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The risk of fracture among patients with psoriatic arthritis and psoriasis: a population-based study

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DATA SHARING: While we are unable to share the datasets, code lists are available upon request.

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Abstract

Objective—To determine the risk of fracture and osteoporosis (OP) among patients with psoriatic arthritis (PsA) and psoriasis, compared with the general population and patients with rheumatoid arthritis (RA).

Methods—A population-based cohort study was performed in The Health Improvement Network in the United Kingdom using data from 1994–2014. Patients aged 18–89 with PsA or psoriasis and up to 5 unexposed controls matched by practice and start date within that practice were included. Patients with RA and matched controls were included for comparison. Severe psoriasis was defined by a code for psoriasis and either phototherapy or a systemic medication for psoriasis. Incidence and adjusted hazard ratios (aHR) for fracture (all, hip, vertebral) were calculated.

Results—Patients with PsA (N=9,788), psoriasis (N=158,323) and controls (N=821,834) were identified. Patients with PsA had an elevated risk of all fracture aHR 1.26 (1.06–1.27). Patients with mild psoriasis had elevated risk of all fractures, vertebral and hip fracture: aHR 1.07 (1.05–1.10), 1.17 (1.03–1.33) and 1.13 (1.04–1.22). Patients with severe psoriasis had significantly elevated risk of all fracture and vertebral fracture: aHR 1.26 (1.15–1.39) and 2.23 (1.54–3.22).

Conclusion—PsA and psoriasis are associated with an elevated risk for fracture.

INTRODUCTION

Osteoporosis (OP) is one of the most common and costly diseases: one in every two women and one in five men will experience a fracture after the age of 50.[1] Hospitalizations for OP fracture are more common than hospitalizations for myocardial infarction and stroke combined[2] and fractures result in pain, immobility, nursing home placement, isolation and depression, in addition to other health problems.[1] Rheumatoid arthritis (RA) is a known risk factor for osteoporosis.[4] Ankylosing spondylitis, despite its association with new bone formation and syndesmophytes, is also associated with vertebral osteoporosis and fractures.

While psoriatic arthritis (PsA) and psoriasis demonstrate a similar Th1 and Th17 driven inflammation to RA and a pathophysiologic link to AS, few studies have addressed the risk of OP in these patients [5, 6] Two studies have reported an increased prevalence of osteopenia or osteoporosis among patients with psoriasis in Taiwan and Israel.[7, 8] Additional studies examined bone mineral density (BMD) in patients with PsA compared to healthy controls, though with conflicting results.[9–13] These studies have been limited by cross-sectional designs and lack of adjustment for obesity, smoking or other risk factors for osteoporosis. To our knowledge, no studies have evaluated the risk of incident fracture in

PsA or psoriasis. Therefore, the objective of this study was to examine the incidence of fracture in patients with PsA and psoriasis and compare this to matched controls from the general population and patients with RA.

METHODS

Study Design

We performed a longitudinal cohort study to examine the risk of incident fracture among patients with psoriasis and PsA compared to patients from the general population and patients with RA.

Data Source

Data from The Health Improvement Network (THIN) in the United Kingdom (UK) between 1994 and January 2014 was used.

Study Population

All patients with PsA or psoriasis between the ages of 18 and 89 at the start date were included if they had observation time in THIN after Vision software implementation. Patients were excluded if they died or transferred out of the practice prior to the implementation of Vision software. Patients with a history of fracture or osteoporosis or a history of bisphosphonate prescriptions were excluded. Patients with psoriasis, PsA and RA were matched to up to 5 unexposed controls from the general population (matching is described in the supplemental methods).

Exposure and Outcome Definitions

PsA, psoriasis, and RA were defined by the presence of at least one READ code consistent with these diseases using previously validated codes.[19–23] Severe psoriasis was defined as a code for psoriasis plus a code for either phototherapy or a systemic medication for psoriasis. The outcomes of interest were fractures (all fractures, hip fracture, and vertebral fracture).[24–27] Disease modifying antirheumatic drugs (DMARDs) and covariates are listed in the supplemental methods.

Person time calculation

Cohort time started at the latest of the following: diagnosis with psoriasis, PsA, or RA (diagnosis date for unexposed controls was the encounter date within 6 months of the matched patient’s diagnosis date), 180 days after registration in the practice, or Vision date (software implementation in the practice). Cohort time ended at earliest of development of the outcome, transfer out of the practice, practice stops contributing to THIN, death, or the end of the study. All covariates of interest were measured prior to cohort entry.

Statistical Analysis

Descriptive statistics were used to examine age, sex, person-time, and covariate distribution between patients with PsA, psoriasis and unexposed controls. The number of events and cumulative incidence of fracture were calculated for each group. Cox proportional hazards

models were used to calculate unadjusted and adjusted hazard ratios with 95% confidence intervals. A purposeful selection modeling approach was used to determine in the most biologically plausible and parsimonious model.[28] The proportional hazards assumption was assessed using log-log plots. Sensitivity analyses are described in the supplementary data.

Ethics Review

This study was approved by the University of Pennsylvania Institutional Review Board and the Cegedim Scientific Review Committee. This paper was prepared according to STROBE guidelines.[29]

RESULTS

After applying inclusion and exclusion criteria, 9,788 patients with PsA, 158,323 patients with psoriasis, and 821,834 matched controls were identified. Baseline demographics are shown in Table 1 and Supplemental Table 1. Time in the cohort was similar among the groups. Approximately 5% of patients with psoriasis had been prescribed a DMARD or received phototherapy. Oral corticosteroids were prescribed for 17% of patients with PsA, 21% of patients with severe 9% of patients with mild psoriasis and controls. PPIs were commonly prescribed for patients with PsA and severe psoriasis (31% each) than controls and those with mild psoriasis (both 15%). Patients with PsA and psoriasis were also more likely to have been prescribed an antidepressant in the baseline period and had a higher prevalence of diabetes than controls. Those with mild or severe psoriasis were more likely to be current smokers, while patients with PsA and severe psoriasis had higher rates of heavy alcohol use.

The number of events, unadjusted incidence per 10,000 person-years, and hazard ratios for fracture are presented in Table 2. Results for RA are included in the table for comparison. After adjusting for OP risk factors, patients with PsA and psoriasis had elevated risk for incident fracture: PsA 1.16 (95% CI 1.06–1.27), mild psoriasis 1.07 (1.05–1.10), and severe psoriasis HR 1.26 (1.15–1.39). Patients with mild psoriasis had an elevated risk for hip fracture 1.13 (1.04–1.22,) and vertebral fracture (HR 1.17, 1.03–1.33). Patients with severe psoriasis had a substantially elevated risk for vertebral fracture: HR 2.23 (1.54–3.22). These results were robust to several sensitivity analyses (Supplemental Table 3–4). Defining fracture by a code for fracture followed by a bisphosphonate prescription resulted in slight increases in the HR. The results did not substantially change when patients with a history of fracture were included.

DISCUSSION

In this study, we found patients with PsA and psoriasis had an increased prevalence of risk factors for OP and fracture (e.g., diabetes, alcohol abuse, smoking, depression, antidepressant use, corticosteroids, methotrexate, and cyclosporine).[3, 30–34]. Additionally, patients with PsA and psoriasis had an increased incidence of fracture compared to the general population by 7–26%. The incidence of vertebral fracture was also increased in patients with severe psoriasis and while hip fracture was elevated in both psoriasis groups, it

was only statistically significant in patients with mild psoriasis relative to matched controls after adjusting for risk factors for osteoporosis. We found that the risk for any fracture in patients with PsA and severe psoriasis was similar to RA. To our knowledge, these are the first population based estimates of the risk for incident fracture and osteoporosis in patients with psoriasis and/or psoriatic arthritis and the first longitudinal cohort study to address this issue.

Strengths of this study include a large cohort of patients with an average of 6 years of follow-up, the use of THIN in which the exposures definitions (codes for PsA, RA, psoriasis) have been validated and fractures have been previously examined[19–23], and the ability to adjust for other measured risk factors for osteoporosis including concomitant medications, BMI and smoking. Additionally, inclusion of a cohort of patients RA for internal comparison provides validity to the results as our estimates for RA were similar to previous studies.[35–37] Similarly, the incidence of hip fracture among controls in our study was similar to population statistics in the UK (10.7 v. 10.3 per 10,000 person-years), further supporting the validity of our results.[38] Finally, the hazard ratios were robust to numerous sensitivity analyses.

Our study also has limitations. There is a risk for misclassification of the outcome when using diagnosis codes to define an event rather than imaging. We addressed this through sensitivity analyses in which we changed the outcome definition; this did not significantly change the results. We also used a secondary definition for fracture in which we required a therapy for osteoporosis to address osteoporotic fractures. Vertebral fracture may be underdiagnosed and thus under recorded.[3] We conducted a sensitivity analysis to examine whether observation bias effected these results and found no difference when we only included patients in the study followed at least once yearly. Next, disease manifestations, disease activity and use of biologic DMARDs are not available in THIN, and therefore we were unable to directly examine their effects on risk of osteoporosis and fracture. We were also unable to account for some lifestyle factors such as degree of immobility or laboratory parameters such as vitamin D. Finally, the relatively small number of patients with PsA and/or severe psoriasis, may have resulted in insufficient power for some of the outcomes, resulting in wide confidence intervals that include 1.0 despite elevated point estimates (e.g., for hip fracture among patients with severe psoriasis).[39]

In conclusion, fractures, in particular osteoporotic fractures, are a major health problem that results in poor outcomes and osteoporosis is largely under-diagnosed. We found that similar to PsA and psoriasis (both mild and severe) were associated with an increased risk for fractures. Screening and management of osteoporosis should still be considered for patients with psoriasis and PsA using guidelines available for the general population.[6, 37]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Demographics

		Control	PsA	Mild Psoriasis	Severe Psoriasis	RA
	N	**821,834**	**9,788**	**149,809**	**8,514**	**39,306**
Age	Mean (SD)	50.18 (17.47)	49.74 (14.09)	46.67 (17.43)	49.29 (15.18)	58.71 (15.33)
Female Sex	N (%)	469,431 (57.12%)	5,029 (51.38%)	79,961 (53.38%)	4,498 (52.83%)	27,198 (69.20%)
Cohort Time*	Mean (SD)	6.75 (4.87)	6.17 (4.67)	6.37 (4.80)	5.50 (4.19)	6.29 (4.67)
Visits in One Year before start	Mean (SD)	4.86 (6.45)	8.03 (8.81)	6.22 (6.72)	10.54 (10.13)	10.02 (9.61)
Cancer**	N (%)	121,488 (14.78%)	1,218 (12.44%)	20,546 (13.71%)	1,264 (14.85%)	6,092 (15.50%)
Chronic Kidney Disease	N (%)	17,335 (2.11%)	188 (1.92%)	2,426 (1.62%)	249 (2.92%)	1,332 (3.39%)
Atrial Fibrillation	N (%)	16,923 (2.06%)	160 (1.63%)	2,425 (1.62%)	142 (1.67%)	1,263 (3.21%)
Diabetes	N (%)	49,554 (6.03%)	743 (7.59%)	8,091 (5.40%)	768 (9.02%)	3,204 (8.15%)
Cardiovascular Disease	N (%)	48,647 (5.92%)	458 (4.68%)	7,640 (5.10%)	479 (5.63%)	3,712 (9.44%)
COPD	N (%)	17,585 (2.14%)	207 (2.11%)	3,262 (2.18%)	233 (2.74%)	1,654 (4.21%)
Liver disease	N (%)	9,653 (1.17%)	182 (1.86%)	1,947 (1.30%)	163 (1.91%)	594 (1.51%)
Dementia	N (%)	3,963 (0.48%)	32 (0.33%)	788 (0.53%)	30 (0.35%)	357 (0.91%)
Stroke	N (%)	21,827 (2.66%)	205 (2.09%)	3,450 (2.30%)	212 (2.49%)	1,613 (4.10%)
Anti-depressant use	N (%)	178,630 (21.74%)	2,861 (29.23%)	33,252 (22.20%)	2,834 (33.29%)	11,805 (30.03%)
Anti-epileptic use	N (%)	25,338 (3.08%)	398 (4.07%)	4,774 (3.19%)	424 (4.98%)	1,877 (4.78%)
Oral corticosteroids	N (%)	77,521 (9.43%)	1,645 (16.81%)	12,811 (8.55%)	1,819 (21.36%)	11,532 (29.34%)
PPI use	N (%)	125,493 (15.27%)	3,021 (30.86%)	22,615 (15.10%)	2,666 (31.31%)	13,408 (34.11%)
Hormone therapy***	N (%)	252,829 (30.76%)	2,643 (27.00%)	40,218 (26.85%)	2,521 (29.61%)	11,158 (28.39%)

		Control	PsA	Mild Psoriasis	Severe Psoriasis	RA
	N	**821,834**	**9,788**	**149,809**	**8,514**	**39,306**
Smoking	Never/ Former (N, %)	561,085 (68.27%)	6,966 (71.17%)	92,044 (61.44%)	5,658 (66.46%)	26,497 (67.41%)
	Current (N, %)	170,562 (20.75%)	2,011 (20.55%)	41,751 (27.87%)	2,322 (27.27%)	8,676 (22.07%)
	Missing (N, %)	*90,187 (10.97%)*	*811 (8.29%)*	*16,041 (10.69%)*	*534 (6.27%)*	*4,133 (10.51%)*
Alcohol Use	Never (N, %)	96,244 (11.72%)	1,150 (11.75%)	16,023 (10.70%)	973 (11.43%)	6,503 (16.54%)
	Some (N, %)	519,079 (63.16%)	6,462 (66.02%)	97,034 (64.77%)	5,600 (65.77%)	23,137 (58.86%)
	Heavy (N, %)	31,735 (3.86%)	477 (4.87%)	5,501 (3.67%)	552 (6.48%)	2,167 (5.51%)
	Missing (N, %)	*174,676 (21.25%)*	*1,699 (17.36%)*	*31,251 (20.86%)*	*1,389 (16.31%)*	*7,499 (19.08%)*
BMI	*Mean (SD)*	26.39 (5.46)	28.03 (5.86)	26.65 (5.60)	28.08 (6.11)	26.69 (5.55)
	Missing (N, %)	*168,709 (20.53%)*	*1,659 (16.95%)*	*30,833 (20.58%)*	*1,327 (15.59%)*	*7,446 (18.94%)*

*Time from index date to end date

**Cancer includes hematologic malignancy and solid tumor malignancies

***Hormone therapy refers to the use of oral contraceptives as well as hormone replacement therapy

Abbreviations: PPI = proton pump inhibitor; BMI = Body Mass Index

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Table 2

Hazard Ratios for Incident Fracture.

	Number of Events	Incidence*	Unadjusted		Age/Sex Adjusted		Fully Adjusted**	
			HR	CI	HR	CI	HR	CI
ALL FRACTURES								
Controls	49,168	92.18	REF		REF		REF	
PsA	575	99.23	1.09	1.00–1.18	1.14	1.05–1.24	1.16	1.06–1.27
Mild Psoriasis	8,470	92.38	1.01	0.98–1.03	1.09	1.07–1.12	1.07	1.05–1.10
Severe Psoriasis	537	119.91	1.33	1.22–1.45	1.42	1.30–1.55	1.26	1.15–1.39
RA	3,460	148.44	1.63	1.57–1.68	1.32	1.28–1.37	1.23	1.18–1.28
HIP FRACTURE								
	Number of Events	**Incidence***	**Unadjusted**		**Age/Sex Adjusted**		**Fully Adjusted*****	
			HR	CI	HR	CI	HR	CI
Controls	5,930	10.71	REF		REF		REF	
PsA	54	8.97	0.86	0.66–1.12	1.27	0.97–1.66	1.17	0.86–1.59
Mild Psoriasis	930	9.78	0.92	0.86–0.99	1.16	1.08–1.24	1.13	1.04–1.22
Severe Psoriasis	55	11.77	1.17	0.90–1.53	1.69	1.29–2.20	1.21	0.88–1.66
RA	730	29.81	2.85	2.64–3.08	1.77	1.64–1.91	1.55	1.40–1.72
VERTEBRAL FRACTURE								
	Number of Events	**Incidence***	**Unadjusted**		**Age/Sex Adjusted**		**Fully Adjusted******	
			HR	CI	HR	CI	HR	CI
Controls	2,009	3.62	REF		REF		REF	
PsA	20	3.32	0.94	0.60–1.46	1.06	0.69–1.65	1.07	0.66–1.72
Mild Psoriasis	371	3.89	1.09	0.97–1.21	1.24	1.11–1.39	1.17	1.03–1.33
Severe Psoriasis	32	6.85	2.02	1.42–2.87	2.35	1.66–3.33	2.23	1.54–3.22
RA	209	8.48	2.40	2.08–2.76	1.70	1.48–1.96	1.53	1.30–1.80

* Incidence per 10,000 person-years

The fully adjusted models for each outcome were slightly different after employing a purposeful selection process. The variables contained within each model are specified as below.

** The all fracture model was adjusted for age, sex, cancer, atrial fibrillation, CKD, diabetes, COPD, liver disease, stroke, dementia, SSRI use, TCA use, anti-epileptic use, PPI use, oral steroids, hormone treatment, cyclosporine, smoking, and categorical BMI

*** The hip fracture model was adjusted for age, sex, cancer, atrial fibrillation, CKD, CVD, diabetes, COPD, stroke, dementia, SSRI use, TCA use, anti-epileptic use, oral steroids, hormone treatment, cyclosporine, smoking, and categorical BMI

**** The vertebral fracture model was adjusted for age, sex, atrial fibrillation, diabetes, COPD, stroke, SSRI use, TCA use, PPI use, oral steroids, smoking, and categorical BMI

Abbreviations: PPI = proton pump inhibitor; BMI = Body Mass Index, COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant