Increased Risk of Diabetes Mellitus and Likelihood of Receiving Diabetes Mellitus Treatment in Patients With Psoriasis

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Objective: To assess the risk of incident diabetes mellitus (DM) in patients with psoriasis and to evaluate DM treatment patterns among patients with psoriasis and incident DM.

Design: Population-based cohort study.

Setting: United Kingdom–based electronic medical records.

Patients: We matched 108 132 patients with psoriasis aged 18 to 90 years with 430 716 unexposed patients based on practice and time of visit. For our nested study, only patients who developed incident DM during our study time were included.

Main Outcome Measures: Incident DM and adjusted risk of pharmacotherapy among those with incident DM.

Results: The fully adjusted hazard ratios (95% CIs) for incident DM were 1.14 (95% CI, 1.10-1.18), 1.11 (95% CI, 1.07-1.15), and 1.46 (95% CI, 1.30-1.65) in the overall, mild, and severe psoriasis groups, respectively. Among those with incident DM and severe psoriasis, the adjusted risk for receiving DM pharmacotherapy was 1.55 (95% CI, 1.15-2.10).

Conclusions: Our results suggest that psoriasis is an independent risk factor for the development of type 2 DM in a dose-dependent manner, and that patients with severe psoriasis who develop DM are more likely to receive systemic diabetic therapies in comparison with patients with DM but without psoriasis.

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PSORIASIS IS A COMMON, chronic inflammatory disease affecting 2% to 4% of the adult population.[1-6] A broad and growing literature has found that psoriasis is associated with myocardial infarction (MI), stroke, metabolic syndrome, and cardiovascular mortality, which is thought to be due to chronic inflammation that characterizes the pathophysiologic mechanisms of these conditions.[7-31] In addition, mechanistic data suggest a link between psoriasis and diabetes mellitus (DM) underscored by T_H1 cytokines, which can promote insulin resistance and disordered metabolism (ie, metabolic syndrome) and promote inflammatory cytokines known to drive psoriasis.[32-35] Despite a growing body of studies examining this relationship, relatively few population-based cohort studies have examined the risk of DM in patients with psoriasis.[36,37]

Qureshi et al[36] demonstrated that a cohort of 1813 normotensive female nurses with self-reported psoriasis had a relative risk of 1.63 (95% CI, 1.25-2.12) for developing DM, independent of risk factors such as age, body mass index (BMI), smoking, alcohol intake, and physical activity. Another study by Brauchli et al[37] included a population-based nested analysis of 1061 patients with DM using the General Practice Research Database and found an odds ratio (OR) of 1.31 (95% CI, 1.13-1.51) for incident psoriasis among people with incident DM while controlling for hyperlipidemia, smoking, hypertension (HTN), infections, and oral steroids use. To date, this is the only study to our knowledge to examine the impact of psoriasis severity, finding an OR of 1.61 (95% CI, 0.90-2.88) for severe psoriasis, as measured by use of oral psoriasis medications, among patients with incident DM. To our knowledge, no studies have evaluated DM treatment patterns among patients with psoriasis and DM.

Our primary aim was to conduct a large, population-based cohort study to determine the risk of incident type 2 DM (T2DM) in patients with psoriasis of vary-

ing severities. Our secondary aim was to determine whether patients with DM and psoriasis are more likely to receive prescription diabetic therapy compared with patients with DM but with no psoriasis. We hypothesized that patients with psoriasis, especially if severe, have an increased risk of developing T2DM, and that patients with DM and psoriasis would have greater utilization of systemic DM medications than patients with DM alone.

METHODS

STUDY DESIGN

Methods conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[38] Using an electronic medical records database, we conducted a population-based cohort study of adults aged 18 to 90 years with psoriasis (ie, the exposed cohort) vs patients without psoriasis (ie, the unexposed comparison cohort). For our secondary aim we performed a nested study including only patients who developed incident T2DM within our study period.

This study was approved by the University of Pennsylvania, Philadelphia, institutional review board. Because only deidentified data were used, no informed consent was required.

SETTING/DATA SOURCE

We used The Health Improvement Network (THIN) data collected from 2003 through October 2008. THIN is an electronic medical records database of more than 7.5 million people and broadly represents 4.6% of the UK population across over 400 medical practices. THIN contains deidentified patient demographics, medical diagnoses, laboratory results, and prescriptions as recorded by general practitioners (GPs), who serve as the primary point of medical contact in the United Kingdom. THIN uses monetary incentives, quality targets, and training to ensure accurate and complete records that include information from hospital and specialty care.

STUDY POPULATION AND DEFINITIONS OF EXPOSURE AND OUTCOMES

Exposed patients were eligible for the cohort if they were 18 to 90 years of age as of January 1, 2010, and had at least 1 medical record Read Code indicating a diagnosis of psoriasis. Psoriasis diagnostic codes in THIN have been shown to accurately reflect a psoriasis diagnosis with a positive predictive value of 90%.[39] We excluded patients with existing DM Read Codes at the time of their first psoriasis code, with undated DM codes, and with a code indicative of any type of DM other than T2DM.

We categorized patients with psoriasis as having severe psoriasis if they had a treatment record for a systemic psoriasis medication (methotrexate, cyclosporine, oral retinoid, azathioprine, hydroxyurea, mycophenolate mofetil, or phototherapy [UV-B or psoralen and UV-A treatment]). We did not include biologic therapies because these were not widely used for psoriasis in the United Kingdom during our study period. Patients with psoriasis without a medical record for any of these treatments were considered to have mild psoriasis.

To construct an unexposed comparison group, each exposed patient was randomly matched to up to 4 patients without a psoriasis Read Code from the same practice who were aged 18 to 90 years and were seen within 60 days of the time the exposed patient received his or her first psoriasis code or registered in the practice (whichever came later).

To identify patients with DM we modified a previously validated algorithm in THIN.[40,41] Patients were identified as having DM if they had received at least 2 diagnostic codes indicative of T2DM on separate occasions or 1 diagnostic code and 1 laboratory value or medication that was indicative of T2DM. For our secondary aim, outcomes measured included use of oral hypoglycemic medications (yes or no) and use of insulin (yes or no).

SAMPLE SIZE AND POWER ESTIMATES

All patients with psoriasis meeting our selection criteria were included in this study, yielding an exposed population of 108 132 patients and a comparison (unexposed) population of 430 716. This sample size ensures that we can detect a hazard ratio (HR) of 1.06 with 80% power assuming 2-sided, .05 α level tests for the primary aim of the study.

IDENTIFICATION OF CONFOUNDERS

Potential confounders were selected based on being known risk factors for DM (age, sex, BMI, use of oral steroids), as well as factors that may be confounders, such as smoking, alcohol intake, HTN, hyperlipidemia, depression, anxiety, MI, and socioeconomic status.

STATISTICAL ANALYSIS

We performed descriptive statistics to summarize and compare patient demographics, covariates of interest, and univariate outcomes using Pearson χ^2 test for dichotomous variables (eg, sex) and t tests for continuous variables (eg, age).

We calculated Kaplan-Meier estimates of time to DM diagnosis for each matched group and compared these estimates using the log-rank test. Observation time started at the latest of the following: (1) the date when the practice began uploading information into the database, (2) the date of patient registration with the practice, and (3) the date of the patient's first psoriasis Read Code, or, in unexposed patients, the closest corresponding visit. We calculated unadjusted and adjusted Cox proportional hazards models in each group and stratified these by psoriasis severity. Censoring occurred when patients transferred out of the practice, died, received a DM code, or reached the end of the study period.

We used a purposeful selection approach for multivariate modeling. In our initial model we included all covariates a priori thought to be clinically important (ie, BMI, age, and sex), as well as any covariates found in the descriptive statistics to have a $P < .10$. Variables were eliminated from the model if their removal did not have a significant effect on the log partial likelihood (using likelihood ratio tests) and did not change the HR estimate of any other covariate by more than 15%. We also evaluated 2-way interaction terms, such as psoriasis and sex, and psoriasis and age, and decided, a priori, to incorporate them in our final model if they were statistically significant ($P < .10$). Each variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log-log survival plots and by tests of the statistical significance of each variable's interaction with time. Model fit was assessed by graphical inspection of Schoenfeld residual plots using standard methods.

For the nested study we included all patients with psoriasis and controls who developed DM within our study window regardless of their initial matching designation. We performed adjusted and unadjusted logistic regressions with use of oral medications and use of insulin as our outcomes and psoriasis status and severity as covariates. The confounding vari-

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Table 1. Characteristics of Study Group[a]

Characteristic	Cohort					
	Psoriasis	Psoriasis Unexposed	Mild Psoriasis	Mild Psoriasis Unexposed	Severe Psoriasis	Severe Psoriasis Unexposed
Qualifying patients, No.	108 132	430 716	101 870	405 819	6229	24 784
Age at start of follow-up, y						
Mean (SD)	46.03 (16.62)	48.40 (16.64)	45.91 (16.71)	48.35 (16.66)	47.99 (15.11)	49.26 (16.32)
Median (IQR)	44.30 (32.31-58.88)	47.47 (34.98-61.24)	44.10 (32.10-58.85)	47.40 (34.89-61.20)	47.17 (36.01-59.38)	48.57 (36.16-62.11)
P value		<.001[b]		<.001[b]		<.001[b]
Sex						
Male	52 420 (48.49)	189 020 (43.90)	49 390 (48.48)	178 060 (43.88)	3030 (48.64)	10 960 (44.22)
Female	55 679 (51.51)	241 583 (56.10)	52 480 (51.52)	227 759 (56.12)	3199 (51.36)	13 824 (55.78)
P value		<.001[c]		<.001[c]		<.001[c]
Transfer from practice	29 197 (27.01)	107 311 (24.92)	27 914 (27.40)	101 040 (24.90)	1283 (20.60)	6271 (25.30)
P value		<.001[c]		<.001[c]		<.001[c]
Patient death	4683 (4.33)	19 157 (4.45)	4330 (4.25)	17 933 (4.42)	353 (5.67)	1224 (4.94)
P value		.10[c]		.02[c]		.20[c]
Censored due to end of follow-up time	78 902 (72.99)	323 292 (75.08)	73 956 (72.60)	304 779 (75.10)	4946 (79.40)	18 513 (74.70)
P value		<.001[c]		<.001[c]		<.001[c]
Confounders						
BMI, mean (SD)	26.46 (5.32)	26.21 (5.20)	26.40 (5.30)	26.22 (5.21)	27.32 (5.63)	26.20 (5.07)
P value		<.001[b]		<.001[b]		<.001[b]
Hypertension	27 182 (25.15)	117 795 (27.36)	25 168 (24.71)	110 711 (27.28)	2014 (32.33)	7084 (28.58)
P value		<.001[c]		<.001[c]		<.001[c]
Hyperlipidemia	10 809 (10.00)	45 800 (10.64)	10 049 (9.86)	42 967 (10.59)	760 (12.20)	2833 (11.43)
P value		<.001[c]		<.001[c]		<.09[c]
DM outcomes						
DM	3992 (3.7)	14 537 (3.4)	3599 (3.5)	13 626 (3.4)	393 (6.3)	911 (3.7)
P value		<.001[c]		.006		<.001[c]
Age at DM onset, y						
Mean (SD)	62.0 (12.3)	62.8 (12.2)	62.3 (12.3)	62.8 (12.2)	59.0 (10.9)	62.8 (12.2)
Median (IQR)	63.4 (54.8-71.6)	64.2 (55.3-72.4)	63.4 (54.2-71.8)	63.8 (54.6-72.2)	59.61 (51.6-66.2)	64.0 (54.8-72.5)
P value		<.001[b]		<.001[b]		<.001[b]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; IQR, interquartile range.
[a] Data are given as number (percentage) except where noted.
[b] *t* Test.
[c] χ^2 Test.

ables are the same as those described herein except that we used smoking and BMI information obtained before the diagnosis of DM whenever possible and included age at T2DM onset as a covariate.

We performed multiple sensitivity analyses to assess the robustness of our results and to ensure they were not explained by systematic error (ie, information bias) or treatment effects.

All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc) and STATA software (version 10; Stata Corp). Statistical significance was determined using 2-sided *P* values at the .05 level (95% CI) unless otherwise noted.

RESULTS

We identified 108 132 patients with psoriasis (exposed cohort) and 430 716 matched patients without psoriasis (unexposed cohort). Among the patients with psoriasis, 101 870 were classified as having mild disease and 6229 were classified as having severe disease based on psoriasis treatment patterns. The most notable differences between the exposed and unexposed groups were age, sex, and current smoking status based on univariate analyses (**Table 1**). Among patients defined as having severe psoriasis, the most commonly prescribed medication was methotrexate (60.5%) (**Table 2**).

In unadjusted analyses the risk of incident DM was increased among patients with psoriasis in a dose-

Table 2. Systemic Psoriasis Treatments Received by 6229 Patients With Severe Psoriasis[a]

Therapy	No. (%)
Methotrexate	3768 (60.49)
Phototherapy (UV-B or PUVA)	1514 (24.31)
Azathioprine	724 (11.62)
Cyclosporine	641 (10.29)
Oral retinoid	272 (4.37)
Hydroxyurea	195 (3.13)
Mycophenolate mofetil	84 (1.35)

Abbreviation: PUVA, psoralen and UV-A treatment.
[a] Percentages do not add up to 100 because patients may have been treated with multiple systemic medications.

response fashion with psoriasis severity (overall psoriasis HR, 1.18; 95% CI, 1.14-1.23; severe psoriasis HR, 1.75; 95% CI, 1.56-1.98). In fully adjusted models that controlled for age, sex, BMI, HTN, and hyperlipidemia, psoriasis was found to be an independent risk factor for incident DM (HR, 1.14; 95% CI, 1.10-1.18), and this risk was greatest in patients with severe disease (HR, 1.46; 95% CI, 1.30-1.65) (**Table 3**). The adjusted attributable risk of developing T2DM among 1000 patients with psoriasis per year is 0.9 extra cases overall, 0.7 cases in those with mild psoriasis, and 3.0 cases in those with se-

Table 3. Incidence of Diabetes Mellitus (DM) by Study Group

Characteristic	Exposed	Unexposed	Mild Exposed	Mild Unexposed	Severe Exposed	Severe Unexposed
Person-time, y						
Mean (SD)	5.17 (3.60)	5.25 (3.62)	5.11 (3.59)	5.22 (3.61)	6.15 (3.58)	5.76 (3.64)
Median (IQR)	4.59 (1.98-7.87)	4.71 (2.03-8.02)	4.58 (1.92-7.78)	4.65 (2.01-7.94)	6.28 (3.05-8.93)	5.60 (2.51-8.58)
Cumulative	545 436	2 208 485	508 599	2 068 935	36 837	139 549
Incident DM rate	0.0077	0.0066	0.0071	0.0066	0.0107	0.0065
(95% CI)	(0.0075-0.0080)	(0.0065-0.0067)	(0.0068-0.0073)	(0.0065-0.0067)	(0.0966-0.0118)	(0.0061-0.0070)
Incident DM, HR (95% CI)[a]	1.18 (1.14-1.23)	1 [Reference]	1.14 (1.10-1.18)	1 [Reference]	1.75 (1.56-1.98)	1 [Reference]
Incident DM, HR (95% CI)[b]	1.14 (1.10-1.18)	1 [Reference]	1.11 (1.07-1.15)	1 [Reference]	1.46 (1.30-1.65)	1 [Reference]

Abbreviations: HR, hazard ratio; IQR, interquartile range.
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, body mass index, hypertension, and hyperlipidemia.

Table 4. Sensitivity Analyses: Hazard Ratio (HR) of Incident Diabetes Mellitus (DM)

Characteristic	Incident DM, HR (95% CI)[a]		
	Psoriasis Overall	Mild Psoriasis	Severe Psoriasis
Original model[a]	1.14 (1.10-1.18)	1.11 (1.07-1.15)	1.46 (1.30-1.65)
Restricting to patients who were seen at least once a year	1.13 (1.09-1.72)	1.10 (1.06-1.15)	1.46 (1.28-1.65)
Excluding patients with psoriatic arthritis	1.13 (1.09-1.17)	1.11 (1.07-1.15)	1.50 (1.29-1.74)
Excluding patients who ever received a systemic steroid, retinoid, or cyclosporine	1.12 (1.07-1.17)	1.11 (1.06-1.16)	1.44 (1.21-1.72)
Restricting to patients who received an oral retinoid or phototherapy	NA	NA	1.52 (1.20-1.93)
Restricting to patients with a diagnosis of DM that occurs at ≥1 y after the start date	1.14 (1.10-1.19)	1.11 (1.07-1.16)	1.45 (1.27-1.65)
Restricting to patients who were seen prior to 2005 (ie, prior to when biologic therapy becoming prevalent for psoriasis treatment in the United Kingdom)	NA	NA	1.54 (1.30-1.83)
Restricting to patients aged ≥50 y	1.15 (1.10-1.20)	1.13 (1.08-1.76)	1.42 (1.23-1.64)

Abbreviation: NA, not applicable.
[a] Adjusted for age, sex, body mass index, hypertension, and hyperlipidemia.

vere psoriasis. These findings remained robust in numerous sensitivity analyses (**Table 4**).

Among patients who developed incident DM we evaluated DM treatment patterns. We observed no difference in use of oral hypoglycemic agents (OR, 1.03; 95% CI, 0.95-1.11) or insulin (OR, 1.06; 95% CI, 0.89-1.25) among patients with mild psoriasis; however, patients with severe psoriasis were more likely to be prescribed oral hypoglycemic agents (OR, 1.53; 95% CI, 1.14-2.07) and had a trend toward being more likely to be prescribed insulin (OR, 1.32; 95% CI, 0.75-2.33) (**Table 5**). These findings remained robust to sensitivity analyses that excluded patients with psoriatic arthritis or restricted the analysis to patients with at least 1 year of follow-up after their DM diagnosis.

COMMENT

The data from this study suggest that psoriasis is a risk factor for the development of T2DM and that this relationship is dose dependent, with severe psoriasis conferring a higher risk than mild psoriasis. Mechanistically, this relationship may be driven by chronic inflammation because both psoriasis and T2DM are associated with elevated levels of T_H1-driven inflammatory markers, and because several studies have pointed to endogenous insulin resistance in patients with psoriasis.[32-35]

With approximately 125 million individuals affected by psoriasis worldwide, we estimate that an additional 115 500 people will develop DM each year owing to the risk posed by psoriasis above and beyond conventional risk factors measured in routine medical practice.[42] Furthermore, our results indicate that people with severe psoriasis who develop T2DM are more likely to receive systemic therapy for their DM, compared with patients with DM without psoriasis. This finding was primarily driven by the use of oral T2DM medications.

Our study advances the existing literature regarding psoriasis and incident T2DM and has several strengths. With more than 100 000 patients with psoriasis, to our knowledge, this study is by far the largest to date to examine the relationship between psoriasis and DM. The large sample afforded us a high degree of precision when we studied subgroups (eg, 6229 patients with severe psoriasis) or excluded large numbers of patients in sensitivity analyses. Because our cohorts were broadly representative and population based, the findings were less likely to have been influenced by bias (ie, good internal validity) and are likely to be generalizable to the psoriasis population at large (ie, strong external validity). We also had access to medical, treatment, and laboratory records that allowed us to precisely define outcomes, confounders, and sensitivity analysis subpopulations. Moreover, to our knowledge, this is the first study to show that patients with T2DM and with severe psoriasis are more likely to

Table 5. Severity and Treatment of Type 2 Diabetes Mellitus in 16 407 Patients

Treatment Type	OR (95% CI)[a]		
	Exposed	Mild Exposed	Severe Exposed
Oral hypoglycemic use	1.06 (0.98-1.15)	1.03 (0.95-1.11)	1.53 (1.14-2.07)
Insulin use	1.07 (0.90-1.26)	1.06 (0.89-1.25)	1.32 (0.75-2.33)
Oral hypoglycemic or insulin use	1.05 (0.97-1.13)	1.01 (0.93-1.10)	1.55 (1.15-2.10)

Abbreviation: OR, odds ratio.
[a] Adjusted for sex, age at diabetes mellitus onset, body mass index, history of smoking, and age at time of outcome.

receive pharmacologic intervention for their T2DM compared with their counterparts without psoriasis, with all other measurable risk factors being accounted for.

Potential limitations in observational studies include selection bias, information bias, misclassification bias, confounding, and statistical error. Herein, we systematically address these potential limitations. Our results are unlikely to be explained by selection bias because all patients (exposed and unexposed) were selected from the same source population. In addition, the potential for information bias is minimized because data on each patient were collected in a similar manner by GPs matched by practice. It is conceivable that patients with severe psoriasis require more frequent visits to their GPs, and therefore DM may be picked up earlier and more frequently in this group.[7,8,10,43] However, we completed a variety of sensitivity analyses accounting for frequency of medical visits as well as restricting to a population of patients routinely screened for DM based on UK pay-for-performance national standards and screening guidelines, and these did not change our results.[44,45] Nevertheless, given the observational nature of this study, we cannot fully exclude information bias as a potential source of error.

We expect some degree of misclassification of mild and severe psoriasis because we used a treatment-based algorithm to define disease severity. Such misclassification would be expected to artificially increase the strength of the association in the group with mild psoriasis and decrease the association in the group with severe psoriasis. Additional analyses with more restrictive definitions of severe psoriasis yielded similar findings.[39] We assessed the robustness of our definition of severe psoriasis by restricting our analysis of severe psoriasis to those receiving highly specific psoriasis therapies (oral retinoids and phototherapy) and by excluding patients with a psoriatic arthritis diagnosis; we also evaluated treatment effects using stratified analyses to ensure that the results were not driven by oral therapies known to promote hyperglycemia. Our overall conclusions were unchanged in these analyses. To confirm that we were capturing incident and not prevalent DM, we restricted our analysis to patients who received a DM diagnosis at least 1 year after their start date and to those with at least 1 year of follow-up after their DM diagnosis. Finally, the results remained robust when restricting the analyses to patients seen on average at least once per year, minimizing the likelihood that detection bias explains the findings.

In all observational studies the possibility of unmeasured or unknown confounders should be addressed. To be thorough, we tested and accounted for numerous confounders in our primary analyses and then completed a large number of sensitivity analyses.

Finally, as with any hypothesis-based analysis, it is possible that our findings may be the result of chance alone (type I error). In order to minimize this type of error, we designed our study to test all of our hypotheses at the .05 α level. Furthermore, the likelihood of type II error (failure to reject the null hypothesis when H_1 is true) is minimized in our study owing to its large sample size, which affords us more than adequate power for each hypothesis under consideration, as demonstrated by our 95% CIs.

In conclusion, our results suggest that psoriasis is a risk factor for the development of DM and that the risk increases with increasing severity of psoriasis. In addition, patients with severe psoriasis are more likely to develop DM that will be treated pharmacologically.

Further research into the extent to which psoriasis and its treatment play a role in the development of T2DM and its complications is warranted. In addition, it is necessary to determine why patients with severe psoriasis who develop DM are more likely to receive prescription hypoglycemic treatments. These findings, combined with the large literature linking psoriasis to cardiovascular and metabolic disease, suggest that patients with psoriasis should be encouraged to lower their risk of DM and its complications by undergoing therapeutic lifestyle changes and appropriate screenings for signs of insulin resistance.

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