Risk Factors Associated with Incident Clinical Vertebral and Nonvertebral Fractures in Japanese Women with Rheumatoid Arthritis: A Prospective 54-month Observational Study

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ABSTRACT. ***Objective.*** To evaluate the association between potential risk factors and incident clinical fractures in Japanese patients with rheumatoid arthritis (RA).

Methods. A total of 1733 female patients with RA over age 50 years were enrolled in a prospective observational cohort study. Participants were followed for 54 months from October 2000 to March 2005, and classified into 4 groups according to incident fracture status since baseline: those without a new fracture; those with a new clinically recognized vertebral fracture; those with an incident nonvertebral fracture at the wrist, hip, humerus, pelvis, or ribs (main nonvertebral fracture); and those with any new nonvertebral fracture. Cox proportional hazard models were used to analyze independent contributions of various risk factors to fracture incidence.

Results. During the followup period, 33, 34, and 98 patients developed a vertebral, a main nonvertebral, and any nonvertebral fracture, respectively. The Japanese Health Assessment Questionnaire (J-HAQ) score was associated with relative risks (RR) of 2.42 (95% confidence interval 1.42–4.14), 1.76 (95% CI 1.07–2.89), and 1.73 (95% CI 1.29–2.32) for vertebral, main nonvertebral, and all nonvertebral fractures. The risks of vertebral and any nonvertebral fractures were increased for age over 70 years compared with age in the 50s (RR 3.25, 95% CI 1.19–8.86; and RR 2.22, 95% CI 1.20–4.10, respectively). Clinical variables and medications were associated with a new fracture.

Conclusion. HAQ, age, history of any prior fracture, and orthopedic surgery for RA appear to be associated with fractures in Japanese women with RA. (First Release Dec 1 2006; J Rheumatol 2007;34:303–10)

Key Indexing Terms:
COHORT STUDIES FRACTURES HEALTH ASSESSMENT QUESTIONNAIRE
RISK FACTORS RHEUMATOID ARTHRITIS WOMEN

Fractures are a major source of disability and impaired quality of life[1]. Patients with rheumatoid arthritis (RA) have an increased risk of osteoporosis and osteopenia[2] and a higher risk of vertebral deformities[3] and hip fractures[4,5] relative to controls. Moreover, many patients with RA receive corticosteroid treatment, which has been shown to increase the risk of vertebral fractures[3,6-9].

Bone mineral density (BMD) has been shown to predict subsequent fractures in patients with RA[6] and in postmenopausal Caucasian women[10]. While low BMD is a major risk factor for vertebral[6,8] and nonvertebral[11] fracture in patients with RA, other clinical factors need to be identified to predict those with increased fracture risk. Detection of high-risk individuals is important because several treatments have been documented to prevent fracture in RA[12-16].

There are relatively few data concerning risk factors for incident vertebral and nonvertebral fracture. The Canadian Multicenter Osteoporosis Study (CaMos), a prospective population-based cohort study, showed the association between various anthropometric measures, disease status, and medications and incident fractures in postmenopausal women[17]. Several cross-sectional and population-based studies reported risk factors for fractures[18,19], both vertebral[6-9] and nonverte-

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bral fractures[11], in patients with RA. Recently, Arai, *et al* reported from a prospective study that Japanese RA patients more than 60 years old who are treated with corticosteroids or who had BMD 80% below normal had high vertebral fracture rates[6]. However, they studied a limited number of potential risk factors (age, BMD, preexisting vertebral fracture, use of corticosteroid and methotrexate, and urinary excretion of N-telopeptide of type I collagen) and evaluated only vertebral fracture risks without multivariate analysis in 117 Japanese female patients with RA[6].

Using data from our prospective observational study of RA in Japan (IORRA: Institute of Rheumatology Rheumatoid Arthritis)[20], we evaluated the associations between potential risk factors at baseline, medications at followup, and subsequent vertebral and nonvertebral fractures over a 54-month period in Japanese women with RA over age 50 years.

MATERIALS AND METHODS

Study cohort. IORRA is a prospective observational cohort study of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University. Details of the study's purpose and methodology are reported[20-22]. A large observational cohort study of RA patients using physicians' assessments and laboratory data has been established in our institute since 2000. Study details were explained to each patient by one of 49 rheumatologists during their clinic visits. Informed consent was received from each patient, and questionnaires were given to them. Each participant was asked to complete the questionnaire at home and mail it back in preaddressed stamped envelopes within 2 weeks.

Participant selection. All female RA patients over 50 years old who participated in IORRA were included in the current study. All had been diagnosed with RA according to the 1987 classification criteria of the American College of Rheumatology[23]. Participants were followed for 54 months from October 2000 to March 2005. Only incident fractures as a result of minimal trauma were included in the analysis[17].

All female patients over 50 years old were subdivided into 4 groups according to their incident fracture status: those without an incident fracture during the 54-month study period (no-fracture group); those with a clinically recognized vertebral fracture (vertebral fracture group); those with an incident nonvertebral fracture at the wrist, hip, humerus, pelvis, or ribs (main nonvertebral fracture group); and those with any new nonvertebral fracture (any nonvertebral fracture group), as reported[17]. The any nonvertebral fracture group included all patients of the main nonvertebral fracture group.

Baseline assessments. The baseline demographic and clinical variables obtained during October and November 2000 were as follows: age, height, weight, body mass index (BMI), current smoking, current alcohol intake, disease duration of RA, rheumatoid factor (RF; IU/ml, Rose-Waaler test), Japanese Health Assessment Questionnaire (J-HAQ) scores[21], erythrocyte sedimentation rate (ESR; mm/h, Westergren method), serum C-reactive protein (CRP; mg/100 ml), patient's assessments of pain [patient's pain visual analog scale (VAS)], patient's global assessment of disease activity (patient's global VAS), physician's global assessment of disease activity (physician's global VAS), tenderness and swollen joint count of 45 joints, and history of any prior fracture, any orthopedic surgery for RA and total knee replacement.

Medications during 54-month followup. All participants were asked about their medications, including disease modifying antirheumatic drugs, corticosteroids, and drugs for osteoporosis, in the questionnaire every 6 months during the 54 months. We defined patients as users of certain drugs if they answered that they took the drug at least one time. In patients with incident fractures, however, we defined patients as users of certain drugs if they took them before the fracture, because some patients started to take the drugs after the fracture occurred.

Fracture assessments. Clinically recognized incident vertebral and nonvertebral fractures were enumerated from self-reports, as documented in the questionnaire. Participants were asked about fractures at the ankle, arm, clavicle, elbow, foot, hand, hip, knee, leg, nose, pelvis, rib, shoulder, thoracic spine, lumbar spine, and wrist every 6 months from October 2000 to March 2005. They were then asked to state whether the fracture was due to a fall, accident, sports injury, or spontaneous event. For verification of fractures and fracture sites, self-reported fractures were confirmed by review of radiology reports or medical records. We excluded patients with self-reported fractures that we could not verify by their radiology reports or medical records, or fractures resulting from a traffic accident. Only the first fracture event reported by the patient was used in this study[24]. Asymptomatic vertebral fractures were not included in this study because routine thoracic and lumbar spine radiographs were not obtained for spinal morphometry[25].

Potential risk factors. Potential risk factors were examined as either continuous or categorical variables. Continuous variables of interest included height (cm), weight (kg), patient's pain VAS (cm), patient's global VAS (cm), physician's global VAS (cm), and J-HAQ scores[21]. Dichotomous variables (yes/no) included current smoking, current alcohol use, history of any prior fracture, any orthopedic surgery for RA, and total knee replacement. Medications used during followup, including corticosteroids, bisphosphonates, active vitamin D_3, and vitamin K_2 (menatetrenone), were further categorical fracture risk factors that were assessed. Categorical variables included age (50s, 60s, ≥ 70 yrs), disease duration of RA [< 5 yrs (median) or ≥ 5 yrs], CRP [< 0.7 (median) or ≥ 0.7 mg/100 ml], ESR [< 37 (median) or ≥ 37 mm/h], RF [negative (< 35 IU/ml) or positive (≥ 35 IU/ml)]. BMI was not included in the potential risk factors because BMI was correlated with weight.

Statistical analysis. To examine the association between baseline risk factors, medications at followup, and incidence of first new vertebral fracture, main nonvertebral fracture, and any nonvertebral fracture, Cox proportional hazard analyses (Cox regression) were performed in 2 steps. First, we performed Cox regression analyses using all possible risk factors; then Cox regression models with stepwise selection were run. For all analyses, relative risks (RR) and associated 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered significant. All statistical analyses were conducted using R statistics software (Internet: http://www.r-project.org/).

RESULTS

In total, 2445 female patients with RA over 50 years old participated in this study at entry. During the 54-month followup period, 335 female participants of IORRA over 50 years old reported their fractures (Figure 1). Of these patients, 107 (31.9%) fractures were excluded from analysis because it was not possible to verify the fractures using their radiology reports or medical records (n = 66, 19.7%), or find their medical records (n = 35, 10.4%), or because the fractures resulted from a car accident (n = 4) or bicycle accident (n = 2).

Among the patients, 97 with verified fractures and 508 without self-reported fractures were excluded because their followup was incomplete or inadequate for this study (Figure 1). A total of 1733 female patients with RA over 50 years old with fractures (n = 131) and without fractures (n = 1602) participated in this 54-month prospective study. Among the 131 patients with both verified fracture and complete followup, 72 were verified with radiology reports and others had their fractures diagnosed in other hospitals. Among the patients with self-reported fractures (n = 335), there were no significant differences in demographic and clinical variables between with-

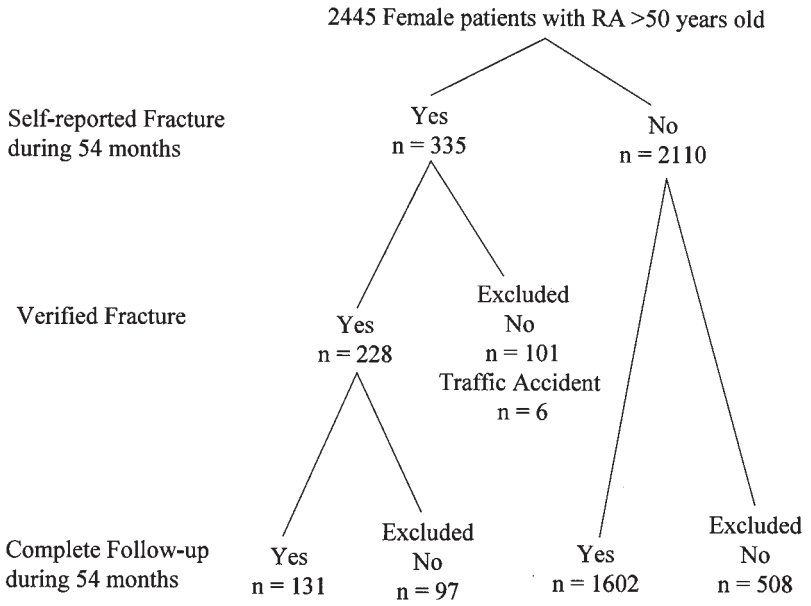

Figure 1. Structure of the study: 2445 female Japanese patients with RA, aged > 50 years.

drawals and 131 patients with both verified fracture and complete followup (data not shown).

Tables 1 and 2 show baseline participant characteristics and medication use during the followup period for all individuals. During the followup period, 131 (7.6%) participants sustained a clinically recognized fracture. Of these patients, 33 developed a vertebral fracture, 34 sustained a main nonvertebral fracture, and 98 developed any nonvertebral fracture. Vertebral fractures occurred at lumbar (61%) and thoracic spine (39%). The most frequent new nonvertebral fractures were the toe (15%), followed by ankle (12%), hip (11%), finger (9%), wrist (8%), rib (8%), knee (7%), elbow (7%), collar bone (4%), leg (4%), shoulder (4%), pelvis (4%), humerus (3%), forearm (1%), and nose (1%). Among patients with new

Table 1. Baseline demographic and clinical variables according to incident fracture status. Values are mean (SD) or number of participants (%) in the category.

Variables	No Fracture, n = 1602	Vertebral Fracture, n = 33	Main Nonvertebral Fracture, n = 34	Any Nonvertebral Fracture, n = 98
Demographic variables				
Age, yrs	61.3 (7.5)	66.0 (7.5)	64.1 (8.2)	62.9 (7.5)
Height, cm	153.5 (5.4)	151.6 (6.1)	151.9 (4.3)	153.1 (5.5)
Weight, kg	50.5 (7.8)	48.5 (6.5)	47.9 (5.6)	49.7 (6.3)
BMI, kg/m^2	21.4 (3.1)	21.2 (2.9)	20.8 (2.6)	21.2 (2.4)
Current smoking (%)	334/1521 (22.0)	5/30 (16.7)	2/32 (6.3)	10/94 (10.6)
Current alcohol intake (%)	237/1534 (15.4)	3/30 (10.0)	5/34 (14.7)	19/98 (19.4)
Clinical variables				
RA disease duration, yrs	10.8 (8.4)	14.7 (11.3)	10.2 (6.6)	12.2 (9.8)
Rheumatoid factor, IU/ml	127.8 (225.1)	196.3 (269.7)	155.4 (219.4)	137.1 (206.4)
J-HAQ score	0.9 (0.8)	1.6 (0.8)	1.1 (0.8)	1.1 (0.8)
ESR, mm/h	41.6 (24.5)	50.7 (29.6)	37.0 (23.3)	38.2 (22.2)
CRP, mg/100 ml	1.5 (2.1)	2.0 (2.4)	1.2 (1.8)	1.3 (1.6)
Patient pain VAS, cm	3.4 (2.6)	4.5 (2.5)	4.2 (2.8)	3.7 (2.7)
Patient global VAS, cm	3.5 (2.4)	4.8 (2.6)	4.2 (3.1)	4.0 (2.7)
Physician global VAS, cm	2.7 (2.1)	2.9 (1.9)	2.6 (2.1)	2.7 (2.0)
Tender joint count (45 joints)	4.7 (5.8)	8.5 (9.2)	4.6 (5.8)	4.8 (5.7)
Swollen joint count (45 joints)	4.0 (4.7)	6.8 (6.0)	3.0 (2.9)	3.9 (4.4)
History of prior any fracture (%)	376/1495 (25.2)	10/29 (34.5)	13/33 (39.4)	34/94 (36.2)
History of prior any orthopedic surgery for RA (%)	329/1537 (21.4)	18/32 (56.3)	8/33 (24.2)	27/95 (28.4)
History of prior total knee replacement (%)	129/1537 (8.4)	7/32 (21.9)	3/33 (9.1)	12/95 (12.6)

BMI: body mass index; J-HAQ: Japenese Health Assessment Questionnaire; VAS: visual analog scale.

Table 2. Medication use during followup period according to incident fracture status. Values are number of participants (%) in the category.

Medications	No Fracture, n = 1602 (%)	Vertebral Fracture, n = 33 (%)	Main Nonvertebral Fracture, n = 34 (%)	Any Nonvertebral Fracture, n = 98 (%)
DMARD	1503/1602 (93.8)	30/33 (90.9)	30/34 (88.2)	93/98 (94.9)
Corticosteroids	964/1602 (60.2)	27/33 (81.8)	26/34 (76.5)	72/98 (73.5)
Bisphosphonates	230/1602 (14.4)	4/33 (12.1)	7/34 (20.6)	11/98 (11.2)
Active vitamin D_3	388/1602 (24.2)	12/33 (36.4)	9/34 (26.5)	26/98 (26.5)
Vitamin K_2	5/1602 (0.3)	1/33 (3.0)	1/34 (2.9)	2/98 (2.0)

DMARD: disease modifying antirheumatic drug.

fractures, 29% had multiple fractures. The vertebral fractures were caused by spontaneous events (67%) and by falls (24%). On the other hand, the nonvertebral fractures occurred by falls (73%) and by spontaneous events (19%).

Incident vertebral fractures. Using a model containing all possible risk factors, the relative risk of sustaining an incident vertebral fracture increased by 3.63 for history of any prior orthopedic surgery for RA (Table 3). Cox regression modeling with stepwise selection indicated that the risks increased by 3.25 for age over 70 years compared with age in the 50s, 2.42 for each 1-point increase in J-HAQ, and 3.77 for history of prior orthopedic surgery for RA (Table 4). Age in the 60s and bisphosphonate use during the 54-month followup also appeared to be associated with fracture risk.

Incident main nonvertebral fractures. No variable was significantly associated with increased risk for main nonvertebral fractures in the all-possible risk factor model (Table 3). Cox regression modeling with stepwise selection estimated that the risks of developing an incident main nonvertebral fracture increased by 1.76 for each 1-point increase in J-HAQ, and decreased by 61% for a patient with CRP > 0.7 mg/dl (median) compared with < 0.7 mg/dl (Table 4). While findings were inconclusive, smoking, history of any prior fractures, and active vitamin D_3 use during the 54-month followup appeared to be associated with fracture risk.

Incident any-nonvertebral fractures. The Cox regression model including all risk factors estimated that the risk of sustaining an incident nonvertebral fracture at any site increased

Table 3. Relative risks (95% CI) for incident fractures: the all-possible risk factor model.

Variables	Vertebral Fracture	Main Nonvertebral Fracture	Any Nonvertebral Fracture
Demographic variables			
Age > 70 years*	2.88 (0.92–8.97)	1.75 (0.52–5.90)	2.00 (1.03–3.87)
Age in 60s*	1.02 (0.37–2.81)	1.70 (0.71–4.04)	1.51 (0.90–2.51)
Height, cm	1.01 (0.93–1.10)	0.99 (0.92–1.07)	1.01 (0.96–1.05)
Weight, kg	0.98 (0.93–1.04)	0.97 (0.91–1.03)	0.99 (0.96–1.02)
Current smoking	0.86 (0.27–2.72)	0.33 (0.08–1.45)	0.49 (0.24–0.99)
Current alcohol intake	0.83 (0.19–3.69)	0.99 (0.29–3.37)	1.21 (0.63–2.33)
Clinical variables			
RA disease duration > 5 years**	1.22 (0.34–4.31)	0.81 (0.33–2.00)	0.91 (0.53–1.56)
Rheumatoid factor-positive	2.01 (0.66–6.09)	0.98 (0.42–2.26)	0.85 (0.53–1.38)
J-HAQ score	1.95 (0.96–3.95)	1.46 (0.72–2.96)	1.66 (1.10–2.50)
ESR > 37 mm/h†	1.65 (0.54–5.03)	0.78 (0.28–2.19)	1.22 (0.69–2.16)
CRP > 0.7 mg/100ml††	1.31 (0.43–4.00)	0.46 (0.17–1.28)	0.58 (0.33–1.04)
Patient pain VAS	0.95 (0.74–1.21)	1.07 (0.81–1.39)	0.95 (0.82–1.10)
Patient global VAS	1.15 (0.88–1.51)	0.98 (0.74–1.32)	1.07 (0.92–1.25)
Physician global VAS	0.69 (0.65–1.08)	1.01 (0.80–1.28)	0.96 (0.84–1.10)
History of any fracture	0.96 (0.38–2.46)	2.02 (0.90–4.53)	2.01 (1.26–3.22)
History of any orthopedic surgery for RA	3.63 (1.30–10.15)	1.07 (0.36–3.16)	0.85 (0.43–1.67)
History of total knee replacement	0.93 (0.32–2.73)	0.72 (0.13–4.02)	1.36 (0.56–3.30)
Medication use during 54-month followup			
Corticosteroids	1.90 (0.61–5.94)	1.94 (0.78–4.84)	1.69 (1.01–2.83)
Bisphosphonates	0.36 (0.10–1.24)	0.62 (0.22–1.72)	0.33 (0.15–0.71)
Active vitamin D_3	0.93 (0.37–2.33)	0.45 (0.17–1.19)	0.56 (0.32–0.96)
Vitamin K_2	4.24 (0.25–71.57)	2.43 (0.19–31.82)	3.07 (0.59–16.04)

See Table 1 for definitions. * RR were calculated compared with the patients with age in the 50s; ** RR were calculated compared with disease duration < 5 years (median); † RR were calculated compared with ESR < 37 mm/h (median); †† RR were calculated compared with CRP < 0.7 mg/100 ml (median).

Table 4. Relative risks (95% CI) for incident fractures: Cox regression models with stepwise selection.

Risk Factors	Vertebral Fracture	Main Nonvertebral Fracture	Any Nonvertebral Fracture
Demographic variables			
Age > 70 yrs*	3.25 (1.19–8.86)	—	2.22 (1.20–4.10)
Age in 60s*	1.28 (0.49–3.34)	—	1.53 (0.93–2.52)
Current smoking	—	0.31 (0.07–1.29)	0.49 (0.24–0.98)
Clinical variables			
J-HAQ score	2.42 (1.42–4.14)	1.76 (1.07–2.89)	1.73 (1.29–2.32)
CRP > 0.7 mg/100 ml**	—	0.39 (0.17–0.88)	0.57 (0.36–0.91)
History of any fracture	—	1.97 (0.89–4.33)	1.95 (1.22–3.11)
History of any orthopedic surgery for RA	3.77 (1.55–9.17)	—	—
Medication use during 54 month followup			
Corticosteroids	-	1.88 (0.78–4.55)	1.62 (0.99–2.73)
Bisphosphonates	0.36 (0.11–1.20)	—	0.35 (0.17–0.73)
Active vitamin D_3	—	0.46 (0.18–1.18)	0.56 (0.33–0.96)

* RR were calculated compared with the patients with age in the 50s; ** RR were calculated compared with CRP < 0.7 mg/100 ml (median).

by 2.00 for age over 70 years compared with age in the 50s, by 1.66 for each 1-point increase in J-HAQ, by 2.01 for history of any prior fractures, and by 1.69 for corticosteroid use during the 54-month followup; and decreased by 51% for smoking, 67% for bisphosphonate use, and 44% for active vitamin D_3 use during the 54-month followup (Table 3).

Cox regression modeling with stepwise selection for any nonvertebral fracture indicated that the risk increased by 2.22 for age over 70 compared with age in the 50s, by 1.73 for each 1-point increase in J-HAQ, and by 1.95 for history of any prior fractures; and decreased by 51% for smoking, 43% for a patient with CRP > 0.7 mg/dl (median) compared with < 0.7 mg/dl, 65% for bisphosphonate use, and 44% for active vitamin D_3 use during the 54-month followup (Table 4). Age in the 60s and corticosteroid use during the 54-month followup seemed to be associated with fracture risk, although data were inconclusive.

DISCUSSION

Associated risk factors of fracture in Japanese patients with RA were evaluated in a prospective 54-month cohort study at a single institute. Our results suggest that in Japanese women with RA the risk factors for (1) vertebral fracture are age over 70, high HAQ disability score, and history of any orthopedic surgery for RA; (2) those for main nonvertebral fracture are high HAQ disability score and low CRP; and (3) those for any nonvertebral fracture are age over 70, high HAQ disability score, history of any prior fracture, not smoking, low CRP, and disuse of bisphosphonates and active vitamin D_3.

Of all the parameters tested in our study, higher HAQ scores were an independent predictor for all vertebral, main nonvertebral, and any nonvertebral fractures (Table 4). This is in agreement with previous reports that HAQ[9], impaired ambulation[18], and lack of physical activity[19] are significantly associated with fractures in patients with RA. Further, previous prospective observations showed that the more disabled patients had significantly greater loss of bone[26] and that HAQ score was negatively associated with hip BMD[27] in RA. Moreover, disturbed physical activity indicated by high HAQ score may relate to falls that are a main cause of fractures[28]. Thus, our results suggest that a high HAQ score is one of the most important risk factors for both vertebral and nonvertebral fractures in older female patients with RA.

Our results also indicated that age over 70 years showed a strong association with both vertebral and any nonvertebral fractures, but not with main nonvertebral fractures, in female patients with RA (Table 4). Age contribution to the susceptibility of fracture is known to be site-specific. Thus, age effects may be difficult to associate with incident fracture when 5 fractures were combined into the main nonvertebral fracture.

History of any prior fractures was significantly independently associated with any incident nonvertebral fractures (Table 3 and 4). Klotzbuecher, *et al* summarized the literature and reported that a history of any prior fractures is an important risk factor for future fractures with relative risks of approximately 2[29]. Our data are consistent with this report, and further indicate that any prior fracture is an important risk factor for nonvertebral fractures in female patients with RA.

History of any prior orthopedic surgery for RA was one of the significant risk factors for vertebral fracture (Tables 3 and 4). Among prior orthopedic surgeries for RA in our study, the most frequent were for total knee replacements (32%), followed by hand joint arthroplasties (8%), total hip replacement (8%), knee synovectomies (7%), knee arthroscopy (7%), finger arthroplasties (7%), hand joint synovectomies (6%), finger synovectomies (4%), toe arthroplasties (3%), elbow synovectomies (3%), finger arthrodeses (3%), hand joint arthrodeses (2%), and elbow arthroplasties (1%). The association between any prior orthopedic surgery for RA and incident vertebral fractures has not been reported before. The patients with total knee or hip replacement may be likely to fall, resulting in fractures[28]. These patients also have systemic

bone fragility. History of any prior orthopedic surgery for RA may also be one of the important risk factors for vertebral fractures in RA, although further studies measuring BMD are needed to be conclusive.

We observed a significant effect of bisphosphonate use for prevention of any nonvertebral fractures, and the bisphosphonate use appeared to be effective for prevention of vertebral fractures (Tables 3 and 4). Bisphosphonates have been proven effective in patients with RA[12,14,15]. Our results confirmed the effects, suggesting that bisphosphonates reduce both vertebral and nonvertebral incident fracture risk in older Japanese female patients with RA.

In our study, active vitamin D_3 analogs were effective in decreasing the risk of any nonvertebral fractures, although bisphosphonates were more effective (Tables 3 and 4). In addition, the use of vitamin D_3 analogs appeared to be effective for the prevention of main nonvertebral fractures (Tables 3 and 4). Although we did not collect data on vitamin D_3 dose and vitamin D supplementation, alfacalcidol (0.5 or 1 μg/day) prescribed by physicians was typically used and self-supplementation is not common in Japan. Nakamura recently reported that the prevalence of vitamin D insufficiency was high (up to about 50%) in inactive elderly people in Japan[30]. Thus, our results suggest that active vitamin D_3 analogs may be recommended for inactive older Japanese female patients with RA to prevent any nonvertebral fractures. However, patients should be carefully monitored because administration of vitamin D_3 is associated with increased incidence of renal stones in Japanese patients with RA[31].

Our results did not confirm the previously reported strong association between corticosteroid use and fractures, although corticosteroid use appears to be a risk factor for both vertebral and nonvertebral fractures (Tables 3 and 4). We chose current corticosteroid use as the variable of interest because reliable data on cumulative dose and longterm use were not available. However, longterm corticosteroid use[3,8] and cumulative steroid intake[9] were reported to be significantly associated with vertebral fractures. Since many RA patients had been taking corticosteroids during the 54-month followup in this study (61%), cumulative intake and longterm use may have affected our results.

Current smoking was associated with a decreased risk of any nonvertebral fracture, although smoking has been reported to be associated with fracture risk[32] (Tables 3 and 4). Previous Japanese studies showed no correlation between fractures and smoking[33,34]. Vestergaard and Mosekilde have suggested that the effect of smoking varied with geographical location[32]. Our data and other studies[33,34] suggest that smoking may not be a risk factor for fractures in older Japanese female patients with RA.

Although severity of RA was reported to be associated with low BMD[35], our study revealed low CRP as a risk factor for both main nonvertebral and any nonvertebral fracture (Table 4). The effects of RA disease activity on incident nonvertebral fracture may be site-specific and difficult to evaluate when 5 fractures of wrist, hip, humerus, pelvis, or rib and any nonvertebral fractures were combined into the main and any nonvertebral fracture group, respectively. This may be because the cause of fracture is different between vertebral and nonvertebral fractures. Most vertebral fractures developed spontaneously (67%), whereas nonvertebral fractures occurred mainly as a consequence of falls (73%) in our study. Klotzbuecher, *et al* reported that most nonvertebral fractures are related to falls or minor trauma, whereas most vertebral fractures are attributable primarily to bone fragility[29]. Seeley, *et al* reported that low bone mass is not associated with about 26% of nonvertebral fractures[36]. Thus, it might be possible that RA disease activity affects vertebral fracture rather than nonvertebral fracture, causing fractures by different mechanisms. The patients with high HAQ disability scores and low RA disease activity might have a high risk of falls and nonvertebral fractures, although further studies are needed in order to be conclusive.

Although the risks of both main and any nonvertebral fracture appeared to be similar (Tables 3 and 4), age and bisphosphonate use were significantly associated with any nonvertebral fracture, but not with main nonvertebral fracture. There may be differences in fracture risks between main and any nonvertebral fracture groups. In support of this, previous studies of postmenopausal women have also reported separate results[17].

Despite the advantages of a prospective, large cohort study in a single institute, our study has some limitations. First, fractures were self-reported, although we verified all fractures with radiology reports or medical records. Thus, fractures may have been underestimated, and we may not have detected asymptomatic fractures. Self-reporting of fractures, however, has been proved to be fairly reliable by several groups[37-40]. This method has been used in fracture studies of RA[11,19] and other recent large studies[41-43]. Second, we did not perform spinal morphometry, which is the best method for detecting spinal fractures[25]. Because most vertebral fractures are asymptomatic[44], or at least unrecognized, we did not investigate the value of risk factors for nonclinical vertebral fractures. Third, we did not analyze the association of fractures with BMD, which is the most sensitive method for screening for osteoporosis, and the best measure for predicting fracture risk[45]. Fourth, we may overestimate or underestimate the effects of medications because we did not analyze the dose or duration of medications, and patients who were withdrawn were significantly less likely to use bisphosphonates and active vitamin D_3 compared with the patients we analyzed (data not shown). Fifth, we may overestimate the effects of age, J-HAQ, and history of any prior fractures because withdrawals without self-reported fractures were significantly older, had higher J-HAQ scores, and had a history of any prior fracture compared with the patients without fractures we analyzed. Finally, we may not have sufficiently addressed clinical implications in our study.

In conclusion, we evaluated the associated risk factors of fractures in Japanese female patients with RA over 50 years of age in a prospective 54-month cohort study at a single institute. Age over 70 years and a high HAQ disability score were associated with both incident clinical vertebral and nonvertebral fractures. History of any fracture and any prior orthopedic surgery for RA were related to nonvertebral and vertebral fractures, respectively. Radiological confirmation studies are needed in order to draw strong conclusions on vertebral and nonvertebral fractures in Japanese patients with RA.

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