score showed negative correlation with age ($r = -0.183$). The subjects with vertebral fractures had significantly lower JOQOL scores than the subjects without fractures. The JOQOL showed a significant correlation with all the scores in each domain of eight of SF-36 ($r = 0.350$–0.839). These results were consistent with that of the preceding study. It is concluded that the reliability and the validity of JOQOL were demonstrated in this study.

Keywords Reliability · Validity · Health-related QOL · Vertebral fracture · Osteoporosis

Introduction

Osteoporosis is a common metabolic bone disease that weakens bone strength, aggravates bone fragility, and increases susceptibility to fracture [1, 2]. The prevalence of osteoporosis increases with aging; in particular, it increases sharply in women around age 45 in the menopausal period. For women in their late seventies, the prevalence exceeds 50% [3]. Vertebral fracture risk is high in patients with osteoporosis. A vertebral fracture brings about many disabilities such as a change in posture (kyphosis), decline in physical functioning, and persistent back pain. These symptoms of the vertebral fracture decrease the quality of life (QOL) of the patient [4]. Thus, in the treatment of the osteoporosis, the consideration of patients' QOL is important [5, 6].

Quality of life has been defined by the World Health Organization (WHO) [7] as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". QOL is roughly divided into two types, such as QOL having a direct connection with health (health-related QOL, HRQOL), and QOL not having a direct connection with health. The HRQOL is a QOL that influences the health of the person directly in terms of physical state, psychosocial state, role function, and well-being. There are two types in the HRQOL, the general HRQOL and disease-specific HRQOL. General HRQOL are generic measures that are broadly applicable and can be used across patient populations. Medical Outcomes Study Short Form 36 (SF-36) [8] is the most widely evaluated measure [9]. EQ-5D (EuroQOL) [10] and the sickness impact profile (SIP) [11] have been also widely used as general HRQOL measurements. Disease-specific HRQOL is focused on aspects of health problems caused by specific disease or impairment. There are many measures that are specific to certain health problems. As disease-specific HRQOL measurements for osteoporosis, Qualeffo [12, 13], OPAQ [14], OQLQ [15, 16], and OPTQoL [17] have been developed in Western countries.

The Japanese Society for Bone and Mineral Research composed the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) to evaluate the disease-specific HRQOL for osteoporosis that is specific to Japanese patients. JOQOL was completed in 2000 [18]. Although many studies have been conducted to evaluate the disease-specific HRQOL of osteoporosis patients with JOQOL [19–23], the reliability and validity of the JOQOL have not been fully confirmed yet. Therefore, the aim of this study was to elucidate the reliability and validity of the JOQOL.

Subjects and methods

Subjects

We enrolled 195 postmenopausal women who had been diagnosed with osteoporosis or osteopenia from January to December 2005. They were recruited from outpatient departments of four hospitals as follows: Obstetrics and Gynecology Department of Atami Hospital of International University of Health and Welfare; Research Institute and Practice for Involutional Diseases; Orthopedic Surgery Department of Medical and Dental Hospital of Niigata University; and Department of Gynecology of Tokyo Women's Medical University.

Because of the exclusion of 2 patients with obvious disabilities (motor paralysis) resulting from a cerebrovascular incident, 193 patients were analyzed in this study.

The study on the test–retest reliability of the JOQOL required repetitive survey with questionnaires and patients' stable conditions. We set the interval from more than 2 to 5 weeks between the test and retest. Among 193 patients, 83 from two hospitals (Obstetrics and Gynecology Department of Atami Hospital of International University of Health and Welfare and Orthopedic Surgery Department of Medical and Dental Hospital of Niigata University) participated in the study to confirm the retest reliability. No patient had experienced a bone fracture or an operation between the period from test to retest. The mean lapse from the test to retest was 23.7 (SD 9.5) days.

Diagnosis

In this study, the diagnosis criteria of osteoporosis or osteopenia were according to the diagnostic criteria for osteoporosis that were established by the Japanese Society for Bone and Mineral Research. These criteria provided that bone mineral density (BMD) <80% of the young adult mean was osteopenia and that <70% was osteoporosis [24].

An orthopedist in charge of the patient diagnosed osteopenia/osteoporosis by BMD of two to four lumbar vertebrae. BMD was measured by dual-energy X-ray absorptiometry (DXA) within 6 months before the start of the survey. The four hospitals used different types of DXA (DPX series from Lunar, QDR series from Hologic, and XR series from Norland), and consequently the criteria were applied to the subjects at each hospital.

Methods

Measures

Development of JOQOL

The development of JOQOL was consistent with widely accepted strategies for scale development.

First, a committee that consisted of orthopedists, internists, gynecologist, epidemiologist, and physiotherapist reviewed the measurements of the disease-specific HRQOL of osteoporosis patients currently used in Western countries. The committee generated a list of items, which was based on the Osteoporosis Assessment Questionnaire (OPAQ) with a version of 79 items, by Silverman et al. [14] and the Qualeffo-41 by Lips et al. [12, 13], both Japanese versions made with the author's permission, and some items particular to the Japanese lifestyle were added.

Second, those items were reduced to 40 items as a result of statistical examination of the reliability and the validity in field-testing [25, 26].

Third, the reliability and validity of the JOQOL (40 items version) were assessed as follows. The subjects were 198 patients of osteoporosis (mean age 70.5 years; SD 9.5 years). Cronbach's alpha, which was the internal consistency of a total score, was 0.808. Test–retest reliability of the JOQOL was assessed in 83 patients 4 weeks apart, and the correlation coefficient was 0.920. There was a significant difference of the score between those with a compression fracture of the vertebrae and those without fracture ($p < 0.001$) [27]. The 40 items version of JOQOL showed generally a good result, but it was recognized that some items were inappropriate as a measurement. Then, the committee revised JOQOL from the study data [28].

The latest JOQOL consists of 38 items with the scale graded from 0 to 4 and a total full score of 152. The total score is converted into percentage; patients' HRQOL is regarded as higher with the higher score. Although 38 items were sorted into six domains according to the contents of questions, the committee recommends use in the total score [18] (see Electronic Supplementary Material). After the revision, reliability and validity of the JOQOL have not been confirmed.

Instrument testing

The reliability of JOQOL was examined in terms of test–retest reliability and internal consistency. The test–retest reliability is the stability of the evaluation with time, and the agreement of the results from two times of evaluation is examined. Internal consistency measures whether the items are those intended to measure the same construct. It is usually measured with Cronbach's alpha, which is a measure based on the correlations between different items on the same test or the same subscale.

To inspect the consistent validity of JOQOL, we examined whether the previous findings about the other disease-specific HRQOLs for the osteoporotic patients were also shown in JOQOL. It is known that the disease-specific HRQOL for the osteoporosis patient is related to whether they have a vertebral fracture, and this deteriorates with age [6, 29, 30]. In addition, to examine the concurrent validity of JOQOL, we estimated the relationship between JOQOL and a general HRQOL. In this study, we selected SF-36 as the general HRQOL. The SF-36 is a widely used general HRQOL measurement with 36 questions. It consists of an 8-scale profile of functional health and well-being scores.

Each patient was asked to complete a self-report questionnaire, which consisted of (1) JOQOL, (2) SF-36, (3) questions on their characteristics, and (4) questions on their performance of activities of daily living (ADL). We obtained the patients' written informed consent and handed them the questionnaire. Then, the questionnaire was completed by them at home and returned by mail. An omission of any answer of the questionnaire was confirmed over the telephone or at the time of outpatient consultation.

The incidence of vertebral fractures was also examined. The number of the vertebral fractures was counted by orthopedists with the thoracic and lumbar vertebrae (T3–L5) X-ray taken in two directions (anteroposterior and lateral). In counting fractures, we used X-ray photographs taken within 3 months before the start of the survey. If a patient had a suspicious incidence of vertebral fracture within 3 months before the start, we obtained a new X-ray photograph.

Statistical analysis

The test–retest reliability of the total score of JOQOL was examined by Pearson's product moment correlation coefficient and paired t test. As a reliability coefficient of each JOQOL item, Kendall's τ (b) rank correlation coefficient was calculated. The internal consistency was examined by a Cronbach's alpha coefficient.

The consistent validity of the JOQOL was examined with t test by comparison of having vertebra fracture or not

of the patients. The concurrent validity of JOQOL, we estimated the Pearson's correlation coefficient between JOQOL and SF-36.

Statistical significance was set at $p < 0.05$ and SPSS (version 12.0 J) was used for the foregoing statistical analyses.

Results

The mean age of the entire group of study subjects was 68.2 (SD 8.0) years, ranging from 48 to 86 years. Their mean height was 150.5 (SD 5.7) cm; mean weight was 50.4 (SD 6.6) kg; mean body mass index (BMI) was 21.8 (SD 3.0) kg/m^2; and mean BMD was 0.759 (SD 0.173) g/cm^2. Among the samples of this study, 58 patients (30.1%) had at least one vertebral fracture and 44 (22.8%) had one to three fractures (Table 1). There was no subject with ADL deficit. Table 2 shows the characteristics of the subjects with or without vertebral fractures. Statistically significant differences were found for age. Table 3 shows the results of the JOQOL and SF-36. The mean score of JOQOL was 71.9 (SD 12.6).

Table 1 Numbers of vertebral fractures

Number	Case	Percent (%)
0	135	69.9
1	18	9.3
2	10	5.2
3	16	8.3
4	2	1.0
5	2	1.0
6	6	3.1
7	1	0.5
8	1	0.5
10	2	1.0
Total	193	100.0

Reliability

The test and retest scores of JOQOL were significantly correlated ($r = 0.973$, Fig. 1). The first and second mean scores of JOQOL were 67.8 (SD 15.3) and 67.7 (SD 15.5), respectively, and no significant difference was observed between them.

We calculated the Kendall's τ for each JOQOL item (Table 4), and all items showed significant correlations at the time of test and retest ($\tau = 0.599$–0.947). The Cronbach's alpha coefficient of JOQOL was 0.918.

Validity

The Pearson's correlation coefficients among scores of JOQOL, patient's age, and BMI were $r = -0.183$, 0.058, respectively. The JOQOL score was significantly correlated with the age of patients. Table 5 shows a comparison of JOQOL and SF-36 scores between a group of patients who had one or more vertebral fractures ($n = 58$) and that of patients without vertebral fracture ($n = 135$). There was a significant difference between these two groups in the JOQOL scores, whereas significant difference was found only in two domains (Physical Functioning and Role Physical) among eight domains of SF-36. As shown in Table 6, scores in each domain of eight of the SF-36 were significantly correlated to the JOQOL score ($r = 0.350$–0.839).

Discussion

Japanese Osteoporosis Quality of Life Questionnaire was already used widely as the disease-specific HRQOL measurement for osteoporosis patients in Japan; therefore, it has been accepted that JOQOL has adequate content validity, among experts. Although the validation of the JOQOL before the minor revision had been confirmed, the validation of the latest JOQOL has not been carried out yet. Therefore, we conducted this study to confirm its reliability and validity.

The JOQOL scores at the time of test and retest showed a high correlation with the mean lapse of 24 days, and this

Table 2 Characteristics of subjects with and without vertebral fractures

	Without vertebral fracture ($n = 135$)		With vertebral fracture ($n = 57$)		p value (t test)
	Mean	SD	Mean	SD	
Age (years)	66.7	7.4	71.8	8.4	0.000
Height (cm)	151.0	5.6	149.3	5.3	0.065
Body weight (kg)	49.0	6.5	49.0	8.0	0.993
BMI (kg/m^2)	21.6	2.9	22.2	3.2	0.256

BMI Body mass index

Table 3 Mean scores of Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) and SF-36

	Mean	SD
JOQOL	71.9	12.6
SF-36 physical function	76.6	23.1
SF-36 role physical	65.5	32.5
SF-36 body pain	65.7	24.8
SF-36 general health	54.2	21.3
SF-36 vitality	56.3	22.3
SF-36 social functioning	80.8	24.1
SF-36 role emotion	69.6	32.7
SF-36 mental health	68.4	21.4

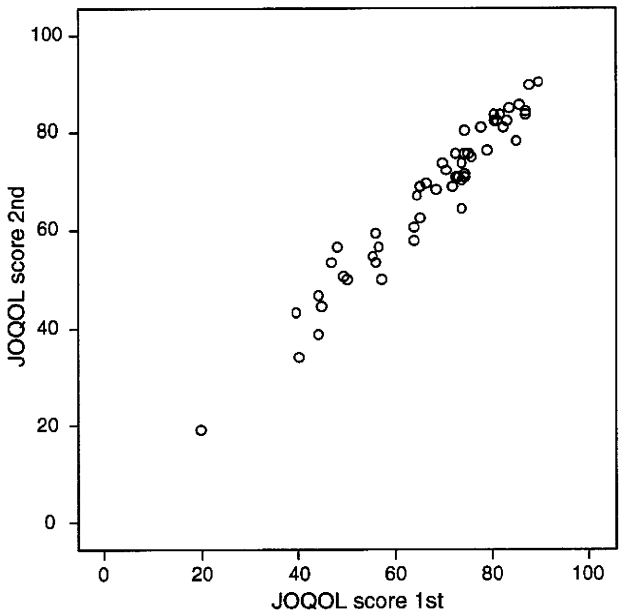

Fig. 1 Correlation between test and retest score of Japanese Osteoporosis Quality of Life Questionnaire (*JOQOL*). Pearson's correlation coefficient: $r = 0.973$, $p < 0.001$

finding indicated their high test–retest reliability. The Cronbach's alpha coefficient of JOQOL was 0.918, which showed high internal consistency. Thus, these results proved the high reliability of JOQOL.

Each of the 38 items that constitute JOQOL showed approximately 0.6 or higher rank correlation coefficients with time lapse, indicating sufficient test–retest reliability of each item of JOQOL. This result suggests test–retest reliability of any measurements that consist of JOQOL items such as a subscale of JOQOL.

The previous studies reported that disease-specific HRQOL for the osteoporosis patient were worsened when there was a vertebral fracture, and there were a large number of vertebral fractures. In the present study, patients without a vertebral fracture comprised 70% of all the subjects. Thus, we divided the subjects into two groups according to the presence of vertebral fracture and compared their JOQOL scores. Then, a significant difference between the two groups was recognized, and the JOQOL score showed a negative correlation with age. These findings were consistent with the results of preceding studies [6, 29–31].

Table 4 The test–retest reliability of JOQOL items

Item	Kendall's τ	p
Q1	0.724	**
Q2	0.691	**
Q3	0.712	**
Q4	0.818	**
Q5	0.749	**
Q6	0.799	*
Q7	0.653	**
Q8	0.787	**
Q9	0.790	*
Q10	0.749	**
Q11	0.850	**
Q12	0.800	**
Q13	0.851	**
Q14	0.790	**
Q15	0.788	**
Q16	0.861	**
Q17	0.798	**
Q18	0.725	**
Q19	0.940	**
Q20	0.947	**
Q21	0.933	**
Q22	0.674	**
Q23	0.828	**
Q24	0.751	**
Q25	0.670	**
Q26	0.758	**
Q27	0.724	**
Q28	0.805	**
Q29	0.666	**
Q30	0.681	**
Q31	0.855	**
Q32	0.631	**
Q33	0.654	**
Q34	0.616	**
Q35	0.730	**
Q36	0.632	**
Q37	0.599	**
Q38	0.675	**

* $p < 0.05$, ** $p < 0.01$

Table 5 Comparison of JOQOL and SF-36 scores between patients with or without fractures

	With vertebral fracture		Without vertebral fracture		p value (t test)
	Mean	SD	Mean	SD	
JOQOL	66.7	15.6	74.2	10.3	0.01
SF-36 domains					
Physical function	66.1	29.0	81.2	18.3	0.00
Role physical	57.3	35.6	69.2	30.4	0.04
Body pain	61.3	27.3	67.6	23.5	0.15
General health	49.7	22.0	56.2	20.8	0.09
Vitality	53.2	22.5	57.7	22.2	0.26
Social functioning	79.0	25.0	81.7	23.8	0.53
Role emotional	65.1	34.7	71.6	31.7	0.27
Mental health	69.3	16.8	68.0	23.2	0.69

Table 6 Pearson's correlation coefficients between JOQOL and SF-36

SF-36 domain	JOQOL	p
Physical function	0.839	**
Role physical	0.463	**
Body pain	0.665	**
General health	0.562	**
Vitality	0.521	**
Social functioning	0.464	**
Role emotional	0.350	**
Mental health	0.483	**

** $p < 0.01$

To confirm the concurrent validity of the JOQOL, it is required to examine the relationship between JOQOL and the other HRQOL. We examined correlation with well-established general HRQOL; it has been a widely used method in this kind of study [6, 13, 29]. In previous studies, EQ-5D, a widely used general HRQOL measurement, showed significant correlation with JOQOL [22, 31]. In this study, SF-36, which is one of the most widely used general HRQOL, was selected. In the subjects, the scores in each domain of eight domains of SF-36 indicated significant correlation with JOQOL. Thus, these results proved the concurrent validity of the JOQOL.

In this study, we were not able to prove the disease specificity of JOQOL sufficiently because the subjects consisted of osteoporosis patients only and because of the omission of a control group and patients with physical impairment or other diseases. This limitation should be a future subject to be resolved.

In conclusion, the reliability and the validity of JOQOL were confirmed in this study. Therefore, JOQOL should be expected to be utilized further as a disease-specific HRQOL measurement for osteoporosis patients in Japan.

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ORIGINAL ARTICLE

Longitudinal change in hip fracture incidence after starting risedronate or raloxifene: an observational study

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Abstract This study examined patients' risk profiles and adherence to treatment in relation to the effect of risedronate and raloxifene on hip fracture incidence. Administrative billing data were used to follow two cohorts of women aged 65 and older after starting therapy with either risedronate ($n = 86{,}735$) or raloxifene ($n = 37{,}726$). The fracture risk profile was described using a 6-month history period before starting therapy. Effectiveness of each therapy was evaluated by comparing the incidence of hip fractures during the first 3 months with the subsequent 12 months among women adherent (medication possession ratio >80%) compared with those non-adherent to treatment. At the start of therapy, the raloxifene cohort was younger than the risedronate cohort (median age 73 vs. 76 years) and had fewer prior fractures ($p < 0.01$ for both). In the first 3 months of therapy, hip fracture incidence was lower in the raloxifene group (0.51 per 100 person-years) compared with the risedronate group (0.94 per 100 person-years). In the subsequent 12 months, the incidence of hip fractures decreased among patients adherent to the risedronate regimen [relative risk (RR) 0.70, 95% CI 0.59–0.84, $p < 0.01$] and did not change significantly among patients adherent to the raloxifene regimen (RR 1.02, 95% CI 0.73–1.44). In poorly adherent patients, neither drug decreased hip fracture risk. Risedronate treatment in adherent patients rapidly decreased the risk of hip fractures, whereas raloxifene treatment did not.

Keywords Bisphosphonate · Hip fracture · Osteoporosis · Raloxifene · Risedronate

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Introduction

Randomized controlled clinical trials are the gold standard for measuring the efficacy of a therapy. All osteoporosis drugs approved to treat postmenopausal osteoporosis have demonstrated reduction of vertebral fractures in placebo-controlled clinical trials. Observations from non-comparative trials suggest that some drugs may reduce the incidence of vertebral fractures more efficiently than others [1–3]. Moreover, evidence for a reduction of hip fractures exists for certain drugs, including risedronate, alendronate, and zoledronate, but not with ibandronate and raloxifene [1, 4]. These apparent differences may pertain to the mode of action and

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distribution of the various drugs, and/or to the clinical characteristics of patients included in the trials. Indeed, recent data suggest that anti-fracture efficacy of osteoporosis drugs may be greater in patients with a higher 10-year fracture probability [5, 6]. Adherence to therapy is another major contributor to drug efficacy. Subjects who maintain a medication possession ratio (MPR) of ≥80% during all the observation time are usually considered adherent to treatment, and in these circumstances a higher level of efficacy is achieved [7–15]. How drug efficacy, baseline fracture risk, and adherence to therapy combine to determine fracture risk reduction in clinical practice however remains to be investigated [16].

Because health data on millions of patients on osteoporosis therapies in real-world clinical practice have been collected through administrative billing, medical records, and registries, many recent observational studies have examined the effectiveness of osteoporosis therapies for reducing clinical fractures [7–15, 17–30]. Some of these studies support that the effectiveness in reducing clinical fractures, particularly hip fractures, in actual patients varies among drugs, in keeping with the respective clinical trials [20, 26, 27, 30]. In the current observational study using administrative billing data, we first sought to describe and compare the fracture risk profile of patients initiating a bisphosphonate (risedronate) and an estrogen agonist/antagonist (raloxifene) therapy. The fracture risk profile included factors known to affect the probability of fracture such as demographic characteristics, co-morbidities, concomitant medication use, and history of prior fractures. We next sought to observe the hip fracture incidence in these patients according to their level of adherence to therapy. For this analysis, we followed two cohorts of women aged 65 and older after starting either risedronate or raloxifene therapy. Within each cohort, the baseline hip fracture incidence was defined by the 3-month period after starting therapy. To assess if therapy resulted in a change in fracture incidence over time, the fracture incidence during the subsequent 12 months on treatment was compared to the baseline incidence (first 3 months on treatment) within each cohort among women adherent to therapy as well as those who were non-adherent. Given the observed differences in the fracture risk profile of patients initiating a bisphosphonate or a selective estrogen receptor modulator, we further explored the hip fracture incidence in a subgroup of risedronate patients whose risk profile was matched more closely to those receiving a selective estrogen receptor modulator and conversely how effective a selective estrogen receptor modulator would be for reducing hip fractures among patients with a risk profile closer to those receiving a bisphosphonate.

Materials and methods

Data source

Computerized records of administrative billing provide a convenient data source for studying filled prescription use and outcomes in large populations. Records include patient-level data concerning: (1) inpatient and outpatient services specified by diagnosis codes of the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM); (2) retail and mail-order pharmacy dispensations specified by national drug codes; and (3) demographic information including sex, age, and eligibility dates of health plan coverage. The data for this study, from January 2000 through December 2008, originated from two mutually exclusive sources: Ingenix® Lab/Rx (Eden Prairie, MN) and Thomson Reuters' MarketScan® (Ann Arbor, MI). During the study period, the average number of eligible enrollees was 13 million in MarketScan, representing multiple health plans, and 12 million in Ingenix, representing a single health plan. Geographically, one half of this population was located in the states of Michigan, California, Florida, Ohio, Georgia, and Texas, and one half in the other 44 states.

Study population

The study population was comprised of two cohorts—one starting risedronate (5 or 35 mg) and one starting raloxifene (60 mg) therapy. Study patients were entered on the date of their initial filled prescription between July 2000 and December 2007. Inclusion criteria were: (1) being women ages 65 and over to provide a study population similar in age to that of the randomized controlled trials and for which clinical fractures are likely to be related to osteoporosis [31]; (2) having at least 3 months of coverage in the data source after cohort entry to provide a minimum observation period; and (3) having no diagnosis of a malignant neoplasm (ICD-9-CM codes 140–208) or Paget's disease (731.0) within 6 months prior to and 3 months after cohort entry to maximize the probability that patients were being treated for either post-menopausal osteoporosis or glucocorticoid-induced osteoporosis. Further description of subject identification is provided in Table 1.

Outcome

After patients were identified, each was followed to identify the first new hip fracture. "Hip fracture" was defined by an inpatient diagnosis of a fracture at the hip (ICD-9-CM code 820, 733.14). "New" was defined as no evidence of hip fracture in the 6 months before cohort entry.

Table 1 Identification of the study population

Risedronate	
Number of women in data source with first use of risedronate 5 mg (daily) (NDC = 001490471) or risedronate 35 mg (weekly) (NDC = 001490472) between July 2000 and December 2007; aged 65 years and over	202,028
Exclude women with less than 6 months of enrollment data before first use of bisphosphonate	−69,475
Exclude women with less than 3 months of enrollment data after first use of bisphosphonate	−7,445
Exclude women with diagnosis of Paget's disease (ICD-9 731.0) during period 6 months before and 3 months after first use of bisphosphonate	−193
Exclude women with malignancy diagnoses (ICD-9 140–208) during period 6 months before and 3 months after first use of bisphosphonate	−14,762
Exclude women with any other use of another **bisphosphonate** form in 6 months before first use of bisphosphonate	−17,025
Exclude women with any use of any *raloxifene* form during period 6 months before and 3 months after first use of bisphosphonate	−6,393
Number of women in bisphosphonate cohort	86,735
Raloxifene	
Number of women in data source with first use of raloxifene 60 mg (daily) (NDC = 000024165) between July 2000 and December 2007; aged 65 years and over	125,139
Exclude women with less than 6 months of enrollment data before first use of raloxifene	−68,314
Exclude women with less than 3 months of enrollment data after first use of raloxifene	−2,616
Exclude women with diagnosis of Paget's disease (ICD-9 731.0) during period 6 months before and 3 months after first use of raloxifene	−30
Exclude women with malignancy diagnoses (ICD-9 140–208) during period 6 months before and 3 months after first use of raloxifene	−5,897
Exclude women with any other use of another **raloxifene** form in 6 months before first use of raloxifene	−4
Exclude women with any use of any *bisphosphonate* form during period 6 months before and 3 months after first use of raloxifene	−10,552
Number of women in raloxifene cohort	37,726

NDC National Drug Code

To increase the probability of only including osteoporotic-related fractures, we excluded likely traumatic fractures by eliminating diagnoses of an open fracture or of a documented cause of injury from a transportation accident (E codes E800–E848).

Risk factors

Risk factors for fracture, which may be confounding variables, include age, fracture history, glucocorticoid use, and diagnosis of rheumatoid arthritis. Age was at the year of cohort entry. Fracture history was any fracture diagnosis at the hip, wrist, humerus, clavicle, pelvis, leg, or vertebrae in the 6 months prior to cohort entry. Glucocorticoid use was receiving 450 mg prednisone-equivalent pills within ±90 days of cohort entry—an approximation of a daily dose of 5 mg prednisone for at least 90 days [32]. A diagnosis of rheumatoid arthritis was any inpatient or outpatient diagnosis (ICD-9-CM code 714.0) within 6 months before and 3 months after cohort entry. Risk factors not available in the data source included bone mineral density, body mass index, smoking, alcohol consumption, and family history of fracture.

Statistical analysis

To calculate change in hip fracture incidence within each therapy cohort, we used a method described previously [30]. Briefly, within each cohort, fracture incidence during the first 3 months of therapy (baseline period) was compared with the fracture incidence during the subsequent 12 months among patients adherent to treatment. Fracture incidence during the baseline period after starting an osteoporosis therapy likely reflects the fracture risk of the cohort independent of any drug effect (i.e., fracture reduction does not begin immediately after the start of therapy). For the calculation of hip fracture incidence during the baseline period, the denominator was the sum of observation time within a cohort during the 3 months, and the numerator was the number of patients within a cohort with a new hip fracture during the 3 months.

For the calculation of hip fracture incidence during the subsequent 12 months, the denominator included all observation time where patients maintained a MPR of at least 80% to filled prescriptions of risedronate (5 or 35 mg) or raloxifene (60 mg). The 80% level utilized for the MPR has been suggested to provide a high level of therapy

effectiveness for bisphosphonates [7–15, 21–25]. The MPR was calculated at 3-month intervals after cohort entry. Therefore, patients with an MPR of at least 80% at the end of 3 months were followed into the subsequent 3-month period. The same process was applied at the end of 6, 9, and 12 months. The numerator was the number of patients with a new hip fracture preceded by a MPR of at least 80%. A simple ratio was used to compare the incidence of fractures between the baseline and subsequent periods. Poisson regression was used to compute the 95% confidence intervals around the ratio.

Two additional analyses were completed to further evaluate the primary analysis. One analysis assessed if there was any change in the hip fracture incidence between the first 3 months of therapy and the subsequent period of 12 months of all observation time where patients had a MPR <80% (i.e., not adherent to treatment). A second analysis attempted to equate the fracture risk profile of the two cohorts by matching. A 1:1 match on year of age (ages 65–100), fracture history (yes or no), and estrogen therapy use (yes or no) was completed so the risedronate cohort matched the raloxifene cohort. Hence, the number of strata matched on was 144 (36 × 2 × 2). If the raloxifene cohort had more patients in a stratum than the risedronate cohort, there was a reduction in the number of risedronate matches (i.e., of the 37,726 raloxifene patients; 37,501 had a match in the risedronate cohort). If the risedronate cohort had more patients in a stratum than the raloxifene cohort, then a random sample of risedronate patients was selected. The results presented in the matched cohort reflect the average of three random samples.

Results

Characteristics of patients starting risedronate or raloxifene

The study population included women 65 years of age and older who entered into a cohort on the date of their initial prescription filling for risedronate 5 mg daily or 35 mg weekly ($n = 86{,}735$) or raloxifene 60 mg daily ($n = 37{,}726$) between July 2000 and December 2007. The data source provided a record of health care utilization for the entire 15-month study period after cohort entry for approximately 75% of each cohort. At cohort entry, the patients receiving risedronate were older, had more prior fractures, had greater use of glucocorticoids, and overall appeared to be at greater risk for hip fracture than patients receiving raloxifene (Table 2).

Table 2 Characteristics of patients starting therapy

Characteristics	Risedronate	Raloxifene
Number of women in cohort	86,735	37,726
Year of cohort entry (% cohort)		
2000–2002	14	43
2003–2005	69	44
2006–2007	17	13
Age at entry (cohort median)	76	73
Age 75 and over (% cohort)	53	38
Any clinical fracture in 6 months before entry (% cohort)	9	4
Glucocorticoid use within 3 months of entry (% cohort)	6	3
Rheumatoid arthritis diagnosis within 3 months of entry (% cohort)	3	2
Estrogen use within 3 months of entry (% cohort)	14	26
Documented osteoporosis diagnosis in 6 months before entry (% cohort)	40	28
Medical specialty seen closest to entry (% cohort)		
Internal medicine/family practice	55	49
Obstetrics/gynecology	4	9
Other/undetermined	41	42
Estimated 10-year probability of hip fracture at cohort entry, cohort median[a]	6.0	4.0

For every characteristic, there is a statistical difference ($p < 0.01$) between raloxifene and risedronate cohorts based upon chi-square test for dichotomous variables and Wilcoxon rank sum test for continuous variables

[a] To summarize the impact of the available risk factors, a partial FRAX™ analysis was used to obtain an estimate of the 10-year probability of hip fracture based on age, fracture history, glucocorticoid use, and rheumatoid arthritis diagnosis, and assuming a body mass index of 25 for all (160 cm and 64 kg) in Caucasian women from the United States [6]. Among all patients in the cohort, the median FRAX value was reported

Incidence of hip fractures during the baseline period

During the 3 months after starting therapy in both cohorts, the incidence of hip fractures was higher among those of older age, prior fracture history, and glucocorticoid use, and lower among those using estrogen therapy (Table 3). During these 3 months, patients receiving risedronate, for whom a higher proportion had these risk factors, had an incidence of hip fractures of 0.94 per 100 person-years, nearly twice as high ($p < 0.01$) as the incidence among

Table 3 Hip fracture incidence in the 3 months after cohort entry by baseline characteristics

Characteristics	Risedronate			Raloxifene		
	Women	Women with fracture	Annualized incidence per 100 women	Women	Women with fracture	Annualized incidence per 100 women
Complete cohort	86,735	204	0.9	37,726	48	0.5
Year of entry						
2000–2002	12,591	32	1.0	16,090	17	0.4
2003–2005	59,778	134	0.9	16,594	24	0.6
2006–2007	14,366	38	1.1	5,042	7	0.6
Age 65–74 years	40,830	37	0.4	23,287	13	0.2
Age 75 and over	45,905	167	1.5	14,439	35	1.0
Clinical fracture prior to entry	8,006	44	2.2	1,466	4	1.1
No clinical fracture	78,729	160	0.8	36,260	44	0.5
Glucocorticoid use	5,261	18	1.4	1,054	2	0.8
No use	81,474	186	0.9	36,672	46	0.5
Hormone therapy use	12,292	10	0.3	9,938	3	0.1
No use	74,443	194	1.0	27,788	45	0.6
Documented osteoporosis	34,764	93	1.1	10,637	21	0.8
No documentation	51,971	111	0.9	27,089	27	0.4
Medical specialty						
Internal medicine	47,508	130	1.1	18,495	28	0.6
Gynecology	3,977	1	0.1	3,349	3	0.4
Other	35,250	73	0.8	15,882	17	0.4
Ten-year hip fracture probability						
1.2–6.0%	45,067	29	0.3	25,698	15	0.2
6.1–34.0%	41,668	175	1.7	12,028	33	1.1

Fig. 1 Follow-up for measure of fracture incidence

	Baseline period	Subsequent period				
	Cohort entry	End of 3 months	End of 6 months	End of 9 months	End of 12 months	End of 15 months
raloxifene cohort						
subjects in data source	37,726	37,726	35,841	33,722	31,715	29,957
adherent subjects		27,073	21,512	16,745	15,075	14,378
(% of available subjects)		(72%)	(60%)	(50%)	(48%)	(48%)
non-adherent subjects		10,653	14,329	16,976	16,640	15,579
risedronate cohort						
subjects in data source	86,735	86,735	81,178	74,887	68,885	63,343
adherent subjects		60,401	41,661	35,697	28,598	25,130
(% of available subjects)		(70%)	(51%)	(48%)	(42%)	(40%)
non-adherent subjects		26,334	39,517	39,190	40,287	38,213

Note: Adherent defined as medication possession ratio of at least 80%

those receiving raloxifene, which was 0.51 per 100 person-years.

Adherence to treatment

Patients with a MPR of at least 80% were considered to be treatment adherent and those with less than 80% MPR were considered to be non-adherent. At the end of the first 3 months, 72% of patients in the raloxifene cohort were adherent, while 70% of the patients were adherent in the risedronate cohort. These numbers continued to decrease during the subsequent 12-month period. At the end of the 15-month observation period, the percentage of patients adherent to treatment was 48% for raloxifene and 40% for risedronate (Fig. 1).

Incidence of hip fractures during the subsequent 12 months

In the subsequent 12 months compared to the baseline period, the incidence of hip fractures decreased among patients adherent to risedronate therapy (RR 0.70, 95% CI 0.59–0.84, $p < 0.01$), whereas no change was seen among patients adherent to raloxifene (RR 0.99, 95% CI 0.72–1.37). In contrast, among those patients not adhering to therapy, hip fracture incidence remained unchanged across the baseline period through the subsequent 12 months for both the risedronate and raloxifene cohorts (Table 4).

Matched analysis

To investigate the contribution of differences in baseline fracture risk between patients treated with risedronate or raloxifene (Table 1) in relation to the effectiveness of these drugs in reducing hip fractures, we attempted to match the risedronate cohort to the lower risk raloxifene cohort based on age, fracture history, and use of estrogen therapy. In this case, the resulting matching was incomplete as differences ($p < 0.01$) in the incidence of hip fractures remained during the baseline period (Table 5). Nevertheless, in the raloxifene-matched risedronate cohort, the initial hip fracture incidence decreased to 0.70 per 100 patient-years (from 0.94 per 100 patient-years in the overall risedronate cohort) (Table 4). In this relatively lower risk group, the incidence of hip fracture in the subsequent 12 months was still significantly reduced with risedronate therapy (Table 5).

Discussion

In this large, observational study of women aged 65 years and older initiating either risedronate or raloxifene therapy,

Table 4 Comparison of hip fracture incidence between baseline period and subsequent period

Cohort (number of patients)	Baseline period			Subsequent period				Ratio (95% CI) of fracture incidence for follow-up/baseline
	Initial 3 months after starting therapy			Subsequent 12 months after baseline period				
	Number patients with fracture	Person-years of observation	Fracture incidence per 100 person-years		Number patients with fracture	Person-years of observation	Fracture incidence per 100 person-years	
Raloxifene ($n = 37,726$)	48	9,432	0.51	Adherent	102	19,594	0.52	1.02 (0.73–1.44)
				Non-adherent	69	14,192	0.49	0.96 (0.66–1.38)
Risedronate ($n = 86,735$)	204	21,684	0.94	Adherent	266	40,214	0.66	0.70 (0.59–0.84)
				Non-adherent	316	34,787	0.91	0.97 (0.81–1.15)

Adherent defined as medication possession ratio of at least 80%
Non-adherent defined as medication possession ratio less than 80%

Table 5 Matched analysis (year of age, fracture history, estrogen use)

Cohort (number of patients)	Baseline period			Subsequent period			Ratio (95% CI) of fracture incidence for follow-up/ baseline
	Three-month period after starting therapy			Subsequent 1-year period adherent to therapy			
	Number subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	Number subjects with fracture	Person-years of observation	Fracture incidence per 100 person-years	
Raloxifene							
Complete cohort (n = 37,726)	48	9,432	0.51	102	19,594	0.52	1.02 (0.73–1.44)
Risedronate							
Matched cohort[a] (n = 37,501)	66	9,375	0.70	81	17,933	0.45	0.64 (0.46–0.89)
Risedronate							
Complete cohort (n = 86,735)	204	21,684	0.94	266	40,214	0.66	0.70 (0.59–0.84)
Raloxifene							
Matched cohort[b] (n = 17,074)	25	4,268	0.59	59	8,730	0.68	1.15 (0.72–1.84)

[a] A 1:1 match on year of age, fracture history (yes or no), and hormone replacement therapy use (yes or no) was completed so the risedronate cohort matched the raloxifene cohort. If the raloxifene cohort had more patients in a stratum than the risedronate cohort, there was a reduction in the number of risedronate matches (i.e., of the 37,726 raloxifene patients, 37,501 had a match in the risedronate cohort). If the risedronate cohort had more patients in a stratum than the raloxifene cohort, then a random sample of risedronate patients was selected. The numbers presented in the matched cohort reflect the average of three random samples

[b] A 1:5 match on year of age, fracture history (yes or no), and hormone replacement therapy use (yes or no) was completed so the raloxifene cohort matched the risedronate cohort. If the risedronate cohort had more than 5× patients in a stratum than the raloxifene cohort, there was a reduction in the number of raloxifene matches (i.e., of the 17,347 needed patients in the raloxifene group, 17,074 had a match in the risedronate cohort). If the raloxifene cohort had more patients in a stratum than 1/5 of the risedronate cohort, then a random sample of raloxifene patients was selected. The numbers presented in the matched cohort reflect the average of three random samples

we made three inquiries: (1) Were there any differences in the fracture risk profile at the time of initial prescription among these women? (2) How effective was each osteoporosis therapy in reducing hip fractures over time considering the adherence level? (3) What is the contribution of the baseline fracture risk to the effectiveness of these drugs in reducing hip fractures?

Consistent with prior observations [27, 33], we observed that patients receiving risedronate had more risk factors for fracture at the time of initial prescription than the population of patients receiving a selective estrogen receptor modulator. These observations suggest that physicians are selectively prescribing osteoporosis therapies based on their appreciation of the patients' risk profile and/or specialty. While these prescription patterns are likely clinically appropriate, selective prescribing creates a meaningful bias for any epidemiological study of drug effects. This bias, confounded by indication, results because the allocation of treatment is not randomized and the indication for treatment is related to the risk of future outcomes [34]. As a result, this bias may lead to a false interpretation of any comparison between treatment groups. While there is no one best way to manage this bias, we utilized a method in this study that makes a comparison within a population rather than between populations. A limitation of our method, which is a comparison in the fracture incidence during the first 3 months of therapy to the fracture incidence during the subsequent 12 months among patients adherent to treatment, is the presumption that fracture reduction does not begin immediately after therapy; consequently, the short baseline period after starting an osteoporosis therapy likely reflects the fracture risk of a cohort independent of any drug effect. One observation supporting this presumption includes changes in bone mineral density, a surrogate marker of therapeutic effect, whose least significant change may not be reached until at least 1 year on therapy [35]. Another supporting observation is that fracture reductions have not been noted earlier than 6 months after start of therapy within post hoc, pooled analysis of clinical trials [36, 37].

Based on our method of measuring effectiveness in this study, we observed that the patients receiving and adherent to risedronate had a reduction over time in the incidence of hip fractures, whereas the patients receiving and adherent to raloxifene had no reduction in hip fracture incidence. The strength of this observation is the consistency between these results and the results of clinical trials [1, 4] and another observational study [38]. Limitations of this observation include the limited availability of information to describe patients (e.g., no bone mineral density results), the inclusion of fracture outcomes not verified by medical charts, and the potential that differences in fracture risk profile at baseline between the risedronate and raloxifene populations may be linked to interpretation of results. In a recent study, McCloskey et al. [5] showed that the bisphosphonate clodronate was effective in women identified by the FRAX® tool (World Health Organization, Centre for Metabolic Bone Diseases, University of Sheffield, UK) to be at high risk even in the absence of bone mineral density information. Kanis et al. [6] showed that bazedoxifene, an estrogen angonist/antagonist, was effective at reducing vertebral and clinical fractures in postmenopausal women at high risk as assessed by FRAX. Thus, the observed differences in the present study may be partly due to the fracture risk profile at baseline.

To control for differences in fracture risk profile at baseline, we attempted to equate the risedronate and raloxifene populations on fracture risk at the time of initial prescription by matching on several major risk factors, including age, prior fracture, and use of estrogen therapy. However, even after matching on these risk factors, there remained significant differences in baseline fracture risk during the initial 3 months of therapy (i.e., matching did not fully control for differences between populations). It remains possible, therefore, that even modest differences in baseline fracture risk have an impact on the effectiveness of these therapies [6]. On the other hand, these results suggest that treating women at lower risk with risedronate might be more beneficial than treating them with raloxifene.

In conclusion, for this observational study of more than 100,000 patients receiving either risedronate or raloxifene, differences existed in the fracture risk profile of patients at the time of initial prescription between those starting different osteoporosis therapies. Among these patients, we found that adherence to risedronate therapy rapidly decreased the risk of hip fractures, whereas raloxifene prescribed to women at lesser fracture risk did not. Hence, cost-effective strategies to reduce the burden of clinical fractures should take into account both drug efficacy and baseline fracture risk.

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The effects of multidimensional exercise on functional decline, urinary incontinence, and fear of falling in community-dwelling elderly women with multiple symptoms of geriatric syndrome: A randomized controlled and 6-month follow-up trial

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ABSTRACT

This study assessed the effects of multidimensional exercises on functional decline, urinary incontinence, and fear of falling in community-dwelling Japanese elderly women with multiple symptoms of geriatric syndrome (MSGS). Sixty-one participants were randomly assigned either to an intervention ($n = 31$) or to a control group ($n = 30$). For 3-month period, the intervention group received multidimensional exercise, twice a week, aiming to increase the muscle strength, walking ability, and pelvic floor muscle (PFM). Outcome variables were measured at baseline, and after intervention and follow-up. The functional decline of the intervention group decreased from 50.0% at baseline to 16.7% after intervention and follow-up ($Q = 16.67$, $p < 0.001$). For urinary incontinence, the intervention group decreased from 66.7% at baseline to 23.3% after intervention and 40.0% at follow-up ($Q = 13.56$, $p = 0.001$), whereas the control group showed no improvement. Intervention group showed greater and significant decrease in the score of MSGS compared to control group ($F = 12.66$, $p = 0.001$). Within the subjects that showed improvement to normal status of MSGS, a significantly higher proportion demonstrated increased maximum walking speed at follow-up ($Q = 6.50$, $p = 0.039$). These results suggest that multidimensional exercise is an effective strategy for reducing geriatric syndromes in elderly population. An increase in walking ability may contribute to the improvement of MSGS.

1. Introduction

The geriatric syndrome such as functional decline, urinary incontinence, and fear of falling are used to capture those clinical conditions that do not fit into discrete disease categories, and are serious problems among the elderly population (Inouye et al., 2007). Many studies have demonstrated that a decline in walking speed, muscle strength and balance ability of the elderly is strongly associated with the development of geriatric syndrome (Vellas et al., 1997; Ishizaki et al., 2000; Maggi et al., 2001).

It is well documented that as age advances, the proportion of people with more than one symptom of geriatric syndrome increases. In addition, people with MSGS have an increased prevalence of functional disability and mortality compared to people with only one or no symptoms present. Several studies have put emphasis on the fact that multidimensional exercises focusing on strength, balance, and mobility improvement, even into advanced age, was helpful in reducing functional decline, urinary incontinence and fear of falling (Nelson et al., 2004; Gitlin et al., 2006; Kim et al., 2007). These previous studies validated the effectiveness of the multidimensional exercises focusing on the improvement of a single geriatric syndrome such as functional decline or urinary incontinence, but did not provide any information on whether the subjects possessed symptoms other than functional decline or urinary incontinence. One study demonstrated (Tinetti et al., 1995) that falls and urinary incontinence were associated with the occurrence of functional decline, and that the identification of shared risk factors associated with falls and urinary incontinence is the key in establishing effective and efficient interventional strategies. However, few multidimensional exercises studies have been performed in community-dwelling elderly persons with MSGS.

In the present study, we hypothesize that deteriorations in muscle strength, walking and balance ability are common risk factors associated with functional decline, urinary incontinence and fear of falling. We conducted a randomized and controlled trial to evaluate the effects of the multidimensional exercises targeted at reducing the symptoms of functional decline, urinary inconti-

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nence, and fear of falling in community-dwelling Japanese elderly women with MSGS.

2. Methods

2.1. Study sample and procedures

Overall health surveys were conducted at the Tokyo Metropolitan Institute of Gerontology (TMIG), aiming at early screening of geriatric syndromes in elderly persons and at developing intervention strategies, which would reduce those geriatric syndromes. As subjects, 1016 women were chosen randomly from the Basic Resident Register as persons aged 70 or older residing in Itabashi ward of Metropolitan Tokyo.

A letter outlining the study and describing its objective, and the way that the personal data would be used was mailed to the elderly women selected, inviting them to participate in the study. The baseline survey was conducted in November 2004, and 669 women aged 70 years and older participated.

The participants were screened based on three geriatric syndromes: functional decline, urinary incontinence, and fear of falling. A person who was reported as having two or more geriatric syndromes present was defined as having MSGS. Out of the 669 women participated, 102 were classified as having MSGS (Fig. 1). A pamphlet containing information on the "Exercise Classes for the Treatment of Geriatric Syndromes" was mailed to the 102 potential participants. A response was obtained from 74 of them, of whom 61 were willing to participate. There were no statistically significant differences in physical fitness, age, and geriatric syndromes between the 61 willing participants and the 41 unwilling ones including those who did not submit any response. The research protocol was approved by the institutional review board, and informed consent was obtained from each participant.

2.2. Randomization

After baseline assessment, subjects were divided into two groups with an allocation ratio of 1:1 according to computer-generated random numbers. There was no attempt to equalize the sizes of the groups based on characteristics or to recruit subjects with specific characteristics. Thereafter, one group was allocated to the intervention ($n = 31$) and the other group to the control ($n = 30$) (Fig. 1).

2.3. Data collection

Data collected by interview and a physical fitness test at baseline, after 3-month exercise, and were reassessed at 6-month follow-up.

2.3.1. Interview survey

A face-to-face interview was conducted to assess the following variables: The functional decline was measured using the TMIG index of competence (Koyano et al., 1991). For each of the 13 items, "yes" was scored as 1 and "no" as 0 (maximum score: 13). A person with a TMIG index score less than 10 was defined as having functional decline. Urinary incontinence was assessed through the question "Have you ever experienced urine leakage during the last 1 year?" If a subject responded with a "yes", we would then ask concerning the frequency of urinary incontinence. The frequency of urinary incontinence was assessed based on a five-point scale through interview (1: several times per year; 2: once or more per month: 3: once or twice per week; 4: once every 2 days; 5: everyday). A person whose response ranged 2–5 was defined as having urinary incontinence (Burgio et al., 1991). The fear of falling was assessed by asking "At this moment, are you afraid of falling?" and classified as "1. not at all", "2. somewhat", "3. very much", and "4. activity restriction due to fear of falling". Subjects who responded within 2 and 4 were assigned to the fear group (Maki et al., 1991).

The effect of the multidimensional exercises on the geriatric syndromes was assessed based on shifts of the responses from the interview, which was conducted at a baseline, completion of the 3-month exercise, and at the 6-month follow-up. The scores of geriatric syndromes were calculated as follows: functional decline, 0 for TMIG index score more than 11, 1 for 10, 2 for 9, and 3 for less than 8; urinary incontinence, 0 for no urine leakage or several times per year, 1 for once or more per month, 2 for once or twice per week, and 3 for once every 2 days or everyday; fear of falling, 0 for not at all, 1 for somewhat, 2 for very much, and 3 for activity restriction due to afraid of falling. The score of MSGS was calculated as add up three geriatric syndrome score (functional decline, urinary incontinence, and fear of falling). And, a participant with a MSGS score less than 1 was defined as improvement of MSGS.

2.3.2. Physical fitness test

Body mass index (BMI) was calculated from body weight (kg) divided by height (m) squared. Physical fitness tests were used for the assessment of muscle strength, walking speed, and balance ability. The following standardized tests were performed: grip strength (Suzuki et al., 2004); adductor muscle strength (Kim et al., 2007); usual and maximum walking speed (Suzuki et al., 2004); one leg standing time with eyes open (Suzuki et al., 2004); tandem walking (Speers et al., 1998); functional reach (Duncan et al., 1990). The staff members who performed the assessments did not know the subjects' group assignments.

2.4. Interventions

2.4.1. Exercise group

The exercise group participated in an intervention comprised of 60-min exercise sessions held at the TMIG Health Promotion Classes, twice per week for 3-month. Weight-bearing exercise: strength training of the thigh, abdominal, and back muscles was performed and included bending the knees, and other similar exercises.

PFM exercise: The exercise regimen was designed to strengthen the fast- and slow-twitch muscle fibers located at the pelvic floor. Participants were initially instructed to perform 10 fast contractions (3-s) with a 5-s relaxation period and 10 sustained contractions (6–8 s) with a 10-s relaxation period in between the contractions. The PFM exercise was performed in sitting, lying, and standing positions with legs apart, emphasizing training of the PFM and relaxation of the other muscles.

Chair exercises: Used in the early stage of the program. The exercises included seated toe and heel raises, seated lift foot and point/flex toes, and others.

Resistance band exercise: Focused on increasing the strength of the muscles of the upper extremities, abdomen, and lower extremities in frail elderly people (arm pull back, leg extension, and others).

Ball exercise: Exercises with a training ball were conducted using a small (diameter: 21 cm) and a large ball (diameter: 45–55 cm), aiming to increment the muscle strength and balance (sitting on the ball and extending legs, and others).

Walking ability training: Focused on maintenance of stability during walking and on the improvement of responses to postural changes during walking (walking with directional changes, gait pattern variations and enhancement, and others).

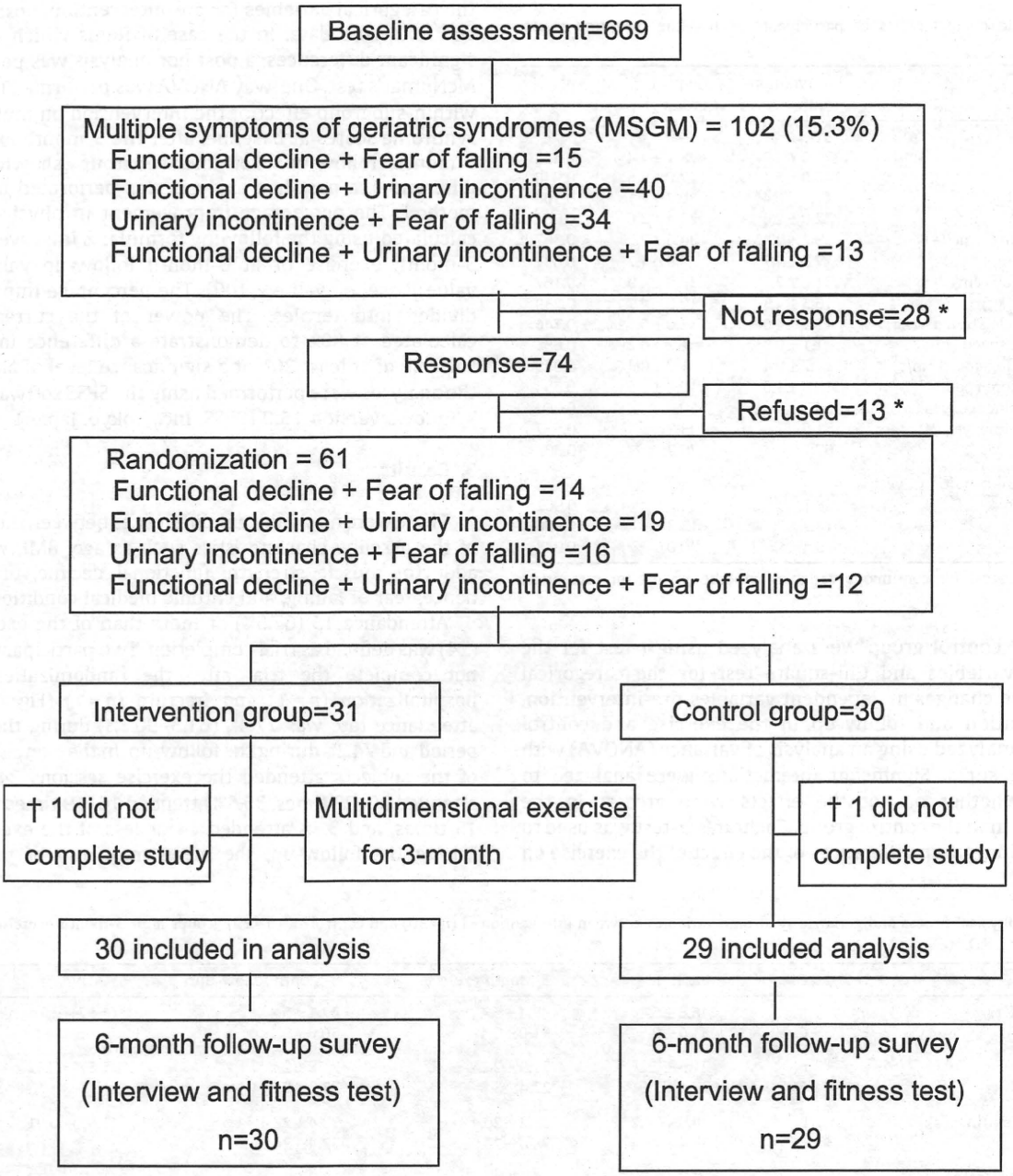

Fig. 1. Flow chart of participants through the randomized controlled trial of the exercise program and analysis. (*) Forty-one of MSGM ($n = 102$) were excluded due to the not response ($n = 28$) and refusal ($n = 13$). (†) Two subjects could not complete the study because of hospitalization ($n = 1$), and fracture ($n = 1$).

Balance training: Focused on the improvement of the static, dynamic, and lateral balancing ability (multidirectional weight shifts, tandem walking, and others).

2.4.2. Control group

The control group attended a general health education class (albumin, osteoporosis, and prevention of malnutrition) held at the TMIG once a month for a 3-month period.

2.5. Follow-up and compliance

During the 6-month follow-up period, subjects of the intervention group attended group exercise classes (60 min) once per month in addition to receiving a home-based exercise program. The home-based exercise program consisted of two to three sets of the 15 exercises and PFM exercise that they had learned during the group exercise session. They were also advised to do the home-based exercises at least three times or more per week for about 30-min per day. In order to accurately monitor the exercise times and the number of sets performed at home during the follow-up period, a pamphlet illustrating the PFM and strengthening exercises and a recording sheet were distributed to the participants, who were instructed to record the time and sets of exercises performed at home everyday. The record sheets were collected once a month at the group exercise class and analyzed in order to calculate the mean exercise frequency per week, and the mean exercise time per day.

2.6. Statistical analysis

Both the mean and standard deviation were calculated for each variable. The differences in the baseline data between the

Table 1
Selected variable characteristics of participants at baseline by study group, mean ± S.D.

Variables	Intervention group	Control group	$p^{\dagger}$
Number	31	30	
Age (year)	79.0 ± 3.9	78.1 ± 4.4	0.424
Height (cm)	146.9 ± 5.4	147.0 ± 5.8	0.940
Body weight (kg)	47.4 ± 6.4	50.7 ± 9.1	0.108
BMI (kg/m^2)	22.0 ± 2.6	23.4 ± 3.6	0.084
One leg standing time (s)	29.2 ± 23.5	34.6 ± 22.8	0.367
Tandem walking (step)	7.2 ± 4.7	7.8 ± 4.7	0.631
Functional reach (cm)	31.0 ± 7.1	33.2 ± 4.9	0.167
Grip strength (kg)	16.5 ± 4.3	17.9 ± 4.7	0.239
Adductor muscle strength (kg)	17.3 ± 4.0	18.0 ± 5.1	0.740
Usual walking speed (m/s)	1.1 ± 0.3	1.2 ± 0.2	0.685
Maximal walking speed (m/s)	1.7 ± 0.4	1.7 ± 0.4	0.979
TMIG index score (point)	10.6 ± 1.6	10.4 ± 1.5	0.654
Urinary incontinence, yes (%)	64.5	50.0	0.252
Functional decline, yes (%)	51.6	43.3	0.517
Fear of falling, yes (%)	67.7	76.7	0.390
Chronic medical conditions, yes (%)			
Hypertension	58.1	60.0	0.902
Stroke	13.2	13.3	0.988
Diabetes	19.4	20.0	0.948

† Two group t-test for continuous variables and the χ^2-test for categorical variables.

exercise and control group were analyzed using t-test for the continuous variables and Chi-square test for the categorical variables. The changes in dependent variables pre-intervention, post-intervention and follow-up in the exercise and control group were analyzed using an analysis of variance (ANOVA) with repeated measures. Significant interactions were analyzed to determine whether or not the effects were greater in the intervention than the control group. Cochran's Q-test was used to evaluate within-group differences of the effect of the exercise on the categorical variables for pre-intervention, post-intervention, and follow-up data. In the case of items which were showing significant differences, a post hoc analysis was performed using McNumar's test. One-way ANOVA was performed to evaluate the within-subgroup effect of the intervention on multiple geriatric syndrome scores at baseline, after the 3-month exercise, and at 6-month follow-up. For the subgroup showing significant differences, a post hoc analysis was performed using Scheffe's method. The percentage improvement in physical fitness was calculated using the following formula: % improvement = {(after 3-month exercise or at 6-month follow-up values − baseline value)/baseline value × 100}. The percentage improvement was divided into tertiles. The power of the current study was calculated at 80% to demonstrate a difference in the outcome variable of at least 20% at a significance level of alpha = 0.05. All the analyses were performed using the SPSS software package for Windows version 15.0 (SPSS, Inc., Tokyo, Japan).

3. Results

There were no significant differences between the groups in any of the baseline characteristics such as age, BMI, walking speed, adductor muscle strength, functional decline, urinary incontinence, fear of falling, and chronic medical conditions (Table 1).

Attendance 15 (62.5%) or more than of the exercise sessions (24) was defined as trial completion. Two participants (3.3%) could not complete the trial after the randomization because of hospitalization ($n = 1$) and fracture ($n = 1$) (Fig. 1). The mean attendance rate was 77.4% (61.3–90.3%) during the intervention period and 74.2% during the follow-up. In the exercise group, 32.3% of the subjects attended the exercise sessions 24 times, 22.6% attended 20–23 times, 35.5% attended 16–19 times, 6.5% attended 15 times, and 3.3% attended 14 or less of the exercise sessions. During the follow-up, the mean frequency of performing the

Table 2
Comparison of physical fitness and geriatric syndrome variables between intervention = I ($n = 30$) and control = C ($n = 29$) groups after 3-month exercise and at 6-month follow-up, mean ± S.D.

Variables	Gr	Baseline	3-Month exercise	6-Month follow-up	ANOVA F=	p=
Body weight (kg)	I	46.6 ± 5.4	47.4 ± 5.4	47.1 ± 5.4	(1,57) = 2.74	0.105
	C	51.0 ± 9.5	51.0 ± 9.4	50.6 ± 9.1		
BMI (kg/m^2)	I	21.5 ± 2.2	21.9 ± 2.2	21.8 ± 2.2	(1,57) = 2.82	0.100
	C	23.4 ± 3.9	23.4 ± 3.8	23.3 ± 3.6		
One leg standing time (s)	I	34.0 ± 24.2	28.2 ± 20.4	32.4 ± 22.6	(1,57) = 0.01	0.920
	C	33.4 ± 23.4	28.8 ± 23.5	32.4 ± 24.6		
Tandem walking (step)	I	7.2 ± 4.7	6.1 ± 4.5	5.9 ± 3.3	(1,57) = 4.70	0.036
	C	7.8 ± 4.7	5.2 ± 3.8	3.5 ± 2.0		
Functional reach (cm)	I	31.7 ± 6.8	33.5 ± 5.13	3.5 ± 4.4	(1,56) = 4.18	0.046
	C	33.7 ± 4.7	32.7 ± 5.3	31.6 ± 8.8		
Grip strength (kg)	I	17.2 ± 4.0	20.9 ± 5.2	17.9 ± 4.7	(1,57) = 0.02	0.874
	C	18.0 ± 4.6	21.5 ± 5.1	18.6 ± 4.8		
Adductor muscle strength (kg)	I	17.2 ± 4.0	18.9 ± 5.1	19.3 ± 4.7	(1,57) = 4.18	0.045
	C	17.9 ± 5.0	18.2 ± 4.01	17.8 ± 3.7		
Usual walking speed (m/s)	I	1.1 ± 0.3	1.1 ± 0.2	1.2 ± 0.2	(1,57) = 13.03	0.001
	C	1.2 ± 0.2	1.1 ± 0.3	1.1 ± 0.3		
Maximal walking speed (m/s)	I	1.7 ± 0.4	1.8 ± 0.5	1.8 ± 0.4	(1,56) = 4.24	0.044
	C	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.4		
Functional decline, yes (%)	I	50.0	16.7	16.7	16.67[a]	<0.001
	C	41.4	31.0	27.6	4.10[a]	0.109
Urinary incontinence, yes (%)	I	66.7	23.3	40.0	13.56[a]	0.001
	C	51.7	44.8	44.8	4.00[a]	0.135
Fear of falling, yes (%)	I	66.7	70.0	70.0	0.17[a]	0.920
	C	75.9	62.1	75.9	2.91[a]	0.234

[a] Cochran's Q-value.