

## **Risk of fractures in dermatitis herpetiformis and coeliac disease: a register-based study**

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***Running Head: Fractures in DH and coeliac disease***

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## Abstract

**Objectives:** Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease. Bone fracture risk is increased in coeliac disease, but little knowledge exists about bone complications in DH. This study aimed to evaluate the risk of hip and other hospital-treated fractures in DH and coeliac disease in a high prevalence area with good adherence to a gluten-free diet.

**Materials and methods:** Hip, proximal humerus, wrist and ankle fractures in 368 treated DH and 1,076 coeliac disease patients between 1970 and 2015 were reviewed from the National Hospital Discharge Register. Hip fracture incidence rates for DH and coeliac disease patients were compared to those for the general population. The overall fracture risk for DH was compared to coeliac disease.

**Results:** The hip fracture incidence rates for DH and coeliac disease patients did not differ from the general population. In females aged 80–89, the hip fracture incidence was higher in DH than in coeliac disease, but the risk for any hospital-treated fracture was lower in DH compared to coeliac disease (adjusted HR 0.620, 95% CI 0.429–0.949). The DH and coeliac disease patients with hospital-treated fractures were diagnosed at an older age, but the degree of small bowel mucosal damage did not significantly differ between patients with and without fractures.

**Conclusion:** The incidence of hip fracture is not increased in treated DH or coeliac disease in an area with high awareness and dietary compliance rates. However, patients with DH seem to have lower risk for fractures overall compared to coeliac disease.

### Keywords:

dermatitis herpetiformis; coeliac disease; fracture; hip fracture; gluten-free diet

## Introduction

Coeliac disease is an immune-mediated enteropathy triggered by dietary gluten affecting 1–2% of the population.<sup>1</sup> Although the disease is classically known as a malabsorption syndrome presenting with gastrointestinal symptoms, presently a wide range of extraintestinal symptoms are increasingly common.<sup>1</sup> Dermatitis herpetiformis (DH), a cutaneous manifestation of coeliac disease, presents in approximately 13% of coeliac disease patients.<sup>2</sup> In DH gluten induces a blistering, itchy rash with pathognomonic granular dermal immunoglobulin (Ig) A deposits. DH patients also suffer from coeliac-type small bowel mucosal villous atrophy or inflammation, and circulating and intestinal IgA class antibodies against transglutaminase 2 at diagnosis are characteristic for both DH and coeliac disease.<sup>1,3</sup> A strict life-long gluten-free diet (GFD) is the treatment of choice for both disorders and the diet heals the small bowel mucosal changes and alleviates the DH rash.<sup>1,3</sup> However, the diet is frequently considered restrictive and difficult to comply with, and the adherence to a strict GFD have ranged from 42% to 91% in different study populations.<sup>4</sup>

Coeliac disease has been linked to decreased bone mineral density (BMD)<sup>5</sup> and also to increased any-type and hip fracture risk<sup>6</sup>, which have been at least partly explained by the small bowel mucosal damage. GFD treatment recognizably increases BMD in coeliac disease<sup>5</sup>, and has a preventive effect against bone fractures.<sup>7</sup> Knowledge concerning bone complications in DH is currently scant, but since the small bowel mucosal damage is more subtle than in coeliac disease, it seems probable that bone deterioration and fracture risk is more minor than in coeliac disease. Two studies have found a lower BMD in DH than in controls, but better than in patients with coeliac disease,<sup>8,9</sup> and three studies found no difference in BMD between DH patients and healthy controls.<sup>10–12</sup> The only published register-based fracture study on patients with DH thus far did not find increased fracture risk associated with DH.<sup>13</sup>

The aim of this register-based study was to evaluate whether patients with DH and coeliac disease have an increased incidence of hip fractures compared to the general

population in an area with high rate of clinically diagnosed cases<sup>14</sup> and with good dietary compliance rates.<sup>15,16</sup> A further aim was to compare any-type hospital-treated fractures between patients with DH and coeliac disease to determine whether the fracture risk varies between these two manifestations of the same disease. This knowledge is of importance when considering the need for BMD measurements in DH and coeliac disease.

## Materials and methods

### Study population

Long term follow-up data were obtained by enrolling all patients diagnosed with DH between the years 1969 and 2000 at the Department of Dermatology at Tampere University Hospital. The department has a special outpatient clinic for patients with DH, where all DH patients within the catchment area of the hospital district are diagnosed. The DH diagnosis of each patient relied on clinical symptoms compatible with DH and demonstration of dermal IgA with direct immunofluorescence examination.<sup>17</sup> The coeliac disease study group comprised all patients in the Tampere area with a small bowel biopsy-based diagnosis made during the same time period as the patients with DH. All patients with a DH diagnosis were excluded from the coeliac disease study group, which thereafter included patients with any other phenotype of coeliac disease than DH. Furthermore, the patients diagnosed with coeliac disease for more than one year prior to a DH diagnosis were excluded from the DH study group. Eventually, our DH study cohort comprised 368 patients, and the coeliac disease cohort 1,076 patients.

After the diagnosis, all DH and coeliac disease patients were advised to adhere to a strict GFD. In addition, DH patients with severe skin symptoms were prescribed dapsone medication to alleviate the intense itching more quickly. The patients with DH were followed up at the Department of Dermatology for at least 1–2 years or until the dapsone treatment was discontinued, and coeliac disease patients were followed up either in primary or tertiary care, depending on the severity of the disease.

## Study design

For both cohorts, the findings of small bowel mucosal specimens at diagnosis were gathered from the medical records. The data on hospital-treated fractures were obtained from the Finnish National Hospital Discharge Register (NHDR). This mandatory register for all hospitals is maintained by the National Institute for Health and Welfare. The database contains variables such as hospital admission and discharge days, primary and secondary diagnosis with ICD-coding (ICD-8 for 1969–1986, ICD-9 for 1987–1995, and ICD-10 since 1996), and all procedures performed during the stay.

The data on inpatient treatment periods were gathered from the NHDR for both cohorts for the time period of 1970–2015. The main outcome was the first hospital-treated hip fracture defined with the relevant ICD-8–10 codes (N820\*, 820\*, S72\*). The hip fracture was chosen as the main outcome because these fractures are practically always treated in the hospital, ensuring comprehensive fracture data deriving from the NHDR. Also, data about the first proximal humerus fracture (N812.0, N812.1, 812\*, S42.2), the first wrist fracture (N813.4, N813.5, N814.0, N814.1, 813\*, S52.5, S52.6) and the first ankle fracture (N824\*, 824\*, S82.5, S82.6, S82.8) causing hospital treatment periods were collected. The dates of death or emigration for the study patients were obtained from the Population Register Centre of Finland. The follow-up time began from the time of the DH or coeliac disease diagnosis or – for those diagnosed before 1970 – on the 1 January 1970. The follow-up ended on the date of the first discharge diagnosis for the studied fracture, the date of the subject's death or emigration, or the end of the study period (31 December 2015), whichever occurred first.

The age- and gender-distributed incidence rates of hospital-treated hip fractures in the Finnish population were reported in the National Institute for Health and Welfare's report concerning the quality of joint replacement surgery in Finland for 2014.<sup>18</sup> These incidences were used in this study as the general population comparison incidences.

The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital (R16090, October 11<sup>th</sup>, 2016) and is in accordance with the

Declaration of Helsinki. In register-based studies the consent from patients is not obtained.

## Statistical analysis

The continuous variables were described with median values and interquartile ranges (IQR), and the categorized values as numbers and percentages. The 95% confidence intervals (CI) were calculated for fracture incidence rates assuming a Poisson distribution. The Mann–Whitney *U* test and the chi-squared test were used for comparing the groups. The Cox Proportional-Hazards Model was used for comparing the fracture risk between the patients with DH and coeliac disease. All testing was two-sided, and  $p < 0.05$  was considered statistically significant. All the statistical analyses were performed with the SPSS version 24 (IBM Corporation, Armonk, NY) in cooperation with a statistician.

## Results

There was female predominance among the 1,076 coeliac disease patients, whereas the gender distribution was equal among the 368 DH patients (Table 1). The median age was higher in DH compared to the coeliac disease patients. The coeliac disease patients were more often diagnosed during childhood, and had more severe villous atrophy at diagnosis compared to DH patients (Table 1). In total, 27% of the patients with DH and 20% of the patients with coeliac disease died during the follow-up period and seven of the coeliac disease patients had moved to another country during the follow-up.

Hip fractures had occurred in 14 (4%) patients with DH and 18 (2%) patients with coeliac disease. The median follow-up time for the first hip fracture was 28 years (IQR 21–34) in the DH cohort and 23 years (IQR 18–29) in the coeliac disease cohort, resulting in 10,003 and 25,033 observed person-years at risk, respectively. Thus, the hip fracture incidences per 100,000 person-years were 140 (95% CI 77–235) in the DH and 72 (95% CI 43–114) in the coeliac disease cohort. Only one DH patient and four coeliac disease patients had suffered a hip fracture under the age of 70 years. Therefore, the hip fracture incidences were studied more specifically in males and females aged 70–79 and 80–89 years

(Figure 1). In total of 410 DH or coeliac disease patients were between the ages of 70 and 89 in 2014, and one hip fracture had occurred in the DH cohort. After these individuals were subtracted from the general population values, the hip fracture incidences in the DH and coeliac disease cohorts did not differ from the general population in any subgroups. The incidences did not differ between DH and coeliac disease patients either, except that in the subgroup of females aged 80–89 years the hip fracture incidence was statistically significantly higher in DH than in coeliac disease cohort (2,435 (95% CI 893–5,300) and 706 (95% CI 146–2,064) per 100,000 person-years, respectively; see Figure 1). In the DH cohort, older patients had been diagnosed at an older age compared to younger patients, since there was a negative correlation between the birth year and the age at the time of the diagnosis ( $r = -0.90$ ,  $p < 0.001$ ).

Hip, proximal humerus, wrist or ankle fractures leading to hospitalization had occurred in 35 (10%) DH and in 105 (10%) coeliac disease patients, resulting in an incidence rate of any-type hospital-treated fracture of 360 (95% CI 251–500) and 435 (95% CI 356–527) per 100,000 person-years, respectively. Patients with DH were at a lower overall risk for hospital-treated fractures compared to patients with coeliac disease when the risk was adjusted for gender and year of birth (Table 2). The adjusted hazard ratio for hip fractures as well as other hospital-treated fractures was also lower for patients with DH, but the difference was not statistically significant (Table 2).

In both cohorts, there was a slight female predominance among those with fractures compared to those without, and the individuals with fractures were diagnosed with DH or coeliac disease at an older age (Table 3). Furthermore, the patients with a fracture in the DH cohort had been diagnosed with DH more formerly than those without (median diagnostic years 1981 and 1985, respectively,  $p = 0.056$ ). The degree villous atrophy did not significantly differ between those with and without fractures in either cohort, but coeliac disease patients with a fracture had more often subtotal or total villous atrophy at diagnosis compared to DH patients with a fracture ( $p < 0.001$ ) (Table 3).

## Discussion

In this large register-based study, we found no increase in the incidence of hip fractures in those diagnosed with DH compared to the general population. Moreover, coeliac disease was not shown to associate with increased hip fracture incidence either. The patient cohorts in the current study were gathered from an area where prevalence of diagnosed DH and coeliac disease is high<sup>2,14</sup> and adherence to GFD is excellent<sup>15,16</sup>, both of which are known to vary between different populations and undoubtedly have affected the results of previous fracture studies<sup>2,4,14,19,20</sup>.

Prior to the current study, only one study has assessed the fracture risk in DH compared to the general population; it found no risk of hip or any-type fractures in DH.<sup>13</sup> The hip fracture incidence in the DH group in that study was closely equal to that in the current study (143 and 140 per 100,000 person-years at risk, respectively), although the follow-up time was rather short, and the population was younger than ours.<sup>13</sup> In turn, the any-type fracture risk has been shown to be increased in coeliac disease in the majority of the performed studies.<sup>6</sup> Furthermore, in coeliac disease a 2- to 4-fold increase in the hip fracture risk has been detected<sup>21–23</sup> although contrary results also exist<sup>24,25</sup>. A recent meta-analysis found a slightly increased (30%) any-fracture risk and a 69% increased hip fracture risk in coeliac disease patients<sup>6</sup>. Discordantly with the meta-analysis, we found no increase in the hip fracture risk in coeliac disease compared to the general population.

In our previous study investigating self-reported fractures, the lifetime bone fracture risk was found to be equal between patients with DH and coeliac disease, except that females with coeliac disease had a higher fracture risk after being diagnosed compared to females with DH.<sup>26</sup> In the current study, the hospital-treated fractures overall were increased in the coeliac disease cohort compared to the DH cohort, which is in line with our previous finding. However, females aged 80–89 in the DH cohort had an increased hip fracture incidence compared to the comparable coeliac disease cohort.

Decreased BMD is a risk factor for bone fractures, and has been explained with a multifactorial aetiology in coeliac disease. The small bowel mucosal villous atrophy in



coeliac disease decreases the absorption of micronutrients necessary for bone metabolism.<sup>5</sup> Also the decreased calcium absorption causing secondary hyperparathyroidism and the persistent inflammation are suggested to cause decreased BMD in patients with coeliac disease.<sup>5</sup> Prolonged diagnostic delay, poor adherence to a GFD, and persistent villous atrophy are factors associated with increased fracture risk in coeliac disease.<sup>7,27,28</sup> In Finland, the diagnostic delay has decreased over the past decades for both coeliac disease and DH.<sup>29,30</sup> Also, the documented adherence to a strict GFD has been shown to be as high as 90% in DH and coeliac disease<sup>15,16</sup>, and persistent villous atrophy in coeliac disease is infrequent.<sup>31,32</sup> These facts at least partly explain the currently found similar hip fracture incidence rates in the DH and coeliac disease cohorts compared to the general population. The detected higher overall fracture risk in coeliac disease compared to DH could instead be explained by the more severe villous atrophy associated with coeliac disease at the time of the diagnosis.

In this study, DH patients with a fracture had been diagnosed earlier compared to patients without a fracture. We have previously shown that the severity of small bowel mucosal damage has become milder in DH<sup>33</sup> and it is generally acknowledged that the importance of a strict adherence to GFD treatment over dapsone has increased during the last decades. Together with decreased diagnostic delay<sup>30</sup> the duration of gluten exposure has thus shortened among DH patients over time and this has most likely had an influence on the decreased fracture risk in those diagnosed with DH in recent times. Moreover, the diagnostic age, and subsequently also the gluten exposure time, of older DH patients in this study was higher than that of the younger ones, which might partly explain the higher hip fracture risk in females aged 80–89 years in the DH cohort compared to corresponding coeliac disease patients.

This study with long follow-up times was conducted with large, well-defined cohorts of patients with biopsy-proven DH and coeliac disease with varying severities of the disease. The gender distributions of the study populations were corresponding to that usually detected in DH and coeliac disease.<sup>3</sup> A hospital-discharge register was used to identify the fractures, and the NHDR has proven to be a reliable source of medical data for epidemiologic studies and its quality and accuracy is well proven for hip fractures.<sup>34</sup>

Even though hospitalization related to proximal humerus, wrist and ankle fractures depends on several factors, such as the severity of the fracture, the operative current care guidelines, the results should be comparable between study groups, as we have no reason to assume vast dissimilarities in the treatment of fractures on the cohort level. A limitation is that in a register-based study, it is not possible to take into consideration various confounding factors such as lifestyle choices and use of medications and long-term illnesses predisposing patients to fractures. In addition, there was no exact data available for the GFD adherence in the study cohorts. However, previously performed studies from the same area and consisting largely of the same DH and coeliac disease patients have shown >90% GFD adherence rates.<sup>16,35</sup> Moreover, improved overall health status, increased body-mass index and an increase in functional ability among the elderly has been also observed in the Finnish population over time,<sup>36</sup> and all of these factors contribute to preventing fractures. Nevertheless, these changes supposedly have affected both study cohorts and also the general population equally. Additionally, it must be emphasized that the general population incidence values were used as reference values for hip fractures instead of matched controls.

To conclude, the risk of hip fractures is not increased in those diagnosed with DH or coeliac disease in an area where adherence to a GFD is good and persistent villous atrophy is infrequent. However, coeliac disease seems to be associated with a slightly higher overall fracture risk compared to DH. Based on these current results, there is no need for routine BMD measurements in DH and not even in coeliac disease. However, since coeliac disease is a known risk factor for fractures, especially in individuals with prolonged diagnosis and in those diagnosed at an old age, the necessity of bone investigations should be considered but still individually assessed based on all of the existing risk factors for fractures. Worth noticing is, however, that the need for BMD evaluation seems to be of higher importance in coeliac disease than in DH.

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## Declaration of interest

The Authors declare no conflict of interests.

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**Table 1.** Demographic data and small bowel mucosal histology at the time of diagnosis for the dermatitis herpetiformis (DH) and coeliac disease study cohorts.

	DH patients (n=368)	Coeliac disease patients (n=1,076)
Female, %*	49	68
Year of birth, median (IQR) *	1946 (1933–1957)	1952 (1940–1967)
Age at diagnosis, %*		
Under 18 years	5	21
18 to 50 years	67	52
Over 50 years	29	26
Small bowel histology at diagnosis, %*		
Normal	29	0
PVA	29	25
SVA/TVA	42	75
Age at the end of the follow-up, median (IQR), years*	67 (57–76)	60 (47–71)

IQR; Interquartile range, PVA; Partial villous atrophy, SVA/TVA; Subtotal/Total villous atrophy

\*  $p < 0.001$  between DH and coeliac disease patients

**Table 2.** Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for hospital-treated fractures in dermatitis herpetiformis patients compared to coeliac disease patients.

	Adjusted <sup>a</sup> HR (95% CI)
All hospital-treated fractures <sup>b</sup>	0.620 (0.429–0.949) *
Hip fracture	0.803 (0.384–1.678)
Other fractures <sup>c</sup>	0.661 (0.423–1.034)

<sup>a</sup>Adjusted for gender and year of birth

<sup>b</sup>Hip, proximal humerus, wrist and ankle fractures combined

<sup>c</sup>Proximal humerus, wrist and ankle fractures

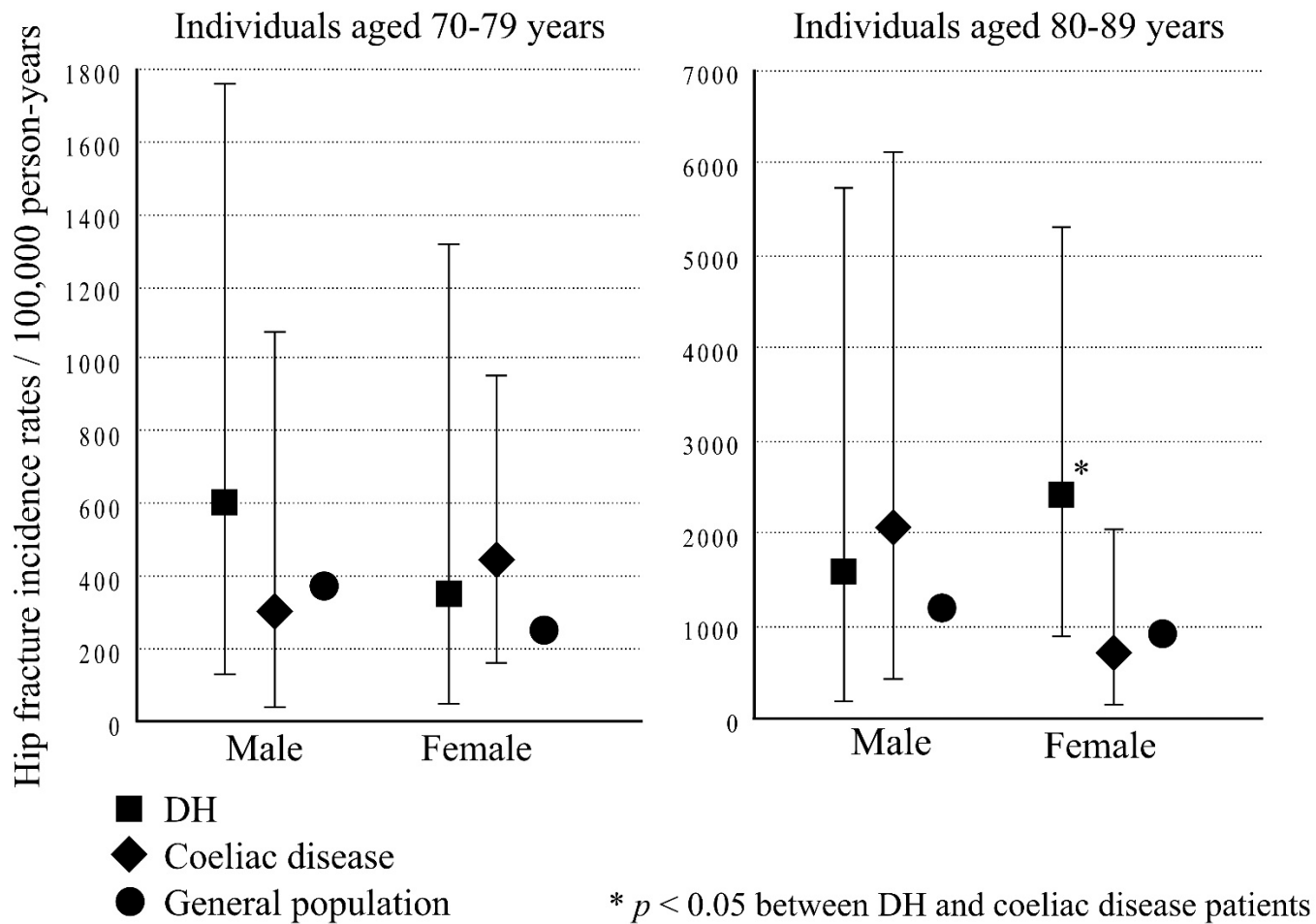
\*  $p = 0.026$



**Table 3.** Demographic and clinical data of dermatitis herpetiformis (DH) and coeliac disease patients with and without fractures.

	DH patients (n=368)			Coeliac disease patients (n=1,076)		
	With fracture (n=35)	Without fracture (n=333)	<i>p</i> -value	With fracture (n=105)	Without fracture (n=971)	<i>p</i> -value
Female, %	63	47	0.083	75	67	0.095
Age at DH or coeliac disease diagnosis, median (IQR), years	54 (35–60)	37 (28–50)	0.002	45 (34–58)	37 (19–50)	<0.001
Year of diagnosis, median (IQR)	1981 (1976–1989)	1985 (1980–1991)	0.056	1990 (1985–1996)	1990 (1985–1996)	0.893
Age at the end of the follow-up, median (IQR), years	71 (56–80)	67 (57–75)	0.309	59 (47–70)	60 (47–71)	0.594
Small bowel histology at diagnosis, %			0.070			0.082
Normal	46	28		0	0	
PVA	14	30		16	26	
SVA/TVA	39	42		84	74	

IQR; Interquartile range, PVA; Partial villous atrophy, SVA/TVA; Subtotal/Total villous atrophy



**Figure 1.** The age- and gender-specific hip fracture incidence rates and 95% confidence intervals for dermatitis herpetiformis (DH) and coeliac disease patients, and the general population of Finland.