Risk of Diabetes Mellitus in Patients with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To examine the risk of type 1 diabetes (T1D) associated with juvenile idiopathic arthritis (JIA).

Methods. Using the IBM MarketScan database, we compared JIA patients with asthma patients and healthy individuals for the risk of incident T1D.

Results. We included patients with 15,210 JIA, 76,050 patients with asthma, and 76,050 healthy individuals matched 1:5 on age, sex, and index date. After adjustment for confounders, the multivariable HR of T1D associated with JIA was 1.48 (95% CI 0.86–2.56) versus asthma and 1.81 (95% CI 1.03–3.17) versus healthy individuals.

Conclusion. JIA appears to be associated with an increased risk of T1D compared to patients with asthma and healthy children. (First Release July 1 2020; J Rheumatol 2020;47:1405–8; doi:10.3899/jrheum.190644)

Key Indexing Terms:
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COHORT STUDY

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases presenting with arthritis of unknown origin before the age of 16 years[1]. The International League of Associations for Rheumatology classifies JIA into different subtypes depending on duration, number of joints involved, and the presence or absence of rheumatoid factors[2]. JIA also shares similarities with rheumatoid arthritis owing to the inflammatory expression of the arthritis and positive rheumatoid factor in a small subset of patients. Higher prevalence of type 1 diabetes mellitus (DM; T1D) has been reported in patients with JIA compared to non-JIA groups, and also the reverse: a higher prevalence of JIA in a T1D population compared to non-T1D[3,4,5]. However, studies assessing the incident cases of DM among patients with JIA are lacking. Data on disease prevalence provides information on the burden of the disease, but it is less useful in studying the disease etiology and how outcome rates differ in individuals with varying exposures[6]. To fill this gap, we conducted a population-based cohort study to identify the incidence rate (IR) of T1D among children with JIA, and assessed the risk of incident diabetes in patients with JIA against 2 comparison groups: patients with asthma and children without significant health conditions.

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MATERIALS AND METHODS

We conducted a cohort study using longitudinal medical and pharmacy claims data collected between 2005 and 2016 in IBM MarketScan, a commercial insurance claims database in the United States. The MarketScan database primarily includes a working population and their dependents insured by employer-sponsored plans across the United States, with information on patient demographics, medical diagnoses, inpatient or outpatient procedures, hospitalizations, physician visits, and pharmacy dispensing records.

The study protocol (no. 2017P001342) was approved by the Institutional Review Board of Brigham and Women's Hospital, and the requirement for patient informed consent was waived.

Study cohort. The study comprised 3 cohorts: JIA, asthma, and healthy children. Children aged between 6 and 18 years were eligible. We identified JIA with 2 or more visits coded for JIA based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) and ICD-10 codes, followed by at least 1 outpatient pharmacy claim for JIA treatment (Supplementary Table 1, available with the online version of this article)[7]. The asthma group was defined with at least 2 diagnoses of asthma followed by at least 1 outpatient pharmacy claim for asthma treatment. The asthma group was chosen for comparison because these patients are likely to see healthcare providers on a regular basis and have a similar exposure to steroids. The healthy group consisted of children who had at least 1

record of a Well-Care visit. Well-Care visits are physician encounters that are recommended once a year for preventive care. Index dates for JIA and asthma patients were defined as the first treatment initiation date after the second diagnosis code, and the index date of a healthy control was the date of the first record of a Well-Care visit. In the asthma group, we excluded those who had a JIA diagnosis during the baseline 365-day period prior to the index date. The control group was required to have no diagnosis of JIA or asthma during the baseline 365-day period. Each patient with JIA was matched to 5 children with asthma and 5 healthy children on age, sex, and index date. Individuals were followed from the index date to the first occurrence of any of the following censoring events: development of diabetes, insurance disenrollment, end of study period, or death.

Definition of outcome. The primary outcome was incident T1D. T1D was defined as at least 1 diagnosis code for T1D followed by at least 1 dispensing of insulin of any type. Secondary outcomes were (1) type 2 diabetes (T2D), defined as at least 1 diagnosis for T2D followed by any antidiabetic agent including insulin; and (2) any diabetes defined as a diagnosis of either T1D or T2D followed by any antidiabetic agent.

Statistical analysis. We estimated the overall and age-subgroup IR of diabetes (6 to 12 yrs vs 13 to 18 yrs) in each group. Multivariable Cox proportional hazards models comparing JIA versus non-JIA groups were calculated adjusting for 12 potential confounders including demographics, comorbidities, cumulative prednisone-equivalent dose of oral steroid, and healthcare use factors. In addition, we calculated diabetes incidence among the patients with JIA stratified by previous use of disease-modifying antirheumatic drugs (DMARD) or biologics. All analyses were performed with SAS (version 9.4; SAS Institute).

RESULTS

After 1:5 matching, there were 76,050 healthy children, 76,050 patients with asthma, and 15,210 patients with JIA (Supplementary Figure 1, available with the online version of this article). The mean followup in the study was 2.68 years (SD 2.34), the mean age in all cohorts was 13.9 (SD 3.4) years, and 67.3% were female (Table 1). A total of 18 incident cases of T1D and 34 cases of either T1D or T2D were observed in the JIA cohort. The IR per 100,000 person-years of T1D in the JIA group was 44 (95% CI 28–70) compared with 29 (95% CI 23–36) in the asthma population and 22 (95% CI 17–28) in the healthy population (Table 2). The IR per 100,000 person-years of T2D in the JIA group was 66 (95% CI 45–96) and 84 (95% CI 60–118) for any diabetes. The fully adjusted HR for T1D associated with JIA was 1.48 (95% CI 0.86–2.56) versus asthma and 1.81 (95% CI 1.03–3.17) versus the healthy children (Table 3). Age subgroup analysis showed similar results (Supplementary Table 2, available with the online version of this article). When IR of any diabetes was stratified by the previous use of DMARD/biologics among the patients with JIA, those with previous systemic drug use had an IR of 79 per 100,000 person-years compared to 87 per 100,000 person-years in those with no use of DMARD/biologics.

DISCUSSION

Our cohort of 15,210 patients with JIA appeared to have a higher risk of developing T1D compared to patients with asthma and the healthy population. However, the absolute risk of the outcomes was low. The estimated IR of diabetes in our study was consistent with the annual IR of diabetes in the United States[8].

Autoimmunity has been a frequent link between diabetes and JIA, supported by findings that there is a higher risk of T1D in patients with JIA[9] and also a higher risk of JIA in patients with T1D[5]. We observed a 1.48-fold increased risk of T1D in patients with JIA compared to patients with asthma and a 1.81-fold increased risk compared to healthy children, which may further support the 2 diseases' association with autoimmunity. However, we also noted elevated

Table 1. Baseline characteristics of study cohorts matched for age, sex, and index date.

Characteristic	Healthy Children, n = 76,050	Asthma Cohort, n = 76,050	JIA Cohort, n = 15,210
Demographic features			
Age, yrs, mean (SD)	13.86 (3.44)	13.86 (3.44)	13.86 (3.44)
Female, %	67.28	67.28	67.28
Comorbidities, %			
Hyperlipidemia	0.58	1.09	1.26
Hypertension	0.42	0.69	1.04
Obesity	1.70	2.69	2.01
Previous medications, %			
NSAID	6.74	10.25	65.71
Inhaled corticosteroids	7.01	57.15	15.31
Oral steroids (past 30 days)	1.01	24.25	28.28
Oral steroids (past 365 days)	6.66	40.49	39.98
Cumulative steroid dose, mean (SD) mg*	31.45 (379.77)	301.15 (2738.23)	454.90 (2612.21)
Healthcare use			
Emergency visit, %	12.69	29.26	27.94
Hospitalization, %	1.58	5.11	7.17
Total no. drugs prescribed, mean ± SD	2.22 ± 2.69	6.09 ± 3.94	6.53 ± 4.63
HbA1c test performed, %	1.42	2.31	2.79

*Cumulative prednisone-equivalent dose of oral steroids prescribed 365 days prior to index date. JIA: juvenile idiopathic arthritis; NSAID: nonsteroidal antiinflammatory drugs; HbA1c: hemoglobin A1c.

Table 2. Incidence rates (IR) of diabetes mellitus per 100,000 person-years in patients with juvenile idiopathic arthritis (JIA) compared to healthy population and patients with asthma. Study cohorts were matched for age, sex, and index date.

	Healthy Children			Asthma Cohort			JIA Cohort		
	Diabetes Cases	Person-yrs	IR (95% CI)	Diabetes Cases	Person-yrs	IR (95% CI)	Diabetes Cases	Person-yrs	IR (95% CI)
Primary outcome									
Type 1 diabetes	62	278,294	22 (17–28)	76	258,899	29 (23–36)	18	40,722	44 (28–70)
Secondary outcome									
Type 2 diabetes	138	278,169	50 (42–59)	187	258,668	72 (62–83)	27	40,710	66 (45–96)
Composite diabetes	149	278,135	54 (46–63)	197	258,624	76 (66–87)	34	40,686	84 (60–118)

Table 3. HR of diabetes mellitus in patients with juvenile idiopathic arthritis (JIA) compared to the healthy population and patients with asthma.

	JIA vs Asthma		JIA vs Healthy Children	
	Age, Sex, Index Date-matched HR (95% CI)	Fully Adjusted HR* (95% CI)	Age, Sex, Index Date-matched HR (95% CI)	Fully Adjusted HR* (95% CI)
Primary outcome				
Type 1 diabetes	1.46 (0.87–2.44)	1.48 (0.86–2.56)	1.89 (1.11–3.19)	1.81 (1.03–3.17)
Secondary outcome				
Type 2 diabetes	0.95 (0.64–1.43)	1.01 (0.66–1.54)	1.33 (0.88–2.02)	1.22 (0.79–1.90)
Composite diabetes	1.11 (0.77–1.60)	1.18 (0.80–1.73)	1.52 (1.05–2.21)	1.40 (0.94–2.09)

* The full model included age, sex, index date, region, calendar year (continuous), hyperlipidemia, hypertension, obesity, inhalation steroid dose, cumulative steroid dose (prednisone-dose equivalent) in the 365 days prior to index date, emergency room visit, and hospitalization.

risk of T2D in patients with JIA, although to a lesser extent. The pathophysiology of T2D differs from that of T1D, and the risk of T2D in patients with JIA may be attributable to the link between systemic inflammation and insulin resistance. Correlation between high-density lipoprotein cholesterol and well-studied inflammation markers (e.g., MRP8/14) in JIA populations may indicate that a series of inflammatory reactions can contribute to the onset of metabolic diseases[10].

Several limitations in our study should be acknowledged. First, the claims data cannot accurately define the heterogeneous expression of JIA such as its subtypes. Also, by defining our outcome with a diagnosis and a prescription claim, we included only pharmacologically treated diabetes cases (i.e., not including those undertaking lifestyle modification), which may lead to underestimation of true IR in the population. In addition, we identified use of nonsteroidal antiinflammatory drugs (NSAID) as a part of JIA-related medications, but the use of NSAID might not be specific enough for the cohort definition. Further, the pharmacy claims data used in the study cannot reliably identify the actual intake of medications.

Owing to lack of information in the study database, our observational cohort study is subject to residual confounding by race/ethnicity, body mass index, diet pattern, nutrition status, socioeconomic status, and baseline HbA1c level.

Misclassification bias is also a possibility because we relied on diagnosis codes and prescription claims to define our cohort and outcomes. And because of left truncation in the data, patients in the JIA or asthma cohorts are not necessarily followed from the onset of disease.

Our study indicates that the absolute risk of diabetes in patients with JIA was low. Our findings support previous reports on the increased risk of T1D in patients with JIA compared to healthy individuals and suggest that a similar association may be present in T2D. Considering the chronicity of the disease, appropriate clinical investigations may be needed in patients with JIA who have risk factors for diabetes. Future studies assessing the onset of diabetes in combination with other autoimmune or metabolic diseases are needed to shed light on the complex association between JIA and its related endocrinopathies.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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