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Adult atopic dermatitis and the risk of type 2 diabetes



To the Editor:

Atopic dermatitis (AD) is a common chronic pruritic inflammatory skin condition, which typically begins in early childhood and has a lifetime prevalence of 10% to 20%.¹ Although it was previously assumed that most patients would outgrow their condition, it is now acknowledged that many patients continue to experience AD symptoms in adulthood.¹ Importantly, a recent US study showed a higher prevalence of type 2 diabetes (T2D) in patients with AD than in the general population.² Possible explanations for the putative relationship include shared genetic risk loci between AD and T2D,³ diabetogenic effects of chronic systemic low-grade inflammation in moderate-to-severe AD,⁴ or sedentary lifestyle associated with AD.^{2,5} In this cohort study, we investigated the risk of new-onset T2D in a large cohort of Danish adults with AD.

The Danish National Health Service provides free health care to all Danish residents, and information on vital statistics, morbidity, medication use, and tax-reported income is stored in nationwide registries and made available for research. As cases, the study cohort comprised all Danish citizens 18 years or older with a hospital diagnosis of AD starting from January 1, 1997, and followed until December 31, 2011, migration, death, or the occurrence of T2D, whichever came first. T2D was defined as the first claimed prescription of a glucose-lowering drug

TABLE I. Baseline characteristics

Characteristic	Reference population (n = 148,428)	AD (n = 30,079)
Age (y), mean $\pm$ SD	28.45 $\pm$ 14.81	28.75 $\pm$ 15.13
Women, n (%)	81,049 (54.60)	16,411 (54.56)
Sex: men, n (%)	67,379 (45.40)	13,668 (45.44)
Socioeconomic status, mean $\pm$ SD	2.00 $\pm$ 1.41	2.00 $\pm$ 1.43
Smoking, ever, n (%)	7,639 (5.15)	2,415 (8.03)
Comorbidities, n (%)		
Alcohol abuse	1,957 (1.32)	582 (1.93)
Hypertension	2,890 (1.95)	762 (2.53)
Inflammatory bowel disease	327 (0.22)	163 (0.54)
Rheumatoid arthritis	193 (0.13)	74 (0.25)
Medication use, n (%)		
Topical corticosteroids	6,630 (4.47)	11,243 (37.38)
Systemic corticosteroids	1,461 (0.98)	2,145 (7.13)
Systemic anti-inflammatory (nonsteroids)	364 (0.25)	669 (2.22)
Topical calcineurin inhibitors	497 (0.33)	1,972 (6.56)
Cholesterol-lowering drugs	1,661 (1.12)	373 (1.24)

Baseline characteristics regarding age, sex, socioeconomic status, comorbidities, and medication use in the AD group and reference population, respectively.

excluding insulin. Each case was matched (on age, sex, and calendar time) with 5 individuals from the reference population (henceforth “controls”). Individuals with any form of diabetes or polycystic ovary syndrome before study start were excluded. Crude and adjusted hazard ratios (HRs) were estimated using multivariable Cox regression models. For detailed description of the methodology, please see this article’s Online Repository at www.jacionline.org.

A total of 5,644,572 Danish citizens 18 years or older were identified, and served as the source population. The final study cohort comprised a total of 30,079 adult patients with AD and 148,428 matched controls (a study flowchart is shown in Fig E1 in this article’s Online Repository at www.jacionline.org). The mean age was 28.5 $\pm$ 14.8 and 28.8 $\pm$ 15.1 years in the control group and the AD group, respectively, with a slight female predominance (54.6%) in both groups. Overall, the baseline prevalence of comorbidities, smoking, and use of prescription medication was higher in the AD group than among controls (Table I).

A total of 3560 incident cases of T2D were registered during the study period. Incidence rates (95% CI) of new-onset T2D per 1000 person-years were 1.92 (1.86-2.00) and 1.96 (1.80-2.13) in the reference population and the AD group, respectively. The mean age of new-onset T2D in AD versus controls was 46.8 $\pm$ 16.8 and 48.9 $\pm$ 17.3 years, respectively. Cox regression analyses yielded a nonsignificant age- and sex-adjusted HR (95% CI) estimate for patients with AD (HR, 0.97; 95% CI, 0.90-1.05). However, in multivariable analysis with further adjustment for socioeconomic status, smoking, comorbidity, and medication use, the independent risk of T2D was significantly decreased (adjusted HR, 0.76; 95% CI, 0.68-0.83). Notably, multivariable analyses showed that T2D was significantly associated with age, smoking, alcohol abuse, and topical as well as systemic corticosteroid use (Table II). However, topical calcineurin inhibitors and systemic nonsteroid immunosuppressive agents were not associated with an increased risk of T2D.

TABLE II. Risk of type 2 diabetes in patients with AD

Patient characteristic	Age- and sex-adjusted			Multivariable model		
	HR	95% CI	P value	HR	95% CI	P value
AD	0.97	0.89-1.05	.372	0.76	0.68-0.83	<.001
Age	1.04	1.04-1.05	<.001	1.04	1.03-1.04	<.001
Sex	0.98	0.92-1.05	.575	1.03	0.96-1.10	.887
Topical corticosteroids	1.39	1.30-1.38	<.001	1.34	1.25-1.44	<.001
Systemic corticosteroids	1.48	1.37-1.61	<.001	1.32	1.22-1.44	<.001
Systemic anti-inflammatory (nonsteroids)*	1.21	0.91-1.49	.245	1.02	0.81-1.28	.848
Topical calcineurin inhibitors	0.98	0.80-1.19	.805	0.93	0.75-1.14	.476
Rheumatoid arthritis	1.30	0.92-1.83	.140	1.07	0.76-1.52	.694
Inflammatory bowel disease	1.51	1.12-2.03	.007	1.27	0.94-1.71	.118
Smoking	1.73	1.57-1.89	<.001	1.50	1.37-1.65	<.001
Alcohol abuse	1.85	1.61-2.13	<.001	1.58	1.37-1.83	<.001
Socioeconomic status						
Lowest	0.80	0.68-0.93	.003	0.85	0.73-0.99	.035
Below average	0.59	0.50-0.70	<.001	0.64	0.54-0.75	<.001
Average (reference)	1	—	—	1	—	—
Above average	1.45	1.31-1.61	<.001	1.36	1.23-1.52	<.001
Highest	1.02	0.91-1.13	.755	1.00	0.89-1.11	.949

Multivariable Cox regression analysis was used to estimate the T2D risk in patients with AD compared with the reference population.

*Azathioprine, methotrexate, cyclosporine, mycophenolate mofetil.

The lack of association between adult AD and T2D contrasts the findings from a recent US population-based study in which AD was associated with both prediabetes (adjusted odds ratio, 1.77; 95% CI, 1.42-2.22) and adult-onset diabetes (adjusted odds ratio, 1.37; 95% CI, 1.16-1.63).² The apparent discord between our study and that by Silverberg and Greenland² could be due to their lack of adjustment for corticosteroid use in fully adjusted models. Another explanation for the difference in the observed T2D risk in Danish and American patients with AD could be international differences in prescription patterns of systemic corticosteroids. A recent survey revealed that Danish dermatologists are among the most restrictive users of systemic corticosteroids in children with severe AD when compared with other European dermatologists.⁶ Moreover, an increased risk of adverse cardiovascular outcomes such as ischemic stroke and myocardial infarction was reported in patients with AD from the United States and Taiwan,^{7,8} whereas we recently showed that excess cardiovascular risk in Danish patients with AD was explained by the presence of comorbidities and modifiable cardiovascular risk factors, rather than the condition itself.⁵

Several strengths and limitations apply to this study. The high accuracy of the Danish registries, as well as the available information on socioeconomic status, medication, and comorbidities, allows for large-scale nationwide analyses, in which selection and recall bias is minimized. Because of the observational nature of our study, we cannot determine causality. Notably, we only included patients with AD treated in hospitals (both inpatients and outpatients), and these patients are likely to have more severe disease than their counterparts managed by general practitioners. This may limit the generalizability of our results; however, these patients also are more likely to display a typical clinical profile that fits the diagnostic criteria of AD. Although the registries used in this study contain information on a wide range of potential confounding factors, information on risk factors such as body mass index (BMI) is missing. However, in a Danish

cohort study including 344 adults with AD and 2999 general population controls, differences in BMI were investigated, and previously unpublished data from this cohort revealed a mean BMI of 25.92 ± 5.24 and 25.93 ± 4.62 kg/m² in patients with AD and the general population, respectively, indicating that BMI would not likely have biased our results significantly.

In conclusion, we show that adult patients with AD treated as inpatients or outpatients in the Danish national hospital system do not have an increased risk of new-onset T2D compared with matched controls. However, multivariate analyses revealed that age, smoking, alcohol abuse, and topical as well as systemic corticosteroids were associated with the risk of diabetes. This suggests that AD in Danes is not likely an independent risk factor for diabetes. Nevertheless, the significant association between the diabetes risk and the use of corticosteroids in our cohort warrant further attention and investigation.

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Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria



To the Editor:

Omalizumab (anti-IgE) has been shown to be effective in chronic spontaneous urticaria (CSU) in a number of clinical trials.¹ However, in clinical practice, some patients with CSU are fast responders to their first injection of omalizumab, often within days, whereas others are slow responders, with therapy taking weeks to be effective. This letter examines the possible underlying mechanisms.

Sixty-four patients with CSU (46 women) whose symptoms were not controlled with H₁-antihistamines up to 4 times the recommended dose were treated with omalizumab at the Charité Department of Dermatology. Their median age was 47 (range, 23-85 years) years, and the median duration of their CSU was 3 years (range, 4 months to 40 years). Seven patients had received omalizumab in the past but not for at least 6 weeks before enrolment in the study, and their symptoms had returned in full. All analyses were performed according to the Declaration of Helsinki and approval was obtained from the Charité Ethics Committee (EA1/268/13). All patients gave signed informed consent.

Omalizumab 300 mg was injected subcutaneously 3 times at 4-week intervals. The first day of response was defined as the first of 7 continuous days when the 7-day urticaria activity score² was 6 or less. Venous blood was taken before the first omalizumab treatment and centrifuged at 2500 rpm for 10 minutes.

By the end of week 12, 56 (88%) had responded to omalizumab and 8 (12%) were nonresponders (Fig 1, A). Of the 56 responders, 39 patients (70%) responded within 8 days (fast responders) and 18 (32%) within the first day. Seventeen patients (30%) responded between 8 days and 3 months (slow responders). The cutoff time of 8 days between fast and slow responders was chosen because it

corresponds with the peak plasma level of omalizumab after its initial injection.³

We hypothesized that a slow response to omalizumab occurs in patients with CSU in whom IgG antibodies to unoccupied IgE receptors (FcεRI) activate mast cell mediator release to cause wheal and angioedema formation.⁴ This hypothesis is based on the knowledge that omalizumab first complexes soluble IgE then sequesters IgE released from mast cells, thus uncovering membrane FcεRI, which subsequently decays slowly over several weeks.⁵

To test this, the basophil histamine release assay (BHRA) was used. This assay may be used to detect serum autoantibodies directed against either the cell-bound IgE or unoccupied FcεRI. In this study, basophils were stripped of their IgE to assess FcεRI only. The BHRA was done as previously described (see this article's Online Repository at www.jacionline.org).⁶ Analysis of the omalizumab responders showed that most BHRA-positive patients responded only after the second injection (Fig 1, B), with a median time to response of 29 days, whereas BHRA-negative patients had a median time to response of only 2 days (Fig 1, C). Furthermore, only 1 of the 39 fast responders was BHRA positive, whereas 8 of the 17 slow responders were BHRA positive ($P = .0001$; Fisher exact test; Fig 1, D).

The hypothesis was also tested using the autologous serum skin test (ASST)⁷ in which 50 μL of fresh undiluted autologous serum was injected intradermally into the volar forearm. Similar volumes of 0.9% NaCl saline and 100 μg/mL histamine were used as negative and positive controls. The ASST was taken to be positive when the serum-induced wheal had a diameter at least 1.5 mm greater than the saline-induced wheal at 30 minutes. For clinical reasons, the ASST was performed on 51 patients only. Twelve of the 33 fast responders were ASST positive, whereas 10 of the 13 slow responders showed a positive ASST result ($P = .012$; Fisher exact test; Fig 1, E and F).

There were no statistical differences between fast and slow omalizumab responders with respect to age, body mass index, or disease activity or duration. Similarly, pretreatment IgE levels, neutralization rates of IgE, and free IgE and omalizumab levels posttreatment were not significantly different between slow and fast responders to omalizumab (Table I).

When comparing BHRA with ASST, it must be realized that BHRA is more specific in that it was designed to identify serum IgG antibodies to FcεRI. However, it is time consuming and may not be available in all clinics. In contrast, the ASST is easy to perform clinically but is less specific, because it will also detect IgG antibodies against mast cell-bound IgE, and may contain other histamine-releasing factors that can lead to a positive ASST response.⁷ Even so, there was a significant relationship between BHRA and ASST results (Spearman $\rho = 0.448$, $P < .01$). All BHRA-positive patients were ASST positive. BHRA-positive and ASST-positive omalizumab responders are 4.5 and 5.5 times more likely to have a slow response to treatment compared with BHRA-negative and ASST-negative responders; the relative risks with 95% confidence limits were 4.54 for BHRA (2.42-8.53, z test $P < .001$) and for ASST 5.50 (1.37-22.11, z test $P < .05$).

The strength of this study is the highly significant correlation between the length of time to the onset of activity of omalizumab and BHRA, strongly suggesting that a positive BHRA may predict a slow response to omalizumab. Limitations of the study

E- Supplementary

The study was approved by the Danish Data Protection agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-suite 02736). Register studies do not require approval from an ethical committee in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.¹

Data sources

In Denmark, population characteristics are continuously registered in nationwide registers including information on health utilization and medication use, and the data are made available for research purposes. A unique personal identification number which is given to all citizens of Denmark at birth or immigration allows for individual-level linkage across these nationwide registers. The Danish National Health Service provides all Danish citizens with tax-supported healthcare, which guarantees free and equal access to general practitioners and hospitals. The Danish National Patient Register contains information on all hospital admissions, treatment procedures and outpatient (ambulatory) visits. Hospital discharge diagnoses are coded by the treating physician according to the Danish version of the International Classification of Disease (ICD)-8 classification from 1978 to 1994, and ICD-10 classification from 1994 to present.² The Danish Registry of Medicinal Products Statistics contains information on all prescription-based drugs. Drugs are coded by the international Anatomical Therapeutic Chemical (ATC) classification.³ Drug expenses are partially reimbursed by Danish healthcare authorities, ensuring complete registration and minimal incentives to claim drugs through other sources. Information on tax-reported household income is recorded by Statistics Denmark.⁴

Study population

The entire Danish population aged ≥ 18 years from 1st of January 1997 until 31st of December 2012 served as the source population. We excluded all patients with polycystic ovary syndrome (PCOS), individuals with missing information on migration, and individuals with a history of any form of diabetes (i.e. a hospital inpatient or outpatient diagnosis of diabetes, or use of any type of glucose-lowering agents) prior to study

start. Cases were identified by their first inpatient or outpatient hospital diagnosis of AD (ICD-8 691 or ICD-10 L20) and were matched with 5 controls (on age, sex and calendar time) randomly sampled from all non-cases in the Danish population, using risk-set sampling. The index date for controls was the index date of the corresponding case. As a substantial proportion of AD diagnoses are given before the age of 18, patients with prevalent AD were included in the study at the latter of either 1st of January 1997 or their 18th birthday. Cases and controls were followed until the first of either 31st of December 2012, migration, death, or occurrence of T2D.

Covariates

The selected covariates in the study included rheumatoid arthritis, inflammatory bowel disease, smoking, alcohol abuse, and hypertension as these have previously been associated with AD.^{5,6} Rheumatoid arthritis and inflammatory bowel disease were identified by ICD codes, and hypertension was defined by either a hospital diagnosis, or if a patient within 90 days received treatment with at least two of the following classes of antihypertensive drugs: α -adrenergic blockers, non-loop diuretics, vasodilators, β -blockers, calcium channel blockers, and renin-angiotensin system inhibitors, as previously validated with a positive predictive value of 80% and a specificity of 95%.⁷ Collection of data on smoking history and alcohol abuse was performed as described elsewhere.^{8,9} We identified prescribed medications *before* the occurrence of an outcome, i.e. only prescriptions claimed before onset of diabetes, or censoring, were included.

Corticosteroids administered orally or by injections were categorised as systemic (ATC code group H02) and ointments and creams were categorised as topical (ATC code group D07). In Denmark, all topical corticosteroids are prescription-based, apart from hydrocortisone 1%, which is prescription-based as well as available over the counter. Non-steroid oral immunosuppressive agents included azathioprine (L04AX01), methotrexate (L04AX03), cyclosporine (L04AD01) and mycophenolate mofetil (L04AA06). An age-standardised index of socioeconomic status was calculated based on the mean income during a 5-year period prior to study inclusion.

Outcome and sensitivity analyses

The primary study endpoint was defined as the first claimed prescription of a glucose-lowering drug excluding insulin (ATC code group A10B).

As a sensitivity analysis, we performed a Cox regression analysis where the topical and systemic corticosteroids were excluded from the fully adjusted model, as this variable is strongly associated with the exposure, and can also be considered as a part of the causal pathway. Corticosteroids administered through inhalation or as nasal sprays were included as a covariate in a separate sensitivity analysis. Furthermore, we conducted a sensitivity analysis where only patients with incident (new-onset) AD were included as study cases, while the rest of the methodology remained the same. Finally, we performed an analysis where patients with new onset T2D within a year after index were deleted, to investigate possible surveillance bias in AD patients.

Statistical analysis

Categorical variables were presented as frequencies with percentages and continuous variables as means with standards deviations (SD). Incidence rates were presented per 1,000 person-years at risk. Hazard ratios (HRs) were estimated by Cox proportional hazards models, in sex- and age adjusted and multivariable analyses, respectively. The proportional hazards assumption was tested and found to be valid. Results were presented with 95% confidence intervals (CIs) where applicable, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed with the STATA software version 13.0 (StataCorp, College Station, TX, USA) and SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results of sensitivity analyses

When topical and systemic corticosteroids were excluded from the adjusted model, patients with AD had a modestly decreased risk of T2D (adjusted HR 0.90 [0.82-0.99]) and in sensitivity analyses where only incident cases of AD (n=10,488) in the study period were included, the risk estimates of T2D did not change significantly (adjusted HR 0.69 [0.57-0.83]). In an analysis testing for surveillance bias, the T2D risk estimates were virtually unchanged when we excluded incident cases of T2D within a year after index.

Corticosteroids administered through inhalers and nasal sprays were not significantly associated with T2D in multivariable analysis, and did not change the estimates significantly when included in the model.

Figure e1 Legend:

Study flow chart

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