

DIABETES MELLITUS

The association between allergy and diabetes in the Canadian population: Implications for the Th1-Th2 hypothesis

Robert Dales¹, Yue Chen², Mei Lin² & Jacob Karsh¹

¹Department of Medicine, Ottawa Health Research Institute; ²Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Accepted in revised form 23 May 2005

Abstract. T-lymphocytes may preferentially differentiate towards a Th1 subtype, which is thought to be involved in the autoimmune aspects of diabetes, or a Th2 subtype, which is thought to mediate allergic disease. The activation of one subtype is thought to inhibit the other. To determine if diabetes is less common among those with allergic disease, consistent with the postulated TH1/Th2 paradigm, we used data from the 2000–2001 Canadian Community Health Survey of those at least 12 years of age from 125,159 households. Diabetes requiring insulin was reported in 1% whether or not allergies were reported. The

crude odds ratio between diabetes and allergies for the entire population was 1.06 (95% confidence interval (CI): 0.90, 1.24). Adjusted for household size, number of bedrooms, immigrant status, income adequacy, educational level, smoking status, alcohol drinking status, regular exercise, and age, there was a positive association between allergy and diabetes with an odds ratio of 1.25 (95% CI: 1.06, 1.49). These results do not provide evidence for the existence of the Th1/Th2 paradigm as a determinant of disease patterns in the general population.

Key words: Asthma, Diabetes, Epidemiology, Immunity, Lymphocytes

Introduction

Diabetes in the general population often has an autoimmune basis. Prior to the clinical onset of type 1 diabetes, glutamic acid decarboxylase (GAD) and insulin autoantibodies can be detected in at least 70 and 56%, respectively [1]. Late onset diabetes in adults (LADA) is associated with fewer detectable autoantibodies than in classic type 1 [1, 2]. In clinical type 2 diabetes diagnosed by primary care physicians, the prevalence of antibodies to GAD and islet cells (ICA) were 10 and 6%, respectively [3]. The presence of ICA predicts future need for insulin suggesting islet cell destruction at a slower rate than in clinical type 1 [2, 4, 5]. Inflammatory markers such as interleukin-6, tumor necrosis factor and C-reactive protein may also modify the risk of developing type 2 diabetes [6–8]. Compared to those without diabetes, type 2 diabetics was associated with TNF- α -R2, IL-6, and C-reactive protein [8].

Postulated immune mechanisms underlying allergic disease and diabetes mellitus suggest that in the general population, allergy should be less common in those with diabetes. T-lymphocytes, which respond to antigen-presenting cells, may tend towards a Th1 or a Th2 subtype. Cytokines of one type are thought to inhibit activation of the other cell type. If this were true, an imbalance towards Th1-lymphocyte expression would favor the development of auto-immune

diseases such as some types of diabetes thought to be mediated by Th1 cells and inhibit atopy and asthma [9–11], mediated by Th2 cells.

We looked for evidence to support this hypothesis in a general population survey by determining if those with reported diabetes were less likely to report allergies. We used data from the Canadian Community Health Survey (CCH). Its large size provides good power to detect small effects and provide relatively stable estimates. Another advantage is the ability to assess the prevalence and burden of disease in the general population. Finally, it is less susceptible to the selection biases that may occur when subjects are volunteers or drawn from a clinic.

Materials and methods

This analysis was based on the data from the CCHS conducted by Statistics Canada in 2000–2001. The design and execution of the survey have been detailed elsewhere [12–15]. In brief, target population included household residents aged 12 years or older in all the 10 provinces and three territories. Persons living on Indian Reserves or Crown lands, clientele of institutions, full-time members of the Canadian Armed Forces and residents of certain remote regions were excluded from this survey. The CCHS covered approximately 98% of the Canadian population aged

12 years or older. The CCHS primarily applied an area frame designed for the Canadian Labour Force Survey (LFS), which is a multistage stratified cluster sampling design. In total, 136,937 households were selected, and 125,159 households participated in the CCHS, with an overall household-level response rate of 91.4%. Among these responding households 142,421 individuals were selected, and 130,827 participated in the survey, with an overall person-level response rate of 91.9% and a combined response rate of 84.7 at the Canada level. Among the households from the area frame, one person aged 12 or older was randomly selected from among 82% of the sampled households and two persons (12 or older) were randomly chosen in the remaining 18%. The rule for selecting persons from households in the area frame was defined as a function of the household composition.

Allergies, asthma and diabetes were defined as 'yes' responses to the following question: 'Do you have [name of disease] diagnosed by a health professional?' Current smokers were defined as respondents who reported smoking cigarettes every day at the time of the survey. Ex-smokers were those who reported smoking cigarettes daily in the past, but not smoking at the time of survey. A positive history of allergy was indicated if an affirmative response was given to either of the questions: 'Do you have any food allergies diagnosed by a health professional?' or 'Do you have other allergies diagnosed by a health professional?' Other variables included in the analysis were age (12–14, 15–19, 20–24, 25–29, ..., 70–74, 75–79, 80+ years), immigrant status (yes, no), marital status (married or common law, widow/divorce/separated, single), number of bedrooms (<3, ≥3), alcohol drinking status (regular drinker, former drinker, never or occasionally drank), regular exercise (yes, no), body mass index (BMI: <20.0, 20.0–24.9, 25.0–29.9, ≥30.0 kg/m²), education level (low, high) and income adequacy (low, middle, high). Subjects in the low education category did not proceed beyond secondary school; the high education category included subjects admitted to college or university, as well as those with a post-secondary school certificate or diploma. A regular drinker was defined as a person

who drank alcoholic beverages at least once a month. A regular exerciser was defined as a person who engaged in physical activities that lasted more than 15 min at least 12 times a month.

The overall prevalence of diabetes was calculated and then stratified by characteristics that would increase the risk of clinical type 1 diabetes being present; age less than 40 years, need for insulin, and need for insulin within 1 year of diagnosis [16, 17]. Prevalence of diabetes with insulin taken was further calculated by status of allergies, and compared with corresponding prevalence of asthma. Logistic regression models were used to assess the relationship between prevalence of diabetes and any allergies.

The CCHS employed a complex survey design. We took the population weight and design effect (DEF) [18] into consideration by using the Rao–Wu bootstrap method [19, 20], which has been described in detail in a previous analysis [18]. SAS macros for the bootstrap approach were developed by Statistics Canada, and the statistical analyses conducted using SAS 8.2 [21].

Results

Diabetes was reported in 4.4% of males and 3.9% of females at least 12 years of age (Table 1). The prevalence was 7–9-fold higher among those over 40 years of age. Insulin was required in about ¼ of all cases of diabetes, and almost ½ of those under 40 years of age. In the younger group requiring insulin, insulin therapy began within 1 year of diagnosis in 92% of males and 84% of females. Reported allergies were very common, 22% of men and 33% of women, and strongly related to asthma (Table 2). Those with diabetes were equally or more likely to have allergies. The crude odds ratio for the association with allergies was 1.05 (95% CI: 0.90, 1.24) with no difference between males and females (Table 3). Adjusted for sex, age, immigrant status, marital status, number of bedrooms, smoking status, alcohol drinking, regular exercise, body mass index, education level and income adequacy the odds ratio was 1.25 (95% CI: 1.06, 1.49). When only diabetes requiring insulin

Table 1. Prevalence (%) of diabetes and diabetes with insulin taken (%) among Canadians aged 12 years and over: Canadian Community Health Survey (CCHS) Cycle 1.1 (2000–2001)

	Males					Females				
	Diabetes			Diabetes with insulin taken		Diabetes			Diabetes with insulin taken	
	No.	Case	%	Case	%	No.	Case	%	Case	%
Total	60514	3079	4.36	735	1.08	70366	3243	3.86	779	0.93
Age (years)										
12–39	26951	229	0.81	128	0.40	29660	302	0.86	127	0.37
40+	33563	2850	7.71	607	1.71	40706	2941	6.42	652	1.40

Table 2. Percentage (number) of asthma and diabetes with insulin taken (%) by sex, any allergies and age among Canadians aged 12 years and over: Canadian Community Health Survey (CCHS) Cycle 1.1 (2000–2001)

Age (years)	No.	Asthma	Diabetes with insulin taken	Stomach/intestinal ulcers
Males with allergies				
12–39	7270	19.30(1478)	0.41(37)	2.53(205)
40 +	6419	13.48(852)	2.10(126)	5.17(388)
Total	13689	16.79(2330)	1.14(163)	3.67(593)
Males without allergies				
12–39	19681	4.37(925)	0.40(91)	1.54(335)
40 +	27144	3.55(1039)	1.61(481)	3.28(1087)
Total	46825	3.93(1964)	1.06(572)	2.48(1422)
Females with allergies				
12–39	10287	22.30(2325)	0.36(47)	3.38(393)
40 +	13067	16.67(2169)	1.52(227)	5.77(872)
Total	23354	19.38(4494)	0.96(274)	4.62(1265)
Females without allergies				
12–39	19373	5.80(1359)	0.38(80)	1.38(332)
40 +	27639	4.62(1359)	1.34(425)	3.13(958)
Total	47012	5.15(2484)	0.91(505)	2.34(1290)

within 1 year of diagnosis was considered, the corresponding crude and adjusted odds ratios were 1.03 (95% CI: 0.88, 1.23) and 1.15 (95% CI: 0.95, 1.40), respectively.

Discussion

Diabetes and allergic diseases are very common in our society and yet there are very few studies addressing the association between diabetes and allergy in the general population. Given the reciprocal relation observed between allergy and infectious disease, one would expect that a disease often with autoimmune mechanisms, such as diabetes which are also thought to be Th1-mediated, would reduce the risk of Th-2 mediated allergic diseases. Rather than an inverse relation, we found a statistically significant positive relation between the two diseases, suggesting that the Th-1/Th-2 paradigm does not hold for non-infectious diseases.

This survey represents the Canadian national population but the trade-off for such a large sample

size is the difficulty of collecting detailed clinical information on individual subjects. We did not have autoimmune or inflammatory markers. However, using aggregate data, the group with diabetes are more likely than those with allergies to have autoimmune characteristics associated with Th1, and those with allergies more likely to have Th2 mediated mechanisms allowing us to assess the Th1–Th2 association. Although several types of diabetes have been associated with autoimmunity, classic type 1, LADA, and more recently type 2, we identified a younger subgroup taking insulin to increase the likelihood of isolating type 1 diabetes, the subgroup with the strongest evidence of autoimmunity. The report that the majority of this group started insulin within 1 year of diagnosis supports this assumption. Having a more accurate measure of autoimmunity in both the allergy and diabetes groups however would likely have strengthened the observed odds ratios.

Atopic allergy is very common, the reported prevalence depending on the definition used. Among 13 year olds participating in a New Zealand birth cohort study, Sears et al. found that 29% of boys and

Table 3. Odds ratios(ORs) for prevalence of diabetes with insulin taken in relation to allergies among Canadians aged 12 years and over: Canadian Community Health Survey (CCHS) Cycle 1.1 (2000–2001)

	Males		Females		Total	
	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
Total	1.08 (0.82, 1.42)	1.33 (1.01, 1.76)	1.07 (0.85, 1.35)	1.19 (0.95, 1.48)	1.06 (0.90, 1.24)	1.25 (1.06, 1.49)
Age (years)						
12–39	1.00 (0.61, 1.66)	1.00 (0.61, 1.65)	0.94 (0.54, 1.62)	0.89 (0.52, 1.53)	0.96 (0.67, 1.38)	0.95 (0.66, 1.37)
40 +	1.31 (0.95, 1.81)	1.43 (1.03, 1.97)	1.15 (0.90, 1.49)	1.24 (0.97, 1.60)	1.18 (0.99, 1.42)	1.33 (1.10, 1.61)

Note: COR – Crude odds ratios; AOR – Adjusted odds ratios for number of bedrooms, immigrant, marital status, income adequacy, educational level, smoking status, alcohol drinking status, regular exercise, body mass index, and age; Reference level for OR – No allergies.

22% of girls had at least two positive allergen skin tests [22]. Allergy is characterized by IgE-mediated mast cell degranulation, which is influenced by Th2 cell derived-cytokines such as IL-4 and IL-5 [9]. Diabetes on the other hand affects one out of every 200 children and 2% of adults. The EURODIAB study reported an annual increase in incidence of 3% for diabetes [23]. In the United States the prevalence of diabetes among those between the ages of 30 and 75 years was 4.3% between 1976 and 1980s [24]. Based on the data from the National Population Health Survey, approximately 4–5% of Canadian adults reported having diabetes (Statistics Canada). The prevalence was higher in men (6.6%) than in women (5.1%) 40 years of age or more [25], while sex-difference is the opposite for asthma. The immunological destruction of islet B-cells is thought to be mediated by a mechanism involving Th1-lymphocytes. The presence of detectable antibodies to islet cells is not limited to the young, consistent with the current belief that type 1 diabetes is now recognized to occur at any age [10].

One explanation for the increasing prevalence of allergies is that reduced early childhood exposure to infections diminishes Th1 responses and polarizes the TH1/Th2 balance towards Th2 cells favoring allergic responses. Evidence for this includes an original report by Strachan in 1989 that reported hay fever was lower among children with siblings (presumably vectors for infection), especially older siblings [26]. Allergen skin test reactivity was inversely related to serological evidence of hepatitis A among Italian military students [27], and number of siblings [28]. IgE levels were found to be lower among those with positive tuberculin skin tests in Southern Honshu, Japan [29].

Although the Th-1/TH-2 paradigm may be consistent with relations between infectious and allergic disease, the same may not be true for allergic and autoimmune diseases. Sheikh et al. found no relation between atopy and history of autoimmune disorders in the American Third National Health and Nutrition Examination Survey (NHANES III) with an odds ratio of 1.01 (95% CI: 0.61, 1.67). The Scottish Continuous Morbidity Recording project based on 47 general practices, reported a positive association between allergic and autoimmune diseases, odds ratio 1.28 (95% CI: 1.19, 1.37) [30]. Consistent with our findings of a statistically significant positive relation between allergy and diabetes, a positive relation between asthma and celiac disease or rheumatoid arthritis was also found in Finland based on data from several linked population-based datasets [10]. A review by Bach contrasted the decline in infectious diseases with the rise in both allergic and autoimmune diseases, and postulated mechanisms mediated by interleukin-10, TGF- β , and/or Toll-like receptors could downregulate both Th1 and Th2 subsets [31]. In summary it appears that allergy may have a

reciprocal relation with infection, a Th1-mediated disease, but not with autoimmune diseases also thought to be Th1-mediated. To quote Sheikh et al., 'the TH1/TH2 model, as currently formulated, might be an oversimplification' [32].

Acknowledgement

This research was supported by a National Health Research and Development Program Grant (6606-06-1998/2640023) and a Canadian Institutes of Health Research Grant (200207SSD-105297). Y. Chen currently holds a Canadian Institutes of Health Research Investigator Award.

Reference

1. Zimmet PZ. The pathogenesis and prevention of diabetes in adults. *Diabetes Care* 1995; 18(7): 1050–1064.
2. Palmer JP. What's in a name: Latent autoimmune diabetes of adults, type 1.5, adult-onset, and type 1 diabetes. *Diabetes Care* 2003; 26(2): 536–538.
3. Shaw JE, Zimmet PZ, McCarty D, de Courten M. Type 2 diabetes worldwide according to the new classification and criteria. *Diabetes Care* 2000; 23(2): B5–B10.
4. Gottsater A, Landin-Olsson M, Fernlund P, Lernmark A, Sundkvist G. Beta-cell function in relation to islet cell antibodies during the first 3 year after clinical diagnosis of diabetes in type II diabetic patients. *Diabetes Care* 1993; 16(6): 902–910.
5. Landin-Olsson M, Nilsson KO, Lernmark A, Sundkvist G. Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus. *Diabetologia* 1990; 33: 561–568.
6. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin-6, and risk of developing type 2 diabetes mellitus. *J Am Med Assoc* 2001; 286(3): 327–334.
7. Spranger J, Kroke A, Mohlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: Results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003; 52(3): 812–817.
8. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; 53(3): 693–700.
9. Durham SR, Till SJ, Corrigan CJ. Organ-specific effects of systemic inflammatory activation – T-lymphocytes in asthma: Bronchial versus peripheral responses. *J Allergy Clin Immunol* 2000; 106(5): S221–S226.
10. Atkinson MA, Eisenbarth GS. Type 1 diabetes: New perspectives on disease pathogenesis and treatment. *Lancet* 2001; 358: 221–229.
11. Kero J, Gissler M, Hemminki E, Isola E. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: A registered study. *J Allergy Clin Immunol* 2001; 108(5): 781–784.

12. Statistics Canada. National Population Health Survey 1994–1995. Ottawa, Ontario: Statistics Canada, 1995.
13. Cycle 2 and beyond: Preparing and storing longitudinal data of the National Population Health Survey. Proceedings of Statistics Canada Symposium 98. 1998.
14. Peaudet MP, Chen J, Perez C, et al. National Population Health Survey Overview 1996/1997. Ottawa, Canada: Statistics Canada, 1998.
15. Chen Y, Dales R, Tang M, Krewski D. Obesity in women but not in men may increase the incidence of asthma: Longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol* 2002; 155(3): 1–7.
16. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes* 1979; 1039–1057.
17. Krolewski AS, Warram JH, Rand LI, Kahn CR. Epidemiologic approach to the etiology of type I diabetes mellitus and its complications. *NEJM* 1987; 317(22): 1390–1398.
18. Skinner CJ, Holt D, Smith TMF. Analysis of Complex Surveys. New York, NY: John Wiley & Sons Ltd, 1989.
19. Rao JNK, Wu CFJ. Resampling inference with complex survey data. *J Am Statist Assoc* 1998; 83: 231–241.
20. Rao JNK, Wu CFJ, Yue K. Some recent work on resampling for complex surveys. *Surv Methodol* 1992; 18: 209–217.
21. SAS Institute I. SAS Procedures Guide. 6.12. Cary, NC: SAS Institute, Inc., 1996.
22. Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood I gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy* 1993; 23(11): 941–948.
23. Anonymous. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 2000; 355: 873–876.
24. Saydah . Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol* 2002; 156: 714–719.
25. Tang M, Chen Y. Prevalence of diabetes in Canadian adults aged 40 years or older. *Diabetes Care* 2000; 23: 1704–1705.
26. Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; 299: 1259–1260.
27. Matricardi PM, Rosmini F, Ferrigno L, et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis a virus. *Br Med J* 1997; 314: 999.
28. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmeir P, Thiemann H-H. Skin test reactivity and number of siblings. *Br Med J* 1994; 308: 692–695.
29. Shirakawa T, Enomoto T, Shimazu SI, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; 275: 77–79.
30. Simpson CR, Anderson WJA, Helms PJ, et al. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general data. *Clin Exp Allergy* 2002; 32: 37–42.
31. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *NEJM* 2002; 347(12): 911–920.
32. Sheikh A, Smeeth L, Hubbard R. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: Lack of support for the hygiene hypothesis. *J Allergy Clin Immunol* 2003; 111: 131–135.

Address for correspondence: R. Dales, Ottawa Hospital, 501 Smyth Road, Room 1805, Ottawa, Ontario K1H 8L6, Canada
 Phone: +613-737-8198; Fax: +613-739-6266
 E-mail: rdales@ohri.ca