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Alimentary Tract

Mortality and causes of death in different celiac disease phenotypes during long-term follow-up

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ABSTRACT

Background: Celiac disease has been associated with increased mortality, but data on long-term mortality are scarce.
Aims: To determine long-term mortality in celiac disease.
Methods: The study cohort consisted of all celiac disease patients (n=1,392) diagnosed in Tampere University Hospital catchment area 1960 – 2000. Patients were categorized into subgroups based on demographic (age, gender, decade of diagnosis) and celiac disease characteristics (e.g., phenotype, severity of villous atrophy) collected from medical records. Overall and cause-specific mortality was compared to those of age-, sex-, and place of residence matched reference individuals (n=4,177) over time.
Results: During the 41 years of follow-up (median 26.5 years), 376 celiac disease patients and 1,155 reference individuals died. All-cause mortality was not increased (hazard ratio (HR) 0.96, 95% confidence intervals (CI) 0.85–1.08). Mortality from lymphoproliferative diseases and diseases of the central nervous system was increased (HR 2.42, 95% CI 1.38–4.24 and HR 2.14, 95% CI 1.05–4.36 respectively) while the risk from alcohol related diseases was decreased (HR 0.31, 95% CI 0.09–1.00). Examination of various celiac disease phenotypes revealed no significant differences in mortality
Conclusions: Overall mortality was not increased in any celiac disease phenotype during a very long-term follow-up.

1. Introduction

Celiac disease has been associated in numerous studies with 1.2- to 2-fold increased mortality [1–5], mainly caused by lymphoproliferative malignancies and cancers of the gastrointestinal tract [6,7]. On the other hand, risk estimates similar to those in general population have also been reported [8–10]. In most studies the mean follow-up has not exceeded 5 – 13 years and therefore persistence of increased mortality during prolonged follow-up after diagnosis is uncertain [1,4,5,8,9]. The only study with a longer follow-up (mean 30 years) included 602 celiac disease patients [3]. In that study, overall mortality initially seen to increase (SMR 1.4) compared to general population, but over time to decrease, the increase after 15 years from celiac disease diagnosis being no longer significant.

Celiac disease can manifest with a multitude of symptoms arising from different organ systems and with varying severity. In addition to frequently encountered diarrhea and malabsorption, the disease may present with dermatitis herpetiformis (the skin involvement of celiac disease), arthralgia, osteoporosis, growth retardation, infertility, and neurological disorders. These distinct celiac disease presentations may result in different prognoses; lower mortality rates have been reported in dermatitis herpetiformis [10–12] and screen-detected celiac disease [13–15] than in other celiac disease phenotypes. Moreover, variations in symptom severity, as well as gender, and age at celiac disease diagnosis have been suggested as possible factors confounding detected mortality risks [1,3,16,17].

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The aim of this study was to ascertain celiac disease-associated mortality during a long follow-up of up to 41 years using a well-defined cohort of celiac disease patients including all celiac disease phenotypes. Special attention was paid to the mortality risks in different celiac disease phenotypes.

2. Materials and methods

2.1. Study population

All patients (n=1,460) with biopsy-proven celiac disease including dermatitis herpetiformis diagnosed in the Tampere University Hospital catchment area between January 1960 and December 2000 were prospectively collected to form the celiac disease cohort [18]. Sixty-eight patients were excluded from further analysis: two patients had died before the start of follow-up (January 1, 1978) and 66 patients had inadequate baseline data preventing selection of reference individuals. Thus, the study population eventually comprised 1,392 celiac disease patients. The diagnoses were based on approved diagnostic guidelines i.e., duodenal villous atrophy and crypt hyperplasia in celiac disease, and granular IgA deposits of the dermal papillae of the skin in dermatitis herpetiformis. In celiac disease the date of duodenal biopsy was set as the date of diagnosis. In dermatitis herpetiformis the date of diagnosis was assigned to be the date of immunofluorescence examination, except for patients diagnosed before the test became available in clinical practice in the 1980s. In such cases the date of diagnosis was taken to be the date of clinical diagnosis rather than the date of confirmatory immunofluorescence test performed at a later timepoint. Eighty-seven percent of dermatitis herpetiformis patients also had duodenal biopsy results available and villous atrophy was detected in 71% of them while 29% had normal villous architecture.

2.2. Reference group

Three reference individuals matched for age, gender, and place of residence at the time of diagnosis of celiac disease index case were selected for each celiac disease patient from the Finnish Population Information System (PIS) maintained by the Digital and Population Data Services Agency (n = 4,182). After excluding the five individuals who died before initiation of follow-up, the reference group eventually comprised 4,177 persons. The PIS contains basic information on all Finnish and foreign citizens permanently resident in Finland, each of whom can be identified by a unique personal identification code.

2.3. Review of medical records and stratification

The medical records of the celiac cohort were reviewed in 2015. All data available on patient and celiac disease characteristics and on adherence to gluten-free diet were collected for each patient. Patient records of 88 deceased patients were no longer available.

The cohort was stratified into subgroups according to the following characteristics: gender; age at diagnosis ($<$ 20, 20 – 39, 40 – 59 and $\geq$ 60 years); decade of diagnosis ($\leq$ 1980, 1981 – 1990, 1991 – 2000), and duration of follow-up since diagnosis ($<$ 2, 2 – 4.9, 5 – 14.9, 15 – 29.9, $\geq$ 30 years). In addition, patients were divided into the following five celiac disease phenotype categories based on the main presenting symptom: 1) gastrointestinal symptoms, including diarrhea, abdominal pain, reflux, obstipation, 2) malabsorption, including weight loss, anemia or deficiencies of iron, cobalamin, folic acid or calcium either alone or in combination, 3) dermatitis herpetiformis including patients with itchy and blistering rash at typical locations, 4) other extraintestinal symptoms including osteoporosis, infertility, neurological manifestations, arthralgia and childhood growth retardation, 5) screen detected patients including individuals with few or no symptoms who were screened due to having either an autoimmune disease e.g. type 1 diabetes, autoimmune thyroiditis, arthritis or IgA nephropathy or celiac disease in the family. Moreover, all celiac disease patients with small bowel biopsy results available were categorized into the following three subgroups according to the degree of small bowel mucosal damage: total or subtotal villous atrophy corresponding to Marsh-Oberhuber 3b-c [19,20], partial villous atrophy corresponding to Marsh-Oberhuber 3a, normal villous architecture corresponding to Marsh 0-2. Finally, patients were divided to two subgroups according to response to gluten-free diet. Response was considered to have been achieved if villous atrophy appeared alleviated in follow-up biopsies. The no-response group included patients with no histological villous improvement and those not adhering to gluten-free diet.

2.4. Mortality data

The Registry of Causes of death is maintained by Statistics Finland and covers more than 99% of all deceased residents of Finland since 1936 [21]. Immediate, underlying, and contributary causes of death are derived from death certificates [21]. The causes of death are classified into 54 groups according to the underlying cause of death [22], and these groups were used when analyzing cause-specific mortality. Alcohol-related causes of death include all alcohol-related codes in all the different disease categories of the Tenth Revision of the International Classification of Diseases (ICD-10), e.g. alcohol associated liver diseases (K70) or alcohol poisoning (X45), but not deaths caused by accidents and violence [22]. The personal identification codes of celiac disease patients and reference individuals were linked with the Registry. The dates of death were acquired until August 10, 2020, whereas causes of death were available until the end of 2018.

2.5. Statistical analysis

Follow-up was set to begin from January 1, 1978 or from the date of diagnosis of celiac disease or dermatitis herpetiformis (and corresponding dates in reference individuals), whichever was later. Follow-up continued until death, emigration, or August 10, 2020, whichever came first. Categorical variables were reported as frequencies and percentages and continuous variables as medians and ranges. To determine celiac disease-associated mortality overall and for different causes of death, crude mortality rates per 10,000 person-years at risk were calculated. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to estimate the risk of death using Cox proportional hazards model. Potential risk factors for stratified analyses were chosen according to the literature. All-cause mortality in each stratified subgroup was assessed comparing celiac disease patients to their designated reference individuals. Particular attention in stratified analyses was paid to duration of follow-up and to the various celiac disease phenotypes. In addition, a separate analysis was performed to ascertain whether the previously reported discrepancy in mortality risks between dermatitis herpetiformis and all the other celiac disease phenotypes combined persisted. All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY).

2.6. Ethics

Data permits were granted by Statistics Finland (TK-53-679-20), Digital and Population Data Services Agency (DVV/4482/2020-2), and Tampere University Hospital Science Center (R17554). All patient data were pseudonymized prior to analyses. According to Finnish legislation, no informed consent or approval by an ethics

Table 1
Characteristics of the study cohort and their designated matched reference individuals.

Characteristic		Celiac disease patients n = 1,392		Reference individuals n = 4,177	
		n	%	n	%
Gender					
	Female	880	63.2	2,639	63.2
	Male	512	36.8	1,538	36.8
Age at diagnosis					
	< 20 years	264	19.0	792	19.0
	20 – 39 years	450	32.3	1,351	32.3
	40 – 59 years	492	35.3	1,477	35.4
	≥ 60 years	186	13.4	557	13.3
Decade of diagnosis					
	– 1980	181	13.0	544	13.0
	1981 – 1990	602	43.2	1,806	43.2
	1991 – 2000	609	43.8	1,827	43.7
Follow–up from celiac disease diagnosis					
	< 2 years	16	1.1	57	1.3
	2 – 4.9 years	27	1.9	79	1.9
	5 – 14.9 years	114	8.2	335	8.0
	15 – 29.9 years	745	53.5	2,287	54.8
	≥ 30 years	490	35.2	1,419	34.0
Follow–up time					
	Median, years (range)	26.5 (0.1 – 41)		25.7 (0.0 – 41)	
	Person-years at risk, years	38,183		113,360	
Median age at diagnosis, years (range)		39.3 (0.8 – 84.8)		39.3 (0.6 – 84.8)	
Median age at the end of follow-up, (range)		65.7 (8.9 – 99.0)		65.6 (17.5 – 102.5)	

committee is required for registry-based studies when the study participants are not contacted.

3. Results

The study cohorts included 1,392 celiac disease patients and 4,177 reference individuals diagnosed at a median age of 39 years (range 0.8 – 84.0) (Table 1). Follow-up extended up to 41 years (median 26.5 years) producing 38,183 and 113,360 person-years of follow-up for celiac disease patients and reference individuals respectively. Throughout follow-up, altogether 376 celiac disease patients and 1,155 reference individuals died, thereby yielding respective mortality rates of 98.5 and 101.9 per 10,000 person-years (Table 2). Thus, overall mortality in the celiac cohort was equal to that among the reference individuals (HR 0.96, 95% CI 0.85 – 1.08). When examining overall mortality in the subgroups based on celiac disease phenotype and other clinical and demographic characteristics, no significant differences in relative risks were observed in comparison to reference individuals (Table 3). Overall mortality in dermatitis herpetiformis (HR 0.87, 95% CI 0.70 – 1.01) did not differ significantly from that observed in all the other celiac disease phenotypes combined (HR 0.99, 95% CI 0.87 – 1.14).

Assessment of specific causes of death throughout follow-up revealed an increase in mortality from lymphoproliferative diseases (HR 2.42, 95% CI 1.38 – 4.24), and especially from non-Hodgkins lymphoma (HR 4.61, 95% CI 1.20 – 10.65) and T-cell non-Hodgkins lymphoma (HR 7.46, 95% CI 1.45 – 38.46). The increased risk was apparent particularly in patients diagnosed with celiac disease after 40 years of age (Table 4), while no cases of lymphoproliferative diseases were detected among patients diagnosed with celiac disease before 30 years of age. Mortality from diseases affecting the central nervous system (not including Alzheimer's disease) was increased in celiac disease (HR 2.14, 95% CI 1.05 – 4.36) due to various causes; 6 Parkinson's disease, 2 Amyotrophic lateral sclerosis, 2 familial spinocerebellar ataxia (siblings), 2 other specified neurodegenerative diseases, and 1 Lewy body dementia. Conversely, risk of dying from alcohol related diseases was decreased in the celiac cohort (HR 0.31, 95% CI 0.09 – 1.00). Mortality from malignancies overall and from gastrointestinal malignancies, as well as from cardiovascular diseases and digestive diseases was not increased among celiac disease patients.

In the stratified analysis assessing the development of trend in mortality over time after celiac disease diagnosis, mortality from lymphoproliferative diseases increased significantly 2 – 5 years after diagnosis and from diseases of the central nervous system 5 – 15 years after diagnosis and diminished in both thereafter (Table 4). No alterations were noted in mortality over time from malignancies overall (Table 4) nor from gastrointestinal malignancies or cardiovascular diseases (data not shown).

4. Discussion

Celiac disease-related long-term mortality showed no increase in this study, which was conducted in a well-defined large cohort of celiac disease patients within a very long follow-up. Furthermore, mortality risk remained largely the same during the entire follow-up. This is a reassuring finding, as over half of the celiac disease patients in our series were diagnosed before the age of 40 years, thus having a long life expectancy ahead of them. It could also be interpreted as an indication of the beneficial effects of a long-lasting gluten-free diet. Even though we were not able to evaluate the long-term adherence to gluten-free diet in our cohort, the 91% response rate observed in duodenal control biopsies suggests reasonable compliance with the diet. In addition, the response rate is also in line with those of earlier studies showing good long-term compliance in Tampere celiac disease (88-93%) and dermatitis herpetiformis (98%) cohorts [10,23,24]. On the other hand, the beneficial effect of gluten-free diet on overall mortality is not self-evident as a strict diet is not nutritionally ideal. The diet itself may be associated with lower fiber, vitamin, and mineral intake as well as higher sugar and fat consumption [25], which may in turn predispose to other comorbidities like obesity, fatty liver, cardiovascular diseases, and even cancer [26,27].

Our mortality result contradicts the higher mortality (1.3- to 2-fold) reported by many others [1,3,4,6,28,29] (Supplementary Table 1). In a recent large Swedish study the mortality risk ob-

Table 2
Mortality rates per 10,000 person-years and hazard ratios (HR) for overall and cause-specific mortality [a] in patients with celiac disease and in the reference group during up to 41 years of follow-up (median 26 years).

Cause of death [20]	Celiac cohort [b] (n=1,392)			Reference group (n=4,177)				
	n	% [c]	Rate [d]	n	% [c]	Rate [d]	HR	95% CI
Overall mortality [a]	376	2.9	98.5	1155	3.0	101.9	0.96	0.86 – 1.08
Malignancies overall	88	23.4	24.4	310	26.8	28.9	0.84	0.66 – 1.06
Gastrointestinal [e]	26	6.9	7.2	79	6.8	7.4	0.97	0.62 – 1.52
Lymphoproliferative	22	5.9	6.1	27	2.3	2.5	**2.42**	**1.38 – 4.24**
NHL	14	3.7	3.9	9	0.8	0.8	**4.61**	**2.00 – 10.65**
T-cell NHL	5	1.3	1.4	2	0.2	0.2	**7.46**	**1.45 – 38.46**
Breast [f]	8	3.9	3.5	34	5.6	4.9	0.70	0.33 – 1.52
Gynecological [f]	2	1.0	0.9	18	2.9	2.6	0.33	0.08 – 1.44
Prostate [g]	2	1.2	1.5	17	3.1	4.4	0.34	0.08 – 1.47
Central nervous system diseases	13	3.5	3.6	18	1.6	1.7	**2.14**	**1.05 – 4.36**
Alzheimer's disease	30	8.0	8.4	105	9.1	0.8	0.83	0.56 – 1.25
Digestive diseases	18	4.8	5.0	35	3.0	3.3	1.52	0.86 – 2.68
Cardiovascular diseases	105	27.9	29.1	305	26.4	28.4	1.02	0.82 – 1.27
Ischemic heart disease	72	19.1	19.9	212	18.4	19.8	1.01	0.77 – 1.32
Cerebrovascular diseases	21	5.6	5.8	90	7.8	8.4	0.69	0.43 – 1.11
Respiratory diseases	16	4.3	4.4	58	5.0	5.4	0.82	0.47 – 1.42
Infectious diseases	3	0.8	0.8	15	1.3	1.4	0.60	0.17 – 2.06
Accidents and violence	25	6.6	6.9	73	6.3	6.8	1.02	0.65 – 1.60
Alcohol related diseases	3	0.8	0.8	29	2.5	2.7	**0.31**	**0.09 – 1.00**

CI, confidence interval; HR, hazard ratio
[a] Follow-up for overall mortality until August 10, 2020 and for cause-specific mortality until December 31, 2018
[b] Includes all celiac disease phenotypes including dermatitis herpetiformis
[c] Percentage of all deaths in the group
[d] Mortality rate per 10,000 person-years
[e] Including cancers of the liver, pancreas, and gastrointestinal tract
[f] Analyzed only for females
[g] Analyzed only for males

Table 3
All-cause mortality in celiac disease subgroups and compared to reference individuals.

Group	Number		Number of events (%)		
	Celiac cohort	Reference individuals	Celiac cohort	Reference individuals	HR (95% CI)
All	1,392	4,177	378 (27.2)	1,159 (27.7)	0.96 (0.85 – 1.08)
Gender					
Male	512	1,538	172 (33.6)	544 (35.4)	0.92 (0.77 – 1.09)
Female	880	2,639	204 (23.2)	611 (23.2)	0.99 (0.85 – 1.16)
Age at celiac disease diagnosis (years)					
< 20	264	792	10 (3.8)	19 (2.4)	1.55 (0.72 – 3.34)
20 – 39	450	1,351	38 (8.4)	142 (10.5)	0.78 (0.55 – 1.12)
40 – 59	492	1,477	169 (34.3)	523 (35.4)	0.92 (0.77 – 1.09)
≥ 60	186	557	159 (85.5)	471 (84.6)	1.02 (0.86 – 1.23)
Decade of diagnosis					
– 1980	181	544	59 (32.6)	299 (36.8)	0.82 (0.61 – 1.10)
1981 – 1990	602	1,806	173 (28.7)	541 (30.0)	0.96 (0.81 – 1.13)
1991 – 2000	609	1,827	144 (23.6)	414 (22.7)	1.05 (0.96 – 1.26)
Presenting phenotype at celiac disease diagnosis [a]					
Gastrointestinal	443	1,329	95 (21.4)	318 (23.9)	0.86 (0.69 – 1.08)
Malabsorption	221	663	55 (24.9)	168 (25.3)	0.97 (0.72 – 1.32)
Dermatitis herpetiformis	299	897	107 (35.8)	344 (38.4)	0.87 (0.70 – 1.09)
Other extraintestinal	182	546	38 (20.9)	109 (20.0)	1.04 (0.82 – 1.51)
Screen detected	153	459	31 (20.3)	74 (16.1)	1.30 (0.85 – 1.97)
Degree of villous atrophy at celiac disease diagnosis					
Normal	86	258	39 (45.3)	121 (46.9)	0.83 (0.58 – 1.20)
Partial villous atrophy	322	964	81 (25.2)	261 (27.1)	0.90 (0.70 – 1.15)
Subtotal or total villous atrophy	861	2,583	186 (21.6)	575 (22.3)	0.95 (0.80 – 1.12)
Response to gluten-free diet					
Yes	824	2,472	196 (23.8)	609 (24.6)	0.94 (0.80 – 1.10)
No	79	236	25 (31.6)	69 (29.2)	1.04 (0.66 – 1.64)
Follow-up from celiac disease diagnosis					
< 2 years	1,392	4,177	14 (1.0)	54 (1.3)	0.97 (0.53 – 1.76)
2 – 4.9 years	1,376	4,120	27 (2.0)	73 (1.7)	1.18 (0.75 – 1.85)
5 – 14.9 years	1,349	4,041	113 (8.1)	328 (7.9)	1.13 (0.91 – 1.40)
15 – 29.9 years	1,235	3,706	173 (12.4)	542 (13.0)	0.96 (0.81 – 1.14)
≥ 30 years	490	1,419	49 (3.5)	158 (3.8)	0.87 (0.63 – 1.20)

CI, confidence interval; HR, hazard ratio
[a] HR for a combination of celiac disease phenotypes excluding dermatitis herpetiformis 0.99, 95% CI 0.87 – 1.14

Table 4
Specific relative mortality risks in celiac disease patients [a] compared to reference individuals by time since and by age at celiac disease diagnosis

	Malignancies overall		Lymphoproliferative diseases		Central nervous system diseases	
	N CD / Ref	HR (95% CI)	N CD / Ref	HR (95% CI)	N CD / Ref	HR (95% CI)
Time from diagnosis						
< 2 years	6 / 17	1.10 (0.42 – 2.86)	3 / 1	9.36 (0.92 – 94.84)	0 / 1	-
2 – 4.9 years	8 / 18	1.34 (0.58 – 3.11)	5 / 1	**14.50 (1.69 – 124.70)**	0 / 1	-
5 – 14.9 years	25 / 93	0.87 (0.56 – 1.36)	7 / 9	2.27 (0.85 – 6.10)	6 / 2	**12.91 (2.49 – 67.07)**
15 – 29.9 years	40 / 145	0.83 (0.59 – 1.18)	7 / 11	1.92 (0.75 – 4.96)	7 / 13	1.62 (0.65 – 4.07)
≥ 30 years	9 / 37	0.69 (0.33 – 1.42)	0 / 5	-	0 / 1	-
Age at diagnosis						
< 20 years	1 / 4	0.72 (0.08 – 6.48)	0 / 3	-	0 / 1	-
20 – 39 years	11 / 47	0.69 (0.36 – 1.32)	3 / 8	1.10 (0.29 – 4.14)	3 / 3	2.97 (0.60 – 14.71)
40 – 59 years	43 / 153	0.82 (0.58 – 1.15)	7 / 4	**5.20 (1.52 – 17.75)**	7 / 12	1.68 (0.66 – 4.28)
> 60 years	33 / 106	0.96 (0.65 – 1.41)	12 / 12	**3.05 (1.37 – 6.79)**	3 / 2	4.62 (0.77 – 27.66)

CI, confidence interval; HR, hazard ratio
[a] Involves all celiac disease phenotypes including dermatitis herpetiformis.

served was elevated (HR 1.2) [5], but the mortality rate detected among celiac disease patients (9.7%) was similar to ours (9.8%). However, mortality among Swedish reference individuals was lower than in our reference subjects (8.6% vs. 10.2% respectively) indicating some differences between the reference groups of these two studies despite similar matching parameters. Differences in celiac disease presentation and symptom severity could also offer one potential explanation for our lower risk estimate. Most studies investigating mortality in undetected, typically mild or asymptomatic celiac disease reported no excess risk while the risk was higher in patients with severe symptoms [1,2,13–15,30]. Lower mortality risks have also been reported in patients with dermatitis herpetiformis (SMR 0.5 – 0.9) [10–12,31].

Although overall cancer mortality was not shown to be increased in the present study, the risk of death from lymphoproliferative diseases and especially from non-Hodgkins lymphoma was elevated. Nevertheless, our risk estimates were lower than those reported earlier in patient cohorts from the same era [1,3,4,12,28]. Moreover, the risk was more pronounced particularly in patients diagnosed when over 40 years of age and within 2 – 5 years of diagnosis. In comparison, Quarpong et al. [3] detected increased mortality from lymphoproliferative diseases both in childhood- and adulthood diagnosed celiac disease and despite a decreasing trend in risk over time it remained almost significantly increased even after 15 years of follow-up. Since the 1990s the widespread utilization of serological diagnostic tests [32] together with investments in educating health care personnel about celiac disease have succeeded in reducing diagnostic delay [33] as well as a high prevalence of (0.7%) biopsy-proven celiac disease in Finland [34] possibly influencing the mortality risks identified.

The increase in mortality from central nervous system diseases was attributable to various diseases. A similar risk estimate was observed by Peters et al. in a Swedish celiac inpatient cohort [28]. Neurological dysfunction has been shown in up to 67% of newly diagnosed celiac disease patients, the most frequent symptoms being headache, ataxia, and peripheral neuropathy [35]. A possible link to neurological symptoms are the cross reacting transglutaminase antibodies in the brain tissue [35,36]. In the 1990s, collaboration with the neurology clinic was intensive in our hospital, possibly improving detection of celiac disease patients with neurological symptoms [37], which may have an impact on our increased mortality rate from these disorders.

The decreased mortality from alcohol-related causes is a novel finding in celiac disease while in dermatitis herpetiformis it has already been noted (SMR 0.0) [10]. The literature on alcohol consumption among celiac disease patients is scanty. Reilly et al. [38] showed a smaller proportion of alcohol-related liver disease among celiac disease patients with non-alcoholic fatty liver disease (NAFLD) compared to controls with NAFLD (12% vs. 15%) and Hervonen et al. [10] discovered a markedly reduced consumption of beer, but not of strong drinks, among dermatitis herpetiformis patients. In Finland, beer is one of the most widely used alcohol types and avoidance of gluten containing products could lead to diminished beer consumption and further to decreased mortality.

A major strength of our study is the long follow-up of up to 41 years, which enabled us to assess the evolution of mortality in celiac disease in a wider time perspective and also for patients diagnosed in childhood. Another strength is the large and prospectively collected cohort of well-defined celiac disease patients with access to patient records for detailed patient and celiac disease-related information. This allowed a reasonable estimate of mortality in different celiac phenotypes and diagnostic age-groups. At the time our cohort was collected, the diagnostics of celiac disease and dermatitis herpetiformis were primarily centralized to Tampere University Hospital and thus the cohort includes all cases diagnosed during that period. We also had a matched reference group, enabling more precise assessment of relative mortality than comparison to general population [39].

Our study also suffered from some limitations. The information on celiac disease characteristics was collected from patient records and not all the data required were available anymore. We had no information on confounding factors like socioeconomic status, tobacco consumption or concomitant diseases possibly affecting mortality. Furthermore, despite the large cohort of celiac disease patients, the number of deaths remained low in many stratified groups and causes of death, and therefore many analyses were likely underpowered.

5. Conclusions

In conclusion, celiac disease-associated mortality showed no increase in long-term follow-up in a patient cohort covering the whole spectrum of celiac disease presentations. Nevertheless, mortality from lymphoproliferative diseases and non-Hodgkins lymphoma was increased and the risk was most prominent when celiac disease was diagnosed after 40 years of age. Our findings suggest that the prognosis is generally good for celiac disease patients adhering to gluten-free diet.

Conflict of interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.04.016.

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