Risk of Fractures in Youths with Celiac Disease—A Population-Based Study

Cristina Canova, PhD[1], Gisella Pitter, MD[1], Loris Zanier, MD, PhD[2], Lorenzo Simonato, MD[1], Karl Michaelsson, MD[3], and Jonas F. Ludvigsson, MD, PhD[4,5,6,7]

Objective To assess the risk of any fracture requiring hospital care in a cohort of individuals with celiac disease diagnosed in childhood/adolescence compared with reference individuals matched by age and sex.

Study design Our study cohort consisted of 213 635 people born and residing in Friuli-Venezia Giulia Region, Italy, in 1989-2011. We selected, through pathology reports, hospital discharge records, or co-payment exemptions, 1233 individuals with celiac disease (aged 0-17 years at diagnosis) and compared them with 6167 reference individuals matched by sex and year of birth. Fractures were identified through hospital discharge records. We calculated hazard ratios (HRs) for any fracture after celiac disease diagnosis (or index date for reference individuals) with Cox regression and ORs for any fracture before celiac disease diagnosis with conditional logistic regression.

Results During the follow-up period (maximum 23 years), 22 individuals with celiac disease (9394 person-years) and 128 reference individuals (47 308 person-years) experienced a fracture, giving an overall HR of 0.87 (95% CI 0.55-1.37). The risk was not modified by sex, age at diagnosis, or calendar period of diagnosis. We obtained similar HRs when excluding fractures occurring after the age of 18 years and adjusting for maternal education or vitamin D supplementation. The odds of previous fracture also did not differ between subjects with celiac disease and reference individuals (22 and 96 cases, respectively: OR 1.15; 95% CI 0.72-1.84).

Conclusions We did not find any evidence of an increased risk of fractures during childhood and youth among patients with celiac disease. *(J Pediatr 2018;■■:■■-■■).*

Celiac disease is a life-long small intestinal disorder that is triggered by exposure to gluten in genetically sensitive individuals.[1] It is characterized by small intestinal inflammation with villous atrophy and occurs in about 1% of the white population.[2-5]

Given the mucosal abnormalities and ongoing inflammation, many patients present with signs of malabsorption,[1] which may lead to vitamin D deficiency and low bone mineral density. Cohort studies have shown that low bone mineral density may increase the risk of fractures in childhood and adolescence.[6,7] A number of large-scale studies have found an increased prevalence of celiac disease in patients with osteoporosis.[8-12] Such data can guide screening principles[13] but will not help inform patients with diagnosed celiac disease on their risk of future fractures. Finnish researchers[14] pooled data from 15 studies reporting a 30% increased risk of any fracture and a 69% increased risk of hip fractures. However, several of the studies were based on self-reported data and adopted a cross-sectional or case-control design.[14] Results from the few available prospective studies have been less consistent.[15-18]

Because most available literature involved adult populations, it is unknown whether children and adolescents with celiac disease also have a greater probability of subsequent fractures compared with their peers. A large prospective study[17] (roughly 3 times larger than all the other prospective studies combined[15,16,18-20]) showed an increased risk of hip fracture (hazard ratio [HR] 2.6, 95% CI 1.1-6.2) but only a borderline-significant relative risk of any fracture (HR 1.1, 95% CI 1.0-1.2) in people diagnosed with celiac disease during childhood.[17] Most fractures occurred during adulthood, and patients with celiac disease in this study were restricted to inpatients with potentially a more severe type of celiac disease than the average child.[17] We used longitudinal population-based data from the Friuli-Venezia Giulia (FVG) region to examine the risk of any fracture during childhood and adolescence in >1200 patients diagnosed with celiac disease.

FVG	Friuli-Venezia Giulia
HR	Hazard ratio

From the [1]Department of Cardiological, Thoracic and Vascular Sciences, University of Padua, Padua; [2]Epidemiological Service, Health Directorate, Friuli Venezia-Giulia Region, Udine, Italy; [3]Department of Surgical Sciences, Uppsala University, Uppsala; [4]Department Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm; [5]Department of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden; [6]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom; and [7]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Supported by the University of Padua (F.S. 4.18.01.05 [to C.C.]); the funding source had no role in study design, data collection, analysis and interpretation, or writing of the paper. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.02.070

Methods

We examined 213 635 individuals born and residing in the region of FVG in northern Italy between 1989 and 2011. Study participants were identified through the regional Medical Birth Register, which contains information from all hospital and home deliveries in the region. The regional healthcare system in FVG was initiated in the 1980s and aims to collect and pool data on healthcare funded by the National Health Service.[21]

Celiac disease was defined as having at least 1 of the following[21]: a pathology report indicating villous atrophy (SnoMed codes D6218, M58, M58005, M58006, and M58007); a hospital discharge record (*International Classification of Diseases, Ninth Revision, Clinical Modification* code = 579.0); or celiac disease–specific exemption from healthcare copayment (code I0060) according to the national coding system in Italy. We used the earliest date identifiable for celiac disease diagnosis as proxy for disease onset; information was retrieved from 3 sources: pathology, hospital admission, and copayment exemption. We restricted all analyses to individuals with celiac disease diagnosed at <18 years of age.

First, "any fracture" was defined as having a hospital discharge record (*International Classification of Diseases, Ninth Revision, Clinical Modification* code) of 800-829. For each patient with celiac disease, we selected 5 reference individuals from the Medical Birth Register. Reference individuals had to be alive on the date when the matched index individual with celiac disease had received his/her diagnosis. Other matching criteria were sex and birth year. Follow-up began on the date of celiac disease diagnosis (and corresponding date in reference individuals, ie, study entry) and until end of the study (December 31, 2012), death, migration out of the area, or first hospital admission with any fracture, whichever occurred first.

In the analysis of any subsequent fracture, we only examined individuals without a previous fracture. Matched Cox regression was used to estimate HRs and 95% CIs for any fracture subsequent to study entry. Individuals with celiac disease were only compared with references within the same stratum and then a summary HR was calculated. The proportional hazards assumption was examined by studying graphs over the log cumulative hazards function and the Schoenfeld residuals and verified by a global test of rho. In sensitivity analyses, we adjusted for maternal education and for vitamin D supplementation (any vitamin D prescribed, Vitamin A and D in combination [ATCA11CB], Vitamin D and analogues [A11CC]). Finally, we also estimated HRs for having a fracture before the 18th birthday (fracture risk in childhood). The analyses also were stratified by sex, age at celiac disease diagnosis (we used the median age at celiac disease diagnosis as the cut-off: ≤ 5, ≥6 years), and year of celiac disease diagnosis (1989-2004, 2005-2012).

To study the temporal relationship between celiac disease and hospital admission with fracture, we carried out a conditional logistic regression to calculate ORs for having a fracture before study entry. This means that we included incident cases of fractures before celiac disease diagnosis in this latter sensitivity analysis. Statistical analyses were performed with SAS software (version 9.2, SAS Institute, Cary, North Carolina).

The study was approved by the institutional review board of the University of Padua (Italy). Patient data were anonymized and deidentified before analysis. Therefore, no informed consent and no ethics committee approval were required.

Results

Overall, 1233 subjects with celiac disease and 6167 matched references were included in the study (**Table I**) Biopsy confirmation was available for 883 (72%) of the individuals with celiac disease, and 933 (76%) were identified by at least 2 data sources. Median age at celiac disease diagnosis was 6 years (range: 0-17 years); 60% the study participants were female.

During follow-up until maximum age of 23 years, there were 22 fractures in individuals with celiac disease compared with 128 in matched references during 9394 and 47 308 person-years, respectively. This corresponded to incidence rates of 234 and 271 per 100 000 person-years. Individuals with celiac disease were therefore not at increased risk of later fracture (HR 0.87; 95% CI 0.55-1.37) (**Table II**). Sensitivity analyses showed that HR was similar after adjustment for vitamin D supplementation (HR 0.83; 95% CI 0.52-1.33) or maternal education (HR 0.87; 95% CI 0.55-1.37). When we restricted our analysis to fractures occurring before the age of 18 years, risk estimates remained similar (HR 0.95; 95% CI 0.59-1.51) (**Table II**).

Table III shows risk estimates stratified by sex and by age and calendar period at celiac disease diagnosis (index date for references). Risk of any hospitalized fracture did not differ in any of the subgroups. Of 1233 individuals with celiac disease, 22 (1.78%) had an earlier hospitalization for any fracture compared with 96 of 6167 references (1.56%). Individuals with celiac disease were hence not at increased risk of fracture before the diagnosis of celiac disease (OR 1.15; 95% CI 0.72-1.84).

Table I. Characteristics of the study participants

Characteristics	Celiac disease n (%)	References n (%)
Total	1233	6167
Sex		
Male	491 (39.8)	2451 (39.7)
Female	742 (60.2)	3716 (60.3)
Age at celiac disease diagnosis, y		
≤5	660 (53.5)	3300 (53.5)
6+	573 (46.5)	2867 (46.5)
Year of celiac disease diagnosis		
1989-2004	548 (44.4)	2740 (44.4)
2005-2012	3427 (55.6)	3427 (55.6)
Maternal education*		
Up to 8th grade	445 (36.5)	2450 (40.3)
9th-13th grade	616 (50.6)	2842 (46.7)
University	157 (12.9)	788 (13.0)
At least 1 vitamin D prescription*	83 (6.7)	291 (4.7)

Up to 8th grade: primary/middle school; 9th-13th grade: secondary school.
*χ^2 $P < .05$.

FLA 5.5.0 DTD ■ YMPD9849_proof ■ April 19, 2018