Celiac Disease and Risk of Autoimmune Disorders: A Population-Based Matched Birth Cohort Study

Cristina Canova, PhD[1], Gisella Pitter, MD[1], Jonas F. Ludvigsson, MD, PhD[2,3], Pierantonio Romor, MSc[4], Loris Zanier, MD[5], Renzo Zanotti, PhD[1], and Lorenzo Simonato, MD[1]

Objectives To estimate the relative risk of developing type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease in children with celiac disease (CD).

Study design A matched cohort design with linkage of administrative data was adopted. A total of 1215 cases of CD and 6075 references matched by sex and year of birth born in Friuli Venezia Giulia Region (Italy) between 1989 and 2011 were included. Cox regression models were used to estimate hazard ratios (HRs) for autoimmune diseases in patients with CD compared with references, stratified by sex and age at diagnosis.

Results Individuals with CD had an increased risk of subsequent hypothyroidism (HR 4.64 [95% CI 2.88-7.46]) and T1DM (HR 2.50 [95% CI 0.94-6.66]), the latter not statistically significant. Risk of hypothyroidism was higher in males (HR 20.00; 95% CI 5.64-70.87) than females (HR 3.21; 95% CI 1.85-5.57) (*P* value <.01). No differences were observed between males and females risks for diabetes or age at CD diagnosis. The small number of hyperthyroidism cases identified precluded any statistical analysis.

Conclusions Children and youth with CD are at increased risk of developing autoimmune hypothyroidism and to some extent T1DM. This suggests the need for surveillance of children with CD in order to timely detect the onset of such comorbidities. *(J Pediatr 2016;174:146-52)*.

See editorial, p 7

Celiac disease (CD) is an immune-mediated gluten-dependent disorder that occurs in about 1% of the general population.[1] Originally considered a rare malabsorption syndrome of childhood, CD is now recognized as a systemic disorder affecting many organ systems.[2] The pathogenesis of CD involves autoimmunity against tissue transglutaminase in genetically susceptible individuals who carry the HLA DQ2 or DQ8 haplotypes,[3] a genetic background shared by autoimmune diseases such as type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease (ATD).

European and North American guidelines[3-5] recommend serologic screening for CD in patients with autoimmune diseases such as T1DM and ATD because of the high prevalence of CD in these conditions.[6,7] An increased prevalence of T1DM[8,9] and ATD[8,10,11] has been reported in patients with CD, but data are scant and limited to cross-sectional studies in adults. The only 2 population-based cohort studies with linkage of administrative data conducted in Sweden, showed subjects with CD at increased risk of T1DM (hazard ratio [HR] 2.4, 95% CI 1.9-3.0),[12] and autoimmune hypothyroidism (AH−) (HR 4.4, 95% CI 3.4-5.6) and hyperthyroidism (AH+) (HR 2.9, 95% CI 2.0-4.2).[13] Both studies identified autoimmune diseases only by hospital discharge records. No study has, therefore, prospectively investigated the risk of future T1DM and thyroid disease outside Sweden or evaluated the co-occurrence of more than one autoimmune disease in subjects with CD and used multisource definitions to identify cases.

This study aims to follow-up a large population-based birth cohort of children and young adults with CD and matched reference individuals using data from the linked and integrated epidemiologic system of the Friuli-Venezia Giulia (FVG) region (Italy) in order to estimate risks of developing T1DM, AH−, and AH+.

AH+	Hyperthyroidism
AH−	Autoimmune hypothyroidism
ATC	Anatomical Therapeutic Chemical
ATD	Autoimmune thyroid disease
CD	Celiac disease
FVG	Friuli-Venezia Giulia
HR	Hazard ratio
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
NHS	National Health Service
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

From the [1]Laboratory of Public Health and Population Studies, Department of Molecular Medicine, University of Padua, Padua, Italy; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [3]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; [4]Friuli-Venezia Giulia Regional Health Information System, Informatica per il Sistema degli Enti Locali (INSIEL) S.p.A.; and [5]Epidemiological Service, Health Directorate, Friuli Venezia-Giulia Region, Udine, Italy

Supported by the University of Padua (year 2013, F.S. 4.18.01.05 [to C.C.]). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.02.058

Methods

The study was conducted on the FVG region (located in North-East Italy), which has a population of about 1.2 million and approximately 10 000 births a year. The study population consisted of 213 635 subjects (excluding abortions, stillbirths, and neonatal deaths within 30 days of birth) born and resident in the Region in the period 1989-2011. Subjects were identified using the regional Medical Birth Register that includes all hospital and home deliveries and contains sociodemographic data on the parents, details of the pregnancy, labor, and delivery, as well as data on the newborn child.

Italy has a tax-based National Health Service (NHS), which is organized at a regional level and provides universal coverage to all Italian and European Union citizens resident in the country, regardless of income. FVG is covered by a regional integrated healthcare system developed in the 1980s with the goal of automatically collecting and pooling data on healthcare funded by the NHS using a unique regional identification code that has been described in detail previously.[14]

In this study, we used the following health data (up to December 31, 2012): mortality records; pathology reports from all the pathology departments in the Region, coded in the Systematized Nomenclature of Medicine; hospital discharge records collected during episodes of inpatient care occurring within or outside the Region with up to 6 diagnostic codes in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM); exemption from healthcare copayment coded in a national coding system; drug prescription records coded in the Anatomical Therapeutic Chemical (ATC) Classification System (available from 1995).

This retrospective study was approved by the Institutional Review Board of the University of Padua (Italy) that funded the project. No informed consent and no Ethics Committee approval were required because this record linkage study was based on computerized databases of medical records, and all data were deidentified prior to analysis.

We defined CD as having at least 1 of the following[14]: a pathology report of villous atrophy (Systematized Nomenclature of Medicine codes D6218, D6318, M58, M58005, M58006, and M58007); a hospital discharge record with an ICD-9-CM code 579.0 in any diagnosis; an exemption from healthcare copayment with code I0060 according to the Italian national coding system. In Italy, all patients with CD can obtain clinical tests and gluten-free food free of charge from the NHS, provided they have a biopsy-verified CD diagnosis. CD onset was defined as the earliest date identifiable in the 3 sources of information (pathology, hospital admission, and copayment exemption).

Follow-Up for Autoimmune Diseases

We identified individuals with T1DM as those having at least 1 hospital discharge record with a code for diabetes mellitus (ICD-9-CM 250) in any diagnosis or 1 prescription of insulin (ATC A10A). Even though this algorithm cannot distinguish between T1DM and type 2 diabetes mellitus (T2DM), T1DM accounts for roughly 92% of all cases of diabetes among Italian individuals <18 years of age,[15] therefore, misclassification of subjects with T2DM as T1DM is considered negligible.

AH+ was defined as having at least 1 hospital inpatient diagnosis of thyrotoxicosis with or without goiter (ICD-9-CM 242) or 1 prescription of antithyroid preparations (ATC H03BB). The only prescribed antithyroid preparation in our data was thiamazole (ATC H03BB02). AH− was defined as having at least 1 hospital inpatient diagnosis of thyroiditis (ICD-9-CM 245) or 1 prescription of thyroid hormones (ATC H03AA). The only prescribed thyroid hormone was levothyroxine (ATC H03AA01). The same hospital discharge and drug prescription codes have been previously used in a validation study.[16]

The time of onset for each of the 3 diseases was considered as the earliest date identifiable in the 2 sources (hospital records, drug prescription data). The co-occurrence of T1DM, AH+, and AH− was also evaluated.

Data Analyses

We used a matched cohort design in the primary analysis and a case-control design in a secondary analysis (**Figure**; available at www.jpeds.com). For each case with a CD diagnosis, 5 reference individuals (from hereon, references) were selected from subjects in the Medical Birth Register (live birth, after merging with mortality records) on the date of CD diagnosis (index date), matched for sex and year of birth. Matching was implemented to control for confounding and improve statistical efficiency. Follow-up started 15 days after the index date (in order to exclude simultaneous diagnoses) and ended at the earliest of end of the study (December 31, 2012), death, migration out of the area, or first diagnosis of any of the 3 autoimmune disorders separately for each outcome in analyses. Analyses were restricted to subjects with index date ≥1995 (because drug prescription data are available from that year). In the main analysis, separately for each outcome analyses, we excluded subjects with autoimmune diagnoses prior to study entry (index date). Cox regression models were used to estimate the HRs and 95% CIs for each of the outcome in patients with CD compared with references within the same stratum (ie, an individual with CD was only compared with his or her age-matched reference individuals). The risk estimate for each outcome was first estimated for each stratum and then summarized to an overall HR. The assumption of proportional hazards was investigated by studying graphs over the log cumulative hazards function and the Shoenfeld residuals, and verified by a global test of rho.

In sensitivity analyses, we excluded the first year of follow-up to better separate CD and other associated outcomes occurrence, and we also adjusted for maternal education. To increase the specificity of T1DM definition, we included only cases diagnosed before the age of 18 years.