Celiac Disease Does Not Influence Fracture Risk in Young Patients with Type 1 Diabetes

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Objectives To examine the risk of any fractures in patients with both type 1 diabetes (T1D) and celiac disease (CD) vs patients with T1D only.

Study design We performed a population-based cohort study. We defined T1D as individuals aged ≤30 years who had a diagnosis of diabetes recorded in the Swedish National Patient Register between 1964 and 2009. Individuals with CD were identified through biopsy report data between 1969 and 2008 from any of Sweden's 28 pathology departments. Some 958 individuals had both T1D and CD and were matched for sex, age, and calendar period with 4598 reference individuals with T1D only. We then used a stratified Cox regression analysis, where CD was modeled as a time-dependent covariate, to estimate the risk of any fractures and osteoporotic fractures (hip, distal forearm, thoracic and lumbar spine, and proximal humerus) in patients with both T1D and CD compared with that in patients with T1D only.

Results During follow-up, 12 patients with T1D and CD had a fracture (1 osteoporotic fracture). CD did not influence the risk of any fracture (adjusted hazard ratio = 0.77; 95% CI = 0.42-1.41) or osteoporotic fractures (adjusted hazard ratio = 0.46; 95% CI = 0.06-3.51) in patients with T1D. Stratification for time since CD diagnosis did not affect risk estimates.

Conclusion Having a diagnosis of CD does not seem to influence fracture risk in young patients with T1D. Follow-up in this study was, however, too short to ascertain osteoporotic fractures which traditionally occur in old age. *(J Pediatr 2016;169:49-54)*.

Celiac disease (CD), an autoimmune, malabsorptive condition induced by gluten ingestion in genetically at-risk individuals, is associated with osteopenia as well as increased risks of hip and other types of fractures.[1,2] Pretreatment serum vitamin D and other nutrient markers such as iron, prealbumin, and folate are significantly lower in individuals with CD with villous atrophy (vs Marsh I-II histology),[3] and similarly osteopenia in CD appears to correlate with the degree of histologic severity,[4] evidenced by a greater frequency of osteopenia seen in the setting of villous atrophy rather than in potential CD where small bowel inflammation is absent.[5,6] Although malabsorption, disturbances in parathyroid hormone secretion,[7-9] and a chronic inflammatory state[10,11] may be responsible for risks of bone fragility in untreated patients, bone mineral density (BMD) generally improves upon treatment of CD with a gluten-free diet (GFD),[12,13] particularly in children diagnosed with CD at a young age,[7] suggesting that underlying disturbances in bone mineralization may be corrected through reversal of malabsorption with treatment.

Individuals with type 1 diabetes (T1D) also are more commonly osteopenic than individuals without diabetes and have increased risk of fractures.[14,15] Explanations for osteopenia in this population are less apparent and are likely multifactorial, potentially as the result of urinary calcium loss[16,17] or even fragility due to insulinopenia in those with T1D.[18]

T1D shares its underlying genetics with CD,[19] and those with T1D have a significant risk of developing CD.[20-22] Simultaneous diagnosis with these conditions would imply a compounded increase of fracture among individuals with both CD and T1D. There is evidence in small groups of patients to support generally low BMD in young patients with T1D and CD autoimmunity,[23,24] although there are no current data to support whether the risk of fracture is increased beyond the baseline risks associated with each of these conditions independently. This population-based study aims to determine risks of bone fracture among individuals with both T1D and CD.

BMD	Bone mineral density
CD	Celiac disease
GFD	Gluten-free diet
HR	Hazard ratio
ICD	*International Classification of Diseases*
T1D	Type 1 diabetes

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Methods

We linked T1D data from the Swedish National Patient Register with nationwide histopathology data on CD by using a unique personal identifier assigned to all Swedish residents.[25] This project was approved by the Regional Ethical Review Board in Stockholm (2006/633-31/4).

T1D

We defined T1D as having an appropriate *International Classification of Diseases* (ICD) code between 1964 and 2009 according to the Swedish Patient Register[26] (ICD-7: 260, ICD-8: 250, ICD-9: 250, and ICD-10: E10). The identification of patients with T1D has been described in detail,[27] but in short Swedish government agencies identified 42 539 individuals with confirmed T1D and no data irregularities (eg, recording errors such as implausible dates of death). Because the Swedish ICD-7, -8, and -9 classifications did not distinguish between T1D and type 2 diabetes, we have in this, and in other similar projects,[27,28] defined T1D as having a diabetes diagnosis at ≤30 years of age. Type 2 diabetes is still infrequent in diabetes with early onset in Sweden.[29]

CD

Biopsy report data were collected from all 28 pathology departments in Sweden.[30] Although the collection of report data took place in 2006-2008, the biopsies per se had been performed in 1969-2008. We defined CD as having duodenal/jejunal villous atrophy (Marsh stage 3). After removal of duplicates and irregularities, we had data on 29 096 individuals with biopsy-verified CD (this dataset is identical to that in our previous paper on CD and mortality[30]). Previous validation has shown that the positive predictive value of villous atrophy is high (some 95% of individuals with villous atrophy have CD).[31]

Study Participants

Of 42 539 individuals with confirmed T1D, 960 (2.3%) had a diagnosis of CD before December 31, 2009. From the 41 579 individuals with T1D without a record of CD, we selected 4608 matched controls with T1D alone (5 controls per case with CD and T1D). We then excluded individuals with a fracture diagnosis before T1D onset. Hence, our study was based on 958 individuals with both T1D and CD and 4598 reference individuals with T1D only.

Data on Fractures

We used the Swedish Patient Register to identify fractures. Our main outcome measure was "any fractures" (the following ICD-10 codes and corresponding codes in ICD-7 to -9: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, and M80). In a subanalysis we also examined osteoporotic fractures (hip, distal forearm, thoracic and lumbar spine, and proximal humerus) (the following ICD-10-codes and corresponding codes in ICD-7 to -9: S72.0-2, S52.5-6, S22.0-1, S32.0, and S42.2).

Statistical Analyses

Cox regression analysis with CD modeled as a time-dependent covariate was used to estimate fracture risk in individuals with T1D and CD vs those with T1D only. We carried out analyses matched for age at T1D diagnosis, sex, and calendar period at T1D diagnosis. We started follow-up on the date of first T1D diagnosis and ended with first record of fracture, death, emigration, or end of study period (December 31, 2009), whichever happened first.

We examined risk of any fractures and of osteoporotic fractures according to years since CD diagnosis (follow-up <5 years, 5-<10 years, 10-<15 years, and ≥15 years). We calculated incidence rates by dividing the number of fractures with the number of person-years at risk. Given that the prevalence of both T1D[32] and CD[33] seemed to vary by country of birth, we adjusted our analysis for country of birth (Nordic vs not Nordic). We examined the risk of any fractures according to calendar year at T1D diagnosis (1964-1975, 1976-1987, 1988-1999, 2000-2009) as well as age at T1D diagnosis (0-9, 10-19, 20-30 years) (**Table I**). This age categorization was chosen because puberty in Swedish children seldom starts before age 10 years.

We also performed several sensitivity analyses to increase the specificity of T1D. First, through using data from the Prescribed Drug Register,[34] we excluded individuals with a record of oral antidiabetic medication (Anatomical Therapeutic Chemical Classification System codes A10B + A10X). Such individuals may have type 2 diabetes even when recorded as having an ICD-10 code of insulin-dependent diabetes (ICD-10: E10). Second, we used data from the Swedish Medical Birth Register[35] to exclude women who received their first diagnosis of T1D during pregnancy (0-9 months before delivery). Such women could suffer from gestational diabetes instead of T1D. In a third sensitivity

Table I. Characteristics of the study participants

	T1D and CD	T1D
Total	958	4598
Age at T1D diagnosis, y (median, range)	9, 0-30	9, 0-30
Age at T1D diagnosis, y, n (%)		
0-9	566 (59.1)	2653 (57.7)
10-19	261 (27.2)	1291 (28.1)
20-30	131 (13.7)	654 (14.2)
Age at end of study, median; range	21; 4-71	22; 2-71
Entry year, median; range	1996; 1964-2009	1997; 1964-2009
Follow-up years, median; range*	13; 0-46	12; 0-46
Age at CD diagnosis, median; range	12; 1-63†	
Females, n (%)	527 (55.0)	2511 (54.6)
Males, n (%)	431 (45.0)	2087 (45.4)
Calendar year		
1964-1975	101 (10.5)	477 (10.4)
1976-1987	152 (15.9)	745 (16.2)
1988-1999	345 (36.0)	1605 (34.9)
2000-2009	360 (37.6)	1771 (38.5)
Country of birth (Nordic), n (%)	950 (99.2)	4460 (97.4)
Gestational diabetes, n (%)	15 (1.6)	93 (2.0)
Oral antidiabetic medication, n (%)	19 (2.0)	138 (3.0)

*Follow-up time until death, emigration or Dec 31, 2009 (whichever occurred first).
†Ages were rounded to the nearest year. The youngest patient with CD was otherwise diagnosed at 0.64 months of age.