

Atopic allergy and delayed hypersensitivity in children with diabetes

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The prevalence of atopy was studied in 61 children with type I insulin-dependent diabetes mellitus (IDDM) and 72 age- and sex-matched control subjects. The two groups had a similar prevalence of atopic disease and did not differ significantly with respect to history, clinical findings, skin prick test results, total serum IgE levels, or presence of circulating IgE antibodies to allergen. We also studied delayed-type hypersensitivity reactions in 37 of the children with IDDM and 46 of the control subjects. Children with IDDM, as compared with those without IDDM, more often had other autoimmune diseases in their family histories ($p < 0.01$). They also had significantly stronger delayed hypersensitivity reactions than the control subjects, as determined with tetanus toxoid ($p < 0.05$) and mumps antigen ($p < 0.01$). The reactivity to purified protein derivative of tuberculin and Candida antigen was similar in the two groups. The study does not confirm previous suggestions of an inverse relationship between IDDM and atopic disease but does confirm that IDDM is associated with other immunologic disturbances. The different genetic and immunologic traits do not prevent allergic manifestations in children with diabetes. (J ALLERGY CLIN IMMUNOL 1995;96:188-92.)

Key words: Allergy, type I diabetes, immune response, children, delayed hypersensitivity

Juvenile insulin-dependent diabetes mellitus (IDDM) and atopic allergy are both associated with immunologic abnormalities^{1, 2}; the latter is the most common aberration of immunoregulation in human beings.³ Type I diabetes develops after a period of autoimmunity against the beta cells of the pancreas.⁴ An association with viral infections and onset of IDDM has also been reported.⁵ Similarly, onset of allergic symptoms in children has been associated with viral infections of the respiratory tract.⁶ The HLA-DR3 is overrepresented in patients with IDDM.⁷ Such association with a defined major histocompatibility complex antigen has not been demonstrated for atopic individuals. Recent studies indicate that there may be an association between a gene on chromosome 11q and manifest atopic disease in some,⁸ but not all, studied families.⁹ An inverse relationship be-

Abbreviations used

DH:	Delayed hypersensitivity
HbA1:	Hemoglobin A1
IDDM:	Insulin-dependent diabetes mellitus
SPT:	Skin prick test

tween presence of atopic disease and IDDM has been reported in several studies.¹⁰⁻¹⁷ Suggested explanations for this include: individuals with a predisposition for diabetes are less susceptible to atopic disease,¹⁷ and hyperglycemia could protect against allergy in the patient with diabetes.¹¹

Most of the studies indicating an inverse relationship between IDDM and atopic disease were performed more than 20 years ago. The prevalence of both allergic diseases¹⁸⁻²⁰ and IDDM²¹ appears to have increased since then. Because our clinical experience has indicated that allergic reactions are not at all uncommon in children with diabetes, we decided to determine whether they have a frequency of atopic allergy similar to that seen in the general population. We also assessed delayed hypersensitivity (DH) to four common antigens in the two groups because this has been reported to be altered in both patients with IDDM²² and atopic²³ patients.

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METHODS

Study groups

Sixty-one children with IDDM, 7 to 18 years of age (mean age, 12.9 years), attending the Department of Paediatrics at Norrköping County Hospital were invited to participate in the study. All were receiving four or five insulin injections a day, usually fast-acting Actrapid human insulin 15 to 30 minutes before main meals and medium long-acting Monotard human insulin or Protaphan human insulin at bedtime (dose range: 0.40 to 1.52 IU/kg/day; mean dose, 0.95 IU/kg/day). The duration of diabetes was 0.6 to 11.5 years (mean, 4.4 years).

Seventy-eight schoolmates were invited to participate as control subjects. They were nondiabetic, matched for age and sex, and born in Sweden to Scandinavian parents. Two of them refused to take part in the study, and four moved during the study period.

The subjects were asked to complete a questionnaire regarding family and personal history of atopic disease (eczema, urticaria, allergic rhinitis, asthma). Information was also obtained about presence of autoimmune diseases (e.g., diabetes mellitus, thyroid disease, celiac disease, rheumatic arthritis, systemic lupus erythematosus, pernicious anemia, Addison's disease, ulcerative colitis) and immunodeficiency in first- and second-degree relatives. The validity of the questionnaire was assessed by reviewing all of the children's medical records from health care units, school health services, district medical officers, and ear-nose-throat and pediatric clinics in the areas where the patients lived.

All children with diabetes and the skin-tested control subjects underwent a physical examination performed by one investigator. All children and their parents were interviewed at the time of skin testing or by telephone within 2 weeks.

Ethics

The study was approved by the Ethical Committee for Human Research at the Faculty of Health Sciences, University of Linköping.

Skin prick tests

Forty-one children with diabetes and 46 control subjects agreed to undergo skin prick testing. The tests were performed with five to seven allergens administered by use of allergen-coated lancets (Phazet; Pharmacia, Uppsala, Sweden)²⁴: birch, timothy grass, *Dermatophagoides pteronyssinus*, *Cladosporium herbarium*, and each child's own animal if any (dog, cat, horse). Uncoated needles served as negative controls, and lancets coated with histamine 10 mg/ml served as positive controls. The largest wheal diameter and the diameter perpendicular to it were measured after 15 minutes. The test result was considered positive if the mean diameter of the two was greater than 3 mm.

Intradermal tests

Thirty-seven children with diabetes and 46 control subjects agreed to undergo intradermal testing. Four antigens were used for the intradermal tests: tetanus (tetanus vaccine 7.5 Lf/ml; State Bacterial Laboratory, Stockholm, Sweden), mumps test antigen, undiluted (Eli-Lilly, Indianapolis, Ind.), tuberculin 50,000 TU/L (State Serum Institute, Copenhagen, Denmark), and *Candida* antigen 10⁶ PNU/L (Dome-Hollister-Stier, Spokane, Wash.).

Local cutaneous anaesthesia was achieved with a lidocaine/prilocaine emulsion (EMLA cream; Astra Pharmaceutical, Södertälje, Sweden). Five grams of the emulsion was applied to the volar side of the forearm and was wiped off after 60 to 120 minutes.²⁵ The antigens (0.1 ml volume) were injected intradermally. The sites of injection were inspected after 20 minutes to detect any immediate reactions and after 48 hours to register the delayed reactions. The mean diameter of induration was calculated from the sum of the largest diameter and the one perpendicular to it. The sum of the indurations at all positive reaction sites was calculated to obtain a cumulative DH induration score.

Laboratory determinations

Total serum IgE concentration was analyzed with Phadebas IgE PRIST (Pharmacia), as recommended by the manufacturer. Presence of IgE antibodies to a mixture of relevant inhalant allergens was assessed with the Phadiatop test (Pharmacia).

The degree of metabolic control in patients with IDDM was defined according to hemoglobin A1 (HbA1) level, as measured by radioimmunoassay with a commercially available kit (Bio-Rad Laboratories, Richmond, Calif.). Reference values for healthy control subjects were 5.0% to 8.0%.

Statistical methods

Allergic symptoms, hereditary data, and skin prick test (SPT) results in the two groups were compared by means of the chi square test with Yates' correction, when appropriate. Cumulative DH induration score, DH tests versus HbA1, and SPT results versus HbA1 were compared by means of Spearman's correlation coefficient.

RESULTS

The prevalence of eczema, allergic rhinitis, asthma, and urticaria was similar among the children with IDDM and the control subjects (Table I). Also, the prevalence of atopic disease was similar among the first-degree relatives in the two groups. Atopic symptoms, as reported in the questionnaire, were confirmed by medical records in 94% of the patients with IDDM and 82% of the

TABLE I. Prevalence (%) of atopy, elevated IgE, positive Phadiatop and positive SPT results in patients with IDDM and control subjects and history of allergy among their first-degree relatives (i.e., parents and siblings) as assessed by questionnaires

	Patients with IDDM		Control subjects	
	All (n = 61)	Tested (n = 41)	All (n = 72)	Tested (n = 46)
Clinical symptoms				
Eczema	13	15	18	17
Allergic rhinitis	21	22	15	15
Asthma	16	20	13	13
Urticaria	24	22	21	24
Any symptoms	33	39	34	32
Heredity				
Atopic relatives	39	41	51	54
Test results				
Elevated S-IgE (>GM + 2 SD) (%)	NA	24	NA	28
+ Phadiatop (%)	NA	19	NA	16
+ SPT (%)	NA	24	NA	35
Mean no. of + SPT results	NA	3.0	NA	2.4
Mean size of + SPT reaction (mm)	NA	5.9	NA	5.1

The table also shows the mean number of positive (+) SPT results and the mean size of positive test reactions among those with at least one positive test response. None of the differences was statistically significant (chi square with Yates' correction). *NA*, Not applicable; *GM*, geometric mean.

control subjects. In no case were atopic symptoms recorded in the medical records, if denied in the questionnaire.

There was no significant difference in the number of children with serum IgE values of 2 SD or greater, positive Phadiatop test results, or positive SPT results. The mean number of positive SPT results per child tested and the mean size of positive SPT and histamine control wheals were also similar in the two groups. Furthermore, the duration of diabetes (> or ≤ 4 years) did not appear to influence the findings.

Autoimmune disease was more commonly present among the relatives of patients with IDDM than among the families of the control subjects. Thus 61 cases of these diseases were reported by the 61 families of children with diabetes, and 39 cases were reported by the 72 control subjects ($p < 0.01$). Of the individual autoimmune diseases, however, a statistically significant difference was recorded only for thyroid disease, which was present in 21 of the families of children with diabetes and in 12 of the families of the control subjects ($p < 0.05$).

None of the intradermal tests for DH were positive at 20 minutes; that is, there were no immediate-type reactions to any of the four antigens tested. After 48 hours, the mean number of

positive test results was 2.2 in the IDDM group and 2.4 in the control group. The mean cumulative DH induration score was 31.5 ± 16.4 mm (mean \pm SD) for patients with IDDM and 21.3 ± 10.3 mm for control subjects ($p < 0.01$). The mean size of reaction to tetanus antigen was 18 ± 13.4 mm in patients with diabetes and 11 ± 6.1 mm in control subjects ($p < 0.05$). For mumps antigen, the mean size of reaction was 5.4 ± 4.4 mm in patients with diabetes and 3.5 ± 2.4 mm in control subjects ($p < 0.01$). The DH scores were similar for purified protein derivate of tuberculin and *Candida* antigen. They were also similar in children with a positive or a negative SPT result. The rate of immunization to bacille Calmette-Guérin, mumps, and tetanus was similar in both groups.

The mean HbA1c value was 9.8% (range, 6.7% to 15.0%) among the patients with diabetes. There was no correlation between DH score, number of positive reactions, size of individual reactions and HbA1c values, nor duration of diabetes (> or < 4 years).

The DH induration scores in atopic and nonatopic individuals were also compared, both in the control groups and among the patients with IDDM. Neither the number of positive test results nor the size of the reactions was significantly different between patients with allergy and nonallergic subjects in the two groups (data not shown).

DISCUSSION

The prevalence of atopic disease in children with IDDM and their first-degree relatives was similar to that in the general population. This is contrary to the findings of several previous studies in which an inverse relationship between atopy and IDDM was reported.¹⁰⁻¹⁷ Atopic diseases appeared to be uncommon in patients with diabetes some decades ago. It should, however, be noted that these early studies did not include carefully selected reference groups. During the 1970s, atopic diseases were reported more often than before in patients with IDDM, but still only half as often as in nondiabetic subjects.¹⁷ In recent studies (including this one), however, the prevalence of atopic disease, elevated serum IgE levels or positive SPT results in patients with IDDM is similar to that of the general population.²⁶⁻²⁸

It is never possible to prove that there is no difference between groups. We have studied a reasonably large group of patients and control subjects with carefully chosen methods, and as can be seen from our results, there were no differences in symptoms among those who participated in testing compared with those who did not. Furthermore, we validated the questionnaires with data from records and found good agreement. Thus we believe our results to be reliable.

The previously reported difference in allergy prevalence between patients with diabetes and nondiabetic subjects thus appears to have disappeared. At the same time, the prevalence of atopic disease appears to have increased considerably.¹⁸⁻²⁰ This is thought to be caused by environmental triggers of sensitization (e.g., air pollution).²⁹⁻³⁰ The increased environmental load may be strong enough to overcome any moderate difference in liability to develop allergic disease in patients with diabetes and healthy individuals. Another possible explanation is that metabolic control in patients with IDDM was in earlier years often poor, resulting in severe hyperglycemia, which in turn could modify the glycosylation of IgE regulatory factors.³¹ With improved control, blood sugar levels are kept near the normal range most of the time in patients with IDDM, and hyperglycemia for long periods is rare. The quality of insulin has also improved in later years. Previously used crude porcine and bovine insulins often induced IgG antibody formation, but this is not the case with the highly purified monocomponent and human insulins used today.³²

Autoimmune diseases were more frequently encountered in relatives of children with diabetes.

This was reported earlier by several authors.³³⁻³⁴ In this context it is of some interest that we demonstrated a significantly higher cumulative DH score among patients with diabetes, indicating a stronger overall DH reaction in them, as compared with control subjects. This is in accordance with the finding that HLA DR3, which is frequently found in patients with type I diabetes,⁷ is associated with increased cell-mediated responsiveness.³⁵⁻³⁶ It is contrary to the report by Pozilli et al.²² who found no major differences in cell-mediated response, as assessed in vivo by multiple intradermal antigen tests, between normal subjects and patients with type I diabetes. The difference in findings may arise from difference in potency of test antigens, different technique, and the fact that Pozilli et al.²² did not test children but adults. Our patients with diabetes and control subjects were in good nutritional condition, and most patients with diabetes had good metabolic control. They did not have *Candida* infections. All had received tetanus vaccine, and most had received mumps vaccine but not bacille Calmette-Guérin vaccine. The increased DH reaction in diabetic children, especially the one towards mumps, is interesting because mumps has been suspected to have a causal role in IDDM.⁵

We could not confirm previous reports (summarized by Björkstén et al.²³) of depressed DH in atopic individuals. The study was, however, not designed to analyze this, nor was the size of the study population calculated for this purpose.

In conclusion, this study does not confirm previous suggestions of an inverse relationship between IDDM and atopic disease but does confirm that IDDM is associated with other immunologic disturbances.

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