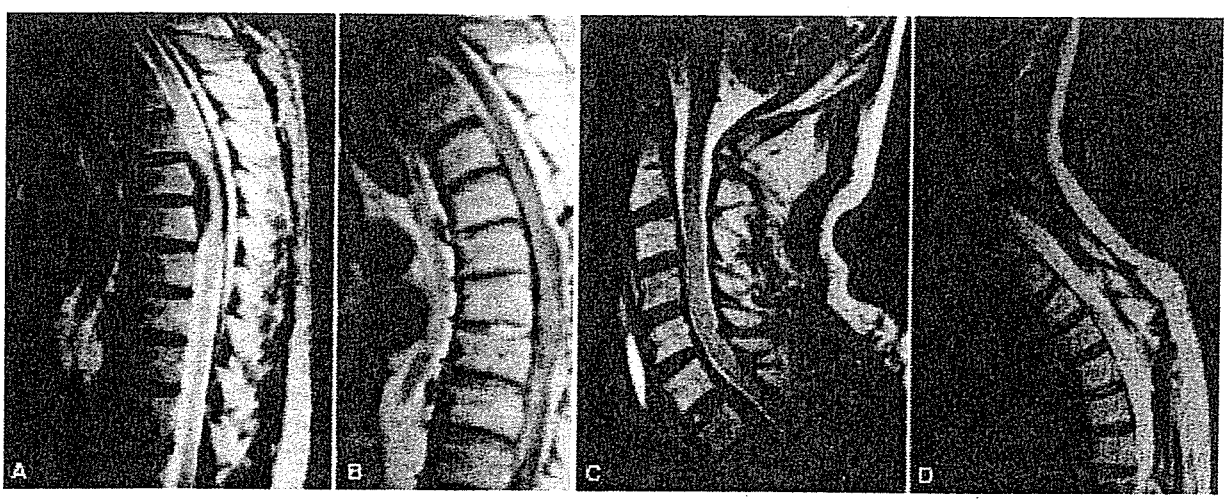

FIG. 1. Case 1. Preoperative and postoperative MR images. A: Sagittal T_2-weighted sequence obtained before the first operation, revealing dorsal and ventral T6–7 cord compression. B: Sagittal Gd-enhanced sequence obtained before the second operation, revealing HSP at the T3–5 level. C: Sagittal T_2-weighted sequence obtained before the third operation, revealing thickened dura at C-6 to T-1. D: Sagittal T_2-weighted sequence obtained after the third operation, revealing decompression of the entire lesion area.