Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: a prospective observational cohort study

Abstract

There are limited data in the literature concerning risk factors for incident fractures in men with rheumatoid arthritis (RA). We evaluated the association between potential risk factors and incident clinical fractures in male Japanese patients with RA. A total of 1050 male patients with RA were enrolled in a prospective, observational cohort study from 2000 to 2005. Participants were followed from 6 to 66 months (median follow-up, 48.7 months) and classified into three groups according to their incident fracture status from baseline: no new fracture, any new nonvertebral fracture, and new clinical vertebral fracture. The associations of potential risk factors were analyzed by Cox proportional hazards models. During follow-up, 30 patients (2.9%) developed a new nonvertebral fracture or a vertebral fracture. The baseline age, history of total knee replacement (TKR), and serum C-reactive protein (CRP) levels were associated with any nonvertebral fracture [baseline age: hazard ratio (HR), 1.08, 95% confidence interval (CI), 1.03–1.14; history of TKR: HR 6.02, 95% CI 1.19–30.42; and CRP: HR 0.60, 95% CI 0.38–0.95]. The baseline Japanese health assessment questionnaire (HAQ) score and daily dose of prednisolone were also associated with the incidence of clinical vertebral fractures (HR 7.74, 95% CI 2.10–28.48, and HR 1.28, 95% CI 1.14–1.45, respectively). Older age, history of TKR, and low serum CRP levels appear to be associated with any incident nonvertebral fracture in Japanese men with RA. High HAQ disability score and baseline doses of daily prednisolone may correlate with incident clinical vertebral fracture in Japanese men with RA.

Key words cohort studies · fractures · male · risk factors · rheumatoid arthritis

Introduction

Fractures are a major source of disability and impaired quality of life in both men and women [1]. Patients with rheumatoid arthritis (RA) have an increased risk of osteoporosis relative to controls in men [2–4], as well as women [5]. Moreover, many patients with RA receive corticosteroid treatment, which has been shown to increase the risk of fractures [6–12].

Although low bone mineral density (BMD) is a major risk factor for fractures in men [13,14], other clinical factors need to be identified to predict those at increased fracture risk [15,16]. The detection of individuals at high risk is important because bisphosphonates have been documented to prevent vertebral fractures in men receiving glucocorticoids [17–19].

There are limited data in the literature concerning risk factors for incident fractures in men with RA, although we [20] and others [6,7,9,10,21,22] have reported the risk factors for fractures in women with RA. Recently, the Osteoporotic Fractures in Men (MrOS) Study, a prospective cohort study, demonstrated predictors of nonvertebral fractures in elderly men [23]: antidepressant use, history of fracture, inability to walk, fall history, age, and depressed mood. That study did not evaluate risk factors in RA patients. van Staa et al. reported that the increased risk of osteoporotic fractures is attributable to a combination of disease activity and use of oral glucocorticoids in patients with RA [12]. They studied fracture risk in 30262 patients with RA, including 8755 males, but did not evaluate male risks separately.

Utilizing data from our prospective, observational study of RA in Japan (IORRA, Institute of Rheumatology Rheumatoid Arthritis) [24], we evaluated the associations between potential risk factors and subsequent nonvertebral and clinical vertebral fractures in Japanese men with RA.
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 (Tokyo, Japan), that was begun in 2000. Details regarding the study’s purpose and methodology have been previously reported [20,24–30]. Study details were explained to each patient by 1 of 49 rheumatologists during their clinic visits. Informed consent was received from each patient. Each participant was asked to complete the questionnaire at home and mail it back in a preaddressed, stamped envelope within 2 weeks.

Participant selection

All male patients with RA who participated in IORRA from 2000 to 2005 were included in the current study. All the patients had been diagnosed with RA according to the 1987 classification criteria for RA by the American College of Rheumatology [31]. The participants were followed from 6 to 66 months (from October 2000 to March 2006). Only incident fractures as a result of minimal trauma were included in the analysis [20,32]. All male patients were classified into three groups according to their incident fracture status from baseline: no new fractures, any new nonvertebral fracture, and clinically recognized new vertebral fracture.

Baseline assessments

The baseline demographics, clinical variables, and medication history obtained at entry into this study were as follows: age, height (cm), weight (kg), body mass index (BMI, kg/m²), current smoking, current alcohol intake, disease duration of RA (years), rheumatoid factor (RF; IU/ml, Rose–Waaler test), RF positive (≥35 IU/ml), Japanese health assessment questionnaire (J-HAQ) scores [27], erythrocyte sedimentation rate (ESR; mm/h, Westergren method), serum C-reactive protein (CRP; mg/100 ml), patient pain visual analogue scale (VAS, cm), patient global VAS, physician global VAS, tender joint count (45 joints), swollen joint count (45 joints), history of any prior fracture, history of any prior orthopedic surgery for RA, and history of TKR at baseline. Current smoking, history of any prior orthopedic surgery for RA, and history of TKR were not included in the potential risk factors for clinical vertebral fracture because no patients with clinical vertebral fracture had any of these factors.

Statistical analysis

The associations of potential risk factors were analyzed by proportional hazards models with time-dependent covariates, from which we calculated the hazard ratio (HR) and associated 95% confidence interval (CI) for each variable, with adjustment for the potential risk factors at baseline. The assumption of proportional hazards was confirmed through the complementary log-log plot. Statistical significance of the differences between groups was determined using a Mann–Whitney U test (continuous variables) and Fisher’s exact test (counts) as appropriate. P < 0.05 was considered significant. All statistical analyses were conducted by R statistics software (Internet: http://www.r-project.org/).

Results

In total, 1483 male patients with RA participated in this study during the 66-month period; 99 and 1384 male participants reported or did not report fractures, respectively (Fig. 1). Follow-up was completed for 76 patients (76.8%) with self-reported fractures and 1105 (79.8%) without self-reported fractures. Among the patients with self-reported fractures and complete follow-up (n = 76), 44 patients (57.7%) were excluded from analysis because it was not possible to verify the fractures using their radiology reports.

Fracture assessments

Clinically recognized incidents of nonvertebral and vertebral 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 2006. They were then asked to state whether the fracture was the result of a fall, an accident, or a sports injury, or a spontaneous event. For verification of fractures, fracture sites and day of 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 radiology reports or medical records, or fractures resulting from a traffic accident or major trauma. Only the first fracture event reported by the patients was used in this study [20,33]. Asymptomatic vertebral fractures were not included because routine thoracic and lumbar spine radiographs for spinal morphometry were not obtained.

Potential risk factors

Potential risk factors were examined as either continuous or categorical variables. Continuous variables of interest included baseline age, BMI, disease duration of RA, CRP, J-HAQ scores [27], patient pain VAS, patient general VAS, physician general VAS, tender joint count, swollen joint count, and daily doses of prednisolone. Dichotomous variables (yes/no) included current smoking, current alcohol intake, history of any prior fracture, history of any prior orthopedic surgery for RA, and history of TKR at baseline. Current smoking, history of any prior orthopedic surgery for RA, and history of TKR were not included in the potential risk factors for clinical vertebral fracture because no patients with clinical vertebral fracture had any of these factors.