Risk of fragility fracture among patients with late-onset psoriasis: a United Kingdom population-based study

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Conflicts of Interest

Zoe Paskins, Rebecca Whittle, Alyshah Abdul Sultan, Sara Muller, Milica Blagojevic-Bucknall', Toby Helliwell, Jon Packham, Samantha Hider, Edward Roddy and Christian Mallen declare that they have no conflicts of interest.

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Abstract

Purpose:

This study aimed to examine fracture risk in patients with late-onset psoriasis and investigate the effect of methotrexate on fracture risk.

Methods:

A cohort study was conducted using primary care records from the UK-based Clinical Practice Research Datalink. Individuals aged 40 years and over, with incident (new onset) diagnoses of psoriasis were identified from 1990–2004 and followed up until 2015. For each exposed individual, up to four age-, gender- and practice-matched controls were randomly selected. Incidence rates of fragility fracture (hip, vertebral, spine, radius or unspecified site) per 10,000 person-years were calculated and hazard rates compared to the unexposed using Cox regression models. The risk of fracture was also estimated, within the exposed group for patients receiving/not receiving methotrexate.

Results:

24,219 patients with psoriasis and 94,820 controls were identified. The absolute rate of fracture in psoriasis patients was 58 per 10,000 person-years (95% confidence interval (CI): 55, 61) and 53 per 10,000 person-years in the matched controls ((CI): 52, 54). Psoriasis patients had a 10% increased risk of fracture compared to their matched controls (hazard ratio (HR) = 1.10; 95% CI: 1.04, 1.16). Methotrexate use was not associated with increased risk (0.91 (0.72, 1.15)).

Conclusions:

Identifying additional clinical factors associated with increased fracture risk is important in improving fracture risk stratification. Further work is needed to determine the relationship between age of onset of psoriasis and fracture risk, explore causative explanations and identify if existing fracture risk stratification tools underestimate fracture risk in patients with psoriasis.

Keywords: psoriasis, fracture, osteoporosis, methotrexate

Mini abstract (max 50 words)

This study aimed to examine fracture risk in patients with late-onset psoriasis. A cohort study was conducted using primary care records from the Clinical Practice Research Datalink. Psoriasis patients had a 10% increased risk of fracture compared to matched controls (hazard ratio (HR) = 1.10; 95% CI: 1.04, 1.16).

Introduction

Psoriasis is a common inflammatory skin condition, usually characterised by well-delineated red, scaly plaques. Between 7 and 42% of patients with psoriasis have associated inflammatory arthritis [1] (psoriatic arthritis: PsA). Psoriasis is associated with several co-morbidities including cardiovascular disease, hypertension, obesity, diabetes, and an excess risk of mortality [2]. As with other inflammatory conditions such as rheumatoid arthritis (RA) [3], it has been theorised that psoriasis may be associated with an increased risk of fragility fracture. Three potential mechanisms link inflammatory diseases with osteoporosis and accelerated bone loss. First, there is a direct effect of pro-inflammatory cytokines (such as IL1, IL6, IL11, IL15, IL17 and TNFα) on bone; these act as primary mediators of accelerated bone loss [4]. Second, some inflammatory disease treatments are thought to be detrimental to bone health. With relevance to the treatment of psoriasis, methotrexate inhibits osteoblastic function, predisposing to fracture [5]. Third, immobility – which may be associated with chronic, particularly musculoskeletal, inflammatory conditions – results in increased bone resorption leading to osteoporosis.

However, previous studies examining bone health and fracture risk in patients with psoriasis have provided conflicting results. An increase in prevalence of osteoporosis has been reported in one cohort study [6], whilst another cohort demonstrated no association with either fracture or reduced bone mineral density [7]. More recently, a large population-based study has suggested that patients with mild psoriasis have a 13% increased risk of hip fracture [8].

A possible explanation for these conflicting results is the heterogeneous nature of the condition. Psoriasis has a bimodal peak of incidence [9] and there is some evidence that

early-onset psoriasis (presenting in individuals aged under 40) and late-onset psoriasis (aged 40 years and over) are distinct conditions with clinical, genetic and immunocytochemical profiles [10].

Further questions persist regarding fracture risk in PsA and the influence on fracture risk of drugs used to treat psoriasis. For patients with psoriasis requiring systemic treatment, and patients with PsA failing to respond to non-steroidal anti-inflammatory drugs, methotrexate is recommended as the first-line drug of choice [11, 12]. Methotrexate has been reported to cause fractures [5], although its use was not associated with increased fracture risk in a large Danish case-control study [13]. Patients with PsA could be expected to be at higher risk of fracture owing to higher inflammatory burden, more common methotrexate use and/or restricted mobility; however, Odgie et al did not find patients with PsA were at higher risk than patients with psoriasis in their population-based study [8].

Understanding factors associated with increased risk is important to allow screening to be targeted at the most appropriate individuals. Current guidance for the management and identification of co-morbidities in patients with psoriasis do not address bone health [2, 11].

This study aimed to examine fracture risk in patients with late-onset psoriasis and PsA and investigate the effect of methotrexate on this risk.

Materials and Methods

We conducted a cohort study using data from the Clinical Practice Research Datalink (CPRD), a large UK primary care medical record database of anonymised patients that covers more than 6.9% of the UK population and is representative in terms of age and sex distribution

[14]. Practices contributing data to CPRD receive training on recording information and the database is subjected to quality checks, with data from a practice only being used when it has reached a certain standard of quality, defined as being up-to-standard (UTS).

The exposed population was defined as patients aged over 40 years with an incident (new onset) diagnosis (Read code) of psoriasis (supplementary table 1) between 1990 and 2004. Huerta et al. [15] carried out external validation of psoriasis diagnosis in CPRD and found that 82% of psoriasis diagnoses were verified by physicians. Each patient was assigned an index date corresponding to the date of their disease diagnosis.

For each exposed patient, up to four controls were randomly selected matched on age (three year age bands), gender and general practice, with the controls' index date anchored to that of their matched exposed patient. Controls were defined as those without psoriasis and without other common inflammatory musculoskeletal conditions (polymyalgia rheumatica (PMR), giant cell arteritis (GCA), gout, ankylosing spondylitis (AS), inflammatory bowel disease, systemic lupus erythematosus, RA and PsA) prior to their index date.

The study end date was defined as the earliest date of: the patient's death; date the patient transferred out of the practice; date of last data collection from that practice; 31st August 2015 and date of first fracture.

The event of interest was time from the index date until the first diagnosis of fracture. Read codes for fractures at sites of major osteoporotic fracture were selected (vertebrae, humerus, wrist and hip) [16] in addition to Read codes for fragility fractures of unspecified site. Patients with the following were excluded: Read code for fracture (as previously defined) prior to their index date; Read code for fracture in the first six months of their

registration with the practice (assumed to be prevalent cases); less than 12 months of UTS follow-up prior to index date and less than 3 years of UTS follow-up after index date.

We extracted information on patient demographics (age and gender) at their index date, on lifestyle-related characteristics (body mass index (BMI), smoking status and alcohol consumption) using the measurement nearest to their index date (ever prior to index and up to 1 year after) and on comorbidities (using the Charlson comorbidity index) and the prescription of medications (corticosteroids, methotrexate, bisphosphonates and proton-pump inhibitors (PPI)) prior to the outcome for both exposed and non-exposed. Those with missing information on BMI, smoking and alcohol were included in separate categories.

Incidence rates were expressed as the number of incident fractures per 10,000 person-years. Cox proportional hazards models were used to obtain estimates of hazard ratios with 95% confidence intervals to assess the association between psoriasis exposure and time to first fracture, based on robust standard errors to account for matching. Unadjusted estimates were obtained, followed by adjustment for confounding factors which affected estimates by >10% (to avoid over-adjustment) from age, gender, BMI, alcohol, smoking, Charlson comorbidity index, bisphosphonate, glucocorticoid and PPI use. The proportional hazards assumption was tested using Schoenfeld residuals. Subgroup analyses were conducted by fracture site, disease severity, age and gender. Disease severity was categorised into three mutually exclusive groups: mild-moderate, severe (defined as prescription for systemic medication (e.g. methotrexate, ciclosporin, relevant biologic drug or psoralens) or having phototherapy Read code) and PsA (≥ 1 PsA Read code). The effect of methotrexate use on fracture risk within psoriasis patients was evaluated by estimating

hazard ratios within the exposed group, comparing patients with any methotrexate use to those with none.

Sensitivity analyses undertaken in patients with no missing category for smoking, alcohol use and BMI were compared to the main results. Sensitivity analyses were also conducted to address the potential misclassification of PsA, by including individuals with both psoriasis and either RA or AS in this category.

All analyses were performed using Stata/MP 14.2 (Stata Corporation, TX. USA). This study was approved by the Independent Scientific Advisory Committee of CPRD (protocol 15_165RA).

Results

The basic characteristics of the exposed and non-exposed populations are given in Table 1. Our study included 24,219 patients with late-onset psoriasis individually matched to 94,820 non-exposed patients, followed up for a median of 11.3 years (Interquartile range IQR (7.32, 14.17). Of the patients with a diagnosis of psoriasis, 1008 (4.2%) also had PsA and of the remaining 23,211 with psoriasis alone, 802 (3.5%) had severe disease and 22,409 (96.5%) had mild-moderate disease. Compared to controls, psoriasis patients had higher BMI (>30kg/m2: 18.2% vs. 13.7%), were more likely to smoke than their matched controls (25.8% vs. 19.4%) and more likely to consume 10 or more units of alcohol weekly (20.7% vs 16.8%). PPI and methotrexate prescriptions were more common among patients with psoriasis compared to controls (49.8% vs. 42.0% and 4.5% vs 0.6% respectively).

Within the exposed population, 1576 (6.5%) patients had a fracture after diagnosis. This corresponded to an absolute rate of 58 per 10,000 (95% confidence interval (CI): 55, 61) person-years (Table 2). Within the non-exposed population, the absolute rate was 53 (52, 54) per 10,000 person years. Psoriasis patients had a 10% increased risk of fracture compared to their matched controls (hazard ratio (HR) = 1.10; 95% CI: 1.04, 1.16). After adjustment for confounding factors, hazard ratios were increased/decreased by less than 10% and hence unadjusted estimates are discussed here, however estimates adjusted for all of the confounding factors listed are presented in Table 2 for comparison. The increased risk compared to controls was slightly higher in males (HR (95% CI): 1.22 (1.09, 1.36)) than females (HR (95% CI): 1.07 (1.00, 1.14)). The increased risk of fracture was similar in the vertebra (HR (95% CI): 1.15 (0.97, 1.35)), hip (1.14 (1.02, 1.27)) and humerus (1.20 (1.04, 1.38)). 1082 (4.5%) psoriasis patients received a methotrexate prescription and there was no significant difference in fracture risk between those receiving and not receiving methotrexate (HR (95% CI): 0.91 (0.72, 1.15)).

Patients with severe disease had similar risk of fracture to those with mild-moderate disease. The estimate of fracture risk in the PsA population was higher than the risk in those with mild-moderate psoriasis, but non-significant (1.26 (0.95, 1.65)).

The sensitivity analysis which excluded those with missing categories for smoking, alcohol use and BMI found similar results (data not presented).The sensitivity analysis including patients with psoriasis and PsA or RA and/or AS Read Codes yielded similar results (HR (95% CI): 1.21 (0.96, 1.54)).

Discussion

This is the first study within CPRD to quantify the increased risk of fragility fracture in people with late onset psoriasis, and to examine the effect of gender and methotrexate. The increased risk was higher in men than women, appeared to be higher in patients with PsA, although this was not statistically significant, and not altered by methotrexate prescription.

Pro-inflammatory cytokines such as IL-17 are known to be associated with osteoclastic bone resorption in other chronic inflammatory diseases such as rheumatoid arthritis [4], leading to osteoporosis and propensity to fracture. It is therefore possible that in psoriasis and psoriatic arthritis, in which IL-17 plays a key role, this mechanism in part explains the increased risk of fracture observed. Furthermore, this study demonstrates the prevalence of risk factors for fragility fractures are higher in patients with psoriasis, such as smoking, alcohol, and use of protein pump inhibitors and glucocorticoids. Oral glucocorticoids are not a treatment modality for psoriasis, but may precipitate the condition; this may explain the apparent higher rate of steroid use in exposed patents.

An increased fracture risk in men with psoriasis has not previously been reported. This may be explained by increased prevalence of risk factors for fracture in men such as excess alcohol consumption [17], which was also observed in our data, although adjustment for these variables did not alter estimates. We found fracture risk in patients with PsA to be higher, compared to patients with psoriasis alone, although non-significant. This finding was as expected although different to that in the previous population study where the risk of fracture appeared lower in those with PsA [8]. Both our study, and that in the THIN database, identified relatively low numbers of patients with PsA.

A previous study examining the incidence of metabolic comorbidities in psoriasis demonstrated that age of onset was associated with risk, with patients with early onset

psoriasis being of higher risk of developing complications such as non-alcoholic fatty liver disease [18]. This, theoretically could be due to longer exposure to pro-inflammatory cytokines. However, in our study, patients with mild-moderate late-onset psoriasis had higher risk of all fractures than that demonstrated in the recently published study using The Health Improvement Network (THIN) database which included patients with any age of onset (10% increased risk, compared with 7%) [8]. The THIN study [8] categorised fractures into all sites, including non-fragility fracture sites e.g. skull which may explain the difference in rates. Furthermore, genetic differences have been observed in early and late onset disease, also associated with gender, which may play a role in fracture risk [19].

By utilising CPRD and selecting all incident cases during the study period, our findings are generalizable to the wider UK population. However, our study is subject to some limitations. As in any database study, it is possible that residual confounding remains and we could not account for factors such as immobility or vitamin D. Although missing data were present in BMI, smoking status and alcohol use, which could bias our estimates, a sensitivity analysis of complete cases did not change our estimates. We relied on general practitioner (GP) diagnoses of psoriasis and fracture: however the diagnoses of psoriasis, hip and spinal fractures have previously been validated in CPRD [15, 20]. Although we cannot account for drugs prescribed in secondary care e.g. biologic treatments, in practice, non-biologic treatments are routinely used prior to biologics and hence most patients will be identified as 'severe' and we used other proxy measures for severity. The proportion of patients with PsA was lower than expected raising the possibility of misclassification; however, sensitivity analysis to account for this did not change our findings. The small number of patients classified as having PsA or severe psoriasis has influenced the precision of risk estimates in

these populations. Finally, there is a risk of misclassification for incident cases of late onset psoriasis that may actually represent recurrence of early onset disease.

In summary, this study suggests that further work is needed to explore the association between age of onset of psoriasis and fracture risk and to explore possible causative mechanisms. As has occurred in diabetes [21], further work is now needed to examine whether existing risk stratification tools such as FRAX underestimate fracture risk in patients with psoriasis or PsA.

Ethics approval and consent: This study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 15_165RA) on 18th May 2016, before data analysis was conducted. Ethical approval is not needed for database studies and ISAC provide the necessary regulatory approvals. Each practice in CPRD has consented to be included; patients within each consented practice are automatically included.

Supplementary Data: 1 (code list)

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Table 1: Basic characteristics of psoriasis exposed and non-exposed patients

Variables	**Exposed N=24,219 n (%)**	**Non-exposed N=94,820 n (%)**
Follow up time; median (IQR)	11.29 (7.32, 14.17)	11.38 (7.52, 14.33)
Male: n (%)	12,320 (50.87)	48,309 (50.95)
Mean age (SD)	58.94 (11.83)	58.83 (11.57)
BMI – Kg/m^2		
<18.5	224 (0.92)	931 (0.98)
18.5-25	6,828 (28.19)	28,678 (30.24)
25-30	7,528 (31.08)	26,699 (28.16)
>30	4,410 (18.21)	13,031 (13.74)
Missing	5,229 (21.59)	25,481 (26.87)
Smoking status		
Current smokers	6,259 (25.84)	18,425 (19.43)
Never/Ex-smokers	14,915 (61.58)	59,285 (62.52)
Missing	3,045 (12.57)	17,110 (18.04)
Alcohol (units per week)		
Never/Ex-drinker	4,323 (17.85)	16,117 (17.00)
1-9	6,174 (25.49)	24,588 (25.93)
≥10	5,005 (20.67)	15,884 (16.75)
Missing	8,717 (35.99)	38,231 (40.23)
Steroid prescription during study period		
None	17,818 (73.57)	76,927 (81.13)
1 prescription	1,719 (7.10)	5,481 (5.78)
More than 1 prescription	4,682 (19.33)	12,412 (13.09)
Median no. steroids prescriptions (IQR)	4 (1, 13)	3 (1, 10)
Median Charlson comorbidity index	1 (0, 3)	1 (0, 2)
Methotrexate use	1082 (4.47)	569 (0.60)
Bisphosphonates use	288 (1.19)	832 (0.88)
PPI use	12,057 (49.78)	39,793 (41.97)
Lithium use	90 (0.37)	202 (0.21)

Table 2: Incidence rates (95% CI) per 10,000 person years of fracture and hazard ratios (95% CI) for fractures in exposed

Variables	Exposed		Non-exposed		HR (95% CI)	Adjusted HR (95%CI)‡
	Number with fracture	Rate (95% CI) per 10,000 person-years	Number with fracture	Rate (95% CI) per 10,000 person-years		
Overall	1576	57.99 (55.20, 60.93)	5693	52.87 (51.52, 54.26)	1.10 (1.04, 1.16)	1.14 (1.08, 1.21)
Gender						
Male	415	30.88 (28.05, 34.00)	1356	25.49 (24.17, 26.88)	1.22 (1.09, 1.36)	1.24 (1.11, 1.38)
Female	1161	84.52 (79.80, 89.52)	4337	79.62 (77.28, 82.02)	1.07 (1.00, 1.14)	1.12 (1.05, 1.19)
Age						
40-49	198	24.30 (21.14, 27.94)	686	21.64 (20.08, 23.32)	1.12 (0.96, 1.32)	1.15 (0.98, 1.35)
50-59	334	40.35 (36.25, 44.92)	1238	37.60 (35.56, 39.75)	1.08 (0.95, 1.22)	1.12 (0.99, 1.27)
60-69	440	67.51 (61.49, 74.12)	1618	61.39 (58.47, 64.45)	1.11 (1.00, 1.23)	1.15 (1.03, 1.28)
70-79	448	130.20 (118.69, 142.84)	1606	115.26 (109.76, 121.04)	1.15 (1.03, 1.27)	1.21 (1.09, 1.35)
≥80	156	196.63 (168.07, 230.04)	545	198.46 (182.48, 215.84)	0.99 (0.83, 1.18)	1.04 (0.87, 1.25)
Fracture site						
Wrist	557	20.50 (18.86, 22.27)	2113	19.62 (18.81, 20.48)	1.05 (0.95, 1.15)	1.16 (1.05, 1.27)
Vertebra	179	6.59 (5.69, 7.63)	621	5.77 (5.33, 6.24)	1.15 (0.97, 1.35)	1.14 (0.96, 1.34)
Hip	413	15.20 (13.80, 16.74)	1445	13.42 (12.75, 14.13)	1.14 (1.02, 1.27)	1.17 (1.05, 1.31)
Humerus	246	9.05 (7.99, 10.26)	813	7.55 (7.05, 8.09)	1.20 (1.04, 1.38)	1.22 (1.06, 1.41)
Non-specified	181	6.66 (5.76, 7.70)	701	6.51 (6.05, 7.01)	1.03 (0.88, 1.22)	1.03 (0.87, 1.21)
Severity						
Severe psoriasis	56	57.28 (44.08, 74.43)	184	52.44 (45.38, 60.59)	1.09 (0.81, 1.45)	1.15 (0.83, 1.60)
Mild-moderate psoriasis	1455	58.19 (55.27, 61.26)	5312	53.30 (51.89, 54.76)	1.10 (1.04, 1.16)	1.13 (1.07, 1.20)
Psoriasis and psoriatic arthritis	65	54.46 (42.71, 69.45)	197	43.70 (38.00, 50.25)	1.26 (0.95, 1.65)	1.62 (1.20, 2.18)

‡Adjusted for age, gender, BMI, alcohol consumption, smoking status, Charlson comorbidity, bisphosphonate, glucocorticoid and PPI use