Fragility Fractures in Patients with Rheumatoid Arthritis and Osteoarthritis Compared with the General Population

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ABSTRACT. ***Objective.*** To determine the rate ratios of hip and distal radius fractures in patients with rheumatoid arthritis (RA), hip osteoarthritis (OA), and knee OA.

Methods. Cohort study using healthcare data (1998–2012) covering the entire population of the Skåne region of Sweden.

Results. We found an increased rate of hip fracture in both female [standardized fracture rate ratio (SFR) 1.54, 95% CI 1.40–1.70] and male patients with RA (SFR 1.81, 95% CI 1.51–2.17). The hip fracture rate in female OA was reduced by 10–20%, and trochanteric fracture tended to have a higher rate ratio compared with the cervical.

Conclusion. The 50–80% increased rate of hip fracture adds to the total burden of RA while the shifted distribution of cervical/trochanteric fractures in OA is in support of subchondral bone alterations. (First Release October 1 2015; J Rheumatol 2015;42:2055–8; doi:10.3899/jrheum.150325)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOARTHRITIS FRACTURES
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The hip and distal radius are two of the most frequent and important sites of fracture[1]. Osteoporosis and increased fall tendency are accepted to be the most important risk factors[2]. Rheumatoid arthritis (RA) has fairly consistently been reported to be associated with low bone mineral density (BMD) and increased risk of fractures[3,4,5,6]. However, there is only limited and conflicting evidence of the fracture risk in patients with osteoarthritis (OA)[7,8,9,10,11,12]. There is a need to gain new knowledge of the actual fracture risk in both these diseases using an approach with less potential for selection bias than classic case-control study designs. Hence, using validated physician-coded healthcare data, covering the first decade of the 21st century and an entire well-defined adult population in Sweden, we determined the fracture rates of the hip and distal radius in all patients with known RA, hip OA, or knee OA, and further related those to the fracture rates of the entire general population.

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MATERIALS AND METHODS

The Skåne Healthcare Register (SHR). The Skåne region is located in the southern part of Sweden. Its population, 1,274,069 as of December 31, 2013, accounts for 12% of the Swedish population. All levels of healthcare are available, i.e., from primary outpatient care to highly specialized in-hospital care. Each single healthcare consultation generates data entries by the healthcare provider that are transferred to central databases. These entries constitute the basis for reimbursement and include, among others, the personal identification number, date of visit, and for public healthcare providers and in-hospital care, diagnostic codes classified by the responsible physician according to the International Classification of Diseases and Related Health Problems (ICD-10) system (www.who.int/classifications/icd/en/index.html).

Our study was approved by the Lund University Ethics Committee.

The Swedish Population Register. For the purpose of our study, on an individual level we linked the SHR with the Population Register to obtain residential data and information on deaths for all inhabitants.

Defining the exposed cohorts and background population. We identified all residents of the Skåne region during the 15 calendar years from 1998 to 2012 aged ≥ 45 years. Subjects were classified as having RA if they had at least 2 visits with an RA diagnosis (ICD-10 code: M05 or M06); at least 1 diagnosis had to come from a specialist in rheumatology or internal medicine. We classified a subject as having hip OA (ICD-10 code: M16) or knee OA (ICD-10 code: M17) if he or she had at least 1 OA diagnosis set by any physician. The validity of the coding in SHR for chronic rheumatic diseases has been high — the positive predictive value of a knee OA diagnosis compared to clinical or radiographic criteria was 88%[13,14,15].

Outcome and the followup period. We defined our outcome as any fracture

of the hip, i.e., cervical (ICD-10: S72.0) or trochanteric (including pertrochanteric or subtrochanteric fractures, ICD-10: S72.1 or S72.2), or fracture involving the distal radius (ICD-10: S52.5, S52.6). Recent work of validating these fracture diagnoses in the SHR has yielded a positive predictive value (compared with a review of medical records and radiologists' report) of 94% for distal radius and 99% for the hip[1].

The start of the followup period for each subject was January 1, 1998 (the beginning of the study period), January 1 of the year of becoming a resident of the Skåne region, or turning 45 years of age. All subjects were followed until their first hip fracture or first distal radius fracture, relocation, death, or the end of study period, December 31, 2012. The followup time was treated as unexposed until the date of fulfilling our criteria for RA or OA, and as exposed after that date.

Statistical analysis. We calculated the standardized fracture rate ratio (SFR) by dividing the observed fracture rate (based on person-time) by the expected fracture rate (direct standardization method using the general population as reference). An SFR > 1 indicates a higher rate of fracture than in the general population. Considering that the proportion of patients with hip OA with total hip replacement is high and that patients with total hip replacement are highly unlikely to sustain a hip fracture on that side, we performed a sensitivity analysis where we censored all subjects in the population at the date of their first hip joint replacement attributable to causes other than hip fracture.

RESULTS

We identified 741,598 subjects aged 45 or older at the time of inclusion eligible for the study population. The mean (SD) age at the beginning of the followup period was 57.7 (13.1) years and 52% were women. We identified 8467 patients with RA, 29,706 patients with hip OA, and 55,753 patients diagnosed with knee OA at risk for hip fracture (Table 1). The corresponding patient numbers eligible for radius fracture are also provided in Table 1. All observed and expected fracture rates in both women and men are provided in the Appendix.

Hip fracture. We found significantly increased rates, as compared with the general population, of hip fracture in female patients with RA (SFR 1.54, 95% CI 1.40–1.70), as well as male patients with RA (SFR 1.81, 95% CI 1.51–2.17; Table 2).

Table 2. SFR for patients with RA and OA compared with the general population.

Cohort	Fracture	SFR (95% CI)	
		Women	Men
RA	Hip	1.54 (1.40–1.70)	1.81 (1.51–2.17)
	Distal radius	0.93 (0.82–1.05)	1.29 (0.90–1.80)
Hip OA	Hip	0.61 (0.56–0.65)	0.77 (0.69–0.85)
	Hip*	0.81 (0.74–0.89)	1.10 (0.96–1.26)
	Distal radius	1.04 (0.97–1.11)	1.08 (0.91–1.26)
Knee OA	Hip	0.89 (0.85–0.93)	1.00 (0.92–1.08)
	Distal radius	1.05 (1.00–1.11)	1.11 (0.97–1.26)

* Sensitivity analysis where subjects were censored at the time of the joint replacement surgery for the hip (n = 17,914). SFR: standardized fracture rate ratio; RA: rheumatoid arthritis; OA: osteoarthritis.

Significantly decreased rates were found for hip fracture in both female and male patients with hip OA (SFR 0.61, 95% CI 0.56–0.65 and SFR 0.77, 95% CI 0.69–0.85, respectively). However, when we censored all subjects at the date of their hip replacement, only the SFR remained statistically significantly reduced for women (SFR 0.81, 95% CI 0.74–0.89).

In patients with hip OA, the rate ratio of trochanteric hip fracture tended to be higher than the corresponding rate ratio of cervical hip fracture. Similar results were also found for patients with knee OA (Table 3).

The observed rate of hip fracture in patients with knee OA was lower in women (SFR 0.89, 95% CI 0.85–0.93), but not in men (SFR 1.00, 95% CI 0.92–1.08) compared with the general population.

Distal radius fracture. We found that the rate of distal radius fracture tended to be elevated in both women (SFR 1.05, 95% CI 1.00–1.11) and men (SFR 1.11, 95% CI 0.97–1.26) with knee OA. For RA and hip OA, we found no statistically

Table 1. Characteristics of the study population (aged 45 yrs or older) by disease exposure status and observed outcomes.

Cohort	Subjects, n	Age, Yrs, Mean (SD)	Women, %	Observed Outcome Hip Fracture	
				Fractures, n	Person Time, Yrs
Population	74,598	57.7 (13.1)	52	33,348	7,389,103
RA	8467	61.0 (10.9)	70	549	56,791
Hip OA	29,706	63.4 (10.9)	58	1119	179,292
Knee OA	55,753	60.5 (11.3)	59	2365	324,253
Cohort	Subjects, n	Age, Yrs, Mean (SD)	Women, %	Observed Outcome Radius Fracture	
				Fractures, n	Person Time, Yrs
Population	741,598	57.7 (13.1)	52	27,764	7,346,597
RA	8517	61.2 (11.0)	70	294	57,453
Hip OA	29,767	63.5 (10.7)	57	1046	178,823
Knee OA	55,103	60.6 (11.4)	59	1785	321,295

RA: rheumatoid arthritis; OA: osteoarthritis.

Table 3. Standardized cervical and trochanteric* fracture rate ratio for patients with RA and OA compared with the general population.

Cohort	Fracture	SFR (95% CI)	
		Women	Men
RA	Cervical	1.58 (1.40–1.78)	1.67 (1.29–2.12)
	Trochanteric*	1.43 (1.24–1.64)	1.91 (1.48–2.43)
Hip OA	Cervical	0.59 (0.54–0.65)	0.65 (0.55–0.75)
	Trochanteric*	0.67 (0.61–0.73)	0.92 (0.80–1.06)
	Cervical†	0.77 (0.68–0.88)	1.00 (0.84–1.21)
	Trochanteric*†	0.91 (0.80–1.03)	1.21 (1.00–1.45)
Knee OA	Cervical	0.86 (0.81–0.92)	0.92 (0.83–1.03)
	Trochanteric*	0.94 (0.88–1.00)	1.10 (0.99–1.23)

* Pertrochanteric or subtrochanteric hip fracture. † Sensitivity analysis where subjects were censored at the time of the joint replacement surgery for the hip (n = 17,914). SFR: standardized fracture rate ratio; RA: rheumatoid arthritis; OA: osteoarthritis.

significant associations, although the point estimates for hip OA were similar to those with knee OA (Table 2).

DISCUSSION

We found RA to be associated with about a 50 to 80% higher rate of hip fracture compared with the general population. Knee and hip OA in women, but not in men, was associated with about 10% and 20% lower rates of hip fracture, respectively. We found a greater likelihood for trochanteric hip fractures in patients with OA. Further, patients with knee and hip OA tended to have a slightly higher rate (about 5–10%) of distal radius fracture than the general population.

On average, patients with RA have been reported to have low BMD[3,4,5]. This is often because of the prolonged use of oral glucocorticoids, and/or the inflammatory disease activity itself[6]. However, low BMD alone does not explain the occurrence of fractures. Increased fall tendency is another crucial component[2,16]. Interestingly, we did not find a similar increased risk of distal radius fracture in the same cohort of patients with RA as for hip fracture. It is plausible that when patients with RA fall, they have less tendency to protect the fall using their hands/arms. Hence, the relatively normal observed rate of distal radius fractures despite being more osteoporotic.

Patients with OA typically have higher BMD than both patients with RA and controls without OA[17,18]. However, muscle weakness, pain, and other factors in OA have also been reported to be associated with increased risks of falling (or severity of the fall) and fractures[9,11]. Additionally, obesity is more frequent in patients with OA and increased soft tissue around the hips (typical in female obesity) may potentially cushion the fall[19]. Altogether, this mixture of protective factors and risk factors makes the sum of risks and its direction complex. It may, for example, explain the sex differences (reduced rate in women only) that we observed for hip fractures in patients with hip and knee OA.

Further, we found a greater relative tendency of trochanteric hip fractures as compared with cervical hip fractures in patients with hip OA, a tendency that has been previously postulated[11,20].

There are several important limitations to our study. We were not able to adjust for confounding effects of the body mass index and lack information on antiosteoporotic treatments. Further, we could not ascertain which side was fractured. Hence, all analyses have been performed at a subject level. Similarly, we were not able to determine the side of the clinically diagnosed OA or prosthesis. Thus, in a sensitivity analysis, we censored all subjects from the date when they received their first known hip prosthesis to limit the potential bias when analyzing hip fracture as the outcome. We included all hip and distal radius fractures in the population aged 45+ years, and a smaller proportion of fractures is caused by high energy trauma or are considered pathologic because of tumor. However, in this middle-aged and elderly population, the fracture of the hip and distal radius are well established to be the most typical fractures associated with older age and frailty[1].

Using uniform methodology of validated 21st century data from an entire population, we found a substantially increased rate of hip fracture in both female and male patients with RA, but decreased rate of hip fracture in female patients with hip or knee OA. Further, we detected a tendency for more frequent trochanteric hip fractures in patients with OA. Finally, we found slightly higher rates of distal radius fracture in both female and male patients with knee and hip OA.

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APPENDIX 1. Observed and expected fracture rates for patients with RA and OA by fracture type. Expected rates are calculated using the sex and age distribution of the general population seeking healthcare.

Cohort	Fracture Type	Rates Per 100,000 Person-yrs					
		Women		Men		All	
		Observed	Expected	Observed	Expected	Observed	Expected
RA	Hip	1066	691	727	401	967	605
	Radius	638	687	207	160	512	532
Hip OA	Hip	742	1228	462	604	624	965
	Hip*	993	1228	657	595	852	962
	Radius	878	845	192	179	585	560
Knee OA	Hip	918	1036	460	460	729	798
	Radius	821	781	184	166	556	524

* Sensitivity analysis where subjects with any hip prosthesis were censored at the time of joint replacement surgery (n = 17,914). RA: rheumatoid arthritis; OA: osteoarthritis.