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The Risk of Diabetes Among Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Psoriasis

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Abstract

Background—We examined the risk of DM among subjects with rheumatoid arthritis (RA), psoriatic arthritis or psoriasis (PsA/PsO), compared with non-rheumatic controls.

Methods—We assembled study cohorts using linked health care utilization data from British Columbia. All persons with at least two diagnoses of RA or PsA/PsO were included and compared with a cohort of persons without any known rheumatic disease. The outcome of interest was a diagnosis of new onset DM, as defined by initiation of an anti-diabetic medication. Incidence rates (IR) per 1,000 person-years and incidence rate ratios (IRR) were calculated and Cox regression models examined to determine the hazard ratio (HR) for diabetes by age, gender, systemic immunosuppressive and glucocorticoid use.

Results—The study cohort consisted of 48,718 subjects with RA, 40,346 with PsA/PsO, and 442,033 without any rheumatic disease. The IR for DM among subjects with RA was 8.6 per 1,000 person-years (95% CI 8.5 – 8.7), PsA/PsO 8.2 (95% CI 8.1 – 8.3), and for non-rheumatic controls 5.8 (95% CI 5.8–5.8). The adjusted HR for RA compared with non-rheumatic controls was 1.5 (95% CI 1.4–1.5) and 1.4 (95% CI 1.3 – 1.5) for PsA/PsO.

Conclusions—RA and PsA/PsO appear to be associated with an increased risk of DM. The ability of potent anti-rheumatic treatments to reverse this trend warrants study.

INTRODUCTION

Cardiovascular disease (CVD) represents an important source of morbidity and mortality in several rheumatic diseases, including rheumatoid arthritis (RA) and psoriatic arthritis// psoriasis (PsA/PsO).[1, 2] Previous studies debate the relative importance of traditional CVD risk factors versus rheumatic disease specific factors.[3, 4] However, the dichotomy between different types of risk factors may be false. Inflammation appears intimately related to insulin resistance, dyslipidemia, and possibly hypertension.[5–7] A number of studies support that insulin resistance is increased in RA. While there seems to be broad agreement about the relation between RA and insulin resistance, only two prior studies have focused on the risk of diabetes mellitus (DM) in RA. One very large study based on health insurance claims calculated an odds ratio of 1.4 for DM among a cohort with RA compared with healthy controls.[9] Another medical records study from a longitudinal cohort found no increased risk

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of DM.[10] In contrast with RA, prior studies of PsA and PsO agree that there is an increased risk of DM. The adjusted relative risks range from 1.2 – 1.6 for PsO and PsA.[11, 12] In prior work, little attention has been paid to systemic immunosuppressives or topical glucocorticoid use.

We examined the risk of DM in population-based cohorts of patients with RA or PsA/PsO, paying close attention to age and gender specific risk, as well as to relevant medication use.

METHODS

Data Source

We studied three cohorts derived from the population-based insurance program of British Columbia Canada. The pharmacy program, PharmaNet, includes the name, dose, and dispensed quantity for all prescription drugs dispensed in British Columbia pharmacies. Up to 25 diagnoses for hospital discharges and one diagnosis for each medical service are recorded, with good specificity and completeness.[15] Because all BC residents are covered for all medical services by the provincial Medical Services Plan (MSP) except for a small number of federal employees and drug dispensings are recorded for all dispensed prescription medications regardless of payer, the study sample is representative of British Columbia's adult population (about 3 million in 2005). [16]

The appropriate Institutional Review Board approved this protocol. Data use agreements are in place between the investigators and British Columbia.

Cohort Selection

The health insurance programs of British Columbia include all citizens and all of their medical and pharmacy claims. The three cohorts encompassed RA, PsA/PsO, and non-rheumatic disease controls. All subjects in the RA cohort had at least two visits for RA (ICD-9-CM 714.0) at least one week apart. Similarly, PsA/PsO subjects were defined by at least two visits for PsA or PsO (ICD-9-CM 696.0 or 696.1) at least one week apart. The non-rheumatic disease controls could have neither a visit coded for RA, PsA/PsO, or any other inflammatory rheumatic disease (ICD-9-CM 287.x, 446.x–447.x, 695.4, 710.x–713.x). We attempted to match 5 controls for each case based on calendar year of study entry. The controls entered the cohort on a physician visit date.

Our study database spanned the period January 1, 1996 through December 31, 2006. All subjects could enter the cohort after qualifying for inclusion, i.e., second diagnosis of RA or PsA/PsO or matched physician visit for controls. We excluded subjects with a diagnosis of DM (ICD-9-CM 250.x) prior to their cohort entry date. Subjects were followed until they experienced an outcome, died, left British Columbia, or follow-up ended (December 31, 2006).

Diabetes Mellitus Outcome

The outcome of interest was the diagnosis of DM or the use of medications specific for DM. We did not have actual laboratory data; thus, the primary definition of DM required at least one prescription for a DM-specific medication. These included all insulin preparations, as well as oral agents. The secondary definition of DM required both a receipt of a DM-specific medication plus a diagnosis of DM (ICD 250.x). Similar definitions have been used in prior studies from Canada and found to have specificities above 90%.[17, 18] Sensitivity analyses considered the type of treatment started for DM, insulin or non-insulin.

Potential Predictors of Diabetes Mellitus

We examined several potential predictors of DM using data from the 12 months prior to cohort entry, including age, gender, comorbid medical conditions, health care utilization, glucocorticoid use, and systemic immunosuppressive use. Age was defined at cohort entry date. The count of comorbid medical conditions encompassed data from the 12 months prior to cohort entry and used the Romano adaptation of the Charlson Index.[19]

Oral and topical glucocorticoids, as well as systemic immunosuppressives, were considered separately based on data from the 12 months prior to cohort entry (see Supplemental file for a list of all preparations).

Statistical Analyses

We compared the baseline characteristics across the three cohorts. Incident DM was identified during follow-up and person-years calculated. This allows for estimation of an incidence rate (IR) for DM. The IRs were estimated for each cohort separately and then stratified by age, gender, systemic immunosuppressive use, and glucocorticoid use. The IRs for RA and PsA/PsO were compared with non-rheumatic controls to calculate an incidence rate ratio (IRR). These were also stratified according to age, gender and medication use. Finally, a Cox proportional hazard regression model was constructed to assess the adjusted hazard ratio (HR) of DM associated with RA, and PsA/PsO. These models were stratified according to age, gender and medication use.

RESULTS

From the total potential population of British Columbia during the study period, 4,310,500 were potentially eligible. We identified 84,480 subjects with at least two diagnoses of RA (1.96%) and 73,909 subjects with PsA/PsO (1.71%). Further exclusions because of prior DM left 48,718 with RA, 40,346 with PsA/PsO and 442,033 non-rheumatic controls.

The baseline characteristics of the study cohorts are shown in Table 1. There were substantial baseline differences in most of the characteristics. Table 2 shows the IRs for each cohort. The IR for diabetes among subjects with RA was 8.6 per thousand (95% CI 8.5 – 8.7), for PsA/PsO 8.2 (95% CI 8.1 – 8.3), and for non-rheumatic controls 5.8 (95% CI 5.8–5.8). The IRs by age stratum demonstrate an increase with older age; as well, IRs were higher for men than women. The IRs were higher among persons using systemic immunosuppressives than those not, likely reflecting a greater underlying disease burden. As expected, persons using oral or topical glucocorticoids experienced higher IRs for DM. The IRs were very similar for the secondary definition of DM (see Supplemental File).

The adjusted HRs are shown in Figure 1. The HR for RA compared with non-rheumatic controls was 1.5 (95% CI 1.4–1.5) and 1.4 (95% CI 1.3 – 1.5) for PsA/PsO. In the adjusted Cox regression models, oral glucocorticoid use (HR 1.3, 95% CI 1.2 – 1.4) and topical (HR 1.3, 95% CI 1.1 – 1.4) were both associated with an elevated risk of DM. While the IRs increase with older age, the HRs are lower with older age in both genders (see Figures 1b and 1c).

Finally, we constructed Cox regression models among persons without any use of oral glucocorticoids or topical glucocorticoids. The adjusted HRs did not change in these restricted models: RA (no oral glucocorticoid use HR 1.4, 95% CI 1.3 – 1.5; no topical glucocorticoid use HR 1.5, 95% CI 1.4–1.5) and PsA/PsO (no oral glucocorticoid use HR 1.4, 95% CI 1.3 – 1.5; no topical glucocorticoid use HR 1.4, 95% CI 1.3–1.4).

DISCUSSION

The relationship between DM and rheumatic diseases is of interest because of the well-documented increased risk of CVD in RA and PsA/PsO.[1–4] Inflammation plays an important role in driving insulin resistance and metabolic syndrome.[5] While substantial literature supports the relationship between insulin resistance and rheumatic diseases, there are surprisingly few data regarding rheumatic diseases and DM. We studied the incidence rate of DM among subjects with either RA or PsA/PsO. Our results confirm an elevated relative risk for incident DM among subjects with PsA/PsO compared with non-rheumatic controls. [9, 11–13] The findings among subjects with RA were remarkably similar – elevated relative risk in both genders but decreasing risk with age. The elevated adjusted HRs observed among subjects not using oral or topical glucocorticoids suggests that this risk is not primarily an adverse effect of such treatments.

While substantial work on insulin resistance has been published, relatively few studies on the risk of DM in RA have been conducted. One study using a large insurance database found an increased risk (prevalence ratio 1.4).[9] The second study to examine DM among subjects with RA utilized a much stronger study design. A longitudinal cohort of subjects with RA was assembled retrospectively from the Rochester Epidemiology Project.[10] Diabetes was not the focus of this study, but in unadjusted the authors found no increase in the risk of new onset DM (RR 0.78). It is important to note that the IR calculated for DM in the study from the Rochester Epidemiology Project --7.9 per 1,000 person-years -- is very similar to the IR calculated in this study (8.6 per 1,000 person-years) and both are in-line with one prior estimate from a large RA cohort (7.6 per 1,000 person-years, calculated from the date presented).[31] Thus, the RR differ between the current study and the study from the Rochester Epidemiology Project because of different IR estimates for the non-RA population -- 10.2 per 1,000 person-years in Rochester Epidemiology Project versus 5.8 in our study.

Limitations of our study include a database that does not include actual blood glucose values, ACR classification criteria, and lack of information on body mass index and family history of DM. Similar algorithms for DM have been previously tested and found to have positive predictive values over 90%.[17, 18] Our findings did not differ much when we ran analyses using slight variations on the coding algorithms for DM (data not shown). Our prevalence calculations for RA are consistent with the literature suggesting minimal misclassifcation.[32] As well, body mass index among subjects with RA is similar to non-rheumatic controls.[1]

Our analyses need to be replicated, especially in RA cohorts. The current epidemiologic analyses add important context to this ongoing area of study. Persons with RA or PsA/PsO and their providers should be aware of the potential link with DM. As these association become better defined, regular DM screening may be called for among these rheumatic disease populations.

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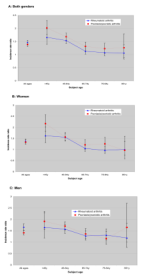

Figure 1.
This figure shows the Cox proportional hazard ratios for diabetes mellitus across age stratum. Panel A shows this for the total cohort, panel B for women, and panel C for men. All models were adjusted for the variables in Table 1.

Table 1

Baseline characteristics of primary cohorts

	Rheumatoid arthritis (n = 48,718)	Psoriatic arthritis/Psoriasis (n = 40,346)	Non-rheumatic (n = 442,033)
	N (%) or mean (± SD)		
Age, years	58 (± 16)	50 (± 17)	53 (± 17)
Gender, female	32,867 (68%)	20,038 (50%)	262,914 (60%)
Physician visits	10 (± 9)	7 (± 7)	6 (± 7)
Number of medications	4 (± 4)	4 (± 3)	2 (± 3)
Prior use of oral glucocorticoids	8,041 (17%)	2,188 (5%)	11,381 (3%)
Prior use of systemic immunosuppressives*	6,989 (14%)	1,354 (3%)	917 (0.2%)
Prior use of topical glucocorticoids*	529 (1%)	4,732 (12%)	2,668 (0.6%)
Comorbidity index	0.35 (± 0.70)	0.16 (± 0.52)	0.35 (± 0.78)

*see text for listing of systemic immunosuppressives and high potency topical glucocorticoids.

Table 2

Diabetes incidence rates (per 1,000 person years), age and gender stratified

	Rheumatoid arthritis			Psoriatic arthritis/Psoriasis			Non-rheumatic		
	# cases	**Person-years**	**Rate (95% CI)**	**# cases**	**Person- years**	**Rate (95% CI)**	**# cases**	**Person-years**	**Rate (95% CI)**
Total cohort	1,949	227,838	8.6 (8.5 – 8.7)	1,564	191,534	8.2 (8.1 – 8.3)	10,732	1,847,202	5.8 (5.8–5.8)
Female	1212	155,599	7.7 (7.7 – 7.8)	730	95,771	7.6 (7.7– 7.8)	6,299	1,118,944	5.6 (5.6 – 5.6)
Male	737	72,239	10.2 (10.1–10.3)	834	95,763	8.7 (8.6 – 8.8)	4,433	728,258	6.1 (6.1–6.1)
Age stratum									
< 45	178	51,994	3.4 (3.4 – 3.4)	295	78,041	3.8 (3.7 – 3.8)	1,093	584,537	1.9 (1.9 – 1.9)
45–64	870	95,342	9.1 (9.1 – 9.2)	745	73,188	10.2 (10.1 – 10.2)	4,432	747,330	5.9 (5.9 – 5.9)
65–74	474	44,078	10.7 (10.6 – 10.8)	318	25,079	12.7 (12.5–12.8)	2,973	309,195	9.6 (9.6 – 9.6)
75–84	345	30,505	11.3 (11.2 – 11.4)	171	13,056	13.1 (12.9 – 13.3)	1,873	176,059	10.6 (10.6 – 10.7)
85+	82	5,918	13.8 (13.5–14.2)	35	2,170	16.1 (15.5 – 16.8)	361	300,81	12.0 (11.9 – 12.1)
Systemic immunosuppressives*									
Yes	269	32,885	8.2 (8.1–8.3)	72	6,388	11.3(11.0–11.5)	50	3,258	15.3(14.8–15.9)
No	1680	194,953	8.6 (8.6–8.6)	1492	185,146	8.0 (8.0–8.0)	10,682	1,843,944	5.8(5.8–5.8)
Oral glucocorticoids*									
Yes	401	36,010	11.2 (11.1 – 11.3)	115	10,166	10.9 (10.8 – 11.1)	387	37,956	9.7 (9.6 – 9.8)
No	1,548	191,828	8.1 (8.0 – 8.1)	1449	181,368	7.6 (7.6 – 7.6)	10,345	1,809,245	5.7 (5.7 – 5.7)
Topical glucocorticoids*									
Yes	26	2,478	10.5 (10.1 – 10.9)	245	22,751	10.8 (10.6 – 10.9)	90	11,099	8.1 (7.9 – 8.2)
No	1923	225,361	8.5 (8.5 – 8.6)	1319	168,783	7.8 (7.7– 7.8)	10,642	1,836,103	5.8 (5.8 – 5.8)

*see text for listing of systemic immunosuppressives and high potency topical glucocorticoids.