Diabetologia (2001) 44: 1051–1053

Diabetologia

Prevalence of coeliac disease in siblings of patients with Type I diabetes is related to the prevalence of DQB1*02 allele

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Abstract

Aims/hypothesis. Coeliac disease is more prevalent among patients with Type I (insulin-dependent) diabetes mellitus and coeliac disease-related antibodies have been reported to increase in frequency in their first-degree relatives. Our aim was to find out if coeliac disease is more common among siblings of children with Type I diabetes than in the normal population.
Methods. IgA endomysium antibodies were measured by indirect immunofluorescence in 550 subjects (mean age 11.8 years, range 3.1–26.9 years) with a sibling with Type I diabetes. We performed jejunal biopsy on as many subjects with positive antibodies as agreed. *HLA-DQB1* genotyping was done in 427 subjects.
Results. Endomysium antibodies were positive in nine subjects (1.6 %). Jejunal biopsy was diagnostic for coeliac disease in five out of seven patients. An additional patient with coeliac disease, one already on a gluten-free diet, was identified by questionnaire. The prevalence of coeliac disease was 1.1 %. Five of six patients with coeliac disease had HLA-DQB1*02 allele, compared with 118 of 421 of those without coeliac disease ($p = 0.009$). The sixth patient was positive for HLA-DQB1*0302 allele, which was also found in 241 of 421 of those without coeliac disease ($p = 0.4$).
Conclusion/interpretation. We found the prevalence of coeliac disease among siblings of children with Type I diabetes to be similar to figures reported from recent population-based studies and to be correlated with the prevalence of coeliac disease associated *HLA-DQB1* alleles. We propose that routine screening for coeliac disease among all first-degree relatives of patients with Type I diabetes is not warranted. [Diabetologia (2001) 44: 1051–1053]

Keywords Endomysium antibodies, Coeliac disease, Type I diabetes, Screening, *HLA-DQ*.

Increased prevalence of coeliac disease in patients with Type I diabetes has been widely reported in Caucasian populations, with figures for prevalence varying from 1.0 to 7.8 % [1]. Certain *HLA* genotypes (especially, those positive for *DR3-DQ2* haplotype) are more frequent in both of these diseases. First-degree relatives of patients with Type I diabetes have an increased risk for developing diabetes, a risk that is proportional to the degree of shared *HLA* risk alleles. It would be plausible then to assume that these relatives also have an increased risk for coeliac disease. The frequent occurrence of coeliac disease-associated antibodies found in these subjects supports this view [2]. Screening for coeliac disease in first-degree relatives of patients with Type I diabetes has been proposed [2].

We have earlier reported a prevalence of 2.4 % of coeliac disease among 776 children with Type I diabetes in Finland [3]. In our study, we analysed IgA endomysium antibodies and jejunal biopsy specimens in non-diabetic siblings of these children.

Received: 11 January 2001 and in revised form: 27 April 2001

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Subjects and methods

During a period of 2.7 years, 801 consecutive families with a child with newly diagnosed Type I diabetes were asked to participate in a nation-wide follow-up study. Of these families, 638 had more than one child, the total number of non-diabetic siblings being 1020. As reported previously, a total of 776 children with diabetes gave a venous blood sample for the screening of coeliac disease and we eventually identified 19 cases of biopsy-proven coeliac disease among them (prevalence = 2.4%) [3]. Blood samples from 550 non-diabetic siblings, collected 2 years after diagnosis of diabetes in the proband, were available for our study. Among these were 16 subjects whose sibling proband had both diabetes and coeliac disease. The samples were kept in deep-freeze until they were analysed. We measured serum IgA endomysium antibodies by indirect immunofluorescence using the human umbilical cord as the antigen [4]. We previously reported a sensitivity of 0.94 and specificity of 1.0 for childhood coeliac disease with this method [4]. Sera were screened at dilutions of 1:5 and 1:50 and positive sera were further diluted. Positive samples were also confirmed using commercial sections of monkey oesophagus (Boule Diagnostics, Scimedx, Denville, N.J., USA) as substrate. We performed jejunal biopsy on as many subjects with positive antibodies who agreed, and diagnosis of coeliac disease was confirmed according to the criteria set by the European Society for Paediatric Gastroenterology and Nutrition. The Childhood Diabetes in Finland study database was checked for cases of coeliac disease reported in questionnaires before the antibody screening. Genotyping of the *HLA DQB1* locus was performed in 427 subjects by a PCR based hybridization assay using lanthanide labelled oligonucleotides and time-resolved fluorometry to detect the presence of Type I diabetes associated alleles [5].

Statistical analysis. Fisher's exact test was used to analyse differences in the prevalence of *HLA DQB1* alleles between the groups. A p value of less than 0.05 was considered statistically significant.

Results

Endomysium antibodies and jejunal biopsies. Among the 550 subjects studied, we found serum endomysium antibodies were positive in 9 (1.6%) (Fig. 1). Seven of the patients agreed to a biopsy and coeliac disease was found in five subjects. Of those two patients who did not consent to biopsy, one had a high titre of endomysium antibodies (1:400), and was also positive for the HLA DQB1*02 allele, making it probable that he had coeliac disease. The other patient who did not have a biopsy had a lower titre of endomysium antibodies (1:50) and her genotype was negative for DQB1*02 suggesting that she probably had false positive endomysium antibodies. A further patient of biopsy-proven coeliac disease, found by questionnaire, was on a gluten-free diet at the time of blood sampling and therefore negative for endomysium antibodies. Taken together, 6 (possibly 7) of the 550 subjects studied had coeliac disease, giving the frequency of 1.1% (95%-Confidence interval, 0.4–2.3%). In two of the six patients with a positive finding in biopsy, the diabetic sibling also had coeliac disease.

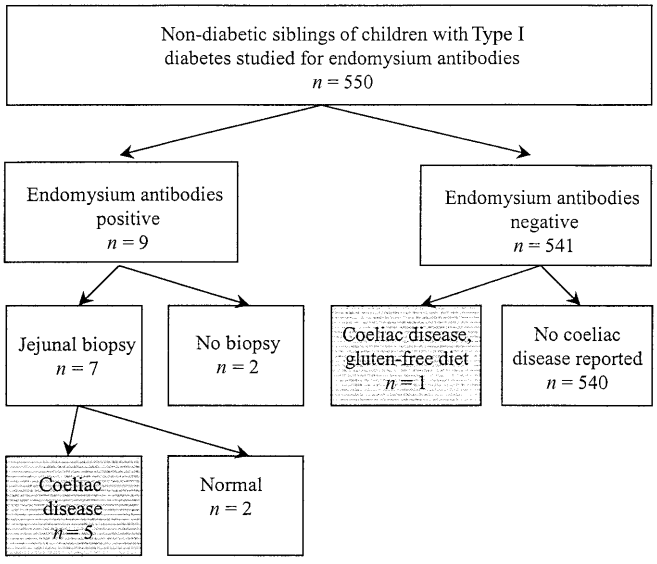

Fig. 1. Results of endomysium antibody screening and jejunal biopsies in siblings of children with Type I diabetes. (*CD* coeliac disease)

HLA DQB1 genotype. Of the six patients for whom coeliac disease was confirmed by jejunal biopsy, five (83%) were positive for DQB1*02. This compares with 118 of 421 subjects (28%) without coeliac disease ($p = 0.009$, Fisher's exact test). The patient with coeliac disease and negative for DQB1*02 was positive for DQB1*0302, a combination found only in this patient (1/6 = 17%) and in 241/421 (43%) of those without coeliac disease ($p = 0.4$, Fisher's exact test). One of the two patients with positive endomysium antibodies but a normal finding in biopsy was positive for DQB1*02 and the other one was not genotyped.

Discussion

Using an endomysium antibody screening with a reported high sensitivity (0.94) for coeliac disease, we found a prevalence of 1.1% of coeliac disease among Finnish children and young adults who have a sibling with Type I diabetes. Before the development of powerful screening methods for coeliac disease, the prevalence of coeliac disease in Caucasian populations was generally estimated to be in the order of 0.1% [6]. During the last few years, the invention of sensitive methods, especially of the assay for endomysium antibodies, has led to a number of reports giving considerably higher prevalence figures, ranging from 0.3% up to 1.2%, among both children and adults [7, 8]. Using the same endomysium antibody method, we previously found a prevalence of coeliac disease of 0.8% among 1070 Finnish adults [9]. Thus, the prevalence of coeliac disease in the present study appears to be similar to that in the general population.

The distribution of *HLA* genotypes in Caucasian patients with coeliac disease shows a very distinctive pattern. HLA DQA1*0501 and DQB1*02 alleles encoding for a distinctive *HLA-DQ2* heterodimer molecule is found in at least 90% of the patients, compared to 20–30% of the control subjects [10]. Because this *HLA-DQ2* molecule is also overrepresented in Type I diabetes, the frequent occurrence of coeliac disease in subjects with diabetes is believed to be connected with genetic predisposition [1]. In the Childhood Diabetes in Finland study, 43% of children with diabetes and 24% of population-based control subjects had the HLA-DQB1*02 allele [5]. Of the 427 non-diabetic siblings analysed in the present study, 29% had HLA-DQB1*02. Therefore, we assume that the prevalence of coeliac disease of 1.1% among these non-diabetic siblings reflects the genetic predisposition to coeliac disease, conferred by the *HLA-DQ* genotype distribution, which is the same as in the general population.

A recent study on 913 offspring of parents with Type I diabetes reported the prevalence of 3.5% of antibodies to tissue transglutaminase (tTG), the newly detected target antigen of endomysium antibodies [2]. However, the actual prevalence of biopsy proven coeliac disease was 1.0% which is very similar to that of our study. In their study, 3 of 12 cases double-positive for endomysium and tTG antibodies did not meet the diagnostic criteria of coeliac disease in biopsy, compared with 2 out of 7 endomysium antibody positive patients in our series. Current sensitive autoimmune-type screening tests also recognize cases with only proliferative changes in the intestinal epithelium, so that these results suggest that those changes could be more common in the family members of patients with autoimmune diseases like Type I diabetes.

In conclusion, we found the prevalence of coeliac disease among siblings of children with Type I diabetes to be similar to that in the general population and less than that anticipated from antibody screening only. We suggest that careful consideration should take place before implementing screening for coeliac disease in all first-degree relatives of patients with Type I diabetes. The occurrence of coeliac disease is strongly associated with certain *HLA* genotypes. Therefore, in those centres which perform routine *HLA* genotyping in family members of the patients with Type I diabetes at least, screening for coeliac disease could be focused on those having genotypes that predispose to coeliac disease, making screening more cost-effective.

Acknowledgements. This work was financially supported by the Foundation for Paediatric Research, Finland, the Sigrid Juselius Foundation, the Finnish Academy of Sciences, and the Finnish Diabetes Research Foundation. The "Childhood Diabetes in Finland" (DiMe) project was also supported by the National Institutes of Health, the Association of Finnish Life Insurance Companies, the University of Helsinki, Nordisk Insulinfond, and the Dorothea Olivia, Karl Walter and Jarl Walter Perklén Foundation. *The Childhood Diabetes in Finland Study Group: Principal Investigators:* H. K. Åkerblom, J. Tuomilehto; *Coordinators:* R. Lounamaa, L. Toivanen, E. A. Kaprio; *Data Managers:* E. Virtala, J. Pitkäniemi; *Local Investigators:* A. Fagerlund, M. Flittner, B. Gustafsson, C. Häggqvist, A. Hakulinen, L. Herva, P. Hiltunen, T. Huhtamäki, N-P. Huttunen, T. Huupponen, M. Hyttinen, T. Joki, R. Jokisalo, M.-L. Käär, S. Kallio, E. A. Kaprio, U. Kaski, M. Knip, L. Laine, J. Lappalainen, J. Mäenpää, A.-L. Mäkelä, K. Niemi, A. Niiranen, P. Ojajärvi, T. Otonkoski, K. Pihlajamäki, S. Pöntynen, J. Rajantie, J. Sankala, J. Schumacher, M. Sillanpää, M.-R. Ståhlberg, C.-H. Strålmann, T. Uotila, M. Väre, P. Varimo; *Special Investigators:* A. Aro, M. Hiltunen, H. Hurme, H. Hyöty, J. Ilonen, J. Karjalainen, M. Knip, P. Leinikki, A. Miettinen, T. Petäys, H. Reijonen, L. Räsänen, A. Reunanen, T. Saukkonen, E. Savilahti, E. Tuomilehto-Wolf, P. Vähäsalo, S. M. Virtanen.

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