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Risk of allergic conjunctivitis in patients with type 1 diabetes mellitus: a population-based retrospective cohort study

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ABSTRACT

Objective In accordance with the dichotomy between T helper type 1(Th1) and T helper type 2 (Th2) responses, the occurrence of allergic conjunctivitis (AC) and type 1 diabetes mellitus (T1DM) is, in theory, inversely related in the individual. However, recent studies investigating the association between the two diseases are controversial.

Design Population-based cohort study.

Setting We used claims data of the National Health Insurance Research Database of Taiwan.

Participants We identified 4160 patients aged 1–30 years with newly diagnosed T1DM and no history of AC at baseline. For each patient with T1DM, four non-T1DM controls (n=16,640) were matched by sex. The mean follow-up time was 6 years.

Primary and secondary outcome measures Multivariate Cox proportional hazards regression analysis was used to evaluate the risk of AC. We additionally evaluated the association between risk of AC and T1DM progression by examining Diabetes Complications Severity Index (aDCSI) changes from the date of diagnosis until the end of follow-up.

Results The overall incidence of allergic conjunctivitis (AC) was higher in the type 1 diabetes mellitus (T1DM) cohort than in the control cohort (23.0 vs 13.5 per 1000 person-years, adjusted incidence rate ratio (aIRR): 1.59, 95% CI 1.47 to 1.71). Relative to that in patients with mildly progressive T1DM, the risk of AC increased as the adapted Diabetes Complications Severity Index (aDCSI) increased (aIRR: 1.68, 3.78 and 18.8, with yearly changes in aDCSI score: 0.51 to 1.00, 1.01 to 2.00, and >2.00 vs <0.51, respectively; for trend <0.001).

Conclusion Patients with T1DM are at an elevated risk of developing AC; this risk increases with T1DM progression. The T helper type 1/T helper type 2 hypothesis is an overly simplistic explanation for this association.

Strengths and limitations of this study

- This is the first population-based retrospective cohort study to examine the risk of allergic conjunctivitis in patients with type 1 diabetes mellitus.
- The study cohorts were large enough to observe the risk variations among subgroups.
- We adjusted for multiple confounding factors, namely, age, sex, urbanisation level, parental occupation, follow-up period and the presence of other atopic disorders in our study.
- We are unable to obtain detailed clinical information (including laboratory data, experimental tests and pathology results) from the National Health Insurance programme.
- This study included only patients in Taiwan; as such, the present results may not be applicable to other populations.

INTRODUCTION

The incidence rate of allergic conjunctivitis (AC) and type 1 diabetes mellitus (T1DM), which are common chronic diseases in children and young adults, has been increasing in the last few decades.[1 2] Approximately 6%–30% of the general population has been diagnosed with AC,[3] which represents more than 90% of all ocular allergies.[4] AC, which is a type of IgE-mediated hypersensitivity of the conjunctiva to allergens such as pollen, animal dander and other environmental antigens,[5] exhibits a similar pathophysiology to that of other atopic diseases and is believed to be associated with the T helper type 2 (Th2) response. In contrast, T1DM is an autoimmune disease caused by cell-mediated immunity against pancreatic islet beta cells, and is viewed mainly as a T helper type 1 (Th1)-mediated disorder.[6] The Th2-associated cytokines, interleukin 4 (IL-4) and IL-13, inhibit the Th1 response; conversely, interferon-γ, which is associated with Th1, downregulates the Th2 response. According to the traditional Th1/Th2 paradigm, AC and T1DM are theoretically inversely related.

However, the results of recent studies investigating the association between the two diseases are controversial.[7–11] These conflicting results may be due to differences in the study design, patient characteristics and geographic location (which leads to variations in allergen exposure) as well as the influence of IL-17 producing T cells (Th17 cells), T regulatory cells (Tregs) and B lymphocytes in both disorders. Although

the pathophysiology of the atopic diseases was similar, the correlation between T1DM and each atopic disease in an identical study population appeared to differ. Furthermore, most previous studies have included allergic rhinitis and AC in the same group (rhinoconjunctivitis); as such, studies that specifically focus on the association between AC and T1DM are rare. Therefore, in order to investigate the association between AC and T1DM, we conducted a population-based cohort study using the database of the Taiwan National Health Insurance (NHI) programme.

MATERIALS AND METHODS

Data source

The NHI programme, which is operated by the National Health Insurance Administration (NHIA), is a single-payer programme, launched on 1 March 1995, that covers approximately 99% of the 23.74 million residents of Taiwan. The NHIA has authorised the National Health Research Institutes to construct and maintain the National Health Insurance Research Database (NHIRD) for researchers. The diagnostic codes were in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Ethics statement

The encrypts patient's personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was found to fulfil the conditions for exemption by the institutional review board (IRB) of the authors' institution. The IRB also specifically waived the consent requirement. The Research Ethics Committee has recommended the approval of studies using claims data from NHI (Protocol title: studies using claims data from NHI, Research Institute: China Medical University Hospital, Protocol No. CMUH104-REC-2-115(CR-1)).

Patients

The T1DM cohort included patients aged 1–30 years who had been newly diagnosed with T1DM (ICD-9-CM codes 250.x1 and 250.x3) between 1998 and 2011. The date of T1DM diagnosis was defined as the index date. We excluded patients older than 30 years, diagnosed with AC (ICD-9-CM codes 372.05, 372.10 and 372.14) at baseline, with type 2 diabetes (ICD-9-CM code 250), gestational diabetes (ICD-9-CM code 648.83), atopic dermatitis (ICD-9-CM code 691.8), vernal conjunctivitis (ICD-9-CM code 372.13), asthma (ICD-9-CM code 493), keratoconus (ICD-9-CM code 371.6), gynaecomastia (ICD-9-CM code 611.1), polycystic ovary syndrome (ICD-9-CM code 256.4), mammary fibroadenoma (ICD-9-CM code 217), adipogenital dystrophy (ICD-9-CM code 272.6), autoimmune thyroid disease (ICD-9-CM codes 242, 244.9 and 245.2), systemic lupus erythematosus (ICD-9-CM codes 710.0 and 695.4), rheumatoid arthritis (ICD-9-CM code 714), or *Sjögren syndrome* (710.0), or for whom age or sex information was missing. For each patient with T1DM, four non-T1DM controls were matched by sex. The patients in both cohorts were followed-up from the index date to the date of AC occurrence or censoring because of loss to follow-up or withdrawal from the NHI programme, or until the end of 2011.

Variables of interest

The sociodemographic variables used in this study were sex, age, urbanisation level and parental occupation. White-collar workers were defined as people with occupations characterised by long indoor work hours such as institutional workers and business and industrial administration personnel. Blue-collar workers were defined as people with occupations characterised by long outdoor work hours, such as fishermen, farmers and industrial labourers. Other occupations included primarily retired, unemployed or low-income populations. The level of urbanisation was divided into four levels based on the NHRI report. (Level 1 was the highest level of urbanisation and level 7 was the lowest. Because few people lived in areas classified as levels 5–7, we grouped the least urbanised populations into level 5.) We identified potential risk factors such as rhinitis (ICD-9-CM codes 472.0 and 477) and urticaria (ICD-9-CM code 708) at baseline. In addition, we evaluated diabetic severity by referring to the Adapted Diabetes Complications Severity Index (aDCSI).[12] The progression of diabetes was defined as a yearly increase in aDCSI score from the date of diagnosis to the end of follow-up; the four progression groups were defined as those with a yearly score increase of <0.51, 0.51–1.00, 1.01–2.00 and >2.0.

Statistical analysis

We conducted χ^2 tests to compare the distribution of the sociodemographic variables and comorbidities between the cohorts with and without T1DM. We assessed the cumulative incidence of AC between the T1DM and non-T1DM cohorts using the Kaplan-Meier method, and determined the differences via a log-rank test. The incidence densities of AC (per 1000 person-years) were estimated for both cohorts by sex, age, urbanisation level, parental occupation, comorbidity and follow-up time. Univariate and multivariate Poisson regression models were used to estimate the incidence rate ratio (IRR) with 95% CIs for AC development. The multivariate model was adjusted for sex, age, urbanisation level and parental occupation, in addition to comorbidities of rhinitis and urticaria. The Cox proportional hazard model assumption was also examined using a test of scaled Schoenfeld residuals. The model evaluating AC risk throughout the follow-up period revealed a significant relationship between Schoenfeld residuals for T1DM and follow-up time, suggesting that the proportionality assumption was violated (p=0.001). In the

subsequent analyses, we stratified the follow-up years to address the violation of the proportional hazard assumption. In order to evaluate the risk of T1DM progression from the date of diagnosis to the end of follow-up (four progression groups (yearly increase in aDCSI scores): <0.51, 0.51–1.00, 1.01–2.00 and >2.0), further analysis was performed to examine whether the progression could be used to predict AC risk. All statistical analyses were performed using the SAS statistical package (V.9.3 for Windows; SAS Institute). Statistical significance was defined at p<0.05.

RESULTS AND DISCUSSION

Results

Table 1 lists the sociodemographic characteristics and comorbidities of the two cohorts. In both cohorts, 53.1% of the patients were female and 47.0% were male. On average, the patients with T1DM were significantly younger than the controls (mean age: 15.6 years, SD: 7.76 vs mean age: 18.0 years, SD: 7.85, p<0.001). Most patients in the T1DM group were younger than 18 years of age (60.8%), and most patients in the control group were aged 18 years or older (54.2%). The mean follow-up duration was longer in the controls than in the cases (6.57 years, SD: 3.99 vs 6.28 years, SD: 4.04, p<0.001). Both cohorts tended to reside in urbanised areas (T1DM cohort: 60.0%, non-T1DM cohort: 57.1%); however, patients with T1DM were significantly more urbanised than the controls (p=0.003). Approximately half of the patients were classified as being in white-collar employment, with a somewhat higher rate of white-collar employment in the controls (T1DM cohort: 53.4%, non-T1DM cohort: 58.2%; p<0.001). The comorbidities were similar between the groups; a history of rhinitis was noted in 28.8% of the patients with T1DM and in 28.9% of the controls, and the proportion of individuals with urticaria in the T1DM and control groups was 10.2% and 10.6%, respectively.

Table 2 shows that the overall incidence of AC was 23.0 per 1000 person-years in the T1DM cohort, which was 1.71-fold higher than in the non-T1DM cohort (13.5 per 1000 person-years), with an adjusted incidence rate ratio (aIRR) of 1.59 (95% CI 1.47 to 1.71). Further, 96% of diagnoses of AC were performed by an ophthalmologist (see online supplementary table 1, which shows the specialties of the physicians who performed diagnoses of AC). We compared the AC risk between the T1DM cohort and the non-T1DM cohort by considering several variables such as sex, age, urbanisation level, parental occupation, the presence or absence of comorbidities, and the follow-up period. The risk of AC in patients diagnosed with T1DM, regardless of stratification, was higher than in the non-T1DM cohort.

Table 3 shows that a higher DCS1(aDCSI) score was associated with an increased risk of AC. Compared with patients diagnosed with mildly progressive diabetes, which was defined by an aDCSI score increase of <0.51 per year, the aIRRs increased with the progression of diabetes (aIRR=1.68, 3.78 and 18.8 with a yearly increase in aDCSI score of 0.51 to 1.00, 1.01 to 2.00, and >2.00 vs <0.51, respectively). The trend of increasing AC risk with T1DM progression was significant (p for trend <0.001).

Table 1 Comparison of demographic characteristics and comorbidities between patients with and without type 1 diabetes mellitus

	Controls (n=16 640) N (%)	Patients with type 1 diabetes mellitus (n=4160) N (%)	p Value
Sex			0.99
Female	8828 (53.1)	2207 (53.1)	
Male	7812 (47.0)	1953 (47.0)	
Age, years, mean (SD)*	18.0 (7.85)	15.6 (7.76)	<0.001
Stratified by age			<0.001
<18	7622 (45.8)	2527 (60.8)	
≥18	9018 (54.2)	1633 (39.3)	
Follow-up duration, years (SD)*	6.57 (3.99)	6.28 (4.04)	<0.001
Urbanisation level†			0.003
1 (Very high)	4590 (27.6)	1181 (28.4)	
2 (High)	4907 (29.5)	1316 (31.6)	
3 (Moderate)	3363 (20.2)	725 (17.4)	
4 (Low)	3780 (22.7)	938 (22.6)	
Parental occupation			<0.001
White collar	9678 (58.2)	2222 (53.4)	
Blue collar	4891 (29.4)	1339 (32.2)	
Others‡	2071 (12.5)	599 (14.4)	
Comorbidity			
Rhinitis	4389 (26.4)	1049 (25.2)	0.13
Urticaria	1645 (9.89)	388 (9.33)	0.44

*Student's t-test, χ^2 test.
†The urbanisation level was categorised by the population density of the residential area into four levels, with level 1 as the most urbanised and level 4 as the least urbanised.
‡Other occupations included primarily retired, unemployed or low-income populations.

Discussion

Our findings revealed that patients with T1DM are at a significantly higher risk of developing AC than non-diabetics. In addition, AC risk was found to increase with T1DM progression. This finding suggests that the traditional Th1/Th2 hypothesis, as an explanation for the association between AC and T1DM, may represent an

Table 2 Comparison of incidence densities of AC and HR between patients with and without type 1 diabetes mellitus by demographic characteristics and comorbidity

	Controls			Patients with type 1 diabetes mellitus				
	Event	Person-years	Rate†	Event	Person-years	Rate†	IRR (95% CI)	Adjusted IRR‡ (95% CI)
All	1470	109 298	13.5	601	26 122	23.0	1.71 (1.58 to 1.85)***	1.59 (1.47 to 1.71)***
Sex								
Male	909	57 662	15.8	394	13 375	29.5	1.87 (1.69 to 2.07)***	1.76 (1.59 to 1.94)***
Female	561	51 637	10.9	207	12 747	16.2	1.49 (1.32 to 1.69)***	1.32 (1.17 to 1.49)***
Stratification by age								
<18	1001	54 591	18.3	413	15 915	26.0	1.41 (1.27 to 1.58)***	1.44 (1.30 to 1.60)***
≥18	469	54 707	8.57	188	10 207	18.4	2.15 (1.91 to 2.41)***	2.16 (1.92 to 2.42)***
Urbanisation‡								
1 (Very high)	473	30 591	15.5	191	7386	25.9	1.67 (1.45 to 1.94)***	1.56 (1.35 to 1.80)***
2 (High)	446	32 252	13.8	204	8304	24.6	1.78 (1.54 to 2.04)***	1.62 (1.41 to 1.86)***
3 (Moderate)	271	22 061	12.3	103	4633	22.2	1.81 (1.52 to 2.16)***	1.66 (1.39* to 1.97)***
4 (Low)	280	24 395	11.5	103	5799	17.8	1.55 (1.30 to 1.84)***	1.51 (1.28 to 1.80)***
Parental occupation								
White collar	911	64 428	14.1	345	14 054	24.6	1.74 (1.56 to 1.93)***	1.52 (1.37 to 1.69)***
Blue collar	406	30 827	13.2	169	8701	19.4	1.47 (1.28 to 1.70)***	1.48 (1.28 to 1.70)***
Others	153	14 044	10.9	87	3367	25.8	2.37 (1.92 to 2.92)***	2.22 (1.80 to 2.73)***
Comorbidity§								
No	871	71 020	12.3	377	17 209	21.9	1.79 (1.62 to 1.97)***	1.68 (1.52 to 1.85)***
Yes	599	38 279	15.7	224	8912	25.1	1.61 (1.41 to 1.83)***	1.43 (1.26 to 1.63)***
Follow-up time								
1 year	258	15 881	16.3	157	3942	39.8	2.45 (2.25 to 2.68)***	1.54 (1.42 to 1.68)***
>1 year	1212	93 417	13.0	444	22 180	20.0	2.15 (1.97 to 2.34)***	1.44 (1.33 to 1.57)***

*p<0.05, ***p<0.001.
†Rate, incidence rate, per 1000 person-years.
‡Adjusted IRR: multivariable analysis including sex, age, urbanisation level, parental occupation, and comorbidities of rhinitis and urticaria.
§Comorbidity: patients with any one of the comorbidities (rhinitis or urticaria) were classified under the comorbidity group.
AC, allergic conjunctivitis; IRR, incidence rate ratio.

Table 3 Incidence and IRR of aDCSI change for allergic conjunctivitis in the type 1 diabetes mellitus cohort

Change in aDCSI score per year	N	Number of events	Rate*	Crude IRR	95% CI	Adjusted IRR†	95% CI
Type 1 diabetes mellitus							
0–0.50	3357	399	18.7	1	(Reference)	1	(Reference)
0.51–1.00	443	81	26.2	1.40	(1.12 to 1.76)***	1.68	(1.34 to 2.10)***
1.01–2.00	244	64	48.2	2.58	(2.01 to 3.31)***	3.78	(2.92 to 4.88)***
>2.00	116	57	183.1	9.81	(7.56 to 12.7)***	18.8	(14.2. 24.7)***
p for trend				<0.001		<0.001	

*Rate, per 1000 person-years, *** p<0.001.
†Adjusted IRR: multivariable analysis including sex, age, urbanisation, parental occupation, and comorbidities of rhinitis and urticaria.
aDCSI, adapted Diabetes Complications Severity Index; IRR, incidence rate ratio.

oversimplification of the relationship between the two conditions.

According to the traditional Th1/Th2 paradigm, AC and T1DM are theoretically inversely related. However, the results of recent studies investigating the association between the two diseases are controversial.[7–11] In 2011, Thomsen *et al* examined the association between T1DM and atopic diseases in a twin population registered in the Danish Twin Registry.[7] They found that the age-adjusted and sex-adjusted risk of atopic dermatitis was lower in patients with T1DM than in non-diabetics, whereas asthma and allergic rhinoconjunctivitis were non-significantly associated with T1DM. In addition, Wahlberg *et al* evaluated the association between early symptoms and known environmental risk factors for atopic diseases with the occurrence of T1DM-related β-cell autoantibodies at the age of 2.5 years.[8] They reported that, at least during the first years of life, there is a positive association between the occurrence of atopic dermatitis or rhinoconjunctivitis and the development of T1DM-related autoimmunity.

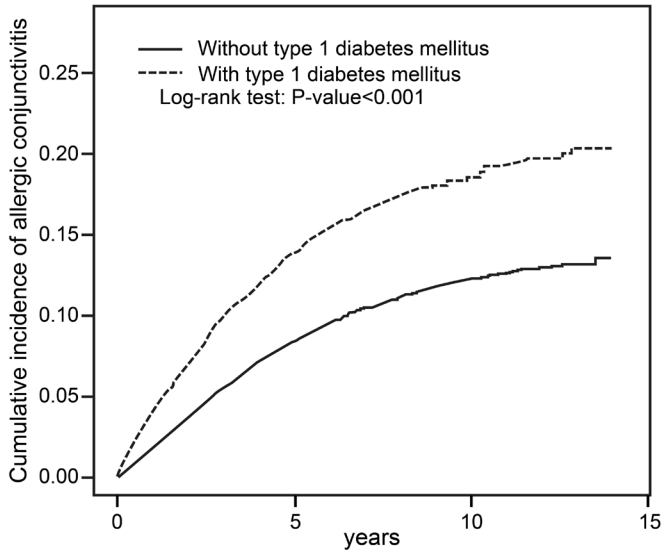

Figure 1 The cumulative incidence of allergic conjunctivitis in T1DM and non-T1DM cohort. T1DM, type 1 diabetes mellitus.

The authors additionally suggested that similar factors may trigger β-cell autoimmunity and atopic symptoms. In 2012, Fsadni *et al* compared the reported national incidence of T1DM with the prevalence of atopic diseases, and found a positive correlation between T1DM and atopic eczema; however, no correlation was observed between the incidence of T1DM and that of rhinoconjunctivitis.[9] In 2015, Klamt *et al* designed a prospective case–control study to investigate the association between the prevalence of T1DM and IgE-mediated allergies.[10] The results implied that T1DM is associated with an increased risk of self-reported IgE-mediated allergies. However, in a large prospective study involving 14 849 individuals from five study populations, including 834 cases with autoimmune disease,[11] Skaaby *et al* did not find a statistically significant association between atopy and the development of any autoimmune disease, including T1DM.

AC is a type of IgE-mediated hypersensitivity that encompasses seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). However, the clinical and pathophysiological features of AKC and VKC differ significantly from those of SAC and PAC.[13] The pathomechanism of AKC involves both IgE-mediated chronic degranulation of mast cells as well as immune mechanisms mediated by Th1-lymphocyte-derived and Th2-lymphocyte-derived cytokines.[13] In order to avoid including patients with AKC, we excluded individuals with atopic dermatitis, as evidence of the latter must be present for a diagnosis of AKC to be made.[13] VKC is a chronic allergic inflammation of the ocular surface; autoimmune diseases have been reported in 2% of patients with VKC.[14] Recent data have suggested that patients with VKC may have a higher frequency of a family history of autoimmune disorders, antinuclear antibodies and autoimmune thyroid disease.[14–17] In addition, VKC is more common in the tropics than in northern climates. However, although VKC is a common disorder, particularly in Asia, most Asian patients with AC are diagnosed as having SAC and PAC.[3] Skin tests and/or serum IgE antibody tests for common allergens often return negative results in patients with VKC; therefore,

VKC diagnosis is mostly based on clinical findings.[18] In addition to excluding patients diagnosed with vernal conjunctivitis based on the ICD-9 code, we excluded disorders commonly associated with VKC, including such as asthma, keratoconus, gynaecomastia, polycystic ovary syndrome, mammary fibroadenoma, adipogenital dystrophy, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis and *Sjögren syndrome*.[18] After the exclusion of patients with AKC and VKC who may have been at higher risk of developing an autoimmune disease, our study revealed that individuals with T1DM are at a significantly higher risk of developing AC than individuals who do not suffer from diabetes. Several potential explanations must be considered.

First, early-life events that trigger AC and T1DM may be identical.[8] The marked increase in the incidence of both diseases in the last few decades implies that this rise is attributable to environmental or lifestyle factors, because the genetic pool could not have altered sufficiently to account for such a dramatic increase in this short period. According to the hygiene hypothesis, exposure, or the lack thereof, to certain infectious agents and other homeostatic factors at an early age may increase the risk of abnormal immune responses, potentially precipitating the onset of allergic diseases and T1DM.[19] Various gene–environment interactions, with the possible involvement of multiple microorganisms, air pollution and dietary factors, including the composition of the gut microbiome with consequent diverse effects on immune response and tolerance,[20] may operate in the aetiology of these two conditions.[21–23] In general, urbanisation is highly likely to represent a strong contributing factor to the increasing prevalence of AC and T1DM. Furthermore, socioeconomic indices may be used to explain the differences in the prevalence of immunological diseases.[19] Therefore, we adjusted for multiple variables, including parental occupation and urbanisation level, when analysing the association between AC and T1DM. We found that the risk of AC in patients diagnosed with T1DM, regardless of stratification of parental occupation and urbanisation level, was higher than in patients without T1DM. These results indicate that, in addition to environmental factors, other mechanisms may underlie the predisposition to both diseases in the same patients.

The dichotomy between Th1 and Th2 responses is a useful framework for describing pathologies; however, in recent years, this paradigm has been considered an incomplete model as Th1 responses have been described as characteristic of atopic disease and Th2 responses of autoimmunity. One recent study has explored the coexistence of several Th1-Th17-Th2-immune mediated disorders, concluding that both Th1 and Th2 responses could exist in the same subjects.[24] Therefore, in addition to the potentially identical early triggers of AC and T1DM, the poor control of immune responses, caused by the aberrant development of regulatory mechanisms, may represent an explanation for the elevated risk of AC in patients with T1DM. Additional insights into the roles of Tregs and B lymphocytes in both disorders are required.[25–27] The control of ocular allergies has been suggested to involve a balance between Tregs and pathogenic T cells, and changes in Treg frequencies have been reported in patients with AC. One study showed that, upon challenge with the *Dermatophagoides pteronyssinus* allergen, patients with PAC exhibited a higher frequency of CD4+CD25+ cells than healthy controls.[28] These cells, however, exhibited reduced Foxp3 expression or were Foxp3−, suggesting that patients with PAC have higher levels of activated effector CD4+ T cells and reduced levels of Tregs. Ferraro *et al* compared peripheral lymph node (PLN)-derived Tregs from patients with T1DM and controls, and found that PLN-derived Treg functions were impaired in the former.[29] In addition, Willcox *et al* analysed postmortem pancreatic samples from patients with T1DM, and found that the lack of Treg cells may be an influential factor in autoimmune pathogenesis in these patients.[30] B-lymphocytes may additionally play a critical role in the development of both atopic disease and T1DM by acting as antigen-presenting cells, thereby advancing the initial stages of the immune response and activating effector T cells. These cells also differentiate into plasma cells, producing both specific autoantibodies as well as allergen-specific IgE antibodies, which are found in numerous atopic diseases. Moreover, the presence of IgE antibodies is not exclusive to atopic diseases, but is also observed in autoimmunity, for example, the occurrence of antiglutamic acid decarboxylase 65 antibodies in T1DM.[31] Overall, recent findings have shown that the traditional Th1/Th2 theory is too simplistic to explain the immune responses involved in AC and T1DM. The complexities of the crosstalk between Th1, Th2, Tregs and B lymphocytes warrant further exploration.

The relationship between the severity of diabetes and atopic disease is unclear. A recent study found that Th17 may play an independent role in the progression of diabetic nephropathy, and that the modulation of IL-17 represents a potential immunologic therapeutic strategy.[32] A significant upregulation of IL-17 has been demonstrated in the skin of patients with atopic dermatitis, and an increase in Th17 cells (both circulating and skin residing) was correlated with disease severity.[33] Increased IL-17 serum levels may be considered a marker of allergy severity in patients with allergic rhinitis.[34] However, the role of Th17 in ocular allergy is poorly understood.[27] We hypothesised that the progression of T1DM, which was defined in this study as a yearly increase in aDCSI score, is positively correlated with the risk of AC development. We found a significant trend in increase of AC risk with the progression of T1DM (p for trend <0.001). To the best of our knowledge, this is the first nationwide retrospective cohort study to investigate the association between T1DM progression and AC risk. However, additional studies are warranted to validate this finding.

Our study had several strengths. First, the use of the administrative database prevented the under-reporting of medical visits.[35] Second, the nationwide population-based

study design was highly representative of the general population, and prevented selection bias. Third, we adjusted for multiple confounding factors, namely, age, sex, urbanisation level, parental occupation, follow-up period and the presence of other atopic disorders in our study.

However, this study was still subject to several limitations. First, the diagnosis of AC was based on ICD-9-CM codes provided by ophthalmologists; however, we were unable to obtain detailed clinical information (including laboratory data, experimental tests and pathology results) from the NHI programme. Although the NHI programme regularly conducts expert reviews of patient charts to randomly confirm claims from all hospitals, bias may arise from miscoding and misclassification. Second, several potential confounding factors that may be associated with AC, such as body mass index, smoking status, education level and food habits, were not included in the database; however, the relationships between these factors and AC remain uncertain. Third, the aDCSI, which was used to evaluate the severity of diabetes in our study, was based on clinical findings without laboratory data; moreover, the aDCSI was an unweighted index that did not independently test adverse outcomes associated with each complication.[36] Finally, the study included only patients in Taiwan; as such, the present results may not be applicable to other populations.

CONCLUSIONS

In conclusion, patients with T1DM are at an elevated risk of developing AC. The risk of AC was found to increase with the progression of T1DM. The traditional Th1/Th2 hypothesis is an overly simplistic explanation for this association. Further elucidation of potential environmental or lifestyle factors, as well as the roles of Th17 cells, Tregs and B lymphocytes, in relation to the development of both diseases, is required.

Contributors YHC: wrote the manuscript. CLL: data analysis and interpretation. DTB: critical discussion. YCH: study design, wrote the manuscript, data interpretation, revised and approved the manuscript.

Competing interests None declared.

Patient consent This study was found to fulfil the conditions for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There were no additional unpublished data from this study.

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