

The Risk of Developing Diabetes Mellitus in Patients with Psoriatic Arthritis: A Cohort Study

Lihi Eder, Vinod Chandran, Richard Cook, and Dafna D. Gladman

ABSTRACT. Objective. To estimate the prevalence of diabetes mellitus (DM) in patients with psoriatic arthritis (PsA) in comparison with the general population and to assess whether the level of disease activity over time predicts the development of DM in these patients.

Methods. A cohort analysis was conducted in patients followed in a large PsA clinic from 1978 to 2014. The prevalence of DM in the patients was compared with the general population of Ontario, Canada, and the age-standardized prevalence ratio (SPR) was calculated. For the assessment of risk factors for DM, time-weighted arithmetic mean (AM) levels of PsA-related disease activity measures were assessed as predictors for the development of DM. Multivariable Cox proportional hazards models were used to compute HR for incident DM after controlling for potential confounders.

Results. A total of 1305 patients were included in the analysis. The SPR of DM in PsA compared with the general population in Ontario was 1.43 ($p = 0.002$). Of the 1065 patients who were included in the time-to-event analysis, 73 patients were observed to develop DM. Based on multivariable analyses, AM tender joint count (HR 1.53, 95% CI 1.08–2.18, $p = 0.02$) and AM erythrocyte sedimentation rate (HR 1.21, 95% CI 1.03–1.41, $p = 0.02$) predicted the development of DM.

Conclusion. The prevalence of DM is higher in patients with PsA compared with the general population. Patients with elevated levels of disease activity are at higher risk of developing DM. (J Rheumatol First Release February 1 2017; doi:10.3899/jrheum.160861)

Key Indexing Terms:

PSORIATIC ARTHRITIS INFLAMMATION EPIDEMIOLOGY DIABETES MELLITUS

Psoriatic arthritis (PsA), a chronic inflammatory arthritis affecting 20%–30% of the patients with psoriasis (PsO)¹, is strongly associated with obesity. Obesity, particularly excess visceral adiposity, is associated with insulin resistance, hyperglycemia, dyslipidemia, and hypertension, which together are termed the “metabolic syndrome.” These metabolic disorders increase the risk of development of Type 2 diabetes mellitus (DM), the most prevalent metabolic disease worldwide; it is characterized by defects in insulin secretion and peripheral insulin resistance². DM is associated with significant

longterm morbidity and premature mortality and has significant implications at the patient and society level³. Subclinical chronic inflammation has been reported as an independent risk factor for the development of DM. Indeed, high levels of inflammatory markers, such as white blood cell counts, high-sensitivity C-reactive protein (hsCRP), and proinflammatory cytokines, predict the development of DM in diverse human populations independently of the initial degree of insulin resistance and obesity^{4,5,6}.

Patients with PsO, in particular those with severe skin disease, have an increased risk of developing incident DM compared with the general population^{7,8,9}. Less information is available about the association between PsA and DM. While several cross-sectional studies reported higher point prevalence of DM in patients with PsA, fewer studies assessed the risk of developing incident DM in patients with PsA^{10,11,12,13,14,15}. Additionally, to the best of our knowledge, no study to date has assessed the association between the levels of PsA disease activity over time and the risk of developing DM. This issue is of interest because there is limited information about the underlying mechanisms driving insulin resistance and DM in psoriatic disease. It is unclear whether PsA-related inflammation is involved, independent of obesity. Finding such a link will support the potential involvement of “treat to target” for prevention of cardiometabolic comorbidities in these patients. In our large cohort study, we assessed the prevalence of DM in PsA in comparison with the general population in Ontario, Canada.

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In addition, we examined the hypothesis that higher levels of PsA disease activity over time predict the development of DM in patients with PsA.

MATERIALS AND METHODS

Patients and setting. A prospective cohort study was conducted in patients followed from January 1, 1978, to November 1, 2014, at the University of Toronto PsA clinic. The cohort consisted of patients with PsA who were referred to the clinic by family doctors and other medical specialists for the management of their PsA. The clinic serves as a primary, secondary, and tertiary referral center; therefore, the spectrum of disease severity of the patients seen in the clinic is broad. The patients were enrolled in an ongoing prospective cohort study aimed at assessing prognostic factors in PsA. Each patient was assessed at 6- to 12-month intervals according to a standard protocol¹⁶. Information collected and stored in a database included demographics, lifestyle habits, medical history, medication use, disease-related outcomes, and laboratory findings. The majority (98%) of the patients in the clinic met the CIASSification for Psoriatic ARthritis criteria for classification of PsA¹⁷. The study included 2 parts: (1) the assessment of the point prevalence of DM in comparison with the general population, and (2) the assessment of predictors for incident DM in patients with PsA. For the assessment of the point prevalence, all patients who were registered in the PsA clinic and were known to be alive were included in the analysis. For the second part, predicting DM in PsA, all patients followed in the clinic from 1978 were included. Patients who had DM at clinic entry and those with only 1 visit to the clinic were excluded. All subjects' written consent was obtained according to the Declaration of Helsinki. The study was approved by the University Health Network Research Ethics Board (08-0630-AE).

Data collection and definitions. The clinic database was searched to identify patients with DM. DM was defined as any of the following: (1) physician diagnosis of DM, (2) use of glucose-lowering medications, or (3) elevated blood glucose level (> 200 mg/dl in at least 2 random blood samples).

The following variables related to PsA activity were assessed as predictors of incident DM: tender (TJC) and swollen joint count (SJC), dactylitis count (no. digits with dactylitis), Psoriasis Area and Severity Index (PASI), and erythrocyte sedimentation rate (ESR). Because these variables were measured at each clinic visit, a time-adjusted arithmetic mean of all measurements from the first visit to the last visit (in those without DM) or to the visit prior to the diagnosis of DM was calculated for each variable. These adjusted mean variables represented the cumulative inflammatory burden in PsA-related domains.

Other known risk factors for DM considered as confounders included age, sex, duration of PsA (at clinic entry), body mass index (BMI; at clinic entry), and cumulative steroid use. Steroid use was measured as the cumulative prednisone dose (in mg) used during the followup period. If other forms of corticosteroid medications were used, the equivalent dose of prednisone was calculated. Synthetic disease-modifying antirheumatic drugs [DMARD; and the effect of methotrexate (MTX) and leflunomide (LEF) individually] and biologic medications [antitumor necrosis factor- α (TNF- α) or interleukin (IL)-12/23 inhibitors] were assessed as effect modifiers. The use of these medications was recorded at each clinic visit.

Comparison group. Comparative data on DM in the general population in the province of Ontario, Canada, were obtained from the Canadian Community Health Survey, a cross-sectional survey examining health determinants, health status, and health system use, carried out by Statistics Canada¹⁸. The survey was conducted by telephone and computer-assisted personal interviews at the provincial level. Summary tables about individuals reporting a diagnosis of diabetes by a health professional subdivided by province and age group were published by Statistics Canada (www5.statcan.gc.ca/cansim) for 2013. These samples included individuals aged > 19 years and living in Ontario, Canada.

Statistical analyses. Statistical analyses were performed using SAS (version 9.3). Baseline descriptive statistics were computed with continuous variables

summarized by their means and SD and categorical variables summarized by proportions. The prevalence of DM in patients followed up in the PsA cohort was compared with information from the general population in Ontario through standardized prevalence ratios (SPR) calculated in the same fashion as the more familiar standardized mortality ratios. The age-standardized prevalence rates (95% CI) of DM in the PsA cohort was estimated using the matched age groups in the general population as the reference for standardization. Only patients registered in the clinic and known to be alive were included in the analysis. The youngest age group (12–19 yrs) was excluded because patients are registered in the PsA clinic only as of 18 years of age. We reported the global SPR and the SPR per age category as well as the age-standardized prevalence rates of DM in PsA.

For the assessment of predictors of incident DM, only patients who had more than 1 visit to the clinic and were event-free (nondiabetic) at clinic entry were included. The time from the date of birth to the date of the diabetes diagnosis was the response of interest; individuals who were event-free at the date of their last visit were censored at that time. Often the exact date of DM diagnosis was unknown because the diagnosis was made by another physician. Thus, the date of diagnosis of DM was imputed as the midpoint between the last visit date without DM and the first visit date with DM. Cox proportional hazards models were fitted with age as the chosen time scale and the age at study entry as the left-truncation time. The time-adjusted mean levels of the following variables were considered as predictors of incident DM: PASI, TJC, SJC, dactylitis count, and ESR. The initial univariate model included each of these predictors as a single covariate in the regression model. Subsequently, each of the above-mentioned predictors was included in a separate multivariable regression model adjusting for age at clinic entry, sex, duration of PsA, cumulative corticosteroid dose, and BMI at clinic entry. All variables that achieved significance at the 10% level were then included in a more comprehensive multivariable model that adjusted for confounders. Medication variables, defined as use of any DMARD, use of MTX, use of LEF, and use of biologics, were assessed as effect modifiers of each of the predictors. These variables were assessed as time-varying covariates. Multiple imputation (with SAS) was used to impute missing data in conjunction with the Cox model. The full conditional specification and predictive mean-matching methods were specified as methods of imputation. The imputation model included the demographic variables, laboratory test results, medications, duration of disease, measures of skin and joint disease activity, and outcomes of interest. Ten imputed datasets were used in our analysis.

RESULTS

Between January 1, 1978, and November 6, 2014, 1305 patients were registered in the University of Toronto PsA clinic database; 722 (55.3%) were men. Mean (SD) age at first clinic visit was 44.2 (4.9) years. The mean (SD) duration of followup was 9.1 (9.1) years. At first clinic visit, the mean (SD) durations of PsO and PsA were 15.4 (12.5) and 6.5 (7.9) years, respectively. One hundred sixty patients developed DM prior to the first visit or during the followup in the clinic. In the majority of the patients, the diagnosis of DM was determined by their family physician (92.5%) and in only 12 cases (7.5%) was the diagnosis based on elevated glucose levels in blood tests conducted in the PsA clinic as part of the followup.

The prevalence of DM in PsA. The standardized prevalence of DM in PsA in 2013 was 11.3% (95% CI 8.9–13.7). The SPR compared with the general population in Ontario was 1.43 (95% CI 1.2–1.7, $p = 0.002$). The SPR was higher in the younger age group (20–44 yrs: SPR 3.0, 95% CI 0.8–5.3); however, the CI was wide and overlapped with those in older

age groups (45–65 yrs: SPR 1.4, 95% CI 1.0–1.7; > 65 yrs: SPR 1.4, 95% CI 1.0–1.8; Figure 1). To address a potential measurement bias due to different criteria for case ascertainment in the population-based survey and the PsA clinic, a sensitivity analysis was conducted after excluding patients with PsA for whom the diagnosis of DM was based on elevated glucose levels in blood tests that were conducted in the PsA clinic. The results were essentially the same with SPR of 1.40 (95% CI 1.12–1.66, $p = 0.005$).

Cohort analysis of predictors for the development of DM in PsA. A total of 1065 patients who were free of DM at clinic entry were included in our analysis. Eighty-four patients were excluded because they developed DM prior to the first visit to the clinic and 157 patients were excluded because they had only a single visit to the clinic. This cohort had a total of 11,006 person-years of followup, with a mean (SD) of 10.3 (8.9) years per person from clinic entry to the last assessment or DM diagnosis. Seventy-three patients developed DM after clinic entry. The characteristics of the study participants at clinic entry are shown in Table 1.

In the univariate analysis, time-adjusted mean levels of TJC (HR 1.40, 95% CI 1.04–1.89), PASI (HR 1.46, 95% CI 1.09–1.97), and ESR (HR 1.14, 95% CI 1.01–1.31) predicted the development of DM (Table 2). Higher levels of TJC and ESR remained independent predictors of DM after controlling for age, duration of PsA, sex, cumulative steroid dose, and BMI.

Multivariable analysis. In multivariable analysis, the following variables were independent predictors of incident

DM: TJC (HR 1.53, 95% CI 1.08–2.18), ESR (HR 1.21, 95% CI 1.03–1.41), female sex (HR 0.42, 95% CI 0.25–0.71), and BMI (HR 1.09, 95% CI 1.04–1.14). The interaction between use of DMARD, MTX, LEF, or biologic medications with each of the measures of PsA disease activity was not statistically significant (data not shown).

DISCUSSION

In our cohort study, we found that the prevalence of DM was 43% higher in patients with PsA than in the general population of Ontario, Canada. Additionally, we found an independent association between higher levels of inflammation and measures of disease activity over time and DM risk. Patients with higher TJC and those with higher ESR levels were at higher risk of developing the disease independently of other known risk factors.

Patients with PsA are at increased risk of developing cardiovascular (CV) events¹⁹. Part of this increased risk may be attributed to the higher prevalence of DM in these patients, which was found in our study. The extent of the excess DM risk found in our study is comparable to that reported in other studies in patients with PsA. Solomon, *et al* found a 40% higher risk of DM in patients with PsA compared with the general population in the province of British Columbia, Canada¹¹. The risk of developing DM in patients with rheumatoid arthritis (RA) in the study was remarkably similar. A slightly higher DM risk (HR 1.72) was found in another population-based study in patients with PsA from the United Kingdom¹². However, in that study, the risk in PsA

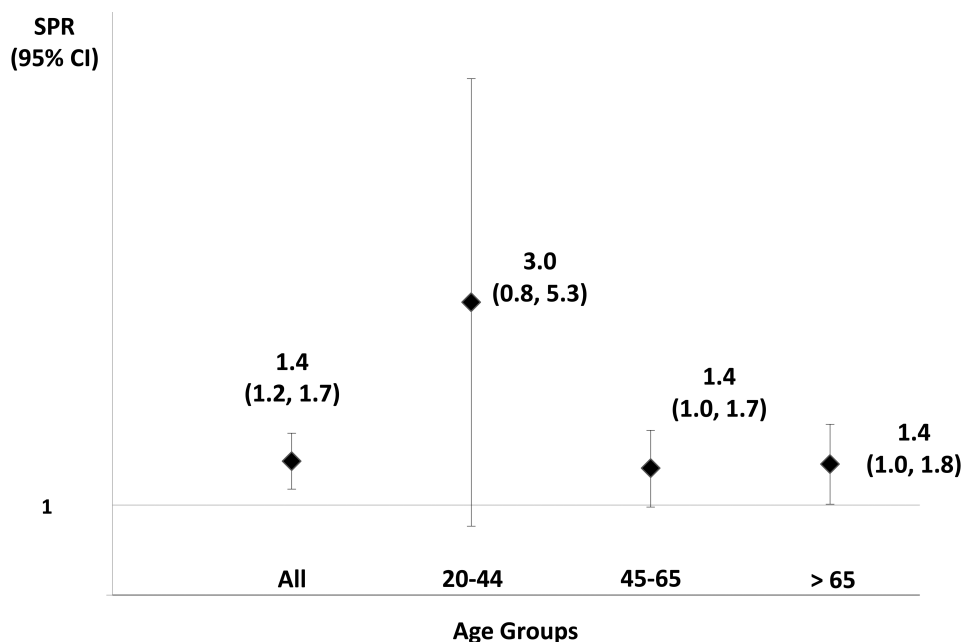


Figure 1. Standardized prevalence ratio (SPR) of diabetes mellitus in psoriatic arthritis in Ontario, Canada, by age group.

Table 1. Characteristics of the study population from the cohort analysis at baseline. Values are mean \pm SD or n (%). N = 1065.

Characteristics	Values
Age, yrs	53.7 \pm 13.9
Female	470 (44.1)
White	943 (88.5)
BMI, kg/m ²	28.2 \pm 5.6
Age at PsO onset, yrs	28.1 \pm 14.5
Age at PsA onset, yrs	37 \pm 13.1
PASI	5.8 \pm 8.5
TJC, max 68	6.8 \pm 8.2
SJC, max 66	3.4 \pm 4.7
Patients with dactylitis	271 (25.4)
Patients with enthesitis	177 (16.6)
ESR, mm/first h	18.2 \pm 16.3
Use of systemic corticosteroids	89 (8.4)
Cumulative corticosteroid dose*	0.37 \pm 2.83
Use of DMARD	478 (44.9)
Use of biologic medications	68 (6.4)

* Equivalent to prednisone in grams. BMI: body mass index; PsO: psoriasis; PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index; TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs.

was significantly higher than in patients with RA (HR 1.12). Overall, the cluster of obesity, insulin resistance, and dyslipidemia, collectively termed the “metabolic syndrome,” tends to be more prevalent in patients with PsA than in those with RA²⁰. Therefore, despite similar characteristics of these 2 conditions that involve chronic inflammatory arthritis and systemic inflammation with Th1 response and elevated levels of TNF- α and additional proinflammatory cytokines that could promote insulin resistance, DM risk is higher in patients with PsA. What could explain this strong link between PsA and DM? Explanations may include higher burden of inflammation because of concomitant skin and joint inflammation, PsA-specific immune mechanisms that

may promote insulin resistance, unhealthy lifestyle that is prevalent among patients with psoriatic disease, or the use of topical corticosteroid preparations.

Chronic inflammation is strongly associated with the development of insulin resistance and subsequent development of DM. Acute-phase proteins such as hsCRP and proinflammatory cytokines including TNF- α , IL-1, and IL-6 are elevated in patients with DM^{21,22}. These proinflammatory markers are associated with insulin resistance independently of the extent of obesity. In animal models, the infusion of TNF- α induces insulin resistance by impairing insulin signaling at the level of the receptor^{23,24}. Further, control of systemic inflammation by blocking TNF- α was associated with improved insulin sensitivity and lower risk of developing DM in patients with RA and psoriatic disease^{25,26,27}, and IL-1 and TNF- α blockade were associated with improved glucose control and reduced insulin resistance in patients with prediabetes^{28,29}. In accordance with these findings, we found that the burden of systemic inflammation and PsA disease activity over time predicted the development of DM. Higher levels of TJC and ESR were independent predictors of DM while more severe PsO, as indicated by higher PASI scores, was also associated with DM risk; however, the strength of association was attenuated after adjusting for obesity and other confounders. Interestingly, TJC was a stronger predictor for DM than SJC. Similarly, TJC was found to be a better predictor of CV outcomes than SJC in previous studies in PsA^{30,31}. This is in contrast to RA, in which SJC is considered a stronger indicator of disease-related inflammation and a better predictor of worse outcomes^{32,33}. The explanation of this finding is not entirely clear. It was suggested that the reliability of detection of swollen joints on physical examination is inferior in PsA compared with RA³⁴, which may have increased the variability in SJC in PsA, resulting in attenuation of the association. An alternative explanation may be that people with PsA tend to have fewer tender joints than patients with RA, suggesting that each tender joint in

Table 2. The association between measures of PsA disease activity and the risk of incident diabetes mellitus by Cox proportional hazard model (n = 1065, 73 events).

Variables	Univariate Analysis		Adjusted RR*		Multivariate Reduced Model	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
TJC**	1.40 (1.04–1.89)	0.025	1.60 (1.14–2.23)	0.007	1.53 (1.08–2.18)	0.02
SJC**	1.28 (0.60–2.72)	0.52	1.80 (0.85–3.32)	0.12		
Dactylitic digit count	1.02 (0.75–1.38)	0.92	0.92 (0.63–1.38)	0.71		
PASI**	1.46 (1.09–1.97)	0.01	1.27 (0.91–1.76)	0.16		
ESR**	1.14 (1.01–1.31)	0.047	1.23 (1.06–1.43)	0.006	1.21 (1.03–1.41)	0.02
Female	0.55 (0.34–0.88)	0.01			0.42 (0.25–0.71)	0.001
BMI	1.08 (1.04–1.12)	0.0003			1.09 (1.04–1.14)	0.0003
Cumulative steroid dose***	1.00 (0.97–1.03)	0.81			0.98 (0.95–1.01)	0.28
Duration of PsA	0.98 (0.95–1.00)	0.10			0.99 (0.97–1.04)	0.65

* Each model is adjusted for cumulative steroid dose, sex, duration of PsA, BMI, and age at clinic entry. ** 10-unit increase. *** In prednisone mg. PsA: psoriatic arthritis; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; ESR: erythrocyte sedimentation rate; BMI: body mass index.

the former group is associated with a higher degree of inflammation³⁵.

In the multivariable regression model, an inverse association was found between female sex and DM risk. This observation may be explained by the higher levels of ESR, BMI, and TJC that were found in women compared with men in our cohort (data not shown).

Our study was limited in several aspects. First, we could not adjust for potential confounding risk factors for DM in our comparison with the general population in Ontario because of the lack of data. Additionally, the definition of DM in the general population was based only on self-reported diagnosis, while in the PsA group the diagnosis of DM relied on physician diagnosis, use of DM medications, or elevated blood glucose, which could have led to measurement bias because of additional testing. To address this potential bias, we performed a sensitivity analysis by excluding the patients in the PsA group for whom the diagnosis of DM was based on elevated glucose levels in blood tests that were conducted in the PsA clinic. Our analysis essentially found the same results, with a higher prevalence of DM in patients with PsA compared with the general population. Second, we acknowledge that the rates of DM in PsA as assessed in our study are based on patients attending a specialty clinic; thus, they may represent a more severely affected group of patients, which may limit the generalizability of the results. However, overall the prevalence of DM in patients with PsA that we found is comparable to that reported in patients with PsA from population-based studies. Third, no information was routinely collected about physical activity. It is expected that the level of physical activity is reduced during flares of PsA, which may be indicated by the increased TJC and the elevated levels of ESR. Reduced physical activity level is a predictor of DM, independently of BMI³⁶. However, this hypothesis could not be tested in our study. Similarly, information about additional confounding factors such as smoking, metabolic syndrome, and CRP was not routinely collected from the beginning of the cohort and thus could not be assessed in our study. It is possible that some of these variables could have modified the identified link between the extent of inflammation and DM risk. Last, in the assessment of risk factors for DM in patients with PsA, more than half of the cases with DM were excluded from the analysis because the event of interest was present at baseline. We accounted for this finding by considering age at study entry as left truncation time. Nevertheless, it is possible that other factors may account for DM risk at earlier stages of PsA. This observation also indicates that patients with PsA are at high risk of having DM at early phases of their disease because of the presence of risk factors for DM, including PsO and obesity, which often precede the onset of PsA. Despite these limitations, our study has several strengths, including the large sample of patients who have been followed for several decades and the comprehensive and accurate phenotyping of

the patients that allowed an estimation of the inflammatory burden of the disease over time.

In our longitudinal study that assessed the risk of DM in patients with PsA over a period of more than 3 decades, we found that the patients with PsA were at a higher risk of having DM compared with the general population. Patients with PsA who have higher levels of disease activity are at a particularly increased risk of developing DM. This finding highlights the need to screen for DM in patients with PsA, especially in those with more active joint disease and elevated inflammatory markers. The control of inflammation may reduce the risk of developing DM in patients with PsA.

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