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

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Abstract

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 1964–2009. Individuals with CD were identified through biopsy report data between 1969–2008 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 4,598 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.

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The authors declare no conflicts of interest.

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.

Keywords

Celiac disease; type 1 diabetes; bone mineral density; gluten-free diet

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} Pre-treatment serum vitamin D and other nutrient markers such as iron, prealbumin, and folate are significantly lower in CD individuals with villous atrophy (versus Marsh I–II histology)³ and similarly osteopenia in CD appears to correlate with the degree of histologic severity⁴, 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 age⁷, 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 non-diabetic individuals and have increased risk of fractures.^{14, 15} Explanations for osteopenia in this population are less apparent and are likely multifactorial, potentially due to urinary calcium loss^{16, 17} or even fragility due to insulinopenia in those with T1D.¹⁸

T1D shares its underlying genetics with CD¹⁹, 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}, though 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.

METHODS

We linked T1D data from the Swedish National Patient Register with nationwide histopathology data on CD 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).

Type 1 Diabetes

We defined T1D as having an appropriate international classification of disease (ICD) code between 1964 and 2009 according to the Swedish Patient Register²⁶ (ICD-7: 260, ICD-8: 250, ICD-9: 250 and ICD-10: E10). The identification of patients with T1D has been

described in detail²⁷, 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

Celiac Disease

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 data set is identical to that in our earlier paper on CD and mortality³⁰). Earlier validation has shown that the positive predictive value of villous atrophy is high (some 95% of individuals with villous atrophy have CD).³¹

T1D Celiac Disease

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 4,608 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 4581 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 ICD7-9: 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-7-9: 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 dividing the number of fractures with the number of person-years at risk. Given that the prevalence of both T1D³² and CD³³ 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 in order to increase the specificity of T1D. First, through using data from the Prescribed Drug Register³⁴ we excluded individuals with a record of oral anti-diabetic medication (ATC codes A10B+A10X). Such individuals may have type 2 diabetes even when recorded as having an ICD-10 code of insulin-dependent diabetes (ICD10: E10). Secondly, we used data from the Swedish Medical Birth Register³⁵ 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 analysis, we restricted study participants to those having an inpatient diagnosis of T1D.

RESULTS

Some 55% of participants were female, and most were diagnosed with T1D after 1988 (Table I). The median age at T1D diagnosis was 9 years, and the median age at CD diagnosis was 12 years. During a median follow-up of 13 years we identified 17 fractures (1.8%) in patients with both CD and T1D vs. 108 (2.3%) in patients with T1D only (ratio=0.78). Of the 17 celiac fractures, 12 occurred after CD diagnosis and were hence included in the time-dependent Cox regression. These fracture locations included: femur (3), tibia or lower leg (3), metatarsal (1), skull (1), multiple lower extremity fractures (1), os pubis (1), cervical spine (1), and distal radius (1).

Overall fracture risk in relation to CD duration

Among individuals with T1D, CD did not influence the risk of future fractures [adjusted Hazard Ratio (HR)= 0.77; 95%CI=0.42–1.41]. The risk estimates were independent of follow-up time (Table II). HRs for fractures were slightly lower in males with CD (HR=0.61) than in females with CD (HR=1.09) but 95% CIs were overlapping. Due to lack of future fractures among individuals with T1D and CD we were unable to calculate HRs for the first two calendar periods, but in the two most recent calendar periods (1988 and onwards), risk estimates were almost identical (HR=0.96 and 0.92) (Table III). Similarly lack of individuals with T1D diagnosed after the age of 20 years with concomitant CD, HRs for fractures could not be calculated for that age strata. For younger individuals HRs were similar. Adjusting for country of birth did not change our risk estimates (data not shown).

Sensitivity analyses

Restricting our dataset to individuals with T1D without any record of oral anti-diabetic medication did not influence our risk estimate (adjusted HR=0.78; 95%CI=0.43–1.42). Neither did the HR change when we excluded individuals with a record of gestational diabetes at some time (adjusted HR=0.77; 95%CI=0.42–1.40), or when we only looked at individuals with an inpatient diagnosis of T1D (adjusted HR=0.77; 95%CI=0.42–1.40). Expanding our analyses to include the five fractures occurring prior to diagnosis with CD

(and modeling CD as a fixed covariate and not as a time-dependent covariate) resulted in a nearly identical HR to that found when these fractures were excluded (adjusted HR=0.73; 95% CI 0.44–1.22).

Osteoporotic fractures

Only one of the 12 celiac fractures was classified as an osteoporotic fracture. Individuals with T1D and CD were hence at no increased risk of osteoporotic fractures compared with individuals with T1D only (HR=0.46; 95% CI=0.06–3.51).

DISCUSSION

This population-based study compared fracture risk between individuals with T1D and those with both CD and T1D, and demonstrates that risk of fracture is not increased in young patients with T1D with the additional diagnosis of CD. Further, duration of time with CD did not impact fracture risk estimates among those with T1D. These findings are surprising given that fracture risk has been independently associated with both of these conditions.

We performed a separate analysis which included those fractures which had occurred prior to diagnosis with CD, as these individuals may have had undiagnosed CD at the time of sustaining the fracture. Incorporating these fractures did not change fracture risk estimates for those with CD and T1D. This is likely because including these fractures resulted in more follow-up time being assigned to those with CD, rather than initiating follow-up at the time of CD diagnosis.

The median age of patients with T1D and CD and T1D alone may explain the lack of fracture risk associated with the additional diagnosis of CD. Younger patients with T1D are more likely to be diagnosed with CD^{36, 37} and given the typical age at diagnosis with T1D, patients followed in this study were overwhelmingly young at study entry. Zanchi et al demonstrated that children diagnosed with CD at a younger age showed the most robust BMD recovery versus older children and adolescents.⁷ Even though vitamin deficiencies, presumably the result of malabsorption, are common in CD at diagnosis and may contribute to fracture risk^{3, 38}, despite the initially depressed BMD³⁹, following treatment with a GFD both adults and young patients with CD will show improvements in BMD.^{12, 13} Risks of falls⁴⁰ and bone loss⁴¹ increase with age, resulting in the overwhelming majority of osteoporotic fractures occurring in the elderly, particularly women.⁴² At least 90% of bone mineral content is accrued by age 18 years⁴³, allowing younger patients with BMD deficits greater opportunity for recovery. Jafri et al demonstrated a direct relationship between age at diagnosis with CD and fracture risk over a 50-year follow-up period⁴⁴, suggesting that there may be a window of time during which BMD recovery in young individuals with CD may protect from future fracture risk.

Although recovery of BMD following treatment has been reported in those with CD, concerning those with T1D alone, there is no direct evidence that fracture risk changes in any respect with duration of disease. Although those with more complicated T1D appear to have greater fracture risk⁴⁵ and more disease complications may be an indirect indication of duration of disease in some cases⁴⁶, BMD does not necessarily improve after diagnosis with

T1D (for example, osteopenia in children and adolescents with T1D does not appear to be related to glycemic control¹⁶). Further, as in CD, it may be more difficult to improve bone mineralization in T1D as time after diagnosis elapses.⁴⁷

Increased vigilance for the development of CD among those with T1D may impact fracture risk among these patients, given that timely detection of CD facilitated through screening may prevent longstanding disease associated with greater nutritional compromise. Fracture risk among adults with CD is increased in those with undiagnosed or undertreated CD.⁴⁸ Although individuals with CD are at increased risk of later developing T1D⁴⁹ approximately 85% of those with T1D and CD will develop T1D first⁵⁰, implying that these individuals will subsequently be subject to increased medical surveillance. Those with T1D are often explicitly screened for CD as a part of routine care, reducing the likelihood that CD may develop unnoticed.

This study has several limitations. Even though the advantages of using a population-based approach are clear, the drawbacks are a lack of detailed information about individual patients. We were not able to verify how strictly patients with CD adhered to a GFD, although an earlier patient chart review of a random subset of individuals with villous atrophy found that 15/86 (17%) had evidence of poor adherence.³¹ Nor do we know how tightly controlled blood glucose was for those with T1D, though glucose control has not been shown to be a factor in bone loss among those with T1D. We also do not have detailed data regarding supplement use, such as non-prescription calcium and vitamin D or access to baseline serum levels of vitamin D, B vitamin levels, or other nutritional markers, data which may have clarified subgroups at greater risk of fracture.^{3, 38} In addition, low coverage of the Patient Registry prior to 1988 may have resulted in an underestimate of fracture incidence in this population. Given this consideration, the limited number of fracture events noted is an additional limitation. Further, hospital-based outpatient data were added to the Registry in 2001, so follow-up occurring prior to this point may also have led to an underestimate of fracture incidence. There is also a possibility that many patients with T1D alone actually had undiagnosed CD, potentially resulting in an overestimation of fracture risk among those with T1D alone. Lastly, although duration of follow-up was considerable for many individuals (up to 46 years), follow-up time was limited for other patients (median 13 years). So even though the young age of our study population gives insight into the fracture risk of young patients, when considering long term fracture risks our results should be interpreted with some caution.

Despite the inherent limitations of a nationwide study, this study provides insight into fracture risk for young patients with two potentially debilitating chronic conditions. Although fracture risk does not worsen in patients with T1D following diagnosis with CD, such risks do persist with time, despite treatment for both diseases. Patients with T1D, with or without CD, must be monitored for signs of compromised bone density to optimize nutritional and pharmacologic measures to prevent fractures.

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Abbreviations

BMD	Bone mineral density
BMI	Body mass index
CD	Celiac disease
CI	Confidence Interval
GFD	Gluten-free diet
HR	Hazard ratio
ICD	International Classification of Disease (codes)
IGF	Insulin-like growth factor
T1D	Type 1 diabetes
VA	Villous atrophy

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Table 1

Characteristics of the Study Participants

	Type 1 Diabetes and Celiac Disease	Type 1 Diabetes
Total	958	4598
Age at T1D diagnosis, years (median, range)	9, 0–30	9, 0–30
Age at T1D diagnosis		
<i>Age 0–9 (%)</i>	566 (59.1)	2653 (57.7)
<i>Age 10–19 (%)</i>	261 (27.2)	1291 (28.1)
<i>Age 20–30 (%)</i>	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 (%)	527 (55.0)	2511 (54.6)
Males (%)	431 (45.0)	2087 (45.4)
Calendar year		
<i>1964–1975</i>	101 (10.5)	477 (10.4)
<i>1976–1987</i>	152 (15.9)	745 (16.2)
<i>1988–1999</i>	345 (36.0)	1605 (34.9)
<i>2000–2009</i>	360 (37.6)	1771 (38.5)
Country of birth (Nordic)	950 (99.2)	4460 (97.4)
Gestational diabetes	15 (1.6)	93 (2.0)
Oral anti-diabetic medication	19 (2.0)	138 (3.0)

* Ages were rounded to the nearest year. The youngest patient with celiac disease was otherwise diagnosed at 0.64 months of age.

Follow-up time until death, emigration or Dec 31, 2009 (whichever occurred first).

Risk of fracture in type 1 diabetes and celiac disease in relation to time since celiac disease diagnosis.

Table 2

Follow-up	CD - observed fractures	CD - expected fractures [†]	Hazard ratios, 95% CI*	P-value	Absolute risk/100,000 PYAR	#Excess risk/100,000 PYAR
Overall	12	16	0.77; 0.42–1.41	0.398	140	-41
Year <5	4	6	0.68; 0.30–1.54	0.353	101	-48
5-<10	4	5	0.86; 0.31–2.35	0.765	159	-26
10	4	4	1.12; 0.27–4.66	0.880	192	20

CD, celiac disease; HR, hazard ratio; CI, confidence interval; PYAR, person-years at risk.

[†] Reference group refers to individuals with type 1 diabetes without celiac disease.

* Adjusted for age, sex and calendar period (see text).

Table 3
Subgroup analyses. Celiac disease in patients with type 1 diabetes and risk of fracture.

Subgroup	CD - observed fractures	CD - expected fractures	Hazard ratios, 95% CI adjusted	P-value	Absolute risk/100,000 PYAR	Excess risk/100,000 PYAR
<i>Sex</i>						
Males	6	5	1.09; 0.46–2.61	0.845	122	10
Females	6	10	0.61; 0.26–1.40	0.244	165	-106
<i>Age at T1D diagnosis</i>						
0–9 yrs	10	13	0.79; 0.40–1.53	0.477	197	-53
10–19 yrs	2	3	0.62; 0.15–2.64	0.519	91	-56
20–30 yrs			NC			
<i>Calendar period</i>						
1964–1975			NC			
1976–1987			NC			
1988–1999	8	8	0.96; 0.45–2.04	0.917	226	-9
2000–2009	4	4	0.92; 0.32–2.66	0.876	204	-18

CD, celiac disease; HR, hazard ratio; CI, confidence interval; PYAR, person-years at risk. NC, Not calculated. Because of few events in these categories we were unable to calculate HRs.