Increased Fracture Risk in Patients with Rheumatic Disorders and Other Inflammatory Diseases — A Case-Control Study with 53,108 Patients with Fracture

RÜDIGER J. WEISS, MARIUS C. WICK, PAUL W. ACKERMANN, and SCOTT M. MONTGOMERY

ABSTRACT. ***Objective.*** To identify the risk of hip and vertebral fractures in patients with rheumatic disorders (RD) and inflammatory bowel diseases (IBD).

Methods. This population-based case-control study assessed the fracture risk of patients with rheumatoid arthritis, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), systemic lupus erythematosus, polymyositis/dermatomyositis (PM/DM), systemic sclerosis (SSc), Crohn's disease, and ulcerative colitis (UC). The study cohort comprised 53,108 patients with fracture (66% women) and 370,602 age-matched and sex-matched controls. Conditional logistic regression analysis was performed and results were expressed as OR with corresponding 95% CI.

Results. There was a statistically significant increased fracture risk for all RD and for IBD compared with controls. The magnitude of fracture risk was higher for patients with RD (OR 3, 95% CI 2.9–3.2) than for those with IBD (OR 1.6, 1.4–1.8). The OR in RD ranged from 2.6 (1.3–4.9) for SSc to 4 (3.4–4.6) for AS. The largest increased fracture risk for vertebral fractures was seen in AS (OR 7.1, 6–8.4) and for hip fractures in JIA (OR 4.1, 2.4–6.9).

Conclusion. Our results highlight the existence of an increased fracture risk from a variety of underlying causes in patients with RD and IBD. In many inflammatory diseases, implementation of fracture prevention strategies may be beneficial. (First Release Oct 1 2010; J Rheumatol 2010;37: 2247–50; doi:10.3899/jrheum.100363)

Key Indexing Terms:
FRACTURE RISK INFLAMMATORY BOWEL DISEASES RHEUMATIC DISORDERS

Chronic inflammatory diseases, such as rheumatic disorders (RD) and inflammatory bowel diseases (IBD), have cost implications for healthcare provision, employers, and insurers. Some of this expense is due to comorbidity, including bone fractures[1,2,3,4,5,6,7,8,9,10,11]. The multifactorial etiology of fractures includes inflammation in RD, causing low bone mass with periarticular osteoporosis, as well as osteomalacia from malnutrition and malabsorption. The catabolic effect of systemic glucocorticosteroid therapy in these diseases, as well as an increased risk of falling, may also contribute to fracture risk.

This large case-control study examined hip and vertebral fracture risk across a range of inflammatory diseases including RD and IBD.

MATERIALS AND METHODS

Source of data. The Swedish National Hospital Discharge Register (SNHDR), which collects information on all inpatient care in Sweden (including diagnoses using the International Classification of Diseases, ICD), provided the data for this study[12]. Data linkage used the personal identity number issued to all Swedish residents.

Study design. We identified all individuals registered in the SNHDR with ICD-9 and ICD-10 codes of hip fractures (820*, S720*-S722*) or vertebral fractures (805*, 806*, S120*-S127*, S129*, S220*, S221*, S320*-S322*). The study period was 1987 to 2004.

Each patient in the fracture cohort was matched with 7 controls by sex, age, and residential area (using the Total Population Register). We selected both populations (cases and controls) equally, i.e. for all cases it was the first hip or spine fracture. The controls did not have a hip or spine fracture at the time of the matching process or before.

We investigated any hospital admissions due to RD or IBD in cases and

From the Department of Molecular Medicine and Surgery, Section of Orthopedics and Sports Medicine, Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; Clinical Epidemiology and Biostatistics Unit, Örebro University Hospital, Örebro, Sweden; and Department of Radiology, Innsbruck Medical University, Innsbruck, Austria.

Supported by grants from the Karolinska Institutet, the Stockholm County Council, the Swedish Orthopaedic Association, and the Capio Research Foundation.

R.J. Weiss, MD, PhD, Orthopaedic Surgeon; P.W. Ackermann, MD, PhD, Orthopaedic Surgeon, Department of Molecular Medicine and Surgery, Section of Orthopedics and Sports Medicine, Karolinska University Hospital, Karolinska Institutet; M.C. Wick, MD, PhD, Radiology Consultant, Department of Radiology, Innsbruck Medical University; S.M. Montgomery, PhD, Professor of Epidemiology, Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital, Karolinska Institutet, Clinical Epidemiology and Biostatistics Unit, Örebro University Hospital.

Address correspondence to Dr. R.J. Weiss, Department of Molecular Medicine and Surgery, Section of Orthopedics and Sports Medicine, Karolinska University Hospital/Karolinska Institutet, S-171 76, Stockholm, Sweden. E-mail: rudiger.weiss@karolinska.se

Accepted for publication June 14, 2010.

controls prior to the case's admission for fracture using these codes: rheumatoid arthritis (RA; 714A, 714B, 714C, 714W, M05*, M060-M063, M068, M069), juvenile idiopathic arthritis (JIA; 714D, M080), ankylosing spondylitis (AS; 720A, M45*), systemic lupus erythematosus (SLE; 710A, M32*), polymyositis/dermatomyositis (PM/DM; 710D, 710E, M33*), systemic sclerosis (SSc; 710B, M34*), Crohn's disease (CD; 555*, K50*), and ulcerative colitis (UC; 556*, K51*). Rheumatic disorders and IBD could have been the reason for admission or a comorbidity.

The local Ethics Committee of Stockholm North approved the study (DN 2005/1332-31/2).

Statistical analysis. Median values and interquartile ranges (IQR) were used descriptively. Conditional logistic regression analysis based on risk-set (patients with fracture and controls matched for sex, age, and residential area) was performed. The results were expressed as OR with corresponding 95% CI.

Surveillance bias is possible when the exposure disease is a medical condition that may result in a higher probability of detection of outcome in the exposed individuals, so secondary analyses were performed: (1) only the primary diagnoses of the exposure diseases in the SNHDR were included; (2) only matched controls who at least once had been admitted to a hospital were included; and (3) all hospital admissions 1 year prior to fracture were excluded. The risk of fractures for 2 control diseases, hypertension (401*, I10) and nephrolithiasis (592*, N200-N209), were also studied.

Statistical analyses were done using SPSS 15 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population. The fracture cases comprised 53,108 patients (35,174 women; 66%) with a hip or a vertebral fracture, who were compared with 370,602 controls. The median age of the case group was 71 years (IQR 61–78). Among cases, 47,282 (89%) had a hip fracture at a median age of 72 years (IQR 64–79). Vertebral fracture was found in 6216 (12%) cases at a median age of 41 years (IQR 25–58).

We identified 3884 patients diagnosed with RD. Of those, 3379 (87%) had RA, 34 JIA (1%), 265 AS (7%), 136 SLE (3%), 36 PM/DM (1%), and 34 SSc (1%). Among 1238 patients with IBD, 644 (52%) had CD and 594 (48%) had UC.

Risk of fracture. Table 1 illustrates fracture risk for the exposure diseases. The magnitude of fracture risk was higher for patients with RD (OR 3, 95% CI 2.9–3.2) than for IBD (OR 1.6, 95% CI 1.4–1.8), compared with controls. There was a statistically significant increase in risk of fracture for all RD, with OR ranging from 2.6 (95% CI 1.3–4.9) for SSc to 4 (95% CI 3.4–4.6) for AS. The largest increased risk for vertebral fractures was seen in AS (OR 7.1, 95% CI 6–8.4) and for hip fractures in JIA (OR 4.1, 95% CI 2.4–6.9). Both CD (OR 1.8, 95% 1.5–2.1) and UC (OR 1.4, 95% CI 1.1–1.7) had an increased fracture risk compared with controls.

For RD, we divided the study period into 3 time periods and found a decrease in fracture risk for later years [1987-1994: OR 4 (95% CI 3.7–4.3), 1995-1999: OR 2.9 (95% CI 2.6–3.2), and 2000-2004: OR 1.8 (95% CI 1.6–2.1)].

Analyses to tackle surveillance bias did not notably alter the overall results. We identified 3503 patients with nephrolithiasis and there was no associated fracture risk (OR 1.1, 95% CI 0.9–1.2, p = nonsignificant). However, 25,078 patients who had been diagnosed with hypertension had an increased risk of fracture (OR 2.1, 95% CI 2.1–2.2, $p < 0.001$).

DISCUSSION

Hip and vertebral fracture risk of patients with RD is great, with OR between 2.5 and 7.1 compared with controls. Similarly, patients with IBD have a statistically significant increase in fracture risk, of lower magnitude than for RD.

Hip and vertebrae are typical fracture sites in patients with low bone mass due to osteoporosis or osteomalacia. Hip fractures represent serious medical incidents with high economic relevance, often requiring cost-intensive surgical treatments, hospitalization, and longterm rehabilitation. We selected these fracture types as indicators for the assessment of the overall risk of a fracture in the general population.

The results are consistent with other studies showing that patients with RA and JIA have an increased fracture risk[2,3,4,5,13,14,15]. Patients with RA showed a similar risk of hip fractures compared with a Finnish study[4]. However, our fracture risk was more prominent than in earlier reports from the UK[2] and the United States[3]. The risk for vertebral fractures was similar to a report from Spector, *et al*[5].

AS is associated with bone remodeling, especially bone loss in the vertebral bodies and the hip due to axial and articular inflammation[16]. The rigidity of the spine may contribute to an elevated vertebral vulnerability in patients with AS. We found a considerable increase for vertebral and hip fractures in this subtype of RD. This is consistent with Cooper, *et al*, who reported estimates of similar magnitude for clinical vertebral fractures in patients diagnosed with AS[6]. Although other studies showed an overall risk for vertebral fractures, increased hip fracture risk has not always been indicated[7].

The catabolic effect of systemic glucocorticosteroid therapy in SLE and glomerulonephritis with renal impairment, a common involvement in SLE, could have adverse effects on bone mineralization. Patients with SLE had a combined risk for hip and vertebral fractures with an OR of 2.9. An earlier report showed a higher estimate of fracture risk in SLE[8]. In contrast with our study, the latter report analyzed all fracture types in women.

Yuen, *et al*, found the same occurrence of fractures in patients with SSc compared with RA[9]. Although the literature on fracture risk of both PM/DM and SSc is sparse, both disorders have been found to be independently risky for lumbar and femoral osteoporosis[17,18]. This may explain the increase in fracture risk for those disorders in our study.

Many patients with RD are treated with longterm systemic glucocorticosteroids, which may lead to decreased bone mineral density. Nevertheless, we do not believe that this solely explains the increased fracture risk in RD, since an increased fracture risk has also been apparent in patients without glucocorticosteroids[1]. Other risk factors such as

Table 1. Fracture risk in rheumatic disorders and inflammatory bowel diseases.

	All Fractures		Hip Fractures		Vertebral Fractures	
	Population, n	OR 95% CI	Population, n	OR 95% CI	Population, n	OR 95% CI
RA	368,322[a]/2280[b]	2.9	327,662[a]/2165[b]	2.9	43,372[a]/132[b]	2.7
	52,009[c]/1099[d]	2.8–3.1*	46,228[c]/1054[d]	2.7–3.1*	6157[c]/59[d]	2.1–3.4*
JIA	370,583[a]/19[b]	3.5	329,812[a]/15[b]	4.1	43,500[a]/4[b]	1.3
	53,093[c]/15[d]	2.1–5.7*	47,268[c]/14[d]	2.4–6.9*	6215[c]/1[d]	0.2–9†
AS	370,518[a]/84[b]	4	329,752[a]/75[b]	2.5	43,493[a]/11[b]	7.1
	52,927[c]/181[d]	3.4–4.6*	47,218[c]/64[d]	1.9–3.1*	6085[c]/131[d]	6.0–8.4*
SLE	370,513[a]/89[b]	2.9	329,749[a]/78[b]	3.1	43,491[a]/13[b]	2.2
	53,061[c]/47[d]	2.2–3.9*	47,241[c]/41[d]	2.3–4.2*	6210[c]/6[d]	1–4.8†
PM/DM	370,577[a]/25[b]	3.1	329,804[a]/23[b]	3.5	43,502[a]/2[b]	#
	53,097[c]/11[d]	1.7–5.5*	47,271[c]/11[d]	1.9–6.3*	6216[c]/0[d]	#
SSc	370,577[a]/25[b]	2.6	329,803[a]/24[b]	2.6	43,503[a]/1[b]	#
	53,099[c]/9[d]	1.3–4.9**	47,273[c]/9[d]	1.4–5.1**	6216[c]/0[d]	#
CD	370,113[a]/489[b]	1.8	329,413[a]/414[b]	1.8	43,427[a]/77[b]	2
	52,953[c]/155[d]	1.5–2.1*	47,155[c]/127[d]	1.5–2.1*	6184[c]/32[d]	1.4–2.8*
UC	370,114[a]/488[b]	1.4	329,410[a]/417[b]	1.3	43,427[a]/77[b]	1.7
	53,002[c]/106[d]	1.1–1.7**	47,196[c]/86[d]	1.1–1.6**	6195[c]/21[d]	1.1–2.6***

RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis; AS: ankylosing spondylitis; SLE: systemic lupus erythematosus; PM/DM: polymyositis/dermatomyositis; SSc: systemic sclerosis; CD: Crohn's disease; UC: ulcerative colitis. [a] Unexposed/no fracture; [b] exposed/no fracture; [c] unexposed/fracture; [d] exposed/fracture. * $p < 0.001$, ** $p < 0.008$, *** $p < 0.05$, † not significant, # not calculated because of empty cell. Exposed: patients with the respective inflammatory disease.

inflammation and bone quality, including microarchitectural weakness, bone remodeling, bone turnover, and mineralization, may be important as well. This situation is also confounded by an increased incidence of falling in these patients.

Overall, the magnitude of fracture risk for patients with IBD was lower than in RD compared with controls. Different effects on bone metabolism and varying disease severity of the various conditions may explain the lower risk. In agreement with our results, 2 other studies reported a similar relative risk of fractures in patients with IBD[10,11]. We confirm the findings of van Staa, *et al*, who showed a higher fracture risk in patients with CD compared with those with UC[10].

We found a decrease in fracture risk of patients with RD during the study period. It is difficult to determine the reasons for the decreasing risk due to changes in medicinal therapy over time. This is because temporal variations in admissions policies will also have changed the characteristics of the patient population admitted with inflammatory diseases. Patients who experienced fractures during any given time period will have had their RD diagnosed in a variety of different time periods and so their treatment history will be somewhat heterogeneous.

Our study is limited by the lack of information on other explanatory factors such as patient characteristics, lifestyle factors, and medication use, all data not included in the SNHDR. However, validation studies of other medical diagnoses indicate that the accuracy of the SNHDR is close to 90%[12]. By having very large samples in both the fracture and control group, we believe that possible bias through false data entry should be equal in both cohorts. Still, our results may have been biased by an inappropriate classification of the RD and IBD studied. The finding of a positive association between the exposure diseases and fracture risk, which is in line with our primary hypothesis, however, adds to the validity of our data.

Because we are using inpatient diagnoses, our study may identify a subset of the population with these diagnoses who have a more severe disease or possible other sources of adversity that increase both the risk of hospital admission and fracture. It is possible that among patients with less severe diseases, who received only outpatient care, the association with fracture will be lower. Still, our sample in this study represents the most complete inpatient population. While we are less certain about admissions for IBD, we know that in patients with RA, about 50% are admitted to a hospital at some time, as estimated in 2007 (personal communication, J. Askling, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden). It is likely that those admitted will have more severe disease and possibly be more likely to have comorbid conditions that could also be relevant to fracture risk.

Nonvertebral fractures such as hip fractures are usually easy to diagnose, as patients have severe pain and are unable to walk. By contrast, diagnosing vertebral fractures can be more complicated. Therefore our study population represents more precisely a cohort of patients with clinical vertebral fractures, because morphometric fractures of the spine are often missed.

As expected, there was no association between fractures and nephrolithiasis. However, patients with hypertension

also had a higher risk of fractures, which has been described[13]. The authors speculated that the mechanism behind the elevated risk of fractures in hypertension may be an increased loss of calcium in the urine, leading to a negative calcium balance[19].

Our results highlight an increased fracture risk in patients with RD and IBD. Therefore, fracture prevention strategies may be of benefit and warrant further research addressing the important issue of fractures in chronic inflammatory diseases.

REFERENCES

1. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:2044-50.
2. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995;54:49-52.
3. Hooyman JR, Melton LJ 3rd, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984;27:1353-61.
4. Huusko TM, Korpela M, Karppi P, Avikainen V, Kautiainen H, Sulkava R. Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. Ann Rheum Dis 2001;60:521-2.
5. Spector TD, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. BMJ 1993;306:558.
6. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 1994; 21:1877-82.
7. Vosse D, Landewe R, van der Heijde D, van der Linden S, van Staa TP, Geusens P. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis 2009;68:1839-42.
8. Ramsey-Goldman R, Dunn JE, Huang CF, Dunlop D, Rairie JE, Fitzgerald S, et al. Frequency of fractures in women with systemic lupus erythematosus: comparison with United States population data. Arthritis Rheum 1999;42:882-90.
9. Yuen SY, Rochwerg B, Ouimet J, Pope JE. Patients with scleroderma may have increased risk of osteoporosis. A comparison to rheumatoid arthritis and noninflammatory musculoskeletal conditions. J Rheumatol 2008;35:1073-8.
10. van Staa TP, Cooper C, Brusse LS, Leufkens H, Javaid MK, Arden NK. Inflammatory bowel disease and the risk of fracture. Gastroenterology 2003;125:1591-7.
11. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Ann Intern Med 2000;133:795-9.
12. The National Board of Health and Welfare. Stockholm: The Swedish Hospital Discharge Register. [Internet. Accessed July 13, 2010.] Available from: http://www.sos.se/epc/english/pareng.htm
13. Orstavik RE, Haugeberg G, Mowinckel P, Hoiseth A, Uhlig T, Falch JA, et al. Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. Arch Intern Med 2004;164:420-5.
14. Orstavik RE, Haugeberg G, Uhlig T, Mowinckel P, Falch JA, Halse JI, et al. Self reported non-vertebral fractures in rheumatoid arthritis and population based controls: incidence and relationship with bone mineral density and clinical variables. Ann Rheum Dis 2004;63:177-82.
15. Burnham JM, Shults J, Weinstein R, Lewis JD, Leonard MB. Childhood onset arthritis is associated with an increased risk of fracture: a population based study using the General Practice Research Database. Ann Rheum Dis 2006;65:1074-9.
16. Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? J Rheumatol 2002;29:1511-9.
17. Souza RB, Borges CT, Takayama L, Aldrighi JM, Pereira RM. Systemic sclerosis and bone loss: the role of the disease and body composition. Scand J Rheumatol 2006;35:384-7.
18. Stewart WA, Acott PD, Salisbury SR, Lang BA. Bone mineral density in juvenile dermatomyositis: assessment using dual x-ray absorptiometry. Arthritis Rheum 2003;48:2294-8.
19. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. Calcif Tissue Int 2009;84:103-11.