Celiac Disease and Risk of Subsequent Type 1 Diabetes

A general population cohort study of children and adolescents

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OBJECTIVE — Earlier studies suggest that children with type 1 diabetes are more likely to have a subsequent diagnosis of celiac disease. However, research is sparse on the risk of subsequent type 1 diabetes in individuals with celiac disease. We sought to determine the risk of subsequent type 1 diabetes diagnosed before the age of 20 years in children and adolescents with celiac disease in a national, general population–based cohort.

RESEARCH DESIGN AND METHODS — We identified 9,243 children with a diagnosis of celiac disease in the Swedish national inpatient register between 1964 and 2003. We then identified five reference individuals matched at time of diagnosis for age, calendar year, sex, and county (n = 45,680). Only individuals with >1 year of follow-up after study entry (diagnosis of celiac disease) were included in the analyses.

RESULTS — Celiac disease was associated with a statistically significantly increased risk of subsequent type 1 diabetes before age 20 years (hazard ratio 2.4 [95% CI 1.9–3.0], $P < 0.001$). This risk increase was seen regardless of whether celiac disease was first diagnosed between 0 and 2 (2.2 [1.7–2.9], $P < 0.001$) or 3 and 20 (3.4 [1.9–6.1], $P < 0.001$) years of age. Individuals with prior celiac disease were also at increased risk of ketoacidosis or diabetic coma before the age of 20 years (2.3 [1.4–3.9], $P = 0.001$).

CONCLUSIONS — Children with celiac disease are at increased risk of subsequent type 1 diabetes. This risk increase is low considering that 95% of individuals with celiac disease are HLA-DQ2 positive.

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Celiac disease is an immune-mediated disease characterized by small bowel mucosal atrophy triggered by gluten exposure in genetically sensitive individuals (1). The prevalence of celiac disease in the general population is 1 of 100 in Western European countries (2). The large majority of individuals with celiac disease exhibit HLA-DQ2, with a smaller group being positive for HLA-DQ8 (1).

Type 1 diabetes is another immune-mediated disease (3). Children with this disease are at increased risk of celiac disease (2,4), with a prevalence of biopsy-confirmed celiac disease ranging from 1 to 11% (2) (Swedish studies: 3–5% [5,6]). This constitutes a 5- to 10-fold risk increase for celiac disease (7) and may partly be explained by shared HLA in celiac disease and type 1 diabetes (8). In an American study, 22 of 68 (32%) children with type 1 diabetes and HLA-DQ2 expressed transglutaminase autoantibodies compared with 1 of 78 (1.3%) children with type 1 diabetes but without type 1 diabetes–associated HLA (8). It has also been suggested that early gluten introduction may be a common risk factor for both celiac disease and type 1 diabetes (9–11).

Until now, most studies of celiac disease and type 1 diabetes have focused on the risk of celiac disease in individuals with a prior diagnosis of type 1 diabetes. However, Cronin and Shanahan (12) have demonstrated that some 15% of individuals with both diseases (21 of 144) may first receive a diagnosis of celiac disease (12). Despite this, studies of co-occurrence of type 1 diabetes in celiac disease are mostly limited to either cross-sectional studies (13–15) or studies of diabetes-related autoantibodies in patients with celiac disease (16–20). In 2005, Viljamaa et al. (21) found an increased risk of type 1 diabetes in 703 individuals with celiac disease compared with 299 control subjects. However, in that study, no incidence ratios were given for type 1 diabetes. It is also unclear if individuals with type 1 diabetes diagnosed simultaneously with celiac disease were included in the analysis. Hence, there is a need to further study the risk of subsequent type 1 diabetes in patients with celiac disease.

The main objective of this cohort study was to estimate the association of celiac disease with subsequent type 1 diabetes recorded before the age of 20 years in a general population cohort of 9,243 individuals with celiac disease compared with 45,680 age- and sex-matched individuals without a diagnosis of celiac disease. A second objective was to study the risk of type 1 diabetes stratified for age at diagnosis of celiac disease. We hypothesized that celiac disease diagnosed at early age, and consequent early introduction of gluten-free diet, would be associated with a lower risk of subsequent type 1 diabetes (21–23). We also investigated the relationship between celiac disease and severe type 1 diabetes, as indicated by ketoacidosis or diabetic coma recorded before the age of 20 years.

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Abbreviations: SEI, Swedish socioeconomic index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS

— This study was approved by the research ethics committee of the Karolinska Institute. None of the participants were contacted. Individual information was made anonymous before the analyses.

We identified individuals with a hospital inpatient diagnosis of celiac disease between 1964 and 2003 through the Swedish national inpatient register. Celiac disease was defined according to the following ICD codes: ICD-7, 286.00; ICD-8, 269.00 and 269.98; ICD-9, 579A; and ICD-10, K90.0. The inpatient register is maintained by the National Board of Health and Welfare and contains individual-based register data, where every record can be identified through a personal identity number. The personal identity number is a unique number assigned to more than 99.9% of all Swedish residents and immigrants (24). The inpatient register was established in parts of Sweden in 1964 and has been nationwide since 1987.

For each individual with celiac disease, Statistics Sweden identified up to five reference individuals matched for age, sex, calendar year, and area of residence at the time of celiac disease diagnosis through the Total Population Register. The Total Population Register (25) contains information on characteristics such as area of residence, vital status, and dates of immigration or emigration.

We used a diagnosis of type 1 diabetes before the age of 20 years as our main outcome measure. Type 1 diabetes was defined according to the following ICD codes: ICD-7, 260; ICD-8, 250; ICD-9, 250; and ICD-10, E10. We restricted our outcome measure to individuals with an inpatient (hospital discharge) diagnosis of diabetes before the age of 20 years, since earlier versions of the ICD do not distinguish between type 1 and type 2 diabetes. Some 98–99% of Swedish children who are 0–18 years of age at diagnosis of diabetes have type 1 diabetes (26). (Zachrisson et al. [26] reported that only 85 of some 6,000 Swedish children 0–18 years of age had diabetes of a type other than type 1 diabetes [type 2 diabetes, $n = 31$; maturity-onset diabetes of the young, $n = 29$; other specified diabetes, $n = 25$].) We defined ketoacidosis and diabetic coma as complications of type 1 diabetes according to the following ICD codes (not available in ICD-7): ICD-8, 250.07; ICD-9, 250B-C; and ICD-10, E10.0–10.1.

Socioeconomic index

In a subset of individuals ($n = 30,216$), we had data from Statistics Sweden on Swedish socioeconomic index (SEI) (27). Some 6,300 of these were children born after 1990 and were too young to have their own SEI, so they were assigned a socioeconomic code on the basis of the occupation of their mother. Socioeconomic index was based on the 1968 classification of SEI.

Follow-up time

Follow-up time began 1 year after study entry (equal to the date of first inpatient diagnosis of celiac disease or corresponding date in matched reference individuals). Follow-up time ended on the date of first discharge diagnosis of type 1 diabetes, emigration, death, age 20 years, or study period completion (31 December 2003), whichever occurred first. When estimating the risk of type 1 diabetes within the first 5 years after study entry, the follow-up time ended on the date of first discharge diagnosis of type 1 diabetes, emigration, death, age 20 years, 5 years after study entry, or study period completion (31 December 2003), whichever occurred first.

Participants

We identified 9,733 individuals with celiac disease diagnosed between 1964 and 2003 who were <20 years of age at the first recorded diagnosis of celiac disease (400 of these had type 1 diabetes before or after first diagnosis of celiac disease). Of these, 17 were excluded due to data irregularities (such as death) recorded before the first diagnosis of celiac disease (none had subsequent type 1 diabetes). To reduce the risk of surveillance bias, we excluded 233 individuals with type 1 diabetes diagnosed before the first diagnosis of celiac disease (58.2% of all cases with type 1 diabetes) and another 71 individuals (17.8%) with type 1 diabetes diagnosed in the 1st year after celiac disease. Another 169 individuals without type 1 diabetes were excluded due to a shorter follow-up than 1 year. Similar exclusion criteria were applied to reference individuals.

This study was therefore based on 9,243 individuals with celiac disease diagnosed before age 20 years and 45,680 age-, period-, and sex-matched individuals without a diagnosis of celiac disease. All study participants were free of prior type 1 diabetes at the start of follow-up.

Statistics

We used Cox regression to estimate the association of celiac disease with subsequent type 1 diabetes before 20 years of age or within 5 years after the first recorded diagnosis of celiac disease. We also estimated the risk of ketoacidosis or diabetic coma before age 20 years. These survival analyses were conditioned on risk set; therefore, an individual with celiac disease was only compared with his/her age- and sex-matched reference individuals. The proportional hazard assumption was tested with log minus log plots (online appendix [available at http://care.diabetesjournals.org]).

Stratification for sex, as well as age at study entry (≤2 or ≥3 years), was performed in separate analyses. We chose this age cutoff so that the number of children in each age stratum would allow for sufficient study power. We also calculated crude and adjusted risk estimates for type 1 diabetes in a subset of individuals with data on SEI. In separate analyses, we also included the 1st year after study entry in the follow-up, as this may represent a period of more intense bowel inflammation before the influence of a gluten-free diet had been established. In a separate analysis, we calculated the risk of subsequent type 1 diabetes restricted to individuals with a diagnosis of celiac disease. Individuals with celiac disease diagnosed between 0 and <1 year of age ($n = 2,262$) were used as the reference category and compared with those between 1 and <2 ($n = 3,937$), between 2 and 3 ($n = 1,291$), between 4 and 7 ($n = 894$), and ≥8 ($n = 859$) years of age at diagnosis. Ninety-five percent CIs for hazard ratios (HRs) not including 1.00 were considered statistically significant. Statistics were calculated using SPSS (version 11.0; SPSS, Chicago, IL).

Power calculation

At a significance level of 5%, we had an 80% power to detect an increased risk of subsequent type 1 diabetes in individuals with celiac disease if the HR was ≥1.36. For subsequent ketoacidosis or diabetic coma, we had the power to detect an increased HR of ≥1.80.

RESULTS

— The median age of individuals with celiac disease and their reference individuals was 1 year (range 0–19). The majority was female (Table 1). The median age at first recorded diagnosis of type 1 diabetes was 10 years (range 2–19, mean 11) in individuals with prior celiac

Table 1—*Characteristics of participants*

	No celiac disease (reference)	Celiac disease
Total	45,680	9,243
Age at first recorded diagnosis of celiac disease (years)		
0–2	—	7,090 (76.7)
3–19	—	2,153 (23.3)
Sex		
Male	19,210 (42.1)	3,889 (42.1)
Female	26,470 (57.9)	5,354 (57.9)
Calendar period		
1964–1973	1,292 (2.8)	265 (2.9)
1974–1983	13,222 (28.9)	2,671 (28.9)
1984–1993	22,165 (48.5)	4,485 (48.5)
1994–2003	9,001 (19.7)	1,822 (19.7)
SEI		
I	4,707 (10.3)	968 (10.5)
II	5,694 (12.5)	1,278 (13.8)
III	13,979 (30.6)	3,590 (38.8)
Missing data	21,300 (46.6)	3,407 (36.9)

Data are *n* (%). Individuals with >1 year of follow-up after celiac disease diagnosis or corresponding date in matched reference individuals (also see text). For SEI, "I" is the highest category (also see text). For reference individuals, we have given the number of individuals who constituted the basis for the Cox regression. In actuality, we had data on SEI for another 4,048 reference individuals, but these individuals were not part of the internally stratified calculations due to missing values on SEI in the matched individual with celiac disease. When these 4,048 reference individuals are added to those presented above, the proportion of missing values is similar between individuals with celiac disease and reference individuals.

disease and 10 years (range 2–19, mean 11) in reference individuals.

The median duration from diagnosis of celiac disease to first recorded diagnosis of type 1 diabetes was 8.1 years (range 1.0–18.7) and 8.3 years (range 1.0–19.1; equal to the duration from study entry to the first diagnosis of type 1 diabetes) in individuals without a diagnosis of celiac disease.

Type 1 diabetes before the age of 20 years

Children with celiac disease were at a statistically significantly increased risk of subsequent type 1 diabetes (HR 2.4 [95% CI 1.9–3.0]) (Table 2 and online appendix). A formal interaction test revealed no statistically significant difference in risk of type 1 diabetes according to age at first diagnosis of celiac disease ($P = 0.211$), and when we restricted our analyses to those with a diagnosis of celiac disease, age at diagnosis did not influence the risk of subsequent type 1 diabetes (age between 0 and <1 year, HR 1.00 (reference); between 1 and <2 years, 0.8; between 2 and 3 years, 1.0; between 4 and 7 years, 1.6; and ≥8 years, 0.6; all $P > 0.05$).

Adjustment for SEI in a subset of individuals with available data on SEI did not affect the risk of type 1 diabetes (crude and adjusted HRs of 2.4; both $P < 0.001$; based on 58 positive events in 5,836 individuals with celiac disease and 105 positive events in 24,380 reference individuals). When we included the 1st year after diagnosis, the HR for subsequent type 1 diabetes was 3.9 (95% CI 3.2–4.8, $P < 0.001$; based on 167 positive events in 9,484 individuals with celiac disease and 211 positive events in 46,954 individuals without a diagnosis of celiac disease).

Type 1 diabetes within 5 years after diagnosis of celiac disease

Children with celiac disease were at increased risk of type 1 diabetes 1–5 years after the first recorded diagnosis of celiac disease (HR 2.7 [95% CI 1.7–4.2], $P < 0.001$; based on 29 positive events in individuals with celiac disease and 54 positive events in reference individuals). Risk estimates after stratification for age at diagnosis and sex were similar to the risk estimates for type 1 diabetes before the age of 20 years in these groups (data not shown). Adjustment for SEI in a subset of individuals with data on SEI did not affect the risk estimates (crude HR 2.7 [1.5–4.7], $P = 0.001$; adjusted HR 2.6 [1.5–4.6], $P = 0.001$; based on 20 positive events in individuals with celiac disease and 33 positive events in reference individuals). When we included the 1st year after study entry, the HR for type 1 diabetes within 5 years after diagnosis was 7.4 (5.5–10.2, $P < 0.001$; based on 100 positive events in individuals with celiac disease and 67 positive events in reference individuals).

Ketoacidosis or diabetic coma before 20 years of age

Individuals with celiac disease were at a statistically significantly increased risk of subsequent ketoacidosis (HR 2.3 [95% CI 1.4–3.9], $P = 0.001$; also see Table 2 and online appendix). When the analysis was stratified by sex, the association was only statistically significant in female subjects (Table 2). In a subset of individuals with data on SEI, we adjusted for SEI. In this subset, adjustment for SEI resulted in a slightly decreased HR (from 2.2 to 1.8). The reduction of statistical significance in the adjusted analysis compared with the main analysis is due in part to the smaller number of individuals with SEI data available for analysis (crude HR 2.2 [95% CI 1.1–4.3], $P = 0.022$; adjusted HR 1.8 [0.9–3.7], $P = 0.083$; based on 13 positive events in individuals with a diagnosis of celiac disease and 25 positive events in reference individuals). When we included the 1st year after diagnosis, the HR for subsequent ketoacidosis was 3.5 (2.2–5.4, $P < 0.001$; based on 34 positive events in individuals with a diagnosis of celiac disease and 47 positive events in reference individuals).

CONCLUSIONS — We found a statistically significantly positive association of celiac disease with subsequent type 1 diabetes and with ketoacidosis/diabetic coma before the age of 20 years. There was no statistically significant difference in risk of subsequent type 1 diabetes between individuals with a diagnosis of celiac disease at 0–2 years of age and those diagnosed after 2 years of age.

A number of studies have screened individuals with celiac disease or the related disease dermatitis herpetiformis for type 1 diabetes (13–20). These studies are, however, mostly cross-sectional, limited to small numbers, and often comprised of patients selected from large centers. To our knowledge, there exists only one earlier study of celiac disease and subsequent type 1 diabetes (21). Although no incidence ratio for type 1 diabetes is given in that study, the incidence

Table 2—*Risk of subsequent type 1 diabetes before the age of 20 years in relation to celiac disease status*

		Type 1 diabetes			Ketoacidosis or diabetic coma		
	n	Events	HR (95% CI)	*P*	Events	HR (95% CI)	*P*
No celiac disease	45,680	199	1.0		45	1.0	
Any celiac disease	9,243	96	2.4 (1.9–3.0)	<0.001	22	2.3 (1.4–3.9)	0.001
Age at first recorded celiac disease diagnosis (years)							
0–2	7,090	77	2.2 (1.7–2.9)	<0.001	19	2.3 (1.3–3.9)	0.004
3–20	2,153	19	3.4 (1.9–6.1)	<0.001	3	2.9 (0.7–12.2)	0.143
Sex							
Male	3,889	37	1.9 (1.3–2.9)	0.001	8	1.5 (0.7–3.4)	0.301
Female	5,354	59	2.7 (2.0–3.8)	<0.001	14	3.3 (1.7–6.6)	0.001

Events refers to the number of positive events before end of follow-up (diagnosis of type 1 diabetes or ketoacidosis/diabetic coma). Estimates derived from Cox regression internally stratified for sex, age, year of study entry, and county of residence (e.g., children with celiac disease diagnosed before the age of 3 years were at 2.2-fold increased risk of developing subsequent type 1 diabetes before the age of 20 years).

rate of 126 of 100,000 person-years in individuals with celiac disease compared with 6 of 100,000 person-years in control subjects signals a substantially increased risk for type 1 diabetes in individuals with celiac disease (21). These data do, however, originate from one center, and the authors did not appear to take important potential confounding factors into account (21). In contrast, we used a national population-based approach with >9,000 individuals with celiac disease and some 45,000 age- and sex-matched reference individuals. A matched design has the inherent advantage of dealing with problems of potential confounding; our internal stratification means that each individual with celiac disease was only compared with his/her reference individuals. The large number of participants provided this study with high statistical power and allowed for subanalyses, such as the risk of subsequent type 1 diabetes according to age at diagnosis of celiac disease.

The risk increase for type 1 diabetes in this study is consistent with earlier findings by Peters et al. (28). (Individuals with celiac disease in their study were at a threefold increased risk to die from type 1 or type 2 diabetes.) Although that study was based on >10,000 individuals with celiac disease or dermatitis herpetiformis, it was restricted to death certificates, whereas the current study was based on incidence of type 1 diabetes before the age of 20 years. The number of positive outcomes in individuals with celiac disease in our study (almost 300) was five times that seen in the study by Peters et al.

The association of celiac disease with subsequent type 1 diabetes may be due to various factors, such as environmental influences or a common genetic susceptibility. Gluten is a necessary trigger for celiac disease (29), and infant feeding pattern may influence the risk of both celiac disease and type 1 diabetes (9–11,30–32). Both the DAISY (Diabetes Autoimmunity Study in the Young) (9) and the BABYDIAB study (10) found a four- to fivefold increased risk of type 1 diabetes–associated autoantibodies in children exposed to gluten before the age of 4 months (9,10). Celiac disease–associated antibody levels were statistically significantly higher among individuals with an early gluten introduction in the DAISY (HR 5.2) (11) but did not attain statistical significance in the BABYDIAB study (HR 3.8) (10). It may be that the positive association between celiac disease and subsequent type 1 diabetes found in the current study is secondary to the association of both celiac disease and type 1 diabetes with early exposure to gluten.

It is interesting to note that our risk estimates for subsequent type 1 diabetes are substantially lower than what has previously been reported between celiac disease and prior type 1 diabetes (2,33). One explanation for this is that those with more severe autoimmune disease have an earlier symptomatic onset of type 1 diabetes, possibly before the diagnosis of celiac disease; therefore, they would not be included in our study of celiac disease and subsequent type 1 diabetes. Higher risk estimates for type 1 diabetes were found when we included the 1st year of follow-up after study entry. This could be due to surveillance bias, as diagnosis of one disease increases the possibility of a second diagnosis (simultaneous investigation for celiac disease and type 1 diabetes). An alternative explanation is that the inflammation associated with celiac disease remained for a period after diagnosis (34); this inflammation initially increased the risk for type 1 diabetes, but as the inflammation decreased over time, the risk for type 1 diabetes was also reduced. As we excluded the 1st year of follow-up to minimize the influence of surveillance bias, this is another potential explanation for the estimates of association between celiac disease and type 1 diabetes being relatively low. We found no strong evidence to support the hypothesis that an earlier diagnosis of celiac disease, and therefore an earlier introduction of a gluten-free diet, protects against type 1 diabetes.

The positive association between celiac disease and later type 1 diabetes could be a result of shared HLA characteristics or an interaction between food introduction and genetic susceptibility (3,9,10). The concordance rate is 70–80% for celiac disease in monozygotic twins (35) and 40–50% for type 1 diabetes (36). About 95% of individuals with celiac disease express HLA-DQ2 (37). Approximately one-third of all HLA-DQ2–positive individuals with type 1 diabetes express tissue transglutaminase autoantibodies (8). HLA-DQ2 is a positive risk factor for type 1 diabetes (odds ratio 3.5 in European whites) (38); therefore, the increased risk of type 1 diabetes in celiac disease could be entirely attributable to the HLA characteristics of these individuals. In fact, our risk estimate for subsequent type 1 diabetes is lower than expected, considering that 95% of individuals with celiac disease express HLA-DQ2 (37).

This study was based on inpatient diagnoses. Some individuals with celiac dis-

ease may not have been identified through a hospital-based register. Nevertheless, we identified >9,000 individuals with a diagnosis of celiac disease before the age of 20 years. Considering that Sweden has 9 million people, the number of cases with celiac disease in this study is consistent with the results of a large Swedish screening study that found a prevalence of diagnosed celiac disease of slightly >1 in 1,000 among adults in a general population (39).

False-negative celiac disease is unlikely to have affected our risk estimates, since <1% of our reference population should be affected by celiac disease (2,7). Although there is a risk that individuals with celiac disease identified through a hospital-based register have more severe disease than the average patient, many of the patients in this study were diagnosed at a young age, when hospital admission was common in those undergoing small-bowel biopsies and other gastrointestinal investigations. Children and young people with type 1 diabetes are always hospitalized in Sweden; the disease is diagnosed due to investigations and the need to start insulin treatment. Hence, the sensitivity for type 1 diabetes should be high in this study. Also, specificity for celiac disease and type 1 diabetes is high in the current study. Smedby et al. (40) recently found that an inpatient diagnosis of celiac disease in a subset of patients with lymphoma in the inpatient register had a specificity of >85%. The general awareness among Swedish physicians regarding the need to perform a small-bowel biopsy before diagnosis is high (41). The specificity for type 1 diabetes before the age of 20 years should also be high. Although earlier versions of the ICD codes do not distinguish between type 1 and type 2 diabetes, type 2 diabetes and maturity-onset diabetes of the young is very rarely seen before 20 years of age in Sweden; therefore, the vast majority of individuals with diabetes in this study have type 1 diabetes (26).

In conclusion, this population-based cohort study found a two- to threefold risk increase for type 1 diabetes before the age of 20 years in individuals with prior celiac disease. Shared nutritional factors and common HLA profiles may explain this statistically significant risk increase. The risk increase for type 1 diabetes is low, considering that 95% of individuals with celiac disease are HLA-DQ2 positive.

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