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Celiac Disease in Type 1 Diabetes Mellitus in a North American Community: Prevalence, Serologic Screening, and Clinical Features

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Abstract

OBJECTIVES—To estimate the prevalence of celiac disease (CD) in pediatric and adult type 1 diabetes mellitus in a defined population and to describe clinical features and HLA class II genotypes predictive of CD in screened patients with type 1 diabetes.

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PATIENTS AND METHODS—All residents of Olmsted County, Minnesota, with type 1 diabetes mellitus on the prevalence date January 1, 2001, were identified with the use of an established medical records linkage system (Rochester Epidemiology Project) and defined clinical criteria. Consenting patients underwent serologic screening with endomysial antibody and tissue transglutaminase antibody testing and intestinal biopsies to confirm the diagnosis of CD. A subset of screened patients also underwent HLA class II genotyping. Quality-of-life screening (Medical Outcomes Study 36-Item Short-Form Health Survey) was completed in a subset of patients at the time of serologic screening.

RESULTS—Overall, 392 Olmsted County residents with type 1 diabetes on January 1, 2001, were identified. A total of 158 patients with type 1 diabetes were tested, representing 40% (158/392) of the enumerated diabetic population, and 11 had biopsy-proven CD for an estimated point prevalence of 7.0% (95% confidence interval, 3.5%-12.1%). Most CD-positive diabetic patients were asymptomatic and expressed an at-risk CD haplotype with at least one of but not both HLA *DQ*2 or *DQ*8.

CONCLUSIONS—Celiac disease is not rare in North American patients with type 1 diabetes, and most CD-positive diabetic patients are asymptomatic irrespective of age at screening.

Celiac disease (CD) is a chronic disorder characterized by immune-mediated damage to the mucosa of the small intestine.[1] These changes are triggered by ingestion of gluten and related substances found in cereal grains, such as wheat, barley, and rye. Although CD was once believed to be rare in North America, recent studies[2-4] have shown an increasing incidence of CD in both pediatric and adult populations. However, the classic clinical features of CD, comprising diarrhea and weight loss, are observed less commonly in recently diagnosed cases.[4]

An association between CD and type 1 diabetes mellitus has been recognized for more than 40 years.[5] European studies in diabetic populations have estimated the prevalence of CD to be 1.5% to 4.6% in children and 2% to 4.1% in adults, significantly higher than the estimated 0.5% to 1% overall prevalence of CD observed in the general population.[6-15] Both CD and type 1 diabetes are associated with the major histocompatibility complex class II antigen DQ2 encoded by the alleles *DQA1*501* and *DQB1*201*, thus providing a common genetic basis for expression of both diseases.[16,17]

Despite the advent of sensitive and specific serologic testing, routine screening for CD in diabetic populations is neither a universal nor accepted practice in North America, unlike in other jurisdictions.[18-22] Much of the controversy derives from previous epidemiological research that suggests that CD is a rare condition in patients with type 1 diabetes in the United States.[14] Subsequent work that showed a higher prevalence focused on highly selected patients who were referred to academic medical centers and was restricted to either pediatric or adult populations.[9,23,24] A true population-based estimate of the prevalence of CD from childhood onward in type 1 diabetes is not available from the United States. This study examined the prevalence of CD in patients with type 1 diabetes in a North American community across the entire age spectrum. HLA class II genotyping and clinical features are also described.

PATIENTS AND METHODS

Study Setting

Olmsted County is a medically well-defined population in southeastern Minnesota. Population-based studies are feasible because Olmsted County is relatively geographically isolated, and most residents receive their medical care locally through a limited number of medical providers. The major provider is the Mayo Clinic in Rochester, Minn, which has maintained a common medical record with its affiliated hospitals (Saint Marys and Rochester Methodist) for more

than 90 years. Recorded diagnoses and surgical procedures are indexed, including diagnoses for outpatients seen during clinic consultations, emergency department visits, or nursing home care and the diagnoses recorded for hospital inpatients, at autopsy examination, or on death certificates. Medical records of the other health care providers who serve the local population, notably the Olmsted Medical Group and its affiliated Olmsted Community Hospital (Olmsted Medical Center), are also indexed and retrievable. Thus, details of the medical care provided to local residents are available for study through this medical records linkage system (Rochester Epidemiology Project [REP]) as described elsewhere.[25] According to US census data, the population of Olmsted County was 124,277 in 2000. The population is primarily white; however, recent immigration of Southeast Asian and African populations has increased the nonwhite group to approximately 10% of the total.

Case Identification

Type 1 Diabetes Mellitus—After approval of this project by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center, the resources of the REP were used to identify residents of Olmsted County with type 1 diabetes. All patients with diagnostic codes (*Hospital Adaptation of the International Classification of Diseases and International Classification of Diseases, Ninth Revision*) identified for type 1 diabetes and those with diabetes-related complications were included. In addition, existing databases and patient cohorts from the Mayo Clinic Pediatric Diabetes Clinic (aged 0-18 years), the Rochester Diabetic Neuropathy Study,[26] the adult Diabetes Electronic Management System database, and the existing REP Diabetes Study database[27] were searched to ensure a complete enumeration of patients. Information about residency on the prevalence date (January 1, 2001) and vital status was verified using Mayo Clinic, county, and state records.

Medical records were abstracted for weight, height, age, and clinical features at initial diagnosis of diabetes, including initial and long-term insulin use and the presence of autoimmune thyroid disease. Patients were classified as having type 1 diabetes with use of clinical criteria at diagnosis (weight loss, polyuria, polydipsia, the presence of ketones, or diabetic ketoacidosis), body mass index (a measure of weight in kilograms divided by the square of height in meters) (<27 kg/m^2 at the time of diagnosis), and treatment with insulin at diagnosis and for greater than 1 year subsequently, using previously published criteria.[28]

Diabetic patients were recruited for the study in both pediatric and adult clinical settings. Consenting patients underwent blood testing for serologic CD markers (IgA endomysial antibody [EMA], IgA tissue transglutaminase [tTg]) and HLA haplotyping. A questionnaire that detailed clinical and depressive symptoms (Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]) also was completed at serologic screening. Clinical and laboratory records were reviewed for 6 months before diagnosis to derive a mean hemoglobin A_{1c} level.

Confirmation of CD—Each consenting patient underwent serologic testing for EMA and tTg enzyme-linked immunosorbent assay (ELISA).[4] All patients with positive serologic test results were offered and underwent intestinal biopsies to confirm CD. At least 4 samples were taken from the distal duodenum and interpreted by a pathologist who was unaware of the serologic results. The diagnosis of CD required jejunal or duodenal biopsy specimens with partial or complete villous atrophy associated with crypt hyperplasia and a lymphoplasmacytic infiltration in the lamina propria.

Laboratory Methods

Anti-tTg IgA testing was undertaken with a commercially obtained ELISA kit (Inova Diagnostics, San Diego, Calif) and performed as described in detail previously.[29] In brief, stored serum samples were thawed and diluted with horseradish peroxidase diluent and tested

in duplicate at room temperature along with appropriate negative and positive controls. The optical density of each pair of duplicates was converted to an ELISA standard by reference to positive controls. An ELISA cutoff of less than 20 was normal, 20 to 30 was equivocal, and greater than 30 was positive. Anti-EMA IgA was detected by an indirect immunofluorescence assay with monkey esophagus as the substrate.[30] The assays were performed at 3 screening dilutions of 1:5, 1:10, and 1:20. The test result was considered positive when there was a reticulated honeycomb staining of the connective tissue that surrounded the bundles of esophageal smooth muscle.

HLA class II typing was accomplished by the polymerase chain reaction (PCR)-sequence-specific primer (One Lambda, Canoga Park, Calif). This method is a low-resolution test to identify the alleles coded for by the *DR*β*1,2,3,4,5* and *DQ*α1 genes of the HLA class II gene locus by PCR. Because the test is based on DNA analysis, it is not subject to difficulties with lymphopenia, nonviable lymphocytes, poor cell surface antigen expression, or poor cellular reactivity. Preoptimized primers for the amplification of HLA class II genes were represented in different wells of a tray (One Lambda). By selecting specific primers, only products that correspond to the different HLA alleles are amplified. A qualitative indicator of specific DNA amplification is obtained by observation of ethidium bromide fluorescence of anplified DNA (in control and test bands) after quick gel electrophoresis of the PCR products. The presence of a band determines the assignment of HLA alleles. The specificity of the primers is achieved by constructing oligonucleotides in which the DNA sequence is matched at the 3′ end with an allele and mismatched with all other alleles. Polymerase chain reaction amplification occurs only when there is a perfect match of both primer and allele. Even a single-nucleotide mismatch will block PCR amplification. Apparent homozygosity was determined by the failure to identify alternate alleles at a specific locus. For this analysis, we considered *DQB1*0201* and *DQB1*0202* as equivalent. The likelihood of an altemative undetected allele was extremely low.

Statistical Analyses

Continuous variables were summarized as mean ± SD and categorical variables as frequencies and percentages. The 95% confidence intervals (CIs) for percentages were calculated using the exact binomial distribution. Participation bias was examined with use of logistic regression to assess the association among age at diagnosis, sex, and duration of diabetes with participation (agreement to testing [yes/no] as the dependent variable). The association of the presence of CD among tested diabetic patients with clinical variables, physical and mental composite scores, and HLA types was assessed using univariate logistic regression or the Fisher exact test.

RESULTS

Prevalence of CD

Overall, 392 Olmsted County residents with type 1 diabetes on January 1, 2001, were identified using uniform clinical criteria. A nearly equal sex distribution (191 males [49%]) was observed. The mean ± SD age at the prevalence date was 36.7±16.5 years but most patients were younger than 18 yers at the time of diagnosis of type 1 diabetes (235 [60%]). Age, sex, and duration of diabetes were not associated significantly with whether someone was screened for CD (Table 1).

A total of 158 diabetic patients underwent serologic testing, and 11 patients with CD were identified. Four of these patients were discovered on the basis of clinical symptoms and underwent CD testing performed by their physician; the remaining 7 were identified by serologic screening. The estimated crude point prevalence of CD in this diabetic population

was 7.0% (95% CI, 3.5%-12.1%), with a higher rate in females (11.0%; 95% CI, 5.1%-19.8%) compared with males (2.6%; 95% CI, 0.3%-9.2%), which was statistically significant (*P*=.06). If clinically discovered cases of CD were excluded, a revised point prevalence for CD of 4.6% (95% CI, 1.9%-9.1%) was obtained in the screened patients. The prevalence of CD was similar in the 3 pediatric patients (7.3%; 95% CI, 1.5%-19.9%) and adults (6.8%; 95% CI, 3.0%-13.0%), whether we considered their age at testing for CD or the age at diagnosis of diabetes.

Clinical Features of CD

Typical clinical features of CD, including abdominal pain and diarrhea, were absent in most CD-positive patients (Table 2). A single pediatric patient (age, 14 years) had lactose intolerance, and a single adult patient had diarrhea. A single adult female patient with confirmed CD identified by screening subsequently developed dermatitis herpetiformis while continuing to ingest gluten. No difference was observed in the frequency of autoimmune thyroid disease among the total diabetic population, diabetic patients not screened for CD, and patients screened for CD (Table 1). A single patient with CD had autoimmune thyroid disease.

A subset of diabetic patients (n=49) completed an SF-36 form, which was considered a measure of these patients' quality of life. Decreases in the physical (*P*=.33) or mental quality-of-life scores (*P*=.58) were not associated with CD in this diabetic cohort.

Laboratory and Biopsy Results

In all patients with CD found during serologic screening, positive results were confirmed by EMAs. Results from 6 of these patients were positive on tTg IgA antibodies, with 1 patient's results marginally below the cutoff level (20 U). All 7 screened diabetic patients and the 4 patients with clinically discovered disease had at least partial villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes that characterized CD. Histologic features of simple increased intraepithelial lymphomatosis were not observed in any sample. There was no association between the level of EMA or tTg IgA antibodies and the hemoglobin A_{IC} value.

HLA Haplotypes

The HLA haplotypes for 8 (73%) of the CD-positive and 58 (39%) of the CD-negative diabetic patients were obtained in this study. All the tested CD-positive diabetic patients expressed a CD at-risk genotype; 6 patients possessed at least 1 *DQ2* allele, and 2 patients expressed *DQ8* homozygosity. The combination of *DQ2* and *DQ8* was common in patients with CD-negative diabetes (30/58). In contrast, no diabetic patient who carried *DQ2* and *DQ8* together had CD (21/58), suggesting that the combination of *DQ2* with *DQ8* is associated with a lower likelihood of CD vs any other type in the diabetic population (*P*=.048; Fisher exact test).

DISCUSSION

In this community-based study, the overall prevalence of CD in patients of all ages with type 1 diabetes was 7.0%, with similar rates for pediatric and adult groups. Comparable North American studies have focused on selected patients seen at referral centers and observed a prevalence of CD in type 1 diabetes that ranged from 1.4% to 5.1% in pediatric patients and from 3.5% to 6.0% in adults.[9,14,23,24,31-33] Two European studies[34,35] evaluated a combined pediatric and adult type 1 diabetic cohort and observed a biopsyproven prevalence of CD of 3.6% and 5.7%, respectively. However, patient recruitment in both reports was accomplished through convenience sampling at a tertiary care medical center, potentially introducing reporting bias and overestimation of the actual prevalence of CD in patients with type 1 diabetes. Our report, which focused on a community-based sample, indicates that CD is more common in type 1 diabetes than previously reported. Although all Olmsted County

residents with type 1 diabetes were enumerated, not all were screened for CD. However, sex, age, and diabetes duration were not associated with being screened. A similar frequency of autoimmune thyroid disease was observed between the screened and unscreened groups.

It is well accepted that much CD remains undiagnosed in the community.[2,19,36] Therefore, a strategy of case finding among high-risk populations, such as people with type 1 diabetes, may be an effective way to identify unrecognized CD. Because we have enumerated all clinically found CD in the county, we are able to estimate the contribution that screening of the diabetic population would make. Our previous study[4] described 52 Olmsted County residents with CD, 4 of whom had type 1 diabetes. By extrapolating the prevalence rate from those tested to the entire enumerated population of patients with type 1 diabetes, we estimate that 18 patients with CD would be identified among the entire Olmsted County diabetic cohort, in addition to the 4 patients whose conditions were diagnosed clinically. Thus, a screening effort would increase the identified prevalence of CD by more than one third in the county.

Extrapolation of our findings to the wider diabetic population suggests that upward of 66,000 diabetic patients also may have CD, based on an estimated 942,000 patients with type 1 diabetes residing in the United States.[37] Thus, national screening could substantially increase the overall prevalence of diagnosed CD in this group.

Several screening studies in the general population have suggested a real prevalence of CD of just less than 1%, most of which is clinically silent.[15] Therefore, there could be as many as 1.7 million cases of CD in the whole US population. Thus, while screening patients with type 1 diabetes would add substantially to the numbers of diagnosed CD, it would have only a small overall effect on reducing the overall numbers of undiagnosed CD in the community.

Although our study confirms the high prevalence of CD in type 1 diabetes, it is not clear what the consequences of CD are in these patients. Only a few studies[38,39] have reported that treatment of CD improves glycemic control. From a clinical perspective, our patients with CD generally had no serious symptoms. Among our pediatric patients, a single patient had a history of lactose intolerance, whereas another had a sibling with CD. A single adult patient described diarrhea. These findings further confirm the subclinical nature of CD in type 1 diabetes, making diagnosis on purely clinical grounds more difficult.

Despite attempts to make screening convenient and free, many diabetic patients are apprehensive about CD testing. For patients and families, diabetes is a challenging condition that requires daily effort to balance meals, activity, and insulin administration to maintain adequate metabolic control. In adult diabetic patients, the presence of complications is associated with worsened quality of life.[40,41] The effect of an additional chronic disease, such as CD, may substantially affect the quality of life in diabetic patients. Unfortunately, we are not aware of studies that address the psychosocial effect of CD screening in asymptomatic diabetic patients.

Because the prevalence of CD is higher in patients with type 1 diabetes, many institutions have embarked on screening programs as part of routine care. From a medical perspective, numerous advantages may exist in screening asymptomatic diabetic patients, including the potential for improved diabetic control and avoidance of extraintestinal manifestations of CD, notably osteopenia and malignancy.[18,42] In contrast, routine screening is supported by minimal evidence on the long-term outcome of asymptomatic patients with CD, and our review of Mayo Clinic records uncovered no CD-positive diabetic patients with lymphoma, hypocalcemia or symptomatic fractures, which may be reflective of their relatively younger age at diagnosis of CD (mean ± SD age, 29.5±19.4 years). However, if clinicians overlook minor gastrointestinal symptoms or ascribe them to complications of long-standing diabetes, then routine testing may identify these symptomatic patients.

Although it is clear that *DQ2* or *DQ8* are essentially required for CD to occur, our HLA data suggest that the combination of *DQ2* with *DQ8* may be relatively protective against development of CD, as suggested in a large population cohort in Finland.[43] It has been suggested that carriage of both alleles together may reduce the binding or presentation of the gluten peptides to the gluten-reactive T cells in the gut.[16] HLA information from a larger cohort of type 1 diabetes patients may allow a more precise estimation or prediction of celiac risk in these patients and shed light on the common genetic factors that predispose patients to both diseases. The relative proportions of these HLA types may partly explain the variation in the prevalence numbers for CD in different diabetic populations.

This study had several strengths, including the ability to enumerate all diabetic patients (both adults and children) in a defined geographic population. Furthermore. serologic results were confirmed by biopsy and HLA haplotyping analysis, which has not been performed in a population-based sample. The shortcomings of this study may include a small sample size, which would affect wider relevance to other populations. Nevertheless, this study identified CD-positive cases in an at-risk population by using rigorous uniform diagnostic criteria for both type 1 diabetes and CD.

CONCLUSIONS

The prevalence of biopsy-proven CD in a combined pediatric and adult population with diabetes was 7.0% in a defined North American community. This relatively high prevalence rate was associated with minimal or no symptoms or clinical consequences and appeared to affect those with either *DQ2* or *DQ8* but not both haplotypes. This finding indicates that CD in type 1 diabetic populations is not rare and that clinicians caring for those with type 1 diabetes or investigating gastrointestinal symptoms should strongly suspect CD. Ultimately, studies of the outcome of testing for CD in this population are needed before widespread screening of patients with type 1 diabetes can be advocated.

Glossary

CD, celiac disease; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EMA, endomysial antibody; PCR, polymerase chain reaction; REP, Rochester Epidemiology Project; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; tTg, tissue transglutaminase.

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TABLE 1

Baseline Characteristics of Olmsted County, Minnesota, Residents With Type 1 Diabetes Mellitus Screened or Not Screened for Celiac Disease

Diabetic population	No. (%) of patients	Mean ± SD age at diagnosis (y)	Sex (% male)	Mean ± SD duration of diabetes (y)	No. (%) with autoimmune thyroditis
Total	392	17.9±11.6	51	18.8±14.3	33 (8.4)
Not screened	234 (60)	17.7±11.4	53	18.6±13.6	20 (8.4)
Screened	158 (40)	18.1±12.1	48	19.2±15.2	13 (8.2)
P value		.80	.50	.90	.90

TABLE 2

Individual Characteristics of Olmsted County, Minnesota, Residents With Type 1 Diabetes Mellitus and Celiac Disease*

Patient No./ age (y)/sex	Age at diabetes diagnosis (y)	Age at CD diagnosis (y)	Gastrointestinal symptoms	EMA	tTg (U/ mL)	Positive biopsy results†	HbA_{1c}‡	BMI (kg/ m^2)
1/10/F	7	10	No	1:5120	169.0	Yes	7.3±0.3	15
2/14/F	10	10	Yes	1:320	89.6	Yes	6.2±0.6	25
3/17/M	10	17	No	1:80	32.0	Yes	8.3±1.0	22
4/29/F	10	29	**No**§	1:5120	48.0	Yes	6.6±0.4	28
5/34/F	16	28	No	1:640	59:3	Yes	…	27
6/45/M	14	45	No	1:20	19:7	Yes	8.0±0.3	28
7/56/F	22	56	Yes	1:640	139.7	Yes	7.8±0.4	23
8/31/F	3	4	Yes	…	…	Yes	…	15
9/40/F	9	11	Yes	…	…	Yes	…	17
10/65/F	13	41	Yes	…	…	Yes	…	20
11/68/F	12	59	Yes	…	…	Yes	…	22

*Patients identified by serologic screening are indicated in bold-face type. BMI = body mass index (a measure of weight in kilograms divided by the square of height in meters); CD = celiac disease; EMA = endomysial antibody; HbA_{1C} = hemoglobin A_{1C}; tTg = tissue transglutaminase.

†Biopsy positive refers to histologic features of CD observed on biopsy.

‡Mean value 6 months before diagnosis of CD.

§Developed biopsy-confirmed dermatitis herpetiformis. Cases 8 through 11 were clinically discovered with use of small bowel biopsy as the primary means of diagnosis and are included for completeness.