Persistent Mucosal Damage and Risk of Fracture in Celiac Disease

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Context: Celiac disease (CD) is associated with an increased fracture risk, an increase that persists after diagnosis. A significant proportion of patients with CD have persistent villous atrophy (VA) on follow-up biopsy.

Objective: The objective of the study was to determine whether persistent VA impacts long-term fracture risk.

Design: This was a cohort study.

Setting and Patients: We identified all patients in Sweden with histological evidence of CD who underwent a follow-up biopsy and compared patients with persistent VA with those with mucosal healing.

Main Outcome Measures: The following were measured: 1) any fracture; 2) likely osteoporotic fracture (defined as fractures of the hip, distal forearm, thoracic and lumbar spine, or proximal humerus); and 3) hip fracture.

Results: Of 7146 patients, VA was present on follow-up biopsy in 43%. There was no significant association between persistent VA and overall fractures [hazard ratio (HR) of persistent VA compared with those with healing 0.93, 95% confidence interval (CI) 0.82–1.06] or with likely osteoporotic fractures (HR 1.11, 95% CI 0.84–1.46). Persistent VA was associated with an increased risk of hip fracture (HR 1.67, 95% CI 1.05–2.66). Hip fracture risk increased, depending on the degree of VA (HR for partial VA compared with those with healing 1.70, 95% CI 0.82–3.49, HR for subtotal/total VA compared with those with healing 2.16, 95% CI 1.06–4.41).

Conclusions: Persistent VA on follow-up biopsy is predictive of hip fracture risk. The association between persistent VA and hip fractures, but not fractures overall, implies that thinner sc tissue and fall or trauma may be mechanisms by which persistent VA confers an increased fracture risk. **(*J Clin Endocrinol Metab* 99: 609–616, 2014)**

Celiac disease (CD), a multisystem autoimmune disease, is associated with osteoporosis (1). Multiple studies have shown that this association translates into an increased risk of fracture (2–9). The mean age of first fracture is similar in patients with CD and the general population, but the overall rate of fractures is greater in CD patients (2). For this reason, screening for osteoporosis is recommended among patients with newly diagnosed CD (10). Unlike other complications of CD, such as increased mortality risk (11) and the incidence of gastrointestinal

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Abbreviations: BMD, bone mineral density; CD, celiac disease; CI, confidence interval; HR, hazard ratio.

malignancy (12), increments in risk that decrease in the years after the diagnosis of CD, the higher fracture risk may persist in CD patients. Data on this long-term risk are, however, conflicting. Some studies show a persistent long-term fracture risk (2, 3), whereas others found that the risk is confined to the peridiagnosis time period (4, 5, 9) or among those with admitted nonadherence to the gluten-free diet (4).

The heterogeneity of findings regarding the long-term fracture risk in CD may be in part attributable to factors that have previously not been taken into account, such as variable rates of mucosal healing. The characteristic histological finding in CD, duodenal villous atrophy, recedes after patients commence the gluten-free diet. Rates of mucosal healing, however, vary considerably in the literature (13–19). Persistent villous atrophy can be seen, even when CD serologies have normalized (14–16, 19, 20), and may in some cases be a more sensitive indicator of poor adherence to the gluten-free diet (14, 16, 19). Although persistent villous atrophy does not impact overall mortality in CD (21), it may have an effect on morbidity. One study of 15 asymptomatic CD patients with persistent villous atrophy found that this group had higher rates of osteoporosis than patients with CD who achieved mucosal healing (22). It is unknown whether this translates into an increased fracture risk and whether the follow-up biopsy can be used to risk stratify CD patients regarding their risk of subsequent fracture. Moreover, different fracture types have variable strengths in the correlation to bone mineral density (BMD); whereas BMD measured by dual-energy X-ray absorptiometry best predicts fracture risk at the site of measurement, BMD measured at one site predicts all fractures, including hip fracture (23, 24). Because the higher fracture risk in CD patients is probably mainly mediated by lower BMD (25), fracture type needs to be considered.

In this study, we aimed to determine whether persistent villous atrophy, as compared with mucosal healing, is associated with an increased risk of fracture, including type of fracture, among patients with CD undergoing a follow-up biopsy.

Materials and Methods

Subjects

We performed an analysis of a database of patients with histologically confirmed CD diagnosed at all (n = 28) pathology departments in Sweden between July 1969 and February 2008. The details of this database have been described elsewhere (11, 26). In brief, patients were identified in each pathology department via SnoMed codes corresponding to villous atrophy (Marsh class 3) (27). An earlier validation study found that this method corresponded to a clinical diagnosis of CD in 95% of cases and that Swedish pathologists classified 90% of all biopsy samples with villous atrophy correctly (26). We then identified all patients who underwent a second small intestinal biopsy. To maximize the possibility that these second biopsies were done as a routine follow-up and were not done due to a change in clinical status, we restricted this data set to those patients who had their second biopsy between 6 months and 5 years after the initial CD diagnosis, as was done previously (21, 28). On follow-up biopsy, all specimens were classified as having villous atrophy (Marsh stage 3), inflammation (Marsh stages 1 and 2), and normal mucosa. As was performed in previous analyses regarding mucosal recovery, we considered any patient whose histology showed inflammation or normal mucosa as healed (21, 28).

Fracture classification

We excluded any patient with a history of fracture prior to the date of the follow-up biopsy. The three outcomes of interest were the development of the following: 1) any fracture; 2) classical osteoporotic fractures (29), consisting of fractures of the hip, distal forearm, clinical vertebral fractures of the thoracic and lumbar spine, and proximal humerus; and 3) hip fracture. The specification of fracture type was based on *International Classification of Diseases* codes (see Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Any inpatient or outpatient visit associated with one of these codes was included, with the exception of hip fractures, in which only inpatient visits associated with this code were considered because hip fracture is nearly universally associated with an inpatient hospital stay, and patients with an outpatient diagnosis of hip fracture, but no corresponding inpatient diagnosis, may suffer from misclassification (2). The analysis of likely osteoporotic fractures was limited to those patients whose follow-up biopsy occurred on or after January 1, 1997, when the *International Classification of Diseases*, 10th version, was introduced (30). For the analysis of hip fracture risk, any patient who had a history of a hip fracture prior to the follow-up biopsy was excluded (whereas patients with another type of fracture preceding this date were included).

Statistical analysis

We used Cox proportional hazards to measure for an association between persistent villous atrophy and any fracture, any classical osteoporotic fracture, and hip fracture. In this analysis, the observation time (ie, time at risk) started on the date of the follow-up biopsy and ended on the date of fracture, death, emigration, or December 31, 2009, whichever came first. We adjusted for age, gender, calendar period of the follow-up biopsy, the duration of CD at the time of the follow-up biopsy, and educational attainment. For children younger than 18 years, the higher educational attainment of either parent was used.

Because the risk of morbidity and mortality in CD changes over time (11, 12, 31), we tested the proportional hazards assumption by using time-dependent covariates to determine whether the risk of fracture changed during the following three prespecified time strata: less than 1 year, 1–5 years, and longer than 5 years after the follow-up biopsy. We also tested for an association between persistent villous atrophy and fracture risk stratified by gender.

Because risk factors for fracture may vary according to peak bone mass, we performed a post hoc analysis, measuring the risk of any fracture, likely osteoporotic fracture, and hip fracture,

stratified according to age. For that analysis, we tested for the association between persistent villous atrophy and these fractures among individuals younger than 25 and separately among individuals 25 years old and older.

For a subset of patients with villous architectural disturbance, histology was further quantified into partial vs subtotal/total villous atrophy. We therefore assessed for a dose-response effect between the degree of villous atrophy on the follow-up biopsy and the magnitude of subsequent fracture risk.

Hazard ratios (HRs) are reported with their corresponding 95% confidence intervals. All *P* values reported are two sided. All statistical calculations were done using SAS version 9.2 (SAS Institute). The study was approved by the Research Ethics Committee of the Karolinska Institutet.

Results

Of 29 096 patients with CD, 7648 (26%) underwent a follow-up biopsy between 6 months and 5 years after their initial CD diagnosis. After excluding 502 patients who had a fracture prior to the follow-up biopsy, 7146 patients remained (Table 1). The median (interquartile range) age of CD diagnosis was 23 (2–49) years and the median (interquartile range) age of follow-up biopsy was 25 (5–51) years. Nearly half of the patients (46%) were younger than 20 years at the time of follow-up biopsy. Most patients (64%) were female and 45% of patients had their follow-up biopsy between 1 and 2 years after the CD diagnosis. A previous analysis of this cohort found that those CD patients who had a follow-up biopsy differed somewhat from those who did not; they were diagnosed with CD at a younger age (mean 28.4 vs 33.4 y, $P < .0001$), and they had a slightly greater female predominance (63% vs 61%, $P = .0017$) (21).

Table 1. Characteristics of Patients Who Underwent Follow-Up Small Intestinal Biopsy 6 Months to 5 Years After Initial Diagnosis of Celiac Disease (n = 7146)

Characteristic	Number of patients (%)
Age at diagnosis, y	
0–19	3398 (48)
20–39	1271 (18)
40–59	1548 (22)
≥60	929 (13)
Male	2592 (36)
Female	4554 (64)
Interval between diagnosis and follow-up biopsy, y	
0.5–1	1856 (26)
Between 1 and 2	3235 (45)
2–5	2055 (29)
Calendar period of follow-up biopsy	
1989 or before	712 (10)
1990–1999	2796 (39)
2000 or after	3638 (51)
Education level	
< 2 y of high school	1849 (26)
2 y of high school	1435 (20)
3 y of high school	1542 (22)
College/university	2175 (30)
Unknown	145 (2)
Died during follow-up	481 (7)
Emigrated during follow-up	54 (0.8)
Developed fracture during follow-up	975 (14)
Developed hip fracture during follow-up	89 (1.2)

Patients were followed up for a median (interquartile range) of 10.3 (6.8–15.7) years after diagnosis and 8.6 (5.2–13.8) years after follow-up biopsy. More than 15 years of follow-up time were available for 1448 patients, 20% of the cohort. Most patients (51%) had a follow-up biopsy after the year 2000. In the analysis of likely osteoporotic fractures (which was limited to those patients whose follow-up biopsy occurred on or after January 1, 1997), 4669 patients remained, with a median follow-up time of 6.4 years, during which time 33 (0.7%) emigrated and 186 (4%) died. Of the 7146 patients who underwent follow-up biopsy, 3105 (43%) had persistent villous atrophy. As was reported previously, patients with subtotal or total villous atrophy on their initial diagnostic biopsy had a greater prevalence of persistent villous atrophy on follow-up (42%) than those who initially had partial villous atrophy at diagnosis (30%) (21).

All fractures

During the follow-up period, a fracture occurred in 975 patients (14%). The overall incidence of any fracture in this population was 1376 per 100 000 person-years of observation. The rate of any fracture, likely osteoporotic fracture, and hip fracture according to follow-up histology is shown in Table 2. There was no difference in risk of overall fracture when comparing those with persistent villous atrophy with those with mucosal recovery [adjusted HR 0.93, 95% confidence interval (CI) 0.82–1.06]. This null association was present in all prespecified time strata, and a test for interaction between follow-up histology and time with regard to fracture risk was not statistically significant ($P = .3$).

Likely osteoporotic fractures

When considering any osteoporotic fracture as the outcome, there were 220 events during the follow-up period, with 676 fracture cases per 100 000 person-years of observation. There was a nonsignificantly increased rate of likely osteoporotic fractures among those with persistent villous atrophy (HR 1.11, 95% CI 0.84–1.46). HRs for each fracture type (distal forearm, thoracic and lumbar spine, and proximal humerus) are shown in Supplemental Table 2; the association was greatest for fractures of the distal forearm (HR 1.19, 95% CI 0.84–1.69), although

Table 2. Risk of Any Fracture, Likely Osteoporotic Fracture, and Hip Fracture According to Follow-Up Duodenal Histology

	Any Fracture		Likely Osteoporotic Fracture		Hip Fracture	
	Number of Events/ PYO	Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]
Mucosal healing	492/34 409	1.0	124/20 617	1.0	26/37 925	1.0
Persistent villous atrophy	483/36 418	0.93 (0.82–1.06)	96/11 916	1.11 (0.84–1.46)	63/39 851	1.67 (1.05–2.66)[b]
Less than 1 y						
Mucosal healing	50/3999	1.0	11/3078	1.0	4/4284	1.0
Persistent villous atrophy	34/3076	0.95 (0.61–1.47)	16/1561	2.54 (1.15–5.61)[b]	3/3278	0.61 (0.14–2.75)
1–5 y						
Mucosal healing	181/14 276	1.0	61/10 914	1.0	9/15 578	1.0
Persistent villous atrophy	106/11 484	0.80 (0.62–1.02)	41/5659	1.06 (0.71–1.59)	15/12 394	1.36 (0.59–3.12)
More than 5 y						
Mucosal healing	261/16 134	1.0	52/6625	1.0	13/18 064	1.0
Persistent villous atrophy	343/21 858	1.0 (0.85–1.18)	39/4696	0.91 (0.60–1.39)	45/24 179	2.18 (1.17–4.05)[b]

Abbreviation: PYO, person-years of observation.

[a] Adjusted for age, gender, duration of celiac disease, calendar period, and educational attainment.

[b] $P < .05$.

the number of events (n = 142) was small. On time-stratified analysis, the increased risk of likely osteoporotic fracture was significant during the first year after the follow-up biopsy (HR 2.54, 95% CI 1.15–5.61) ($P = .08$ for the interaction between follow-up histology and time.)

Hip fractures

There were 89 hip fractures during the observation period, corresponding to a rate of 114 per 100 000 person-years of observation. Among those with persistent villous atrophy, the rate was 158 per 100 000 person-years of observation, and among those with mucosal healing, the rate was 69 per 100 000 person-years of observation. Persistent villous atrophy was associated with an increased risk of subsequent hip fracture (HR 1.67, 95% CI 1.05–2.66), yielding an absolute excess risk of 63 events per 100 000 person-years. There appeared to be a heterogeneous risk of hip fracture over time, with this increased risk confined to the period beyond 5 years after the follow-up biopsy (HR 2.18, 95% CI 1.17–4.05); interaction between follow-up histology and time with regard to hip fracture risk was not statistically significant ($P = .3$).

Stratified analyses

Risks stratified by gender are shown in Table 3. There was an interaction observed between gender and persistent villous atrophy with regard to the outcome of likely osteoporotic fractures (P for interaction .01). Although this association was nonsignificant among men with persistent villous atrophy, among women there appeared to be an association with likely osteoporotic fractures (HR 1.39, 95% CI 0.98–1.95). The increased risk of hip fracture was similar for men as well as women. The highest risk of hip fracture was seen among patients whose follow-up biopsy occurred before the year 1990; in that cohort, of 21 patients with a hip fracture, 19 occurred among those with persistent villous atrophy (HR 4.94, 95% CI 1.14–21.46). Apart from that association, the relationship between persistent villous atrophy and fracture risk did not vary by era.

On age-stratified analysis, the null association between persistent villous atrophy and overall fracture risk was similar among those younger than 25 years (HR 0.90, 95% CI 0.74–1.09) and those 25 years and older (HR 0.99, 95% CI 0.82–1.99). The association with likely os-

Table 3. Risk of Any Fracture, Likely Osteoporotic Fracture, and Hip Fracture Stratified by Gender

	Any Fracture		Likely Osteoporotic Fracture		Hip Fracture	
<rrt;row>Number of Events/ PYO		Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]
Men						
Mucosal healing	226/12 110	1.0	51/7217	1.0	9/13 718	1.0
Persistent villous atrophy	200/13 130	0.82 (0.67–1.00)	29/4614	0.75 (0.47–1.22)	26/14 683	1.63 (0.76–3.53)
Women						
Mucosal healing	266/22 298	1.0	73/13 400	1.0	17/24 208	1.0
Persistent villous atrophy	283/23 287	1.04 (0.88–1.24)	67/7302	1.39 (0.98–1.95)	37/25 168	1.67 (0.93–2.99)

Abbreviation: PYO, person-years of observation.

[a] Adjusted for age, gender, duration of celiac disease, calendar period, and educational attainment.

teoporotic fractures was null in the younger age group (HR 0.84, 95% CI 0.51–1.40), with a nonsignificantly increased risk in the older age group (HR 1.23, 95% CI 0.87–1.75). [Due to a low number of hip fractures in the younger age stratum (n = 4, all among patients with persistent villous atrophy), a separate risk estimate was not calculable; among patients 25 years old and older, there was a nonsignificantly increased risk of hip fracture in those with persistent villous atrophy (HR 1.51, 95%CI 0.95–2.42)]. The association between persistent villous atrophy and risk of hip fracture was largest among those in the age group 40–59 years (HR 2.10, 95% CI 0.67–6.58) as compared with those older than 60 years (HR 1.60, 95% CI 0.94–2.73), although the wide CIs limit the precision of these estimates.

When considering the subset of patients whose degree of villous atrophy was specified (Table 4), those with subtotal or total villous atrophy were at higher risk for hip fracture (HR 2.16, 95% CI 1.06–4.41) as compared with those with partial villous atrophy (HR 1.70, 95% CI 0.82–3.49).

Discussion

Fracture risk has been previously shown to be increased in patients with CD compared with the general population (2). This is the first study to our knowledge that evaluates fracture risk in CD according to follow-up histology. We found that patients with persistent villous atrophy on follow-up biopsy had an overall fracture risk that was comparable with those with mucosal healing but that their risk of hip fracture was significantly increased. We also found that the degree of villous atrophy was predictive of hip fracture risk, with the highest risk among patients with subtotal or total villous atrophy and a less prominent (and statistically nonsignificant) risk among those with partial villous atrophy.

Fracture risk is a significant consequence of CD, both in terms of the commonness of its occurrence and with regard to its associated morbidity. A recent cost-effectiveness analysis found that the risk of fracture in patients with CD is sufficiently costly to justify testing for CD among symptomatic at-risk individuals (32). Although most stud-

Table 4. Risk of Any Fracture, Likely Osteoporotic Fracture, and Hip Fracture According to Degree of Villous Atrophy

	Any Fracture		Likely Osteoporotic Fracture		Hip Fracture	
	Number of Events/ PYO	Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]	Number of Events/ PYO	Adjusted HR[a]
Mucosal healing	492/34 409	1.0	124/20 617	1.0	26/37 925	1.0
Partial villous atrophy	64/4809	0.75 (0.57–0.98)	28/3455	1.10 (0.72–1.68)	11/5359	1.70 (0.82–3.49)
Subtotal or total villous atrophy	86/4484	1.18 (0.93–1.48)	27/2425	1.39 (0.91–2.13)	11/5085	**2.16 (1.06–4.41)**[b]

Abbreviation: PYO, person-years of observation.

[a] Adjusted for age, gender, duration of celiac disease, calendar period, and educational attainment.

[b] $P < .05$.

ies have quantified an increased risk of fracture in CD (2–7), estimates are variable, with relative risks ranging from a 1.3-fold (3) to a 7-fold increased risk (6). This variability is due in part to differing lengths of follow-up, ascertainment of fracture history, and, according to one study, the degree of adherence to the gluten-free diet (4). Our results suggest that these heterogeneous results may partly be due to the type of fracture and the risk-stratifying effect of mucosal healing after the diagnosis of CD. In a Finnish study of patients with CD and persistent villous atrophy, osteoporosis developed in 58% of patients, as compared with 22% of patients with villous recovery (22). That study was based on a small sample (13 patients with persistent villous atrophy), using an outcome of osteoporosis as opposed to fracture. In another study of 40 newly diagnosed CD patients, the degree of villous atrophy at initial diagnosis correlated with bone density measurement of the lumbar spine (33). The results of the present study indicate that mucosal recovery on the follow-up biopsy can reduce the risk of the clinically significant outcome of hip fracture, the most devastating of all osteoporotic fractures. Hip fractures have a profound impact on societal costs and quality of life, with a low proportion of individuals regaining their prefracture level of function (34, 35). Moreover, a long-lasting higher mortality rate after hip fracture is well recognized (36, 37).

The risk-stratifying effect of follow-up histology was not constant over time. The risk of likely osteoporotic fractures was increased only in the first year after the follow-up biopsy date, with a null relationship in the time strata beyond 1 year. In contrast, the increased hip fracture risk was confined to the period 5 years after the follow-up biopsy. Moreover, the effect of follow-up histology was most pronounced among those who underwent follow-up biopsy before 1990. There are several plausible explanations for these heterogeneous time and era-varying risks. One possibility is that the risk of certain fractures, similar to other measurements of morbidity and mortality in CD, tends to be most pronounced in the early time period after diagnosis (11, 12), a period in which cumulative undiagnosed and untreated morbidity is highest; perhaps the presence of these other conditions may be modifying the relationship between persistent villous atrophy and likely osteoporotic fracture. The increased risk of hip fracture in the pre-1990 period and among those followed up beyond 5 years likely relates to the notion that hip fracture is a late complication of longstanding osteoporosis and is a rare event during the first year after follow-up biopsy. Indeed, in our post hoc analysis, there were few hip fractures in the younger age stratum, and the association between persistent villous atrophy and likely osteoporotic fractures seemed to be restricted to individuals who had passed the age of peak bone mass. Other possibilities are that patients biopsied before 1990 had more severe disease or that access to antiosteoporotic medical therapy has increased over time, leading to a diminishing risk of fracture in more recent years, even among those with persistent villous atrophy.

This study has several limitations. Data regarding clinical symptoms, which may have prompted follow-up biopsy, were not available for all patients. Patients who underwent follow-up biopsy may have done so due to a new clinical development or worsening symptoms. In an earlier validation study involving chart review at one site (Örebro) (26), 98 of 105 follow-up biopsies performed within this time window (93.3%) were done as a routine follow-up, and only 7 (6.7%) were performed due to a clinical development prompting the procedure. The overall fracture incidence of patients who had a follow-up biopsy was remarkably similar to a study of fracture incidence in study of celiac disease patients in Great Britain (3), which supports the notion that patients who underwent follow-up biopsy are similar to those CD patients who did not undergo follow-up biopsy with regard to fracture risk. Because our analysis was restricted to the first follow-up biopsy, long-term mucosal healing rates were not available, and these rates may affect fracture risk.

The increased fracture rate among patients with persistent villous atrophy may be due to an increased rate of severe trauma in this group; details regarding trauma were not available in this database. Information regarding bone density, muscle mass, and fall risk were not retrievable, and these possible mediators could therefore not be tested. Vertebral fractures in this study were limited to those that came to clinical attention, and silent fractures were not ascertained. The use of medication to treat osteoporosis was not available; because the effect of osteoporosis drugs on fracture prevention is generally weaker in the hip than in the spine, it would be valuable to stratify by osteoporosis drug use. Also unavailable were data regarding adherence to the gluten-free diet, but the prior literature supports the notion that persistent villous atrophy is more common among patients whose dietary adherence is poor (14, 16, 19). In a previous validation study involving chart review, we found that in 17% of patients, there were indications of poor dietary adherence (26). The use of diagnostic codes for villous atrophy and for fractures raises the possibility of information bias; this is unlikely to be substantial, given the validation of CD histology codes in this database (26) and of fracture codes (38). The follow-up biopsy represents only a one-time marker of disease activity and adherence to the diet; patients learning of the presence of persistent villous atrophy may have subsequently altered their behavior, thus diminishing the

measured effect between follow-up histology and fractures.

This data set lacked information regarding potential confounders or mediators including smoking, corticosteroid use, anthropometry, physical activity, and diabetes, all of which may impact the risk of fracture (39). For example, mucosal healing in adherent patients may result in an increased body mass index (40); because a higher body mass index is protective against fracture risk, anthropometry may mediate the relationship between mucosal healing and fracture. The relationship between smoking or corticosteroid use and persistent villous atrophy is unknown, but if either of these exposures inhibit mucosal healing, these may serve as positive confounders, given their known association with fracture risk (39). These results inform the question of fracture risk in patients diagnosed with CD but are not applicable to the significant proportion of CD patients who are undiagnosed; such patients have an increased risk of osteoporosis, but fracture risk in that population is understudied (41).

This study also has a number of strengths, most notably its nationwide setting. Its large sample size (which included more patients with CD than any non-Swedish study of fracture risk) provided unprecedented power to test for an association between persistent villous atrophy and fracture. Information on fractures was retrieved from prospectively recorded data in the National Inpatient Registry. The gradation of risk from overall fractures (null) to likely osteoporotic fractures (slight increase) to hip fractures (significantly increased risk) suggests that osteoporosis may be the mechanism by which persistent villous atrophy is associated with fracture risk. Indeed, there is a strong association between metabolic bone disease and hip fracture risk, an association that is more pronounced than for other clinical fractures (23). Moreover, the dose-response relationship between the degree of villous atrophy and the magnitude of hip fracture risk suggests that this association is causal. At the same time, the fact that the significant fracture risk increase was seen only in hip fractures suggests the possibility that other factors, such as a lack of sc fat or risk of falls, may be mediating this relationship. Impaired balance has been shown to be particularly strongly associated with hip fracture risk, (42) and investigating this as a potential mediator may be warranted.

In conclusion, we found that the results of the follow-up biopsy is predictive of hip fractures, but not of fractures overall, in patients with CD. Although the small number of events limits the precision of our subgroup analyses, these results suggest that follow-up histology may be a useful method to risk stratify patients with CD with regard to their fracture risk. Future studies should examine how persistent villous atrophy affects bone density, sc fat, fall risk, and predictors of fractures among patients attempting to adhere to the gluten-free diet.

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