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Risk of type 2 diabetes and cardiovascular disease in an incident cohort of people with psoriatic arthritis: a population-based cohort study

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ABSTRACT

Objectives To determine the risk of Type 2 diabetes (T2D) and cardiovascular diseases in psoriatic arthritis (PsA) patients compared to the general population and patients with psoriasis.

Methods Incident PsA patients aged 18-89 years were identified in the UK Clinical Practice Research Datalink between 1998 and 2014 and were matched (1:4 ratio) to a general population cohort and psoriasis cohort. The incidence of T2D, cerebrovascular disease (CVD), ischaemic heart disease (IHD) and peripheral vascular disease (PVD) was calculated for each study cohort. Conditional Poisson regression was used to calculate adjusted Relative Risks (RR_{adj}).

Results We identified 6,783 incident cases of PsA. The risk of T2D was significantly higher in the PsA cohort than the general population and psoriasis cohorts (RR_{adj}1.40 (CI_{95}1.15-1.70) and RR_{adj}1.53 (CI_{95}1.19-1.97) respectively). The incidence of IHD, PVD, and the three cardiovascular outcomes combined in the PsA cohort was significantly higher than in the general population. No significant differences in risk were observed between the PsA and psoriasis cohorts for any cardiovascular outcome.

Conclusion

The development of T2D in an incident population of PsA is significantly higher than in psoriasis alone or a general population, whereas the increased risk of cardiovascular disease in PsA and psoriasis is similar.

Keywords: Psoriatic arthritis, Type 2 diabetes, cardiovascular disease, psoriasis, cohort study

Key Messages

The development of type 2 diabetes is an important comorbidity following onset of psoriatic arthritis.

There is an increased risk of cardiovascular disease in psoriatic arthritis similar to that seen in psoriasis.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic multisystem inflammatory disease reported to affect 10-40% of individuals with psoriasis [1]. There is strong evidence that patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease morbidity and mortality, likely in part to be linked to inflammation [2], but at present the evidence in relation to PsA as opposed to psoriasis alone is less abundant.

The understanding of cardiovascular risk in PsA is complicated by an increased prevalence of established cardiovascular risk factors, including the metabolic syndrome (at least three of: obesity, hypertension, impaired glucose tolerance and dyslipidaemia) [3, 4] which is also associated with an increased risk of developing Type 2 diabetes (T2D). Many of the earlier studies of cardiovascular disease focussed on patients with psoriasis [5, 6], with later studies looking specifically at PsA [7-10] and a few separating the PsA population from those with psoriasis alone [11, 12]. These have investigated a range of different cardiovascular composite endpoints and have varied in terms of their study design, study population, outcome definitions, comparator groups and consideration of risk factors.

Although several studies have evaluated the incidence of cardiovascular disease events, many have been within all PsA patients and few studies have looked at the risk within a cohort of newly diagnosed, incident patients, where the temporal relationship can be better determined. Therefore we aimed to calculate the risks of cerebrovascular disease (CVD), ischaemic heart disease (IHD), peripheral vascular disease (PVD) and T2D, within a cohort of incident PsA patients in the United Kingdom (UK) and compare these with the risks in matched cohorts of the general population and patients with psoriasis but no PsA.

METHODS

The UK Clinical Practice Research Datalink (CPRD) contains anonymised medical records for ~15 million individuals collected within primary care and is generally representative of the UK population [13].

A cohort of incident PsA patients aged 18-89 and diagnosed between 1-Jan-1998 and 31-Dec-2014 were identified in the CPRD. Patients were required to have ≥1 year of up-to-standard (UTS) data contribution prior to their date of PsA diagnosis (index date). Cases of PsA were matched at a 1:4 ratio to two randomly selected cohorts based on their index date, year of birth, sex and general practice: the first matched cohort (the general population cohort) included patients with no psoriasis, no PsA and no other inflammatory arthritis, and the second cohort (the psoriasis cohort) included patients with psoriasis but no diagnosis of PsA or other inflammatory arthritis. Patients in the comparator cohorts were assigned the index date of the matched case and were required to have ≥1 year of UTS data prior to the index date. Patients were followed from the index date until the date they were no longer eligible for the cohort or were diagnosed with the outcome of interest. Patients in the general population and psoriasis cohorts who developed psoriasis or PsA respectively after the index date had their person-time contribution censored the day before the diagnosis date.

The outcomes of interest were T2D, CVD, IHD and PVD, identified based on Read codes. An algorithm created and utilised in previous investigations was used to identify patients with T2D [14]. A full description of the methods can be found in Online Supplement I.

Ethical approval

Ethical approval was obtained by the CPRD data provider from a Multicentre Research Ethics Committee for all observational studies and the study protocol was approved by the CPRD Independent Scientific Advisory Committee (15_154R). No additional approval or consent was needed.

Statistical analyses

The incidence, per 10,000 person-years, of T2D, CVD, IHD and PVD were calculated for each study cohort. For each outcome, conditional Poisson regression was used to calculate crude and adjusted relative risks (RR) comparing the risk in the PsA cohort with the risk in the general population and psoriasis cohorts. The following covariates were considered for adjustment in the model; smoking status, body mass index, a prior history of hyperlipidaemia including the issue of a statin prescription, treated hypertension, T2D, psoriasis severity on the index date and corticosteroid and non-steroidal anti-inflammatory drug (NSAID) prescribing. The final models were adjusted for all significant covariates (p <0.05), which was based on their contribution to the model as defined by their contribution to the likelihood. Analyses were performed using R 3.3.0 (R Core Team, 2017).

RESULTS

We identified 6,783 eligible incident cases of PsA, 27,132 matched patients from the general population and 27,132 matched psoriasis patients. The median age at PsA diagnosis was 49 years (IQR 39-59). Table 1 shows the baseline patient characteristics for each cohort. The mean duration of follow-up was similar for all cohorts at approximately 5.5 years.

The incidence of T2D was significantly higher in the PsA cohort than both the general population and psoriasis cohorts (RR_{adj} 1.40 (CI_{95} 1.15-1.70) and RR_{adj} 1.53 (CI_{95} 1.19-1.97) respectively) (Table 2). The incidence of any of the cardiovascular outcomes combined in the PsA cohort was significantly higher than in the general population (RR_{adj} 1.29 (CI_{95} 1.12-1.48)) but not in the psoriasis cohort (RR_{adj} 1.09 (CI_{95} 0.95-1.24)). The incidence of IHD and PVD was significantly higher incidence in the PsA cohort than the general population cohort (RR_{adj} 1.27 (CI_{95} 1.05-1.54) and RR_{adj} 1.40 (CI_{95} 1.02-1.92)). No significant differences in risk were observed between the PsA and psoriasis cohorts for any of the cardiovascular outcomes (Table 2). The median age at incident outcomes was similar for all three cohorts, ranging from approximately 60 years for T2D to 69 years for CVD (Supplementary Table 1).

DISCUSSION

This population-based study identified a 50% increase and 40% increased risk of T2D among an incident cohort of PsA patients compared to patients with psoriasis and those in the general population respectively. There was a 29% increase in risk of the combined cardiovascular diseases, a 27% increase in the risk of IHD and a 40% increase in risk of PVD in PsA compared with the general population after taking into account other potential risk factors, but no increase in any of the cardiovascular outcomes compared to the psoriasis population.

The incidence rates and increased risks observed for T2D in our study using data from the CPRD are consistent with those reported elsewhere [12, 15, 16]. A systematic review and meta-analysis of observational studies investigating the association between psoriasis, PsA and T2D reported the highest risk for patients with PsA and a 'dose effect' in the risk for patients with psoriasis, with those with severe psoriasis having the highest risk [17]. Dubreuil et al reported an increased incidence of diabetes in PsA, psoriasis and rheumatoid arthritis compared to cohorts without the corresponding condition in The Health improvement Network (THIN), a similar database to the CPRD [15]. Unlike rheumatoid arthritis the increased risk of diabetes in PsA and psoriasis was not fully accounted by life-style risk factors, leading the authors to postulate that immune-mediated inflammatory processes specific to psoriatic conditions may exert an effect [15].

Herein we have found that the risk of T2D is 50% higher in PsA than in a matched cohort of patients with psoriasis. We adjusted for possible co-variates including BMI, psoriasis severity and corticosteroid and NSAID prescribing all of which could conceivably account for the findings, although cannot exclude residual confounding. It is possible that the additional inflammatory burden associated with arthritis in combination with higher levels of obesity contribute to the higher risk observed in the PsA cohort than the psoriasis cohort, although we were unable to measure inflammatory markers such as C-reactive protein. A study from the University of Toronto PsA clinic has also reported an association between higher levels of inflammation and PsA disease activity and the risk of diabetes [18]. Similarly, the metabolic syndrome and insulin resistance in PsA has been associated with severity of the underlying disease [19]. Other possibilities to explain the increased risk of T2D in PsA

compared to psoriasis alone include unidentified genetic factors unique to PsA and T2D, the contribution from diet and the microbiome, and the influence of exercise. We were unable to adjust for levels of exercise that are likely to be lower in PsA than controls and may influence body composition and insulin receptor levels in favour of development of diabetes.

The lack of a significant increase in risk of cardiovascular comorbidities in patients with PsA compared to those with psoriasis is consistent with another study using the CPRD [12] and a study of patients from the University of Toronto PsA clinic and psoriasis cohort [11]. However, in both studies the specific cardiovascular endpoints were different and in the Toronto study prevalence rather than incidence of cardiovascular disease was calculated. The presence of an increased risk when compared to the general population looking at the three cardiovascular outcomes (CVD, IHD, PVD) combined, but only an increased risk for IHD and PVD when looking at them separately may partly be due to a lack of statistical power.

The population-based nature and large number of PsA patients included in our study are both strengths, as were the use of validated codes to identify psoriasis and PsA and the inclusion of both a psoriasis and general-population matched comparator group. The inclusion of only incident PsA patients was an advantage for looking at temporal relationships, but will have had an impact of the duration of follow-up available and may have resulted in some patients having insufficient follow-up time (mean duration 5.5 years) after their PsA diagnosis to develop the specific cardiovascular outcomes of interest. There may be some degree of both detection and referral bias, with PsA patients being more likely to visit their healthcare professionals regularly and therefore more likely to undergo investigations and receive a comorbidity diagnosis. Also, the absence of data on tumour necrosis factor-alpha inhibitor (TNFi) therapy and PsA disease activity in the CPRD meant it was not possible to explore the effect of TNFi therapy and disease activity on the incidence of T2D and cardiovascular disease.

The results of this study have demonstrated an increased risk of T2D, IHD and PVD amongst patients with PsA compared with the general population, after adjustment for traditional risk factors. These results support the proposal in existing clinical guidelines [20, 21] that in

order to reduce cardiovascular risk in patients with PsA it is important to treat inflammatory disease as well as screen and treat traditional risk factors early in the disease course.

ACKNOWLEDGMENTS

References

1   Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheum Dis Clin North Am 2015;41(4):545-68.

2   Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. Rheumatology (Oxford) 2014;53(12):2143-54.

3   Gelfand JM, Yeung H. Metabolic syndrome in patients with psoriatic disease. J Rheumatol Suppl 2012;89:24-8.

4   Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55(5):829-35.

5   Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. Br J Dermatol 2009;160(5):1048-56.

6   Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296(14):1735-41.

7   Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 2009;68(7):1131-5.

8   Ernste FC, Sanchez-Menendez M, Wilton KM, Crowson CS, Matteson EL, Maradit Kremers H. Cardiovascular risk profile at the onset of psoriatic arthritis: a population-based cohort study. Arthritis Care Res (Hoboken) 2015;67(7):1015-21.

9   Jafri K, Bartels CM, Shin D, Gelfand JM, Ogdie A. Incidence and Management of Cardiovascular Risk Factors in Psoriatic Arthritis and Rheumatoid Arthritis: A Population-Based Study. Arthritis Care Res (Hoboken) 2017;69(1):51-7.

10   Polachek A, Touma Z, Anderson M, Eder L. Risk of Cardiovascular Morbidity in Patients With Psoriatic Arthritis: A Meta-Analysis of Observational Studies. Arthritis Care Res (Hoboken) 2017;69(1):67-74.

11   Husted JA, Thavaneswaran A, Chandran V, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. Arthritis Care Res (Hoboken) 2011;63(12):1729-35.

12   Edson-Heredia E, Zhu B, Lefevre C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. J Eur Acad Dermatol Venereol 2015;29(5):955-63.

13   Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44(3):827-36.

14   Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. Diabet Med 2006;23(5):516-21.

15   Dubreuil M, Rho YH, Man A, et al. Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: a UK population-based cohort study. Rheumatology (Oxford) 2014;53(2):346-52.

16   Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis 2010;69(12):2114-7.

17   Coto-Segura P, Eiris-Salvado N, Gonzalez-Lara L, et al. Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. Br J Dermatol 2013;169(4):783-93.

18   Eder L, Chandran V, Cook R, Gladman DD. The Risk of Developing Diabetes Mellitus in Patients with Psoriatic Arthritis: A Cohort Study. J Rheumatol 2017;44(3):286-91.

19   Haroon M, Gallagher P, Heffernan E, FitzGerald O. High prevalence of metabolic syndrome and of insulin resistance in psoriatic arthritis is associated with the severity of underlying disease. J Rheumatol 2014;41(7):1357-65.

20   Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol 2016;68(5):1060-71.

21   Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75(3):499-510.

Table 1

Baseline characteristics of the PsA, psoriasis and general population cohorts

	PsA		Psoriasis cohort		General population cohort	
	N	%	N	%	N	%
N	6,783		27,132		27,132	
Sex (% male)	3,327	49.05	13,308	49.05	13,308	49.05
Median age[*], years (IQR)	49	(39-59)	49	(39-59)	49	(39-59)
Mean follow-up post index, years (SD)	5.8	(4.1)	5.5	(4.1)	5.5	(4.1)
Mean duration of psoriasis,[*] years (SD)	11.3	(10.9)	11.8	(10.6)	---	---
Body mass index[†]						
<25.0	869	(12.8)	4,190	(15.4)	4,149	(15.3)
25.0-29.9	1,226	(18.1)	4,511	(16.6)	4,257	(15.7)
30.0-34.9	844	(12.4)	2,602	(9.6)	2,254	(8.3)
≥35.0	641	(9.5)	1,746	(6.4)	1,252	(4.6)
Unknown	3,203	(47.2)	14,083	(51.9)	15,220	(56.1)
Smoking status[†]						
Non-smoker	3,059	(45.1)	11,001	(40.6)	13,533	(49.9)
Current smoker	1,605	(23.7)	8,199	(30.2)	6,509	(24.0)
Ex-smoker	2,084	(30.7)	7,480	(27.6)	6,067	(22.4)
Unknown	35	(0.5)	452	(1.7)	1,023	(3.8)
Hyperlipidaemia or ≥1 statin prescription[‡]	1,044	(15.4)	4,137	(15.2)	3,490	(12.9)
Treated hypertension[‡]	1,928	(28.4)	6,574	(24.2)	5,618	(20.7)
Type 2 diabetes[‡]	414	(6.1)	1500	(5.5)	1160	(4.3)
Cerebrovascular disease[‡]	106	(1.2)	582	(2.2)	454	(1.7)
Ischaemic heart disease[‡]	314	(4.6)	1288	(4.8)	979	(3.6)
Peripheral vascular disease[‡]	65	(1.0)	225	(1.1)	225	(0.8)

[*] on the index date [†] closest to and within 3 years prior to the index date [‡] ≥1 diagnosis code on or before the index date

Table 2

Risk of type 2 diabetes and cardiovascular disease in patients with PsA

Comorbidity	PsA compared with a <u>general population cohort</u> (no PsA and no psoriasis)						PsA compared with a <u>psoriasis cohort</u>					
	Unadjusted			Adjusted[†]			Unadjusted			Adjusted[†]		
	RR	CI_{95}	P	RR	CI_{95}	P	RR	CI_{95}	P	RR	CI_{95}	P
Type 2 diabetes	1.72	1.50-1.97	<0.0001	1.40[a]	1.15-1.70	0.0007	1.49	1.30-1.70	<0.0001	1.53[f]	1.19-1.97	0.0009
Cardiovascular disease[‡]	1.43	1.25-1.63	<0.0001	1.29[b]	1.12-1.48	0.0005	1.12	0.99-1.28	0.08	1.09[g]	0.95-1.24	0.23
Cerebrovascular disease	1.40	1.14-1.73	0.0013	1.24[c]	0.99-1.56	0.06	1.08	0.88-1.32	0.48	1.09[h]	0.86-1.37	0.48
Ischaemic heart disease	1.41	1.18-1.69	0.0002	1.27[d]	1.05-1.54	0.02	1.12	0.93-1.34	0.22	1.06[i]	0.87-1.28	0.57
Peripheral vascular disease	1.40	1.02-1.92	0.04	1.40[e]	1.02-1.92	0.04	1.14	0.84-1.56	0.41	1.14[j]	0.84-1.56	0.41

[‡] including cerebrovascular disease, ischaemic heart disease and peripheral vascular disease

[†] The following covariates were considered for adjustment in the model; smoking status, body mass index, a prior history of hyperlipidaemia including the issue of a statin prescription, treated hypertension, type 2 diabetes, psoriasis severity on the index date, corticosteroid and NSAID prescribing. The final models were adjusted for all significant covariates (p <0.05) as following. [a] BMI and hypertension; [b] hypertension; [c] hypertension and hyperlipidaemia; [d] hypertension; [e] No covariates significant and requiring adjustment [f] BMI, smoking, hypertension and NSAID prescribing; [g] smoking and hypertension; [h] smoking, hypertension, hyperlipidaemia and steroid prescribing; [i] hypertension; [j] No covariates significant and requiring adjustment