Celiac Disease Increases Risk of Thyroid Disease in Patients With Type 1 Diabetes: A Nationwide Cohort Study

Matthew Kurien,[1,2] Kaziwe Mollazadegan,[3] David S. Sanders,[1,2] and Jonas F. Ludvigsson[3,4]

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OBJECTIVE

Both type 1 diabetes (T1D) and celiac disease (CD) have been linked to autoimmune thyroid disease (ATD). We examined if individuals with both T1D and CD were at a higher risk of ATD than those with only T1D.

RESEARCH DESIGN AND METHODS

This study was a nationwide population-based cohort study. We defined T1D as having an inpatient or a hospital-based outpatient diagnosis of T1D at age ≤30 years in the Swedish National Patient Register between 1964 and 2009. Data on CD were obtained through small intestinal biopsy reports showing villous atrophy (Marsh histopathology grade III) between 1969 and 2008 at any of the 28 pathology departments in Sweden. ATD included hyperthyreosis and hypothyreosis, defined according to the Swedish National Patient Register. We identified 947 individuals with T1D and biopsy-verified CD. These were matched to 4,584 control subjects with T1D but no CD diagnosis. Cox regression then estimated the risk of ATD.

RESULTS

Among T1D, CD was a risk factor for later ATD. During follow-up, 90 T1D+CD patients developed ATD (expected *n* = 54). Adjusting for sex, age, and calendar period, this corresponded to a hazard ratio (HR) of 1.67 (95% CI 1.32–2.11; *P* < 0.001). This excess risk was highest in those who had CD for 10 years or more (HR 2.22 [95% CI 1.49–3.23]). Risk increases were seen in both males and females. CD was a risk factor for both hypothyreosis (HR 1.66 [95% CI 1.30–2.12]) and hyperthyreosis (HR 1.72 [95% CI 0.95–3.11]).

CONCLUSIONS

Among patients with T1D, CD is a risk factor for the later development of ATD.

Celiac disease (CD) is an immune-mediated enteropathy that has a prevalence of 1% in Western populations (1). It occurs in genetically susceptible individuals after exposure to dietary gluten, which is a protein found in wheat, barley, and rye. Strict adherence to a gluten-free diet is the mainstay of treatment for CD, which reduces the risk of developing serious complications such as lymphoma, osteoporosis, hyposplenism, anemia, and other micronutrient deficiencies (2). CD has been linked to both type 1 diabetes (T1D) and autoimmune thyroid disease (ATD) (3,4). The development of autoimmune conditions in CD may be related to the duration of gluten exposure, although previous findings from the literature are conflicting (5,6).

[1]Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, U.K.
[2]Academic Unit of Gastroenterology, University of Sheffield, Sheffield, U.K.
[3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[4]Department of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden

Corresponding author: Jonas F. Ludvigsson, jonasludvigsson@yahoo.com.

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Further supportive of a link between these three immune-mediated conditions is the higher prevalence of CD in both T1D and ATD (7–10).

Although epidemiological data suggest a common genetic background for all three of these organ-specific T cell–mediated diseases, knowledge on shared susceptibility genes is incomplete (11,12). CD has been shown to be strongly associated with the MHC class II molecules HLA-DQ2 and HLA-DQ8 (11). Regarding CD and T1D, both conditions share similar HLA and non-HLA genetic loci, with HLA genotype DR3-DQ2 and DR4-DQ8 strongly associated with T1D and DR3-DQ2 with CD (13,14). With regard to CD and ATD, studies have shown that HLA-DQ2 and DQ8 are disproportionately represented in patients with autoimmune thyroiditis and Graves disease (15). Interestingly, Ventura et al. (16) have suggested that the introduction of a gluten-free diet in patients with CD may actually decrease the levels of thyroid-related antibodies in these patients.

Diabetes and thyroid disorders are the two most common endocrinopathies seen in clinical practice. They can often coexist within families and in the same individual (17). The reported prevalence of thyroid dysfunction in diabetes is variable, ranging between 4.8 and 31.4%, influenced by the terminology used to define diabetes and thyroid dysfunction in differing studies (12). Given the increased risk of thyroid disease in T1D and the potential for significant morbidity, current guidelines recommend screening of patients with T1D for thyroid disease (18). Although advocated in guidelines, uncertainty remains as to the optimal method of screening, its frequency, and whether it is actually cost-effective (18).

Given the previously reported associations between these diseases, the aim of this study was to examine if CD is a risk factor for future ATD in patients with T1D. This research was conducted through linked data from the Swedish nationwide registries, calculating relative and absolute risks of ATD in 5,531 patients with T1D according to CD status.

RESEARCH DESIGN AND METHODS

T1D

We ascertained T1D using inpatient and hospital-based outpatient data on T1D from the Swedish National Patient Register (19). This registry started in 1964, came nationwide in 1987, and added outpatient data in 2001. T1D was defined as having a relevant ICD code representing T1D (ICD-7: 260, ICD-8: 250, ICD-9: 250, and ICD-10: E10). Older ICD versions in Sweden (7th, 8th, and 9th editions) made no difference between T1D and T2D, and hence we also required the first diabetes ICD code to be at $\leq$30 years of age. In Sweden, forms of diabetes other than T1D are uncommon below this age (3,20), and data by Miao et al. (21) suggest that in Sweden this definition has a 95% positive predictive value for insulin-dependent diabetes.

CD

The CD diagnosis was based on biopsy report data from all pathology departments in Sweden (n = 28). We defined CD as having villous atrophy in the duodenum or jejunum (Marsh histopathology stage III) (22). Although we collected biopsy report data in 2006–2008, the actual biopsies had taken place in 1969–2008. The current study was based on 29,096 individuals with biopsy-verified CD (previously described in our article on mortality in CD [23]). Earlier validation has shown that villous atrophy has a high specificity for CD in Sweden, and 95% of patients had CD when their patient charts were reviewed (24). Although we did not require a positive CD serology for diagnosis, some 88% of those with available celiac serology data at diagnosis were positive, and when two independent reviewers manually examined $>$1,500 biopsy reports with villous atrophy or small intestinal inflammation, diagnoses other than CD were uncommon in villous atrophy (inflammatory bowel disease occurred in 0.3%, and *Helicobacter pylori* in 0.2% of samples) (24). On average, three tissue specimens were obtained per biopsy session (25).

ATD

We again used the Swedish National Patient Register to identify individuals with ATD (hypothyreosis: ICD-7: 253.19, 253.29; ICD-8: 244.09; ICD-9: 244W, 244$\times$; ICD-10: E03; and hyperthyreosis: ICD-7: 252; ICD-8: 242; ICD-9: 242; ICD-10: E05).

Study Participants

Through the Swedish National Board of Health and Welfare, we identified 42,539 individuals with T1D and no data irregularities (see our article on mortality in T1D+CD for details [26]). Among these, 2.3% (n = 960) had a diagnosis of CD before 31 December 2009. From the remaining individuals with T1D, we selected up to five control subjects per T1D+CD patient (in total n = 4,608). Control subjects were matched for age (exact year), sex, and birth year (exact year). Finally, we excluded 36 individuals with a diagnosis of ATD before first T1D diagnosis and one CD individual with other data irregularities. This left us with 947 individuals with T1D+CD and 4,584 individuals with only T1D.

Statistical Analyses

We modeled CD as a time-dependent variable in a Cox regression to calculate hazard ratios (HRs) for future ATD. We began follow-up on the date of the first T1D diagnosis and ended it with the first of the following potential events: diagnosis of ATD, emigration, death, or end of study period (31 December 2010). All Cox models were adjusted for sex, age, and calendar period at T1D diagnosis.

The risk of ATD was determined according to sex of the patient, calendar period of first T1D diagnosis (1964–1975, 1976–1987, 1988–1999, and 2000–2009), and age at T1D diagnosis (0–9, 10–19, and 20–30 years) (Tables 2 and 3). We chose these age categories since the children below the age of 10 years in Sweden have rarely reached puberty (27), and since the third age-group (20–30 years) consists of adults rather than children (and is also cared for by adult medicine physicians). We calculated incidence rated through dividing the number of ATD events with time at risk. Since earlier research on comorbidity in T1D+CD has shown a different pattern in the first 5 years after CD diagnosis (likely due to ongoing inflammation and surveillance bias), we also estimated the risk of ATD according to follow-up ($<$5, 5–9, and $\geq$10 years) (26,28,29).

To rule out that our results were due to misclassification of T1D, we carried out four sensitivity analyses. In one we excluded those individuals who had a record of having oral antidiabetic medication in the Prescribed Drug Register according to relevant ATC codes (A10B and A10$\times$) since this may signal that they have T2D rather than T1D. In a

second sensitivity analysis, we excluded women who were pregnant at the time of their first T1D diagnosis (0–9 months before delivery) since such diabetes may be gestational diabetes mellitus instead of T1D. Data on pregnancy were obtained through the Swedish Medical Birth Registry. In a third analysis, we restricted our analysis to patients with an inpatient diagnosis of T1D. Since earlier research has shown that the prevalence of both CD (30) and T1D (31) varies by country, we performed a fourth sensitivity analysis restricting study participants to those born in the Nordic countries. Finally, we calculated the risk of hypothyreosis and hyperthyreosis according to CD status in patients with T1D.

Ethics

This project (2011/841–31/3) was approved on 15 June 2011 by the Ethics Review Board, Stockholm, Sweden.

RESULTS

Some 55% of study participants were female (Table 1). The median age at first T1D diagnosis was 9 years, and the median age of CD diagnosis (date of biopsy with villous atrophy) was 12 years. Patients were followed up for a median of 13 years. A majority of study participants were diagnosed with T1D in the 1990s and later. The median age of first ATD diagnosis was 25 years in individuals with T1D+CD.

Overall Risk of ATD

During 8,890 person-years of follow-up, there were 90 cases of ATD among patients with T1D and CD (expected n = 54). The incidence rate of ATD was 1,012/100,000 person-years in T1D+CD vs. 607/100,000 person-years in control subjects with an excess risk of 406/100,000 person-years (rounded). Hence, 40% of the ATDs occurring in individuals with T1D and CD could be attributed to the underlying CD (Table 2). The relative risk of ATD in T1D individuals with CD was 1.67 (95% CI 1.32–2.11).

Overall, some 10.8% (n = 102) of T1D+CD patients had a diagnosis of ATD at some stage of life (before or after CD), compared with 7.2% (n = 329) of patients with T1D only. The Supplementary Figure 1 shows a Kaplan-Meier curve of the risk of ATD in individuals with T1D who at some stage in life had a CD diagnosis (be it before or after ATD).

Duration of CD and Risk of ATD

The highest risks of ATD were seen after ≥10 years with CD (Table 2). This is also illustrated by the Kaplan-Meier curve (Supplementary Fig. 1).

Table 1—Characteristics of the study participants

	T1D+CD	T1D
Total	947	4,584
Age at T1D diagnosis, years (median, range)[a]	9, 0–30	9, 0–30
Age at T1D diagnosis		
0–9 years, *n* (%)	564 (59.6)	2,646 (57.7)
10–19 years, *n* (%)	255 (26.9)	1,285 (28.0)
20–30 years, *n* (%)	128 (13.5)	653 (14.2)
Age at end of study, years (median, range)	21, 5–70	22, 2–72
Entry year (median, range)[b]	1996, 1964–2009	1997, 1964–2009
Follow-up, years (median, range)[c]	13, 0–47	13, 0–47
Age at CD diagnosis, years (median, range)	12, 1–63	–
Females, *n* (%)	522 (55.1)	2,498 (54.5)
Males, *n* (%)	425 (44.9)	2,086 (45.5)
Calendar period		
1964–1975, *n* (%)	102 (10.8)	479 (10.4)
1976–1987, *n* (%)	152 (16.1)	746 (16.3)
1988–1999, *n* (%)	341 (36.0)	1,600 (34.9)
2000–2009, *n* (%)	352 (37.2)	1,759 (38.4)
Nordic country of birth, *n* (%)	939 (99.2)	4,449 (97.4)
Gestational diabetes mellitus, *n* (%)	15 (1.6)	93 (2.0)
Oral antidiabetic medication, *n* (%)	19 (2.0)	138 (3.0)
Ever ATD[d]	102 (10.8)	329 (7.2)

[a]Age was rounded to the nearest year. [b]Average entry year. [c]Follow-up time until death, emigration, or 31 December 2010, whichever happened first. [d]Includes patients with ATD before or after CD diagnosis.

Stratified Analyses

Risk estimates were independent of sex, but we found a higher risk of ATD in the first calendar period (P for interaction between CD and calendar period = 0.049) and a lower risk in individuals diagnosed with T1D in early childhood (P for interaction = 0.015) (Table 3).

Sensitivity Analyses

All four sensitivity analyses found similar risk estimates (exclusion of individuals with oral antidiabetic medication: HR 1.63; exclusion of potential gestational diabetes mellitus: HR 1.64; restriction to inpatients: HR 1.68; and restriction to individuals born in the Nordic countries: HR 1.65; all $P < 0.001$).

Type of ATD

Patients with T1D and CD were at increased risk of both hypothyreosis (HR 1.66 [95% CI 1.30–2.12]) and hyperthyreosis (HR 1.72 [95% CI 0.95–3.11]).

CONCLUSIONS

We performed a population-based cohort study of 947 patients with both CD and T1D and compared these to 4,584 individuals with T1D only. During follow-up, 90 patients with T1D+CD developed ATD, representing an excess risk of 67%. Importantly the highest risks were seen after ≥10 years with CD, suggesting that long-term double autoimmunity is a risk factor for ATD.

We believe that our work is the largest study to date to examine whether concomitant CD and T1D influences the likelihood of developing ATD. To our knowledge, there has only been one previous pediatric study from the Czech Republic (n = 251) examining whether ATD occurs more frequently in coexisting T1D and CD compared with T1D alone (32). Findings from that study failed to show that coexisting CD in T1D influenced the occurrence of ATD. The discrepancy between our findings and the previous study may be accountable by the difference in sizes between the two studies, with our cohort over 20 times larger than the previous study's population. In addition, our median follow-up was 13 years compared with 4.9 years in the Czech study. This could potentially have influenced the outcomes obtained as the highest risk of developing ATD from our work was after 10 years or more of having CD and T1D.

Table 2—Risk of ATD according to time with CD among patients with T1D

Subgroup	Observed events	Expected events*	HR (95% CI) adjusted	*P* value	Excess risk/100,000 PYAR	Attributable risk (%)
Overall	90	54	1.67 (1.32–2.11)	<0.001	406	40
0 to <5 years	30	18	1.68 (1.21–2.32)	0.002	305	40
5 to <10 years	23	22	1.05 (0.66–1.66)	0.834	40	5
≥10 years	37	17	2.22 (1.49–3.23)	<0.001	937	55

*Due to rounding, the numbers do not add up. PYAR, person-years at risk.

Given the increased long-term risk of developing ATD in patients with both CD and T1D, our work would support screening for ATD in this high-risk group of patients. Currently, there is a lack of consensus from major endocrine and diabetes societies' guidelines as to which thyroid function tests should be performed and as to when screening should be undertaken (33). Most guidelines advocate screening for ATD in all patients with T1D at the point of diagnosis. Beyond this, the screening intervals are uncertain, with some practice guidelines not specifying a time for repeat screening, whereas others recommend annual or 2-year testing or more frequent testing if patients are antibody positive, have a goiter, or have another autoimmune disease (33). Although uncertainty exists regarding the merits and the cost-effectiveness of these differing screening strategies, findings from our work suggest that patients with both CD and T1D are at particularly high risk of developing ATD. Consequently, a pragmatic approach that we would advocate for is screening in these high-risk patients to measure thyroid peroxidase antibody (TPOAb) and thyroid-stimulating hormone (TSH) at baseline and then annually thereafter.

Other interesting findings from our work are that the highest risk estimates for developing ATD were in the first calendar period (1964–1975) of our study. A potential explanation for this outcome could be that historically screening for ATD in T1D was poorly performed and possibly only considered in those with double autoimmunity, such as those with both T1D and CD. As guidelines have evolved and screening improved over recent years, there has undoubtedly been an increase in the detection of ATD in all T1D patients, which could have caused a reduction in the risk estimates. Another interesting observation from our study is that the lowest risk of ATD was identified in those who were diagnosed with T1D in childhood (0–9 years). A plausible explanation for this finding could be that ATD is most strongly associated with age-groups >45–50 years (34). As our median follow-up was 13 years, this may have been insufficient time for those diagnosed at an early age to have reached the typical age of ATD.

Our work may have clinical implications, as recent work has suggested that patients with concomitant T1D and ATD have diminished quality of life (35). Given the previously recognized reduction in quality of life in patients with CD, clinicians should be mindful that patients with CD, ATD, and T1D have a higher potential risk of psychological problems, which should trigger early referral to health care professionals with relevant expertise if concerns are identified (36).

Among the strengths of our study are the number of patients with both T1D and CD and a follow-up of >8,800 person-years in the CD patients. Furthermore, CD was identified through biopsy records showing villous atrophy. During the study period, biopsy remained the gold standard for diagnosis in both children and adults, and ≥96% of all pediatricians and gastroenterologists in Sweden reported performing a small intestinal biopsy before diagnosis (24). A patient chart review found that 95% of all samples with villous atrophy represented CD, a higher positive predictive value than physician-assigned diagnosis for CD in the Swedish National Patient Registry (37).

Some limitations of this study should also be considered. It has been reported

Table 3—Stratified analyses: ATD in T1D, according to CD status

Subgroup	Observed events	Expected events*	HR (95% CI) adjusted	*P* value	Excess risk/ 100,000 PYAR	Attributable risk (%)
Sex						
Female	68	41	1.67 (1.27–2.19)	<0.001	550	40
Male	22	13	1.65 (1.03–2.66)	0.038	221	39
Age at T1D diagnosis (years)						
0–9	42	32	1.31 (0.94–1.83)	0.0116	184	24
10–19	30	14	2.19 (1.44–3.33)	<0.001	726	54
20–30	18	9	2.04 (1.20–3.48)	0.009	737	51
Calendar period						
1964–1975	16	7	2.32 (1.28–4.19)	0.005	822	57
1976–1987	21	11	1.87 (1.15–3.04)	0.011	510	47
1988–1999	33	22	1.53 (1.03–2.25)	0.031	310	35
2000–2009	20	16	1.28 (0.79–2.08)	0.317	201	22

*Due to rounding, the numbers do not add up. PYAR, person-years at risk.

that the prevalence of CD in patients with T1D is between 1.6 and 12.3% (7). At present, Swedish patients with T1D are screened for CD, but because such screening did not occur in the early part of our study period, we cannot rule out the possibility that some individuals classified as having T1D alone may also have undiagnosed CD. However, because individuals with T1D and undiagnosed CD would not make up >3–4% of our reference group (if the average CD prevalence in T1D is 6% [7]), such misclassification would not affect our risk estimates more than marginally.

In summary, this is the largest study to date demonstrating that concomitant CD and T1D influences the likelihood of developing ATD. Our findings would support the merits of screening for ATD in this group or patients with double autoimmunity.

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