



Risk of Rheumatoid Arthritis in Patients with Type 2 Diabetes: A Nationwide Population-Based Case-Control Study

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Abstract

Objective: Type 2 diabetes is associated with chronic, low-grade inflammation and could potentially trigger the progression of other, more prominent inflammatory diseases such as rheumatoid arthritis (RA). Therefore, we aimed to investigate the risk of incident RA in Taiwanese patients with type 2 diabetes using a population-based health claims database.

Methods: This nationwide, population-based, case-control study used administrative data to identify 1,416 patients with RA (age ≥ 20 years) as cases and 7,080 controls that were frequency-matched for sex, 10-year age group, and year of catastrophic illness certificate application date (index year). All subjects were retrospectively traced back, up to 13 years prior to the index year, for their first diagnosis of type 2 diabetes. Logistic regression analysis was conducted to quantify the association between incident RA and type 2 diabetes.

Results: The odds of developing RA were significantly higher in female (odds ratio [OR] 1.46, 95% confidence interval [95% CI] 1.24–1.72) but not in male (OR 1.00, 95% CI 0.72–1.37) patients who had previously diagnosed with type 2 diabetes. Subgroup analysis indicated that the odds of developing RA were more prominent in younger females (20 to 44 years of age) with type 2 diabetes. In addition, the odds of developing RA in female patients with type 2 diabetes were higher in those with a shorter time interval between the diagnosis of type 2 diabetes and RA.

Conclusions: This large nationwide, population-based, case-control study showed an elevated risk of RA in female Taiwanese patients with type 2 diabetes. Our findings were consistent with the hypothesis that chronic low-grade inflammation in type 2 diabetes may elicit the development of RA in genetically susceptible individuals.

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Introduction

The prevalence of type 2 diabetes has rapidly increased in many Asian populations, including the Taiwanese, thought to be the result of a combination of a sedentary lifestyle and unhealthy dietary habits. In Taiwan, the crude incidence of type 2 diabetes was 8 per 1,000 with a prevalence of 8.3% in 2007 [1]. Type 2 diabetes is characterized by pancreatic β cell dysfunction and insulin resistance. Obesity can trigger chronic low-grade inflammation and the resulting inflammatory mediators are detrimental to β cell function [2,3]. Modulating inflammatory reactions in patients with type 2 diabetes with the use of salsalate has been shown to improve glycemic control [6], strongly suggesting that inflammatory pathways are involved in the metabolic abnormalities of type 2 diabetes.

Rheumatoid arthritis (RA) is a chronic and disabling disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies [7]. The annual incidence of RA in Taiwan was 15.8 cases per 100,000 population with a female to male ratio of 4 to 1 [8]. Inflammatory mediators such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)- α are frequently elevated in patients with type 2 diabetes [4,5] as well as in the sera of patients many years before the clinical onset of RA [9], suggesting a critical role in the immunopathogenesis of this disease. This observation also suggests that low-grade inflammation should have already existed in patients with RA during the preclinical phase. In addition, smoking causes chronic lung inflammation and could subsequently lead to the production of autoantibodies, resulting in the development of RA among genetically susceptible individuals [10]. Therefore, it is plausible that chronic low-grade inflamma-

tion observed in patients with type 2 diabetes could also contribute to the development of RA in these patients. Several studies show the risk of diabetes is higher in patients with RA, but less is known about RA risk in established type 2 diabetes [11,12]. Therefore, the aim of this case-control study was to explore the risk of incident RA in patients with type 2 diabetes using a nationwide health claims database. To our knowledge, this is the first study to investigate the risk of incident RA among patients with type 2 diabetes using nationwide, population-based data.

Materials and Methods

Data sources and study subjects

This study used a nationwide, population-based, case-control study design based on the data available from the National Health Insurance Research Database (NHIRD) in Taiwan [13].

The study protocol was reviewed and approved by the institutional review board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan (No. 10004021). Since the NHIRD datafiles contain only de-identified secondary data, the need for informed consent from individual subjects was waived.

Using the 1997–2010 catastrophic illness datafile, a part of the NHIRD, cases were defined as new and successful applicants for the certificate of catastrophic illness with RA (International Classification of Diseases, ninth revision, clinical modification, ICD9-CM code 714.0). In Taiwan, patients with RA can apply for catastrophic illness certificates from the Bureau of National Health Insurance to become exempt from copayments for healthcare costs related to RA. The certificate is issued to patients only after their medical records, laboratory data, and imaging results have been reviewed by at least two rheumatologists. Because RA and type 2 diabetes occur primarily in adults, patients under 20 years of age were excluded from the study. The index date was defined as the date of first application of catastrophic illness certificate in the cases. A total of 1,416 patients with RA were included in the analyses.

The controls were selected from a random sample of the ambulatory care datafile of the 2000 Longitudinal Health Insurance Database (LHID2000) within the same inclusion period (January 1, 1997 to December 31, 2010) as the cases. The LHID2000 contained the claim data and registration files of both ambulatory and inpatient care expenditures for one million individuals randomly sampled from the 2000 Registry for Beneficiaries of the NHIRD. Any individual who was once a beneficiary of the National Health Insurance program during the period of 1996 to 2000 would be included in the registry. There are approximately 23,720,000 individuals in this registry, which represents more than 99% of the population in Taiwan. The National Health Research Institute confirmed that there were no significant differences in the age and sex between the LHID2000 and all beneficiaries.

Individuals identified as cases were excluded from the selection. Five controls per case were selected based on frequency matching for sex, 10-year age interval, and index year. Therefore, a total of 7,080 controls were included in the statistical analyses. The index year was defined as the same year of the index date of the matched case. The index date for each of the control subjects was assigned by using the date of a randomly selected ambulatory visit for a given index year.

Both the cases and controls were linked to the LHID2000 to obtain their ambulatory care visit data from 1997 to 2010. Patients were identified as having type 2 diabetes if they had at least three instances of ambulatory claims with a diagnosis of A-code A181 or ICD9-CM code 250.xx, except type 1 diabetes (ICD9-CM code

250.x1 or 250.x3). Patients with type 1 diabetes were excluded from this study because the disease is associated with an increased risk of several autoimmune diseases [14]. In addition, patients diagnosed with type 2 diabetes after the index date were excluded from the analyses. Therefore, only incident RA occurring after a diagnosis of type 2 diabetes were included in the final analyses.

Statistical analysis

Sex and age groups between cases and controls were compared with Chi-square test and t-test, as appropriate. Logistic regression was used to determine the odds ratio (OR) and 95% confidence interval (95% CI) of the risk of RA development with type 2 diabetes. A two-tailed *P* value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics software package, version 21.0 (IBM Corp, Armonk, NY, USA).

Results

We identified 1,416 patients newly diagnosed with RA with a certificate of catastrophic illness as cases, and 7,080 non-RA controls frequency-matched for sex, 10-year age interval, and index year. Table 1 shows the distribution of age and time interval between the first diagnosis of type 2 diabetes and index date in the cases and controls, stratified by sex. The mean age was 53.9 years for cases and the female to male ratio was 3.4:1. Since we frequency matched the cases and controls, there were no significant differences in their age distribution, with or without stratification by sex. However, there were significantly more patients with a longer time interval between the first diagnosis of type 2 diabetes and the index date among controls than among the cases ($P=0.003$); this difference was observed in females ($P=0.024$) but not in males ($P=0.118$).

Overall, the prevalence of type 2 diabetes was higher among RA cases (19.6%) compared with controls (15.4%) (Table 2). The odds of developing RA were significantly higher among patients who had previously diagnosed with type 2 diabetes (OR 1.34, 95% CI 1.16–1.55). When the data were analyzed after separating by sex, only female patients showed a significant association between RA and type 2 diabetes (OR 1.46, 95% CI 1.24–1.72). Therefore, we only included females in the subsequent analyses with stratification by age group (Table 3) and the time interval between the first diagnosis of type 2 diabetes and the index date (Table 4).

Subgroup analyses with stratification by age group indicated that the odds of developing RA in patients with type 2 diabetes were highest (OR 3.59, 95% CI 1.99–6.49) for the youngest age group of 20 to 44 years. The magnitude of the association was statistically significant but smaller in the two older age groups. Furthermore, stratification by the time interval between the first diagnosis of type 2 diabetes and the index date in female patients showed an increased odds of developing RA within a shorter time interval. The association was strongest with an interval of <4 years (OR 2.30, 95% CI 1.64–3.22) compared to those with an interval of 4 to <7 years (OR 1.60, 95% CI 1.13–2.26) or an interval of 7 to 11 years (OR 1.40, 95% CI 1.02–1.92). No significant associations were observed in patients with an interval of ≥ 11 years (OR 0.98, 95% CI 0.71–1.34).

Discussion

Previous studies based on healthcare utilization data have reported an increased risk of type 2 diabetes in patients with RA [11,12]. In contrast, our study showed that female patients with type 2 diabetes were associated with a significantly increased risk

Table 1. Characteristics of patients with rheumatoid arthritis and frequency-matched controls (N = 8,496).

Variable	Total			Males			Females		
	n (%)	Controls	P value	n (%)	Controls	P value	n (%)	Controls	P value
	Cases	7,080 (83.3)	>0.999	320 (16.7)	1,600 (83.3)	>0.999	1,096 (16.7)	5,480 (83.3)	>0.999
Age (years)									
20–29	68 (4.8)	340 (4.8)		13 (4.1)	65 (4.1)		55 (5.0)	275 (5.0)	
30–39	161 (11.4)	805 (11.4)		22 (6.9)	110 (6.9)		139 (12.7)	695 (12.7)	
40–49	310 (21.9)	1,550 (21.9)		72 (22.5)	360 (22.5)		238 (21.7)	1,190 (21.7)	
50–59	398 (28.1)	1,990 (28.1)		85 (26.6)	425 (26.6)		313 (28.6)	1,565 (28.6)	
60–69	267 (18.9)	1,335 (18.9)		53 (16.6)	265 (16.6)		214 (19.5)	1,070 (19.5)	
70–79	166 (11.7)	830 (11.7)		60 (18.8)	300 (18.8)		106 (9.7)	530 (9.7)	
80–89	42 (3.0)	210 (3.0)		14 (4.4)	70 (4.4)		28 (2.6)	140 (2.6)	
90–99	4 (0.3)	20 (0.3)		1 (0.3)	5 (0.3)		3 (0.3)	15 (0.3)	
mean (SD)	53.9 (14.1)	53.7 (14.5)	0.749	56.7 (14.4)	56.4 (15.0)	0.765	53.1 (13.9)	53.0 (14.2)	0.842
Interval between T2D diagnosis and index date (years)			0.003			0.118			0.024
<4	72 (25.9)	196 (17.9)		16 (29.6)	51 (18.8)		56 (25.0)	145 (17.6)	
4–<7	66 (23.7)	235 (21.5)		15 (27.8)	64 (23.6)		51 (22.8)	171 (20.8)	
7–<11	76 (27.3)	308 (28.2)		14 (25.9)	74 (27.3)		62 (27.7)	234 (28.5)	
≥11	64 (23.0)	354 (32.4)		9 (16.7)	82 (30.3)		55 (24.6)	272 (33.1)	

% are column percentages except in the header rows where they are row percentages.
T2D, type 2 diabetes.
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Table 2. Association between type 2 diabetes and incident rheumatoid arthritis in male and female patients (N = 8,496).

	Total, n (row %) 8,496 (100)		Sex, n (row %)			
			Male		Female	
			1,920 (22.6)		6,576 (77.4)	
	Cases	Controls	Cases	Controls	Cases	Controls
	1,416 (16.7)	7,080 (83.3)	320 (16.7)	1,600 (83.3)	1,096 (16.7)	5,480 (83.3)
T2D, n (column %)	278 (19.6)	1,093 (15.4)	54 (16.9)	271 (16.9)	224 (20.4)	822 (15.0)
Odds ratio (95% CI)	1.34 (1.16–1.55)	1.00	1.00 (0.72–1.37)	1.00	1.46 (1.24–1.72)	1.00
P value	<0.001		0.978		<0.001	

T2D, type 2 diabetes; 95% CI, 95% confidence interval.
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for incident RA. The increased risk of type 2 diabetes in patients with RA was proposed to be due to the long-term use of steroids during RA treatment [15]. Nevertheless, a Canadian study using a population-based health insurance database demonstrated a similar risk of incident type 2 diabetes in patients with RA, with or without adjusting for the use of oral or topical glucocorticoids [12]. Conversely, decreased insulin sensitivity was reported in patients with RA upon long-term exposure to steroids [16]. Thus, the role of long-term steroid use among patients with RA in the development of type 2 diabetes still requires further investigation. Furthermore, lifestyle changes after diagnosis of RA [17] might also contribute to an increase in the risk of developing type 2 diabetes. One health insurance database study performed in the United Kingdom concluded that the observed association between patients with RA and incident type 2 diabetes could substantially be explained by obesity and lifestyle factors [18].

Our findings also showed that the risks between type 2 diabetes and incident RA were more prominent in younger female patients and in those with a shorter interval between the diagnosis of type 2 diabetes and RA. In the youngest age group of 20 to 44 years, the risk of developing RA was 3.6 times higher in patients with type 2 diabetes compared with patients without type 2 diabetes. Since both RA and type 2 diabetes are primarily chronic diseases of an older population, a strong positive association in young female patients is of concern. It is possible that these patients are genetically susceptible for developing autoimmune diseases, which tends to manifest early in life [19].

Furthermore, the association between type 2 diabetes and incident RA was found to be strongest for patients with the shortest time interval (<4 years) between the diagnosis of type 2 diabetes and the index date. Conversely, patients whose RA appeared 11 years or more after the diagnosis of type 2 diabetes were not significantly associated with the presence of type 2 diabetes. The proximity in the timing between when these two conditions occurred is consistent with the notion that type 2 diabetes and RA are related.

The possible link between type 2 diabetes and incident RA could be explained by the inflammatory responses associated with both conditions. Serum levels of IL-6 and levels of CRP are significantly elevated in patients with RA [20]. Regarding type 2 diabetes, a meta-analysis of ten prospective studies with a total of 19,709 participants revealed a significant dose-response association of IL-6 levels with risk of type 2 diabetes (relative risk, [RR] 1.31, 95% CI 1.17–1.46). This same study, based on the results from 22 cohorts of 40,735 participants, also found that elevated CRP levels were significantly associated with increased risk of type 2 diabetes (RR 1.26, 95% CI 1.16–1.37) [21]. Furthermore, in patients with inflammatory polyarthritis, insulin resistance was closely associated with the presence of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) [22]. These findings suggest an important role for chronic systemic inflammation in the pathogenesis of both RA and type 2 diabetes.

The use of disease-modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine or tumor necrosis factor inhibitor for lowering the inflammatory response in patients with RA has been

Table 3. Association between type 2 diabetes and incident rheumatoid arthritis in female patients, stratified by age group (N = 6,576).

	Age group (years), n (row %)					
	20–44		45–64		≥65	
	1,836 (27.9)		3,282 (49.9)		1,458 (22.2)	
	Cases	Controls	Cases	Controls	Cases	Controls
	295 (16.1)	1,541 (83.9)	573 (17.5)	2,709 (82.5)	228 (15.6)	1,230 (84.4)
T2D, n (column %)	19 (6.4)	29 (1.9)	120 (20.9)	426 (15.7)	85 (37.3)	367 (29.8)
Odds ratio (95% CI)	3.59 (1.99–6.49)	1.00	1.42 (1.13–1.78)	1.00	1.40 (1.04–1.88)	1.00
P value	<0.001		0.002		0.026	

T2D, type 2 diabetes; 95% CI, 95% confidence interval.
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Table 4. Association between type 2 diabetes and incident rheumatoid arthritis in female patients, stratified by the time interval between the first diagnosis of type 2 diabetes and the index date (N = 6,576).

	Time interval between the first diagnosis of type 2 diabetes mellitus and the index date (years), n (row %)					
	<4	4-<7	7-<11	≥11	Cases	Controls
	1,763 (26.8)	1,501 (22.8)	1,594 (24.2)	1,718 (26.1)		
Cases	281 (15.9)	252 (16.8)	269 (16.9)	294 (17.1)	1,325 (83.1)	1,424 (82.9)
Controls	1,482 (84.1)	1,249 (83.2)	1,718 (83.1)	1,424 (82.9)		
T2D, n (column %)	56 (19.9)	51 (20.2)	62 (23.0)	55 (18.7)	234 (17.7)	272 (19.1)
Odds ratio (95% CI)	2.30 (1.64–3.22)	1.60 (1.13–2.26)	1.40 (1.02–1.92)	0.98 (0.71–1.34)	1.00	1.00
P value	<0.001	0.008	0.039	0.876		

T2D, type 2 diabetes; 95% CI, 95% confidence interval.
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shown to reduce the risk of developing diabetes [23,24]. Altogether, these findings suggest that the pathogenesis of type 2 diabetes and RA could be linked by a similar chronic inflammatory response profile. Nevertheless, it should be noted that there is currently no evidence demonstrating that both conditions have shared genetic mechanisms [25].

The data used in this study were based on health claims records and thus could minimize the presence of recall bias as a result of collecting exposure information prior to disease onset in typical case-control studies. Still, there were several drawbacks in our study. First, due to the lack of detailed clinical data in the NHIRD, no information in regards to radiographic reports, biochemical and serological data (such as inflammatory markers, ACPA, and RF), or lifestyle factors such as smoking was available. Although smoking is an important risk factor for RA [26], the prevalence of female smokers is under 5%, and even lower (1.8%) among older women in Taiwan [27]. Thus, the increased risk of RA in female patients with type 2 diabetes should not be affected by smoking. On the other hand, prevalence of smoking was high (45.7%) in males and could confound the association between type 2 diabetes and RA, possibly leading to a lack of association between the two diseases in male patients. Since both the humoral and cell-mediated immune responses are more active in females, it is plausible that the disease expression is related to sexual dimorphism in the immune response [28]. This might also explain a significant association was only found in females, not male patients as well.

Second, although mobility and physical activity could be adversely affected by joint symptoms in individuals many years prior to the definitive diagnosis of RA [29], which in turn can increase the risk of type 2 diabetes, the joint symptoms before the clinical onset of RA are generally mild [30]. Therefore, the effect of immobility and physical inactivity on the development of type 2 diabetes should be minimal.

Third, it is possible that the association between RA and type 2 diabetes might be partially explained by the confounding effect of obesity. Nevertheless, although obesity is a well-established risk factor for type 2 diabetes [31], previous research on the association between body mass index and RA generated inconsistent results. Early studies had indicated a moderate increase in the risk of RA with obesity [32] but newer studies generally reported that obesity was not a predisposing factor for RA [33]. In addition, a comparison study using nationally representative survey data indicated that the prevalence of obesity was lower in Taiwan (7.2%) compared with the United States (33.7%) and England (32.1%) [34]. Furthermore, no significant differences in waist circumference were found between 86 Taiwanese patients with RA and 172 age- and sex-matched population controls [35]. Therefore, it might be premature to attribute the significant association between type 2 diabetes and incident RA to the confounding effect of obesity without further investigation.

In conclusion, this large nationwide, population-based, case-control study suggested that female patients with type 2 diabetes had an increased risk of developing RA. Although our findings are consistent with the hypothesis that chronic inflammation seen in patients with type 2 diabetes could contribute to the development of RA, further investigation with adjustments for possible confounders is needed before conclusions can be drawn. Nevertheless, given the high and increasing prevalence of type 2 diabetes in Taiwanese and other Asian populations, it is important to understand the effects of type 2 diabetes on the development of RA, particularly in young females.

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Author Contributions

Conceived and designed the experiments: MCL STY WYY NSL. Performed the experiments: MCL MK. Analyzed the data: MCL MK. Contributed reagents/materials/analysis tools: MCL STY WYY NSL. Wrote the paper: MCL MK.

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