Tampere University

CAMILLA PASTERNACK

Burden of Dermatitis Herpetiformis

Comparison to Coeliac Disease

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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland
Tampere University, Celiac Disease Research Center, Finland
Tampere University Hospital, Departments of Internal Medicine and Dermatology, Finland

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ABSTRACT

Coeliac disease is an immune-mediated disease in which dietary gluten causes small bowel mucosal damage in genetically susceptible individuals. Coeliac disease was previously considered to be mainly a malabsorption disorder with overt gastrointestinal symptoms, but currently a wide range of extraintestinal symptoms are increasingly seen. Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease presenting in approximately 13% of coeliac disease patients. In DH, gluten induces an intensively itchy and blistering rash, and DH patients additionally have villous atrophy or coeliac-type inflammation in the small bowel mucosa. Both disorders are treated with a life-long gluten-free diet, which heals the small bowel changes and the DH rash.

Untreated coeliac disease patients suffer from impaired quality of life compared to the general population. With gluten-free dietary treatment, quality of life improves, but following a strict gluten-free diet is challenging. Moreover, a number of complications are associated with coeliac disease, one of which is elevated risk for bone fractures. For these reasons and compared to general population, the disease burden related to coeliac disease persists and the quality of life impaired among long-term treated coeliac disease patients. Despite the observed burden of illness associated with coeliac disease, patients' perceptions of health, well-being and quality of life in DH have been very little studied.

This dissertation studies the burden related to DH. In Study **I**, quality of life and self-perceived experiences were evaluated prospectively in 52 DH patients at the time of the diagnosis and after one year on a gluten-free diet. In addition, the use of medication and health care services during the year preceding and the year following the diagnosis were investigated. Further, the effect of gastrointestinal symptoms on the burden was assessed. Study **II** evaluated quality of life and presence of gastrointestinal symptoms in 78 long-term treated DH patients compared to 371 long-term treated coeliac disease controls and 110 healthy controls.

The self-reported bone fractures were compared between 222 DH patients and 129 coeliac disease controls and further, factors associated with fractures were evaluated (Study **III**). A large register-based hospital-treated fractures study,

focusing specifically on hip fractures, included 368 long-term treated DH patients and 1,076 long-term treated coeliac disease controls (Study **IV**).

The data in Studies **I** and **III** were gathered with questionnaires designed for the purpose of each study and in Study **II** by interview. Quality of life was assessed with the Psychological General Well-being (Studies **I–III)** and with Short-from 36 questionnaires (Study **II)**. Severity of gastrointestinal symptoms was assessed with the Gastrointestinal Symptoms Rating Scale questionnaire in Studies **II** and **III**. The National Hospital Discharge Register was used in Study **IV**.

The DH patients were shown to have impaired perceptions of their health and poorer quality of life at the time of the diagnosis compared to the healthy controls. Further, DH patients with gastrointestinal symptoms were shown to have lower quality of life at diagnosis compared to those without gastrointestinal symptoms (PGWB total median 89 vs. 100, $p = 0.003$). However, after one year's adherence to a gluten-free diet, quality of life in DH patients with and without gastrointestinal symptoms was shown to be comparable to that of healthy controls. Likewise the quality of life of long-term treated DH patients did not differ from that of controls (PGWB total median 104 vs. 107, $p = 0.150$), and treated DH patients were shown not to suffer from persistent gastrointestinal symptoms. The self-reported life-time bone fracture risk was similar in DH and coeliac disease, but the fracture risk after DH or coeliac disease diagnosis was lower in female DH patients than in female coeliac disease controls (hazard ratio, HR 0.473, 95% confidence interval, CI: 0.25–0.88). The DH patients and coeliac disease controls with fractures reported more severe reflux symptoms and used proton-pump inhibitor medication more often than those without fractures. The risk of hospital-treated fractures after being diagnosed was found to be lower in DH than in coeliac disease (HR 0.620, 95% CI: 0.43–0.95), but the hip fracture incidence rates in both DH and coeliac cohorts were comparable to those in the general population of Finland.

The present study showed an increased burden related to untreated, but not to short- and long-term treated DH. Further, the presence of gastrointestinal symptoms at the time of diagnosis had a significant impact on the burden, but long-term treated DH patients were shown not to suffer from persistent gastrointestinal symptoms. After diagnosis, bone fracture risk in coeliac disease seemed to be higher than in DH. Surprisingly, hip fracture risk was shown not to be increased in DH, nor in coeliac disease, which in earlier studies has been linked to increased hip fracture risk.

TIIVISTELMÄ

Keliakia on immuunivälitteinen sairaus, jossa ravinnon gluteeni aiheuttaa ohutsuolen limakalvon vaurion geneettisesti alttiilla yksilöillä. Aiemmin keliakia ilmeni pääosin vaikeina vatsaoireina ja imeytymishäiriönä, mutta nykyään yhä useammin keliakiaa sairastavat kärsivät erilaisista suoliston ulkopuolisista oireista. Ihokeliakiassa, keliakian ihoilmentymässä, ravinnon gluteeni aiheuttaa kutisevan ja rakkulaisen ihottuman. Myös ihokeliakiaa sairastavilla todetaan ohutsuolessa keliakialle tyypillisiä muutoksia, mutta usein lievempiasteisena kuin klassisessa keliakiassa. Ihokeliakiaa esiintyy noin 13 % keliakiapotilaista. Sekä keliakiaa että ihokeliakiaa hoidetaan elinikäisellä gluteenittomalla ruokavaliolla, joka parantaa ohutsuolivaurion sekä ihokeliakiaan liittyvän ihottuman.

Diagnoosivaiheessa keliakiapotilaat kärsivät alentuneesta elämänlaadusta ja käyttävät terveyspalveluita ja lääkkeitä väestöä enemmän. Ruokavaliohoidon myötä tautitaakka vähenee, mutta dieetin noudattaminen on haastavaa. Lisäksi keliakiaan liittyy komplikaatioita, joista yksi on lisääntynyt riski luunmurtumille. Näistä syistä hoidettuunkin keliakiaan liittyy lisääntynyttä tautitaakkaa ja elämänlaatu on alentunut verrattuna normaaliväestöön. Keliakiaan liittyvästä tautitaakasta huolimatta ihokeliakiaan liittyvää tautitaakkaa ja elämänlaatua ei ole juurikaan tutkittu.

Tämä väitöskirja tutkii ihokeliakiaan liittyvää tautitaakkaa. Osatyössä **I** tutkittiin 52 ihokeliakiapotilaan elämänlaatua ja kokemuksia terveydestä diagnoosihetkellä sekä vuoden kestäneen gluteenittoman ruokavaliohoidon jälkeen. Lisäksi verrattiin terveyspalveluiden ja lääkkeiden käyttöä vuotta ennen ja jälkeen diagnoosin, ja kartoitettiin vatsaoireiden vaikutusta tautitaakkaan. Osatyössä **II** tutkittiin pitkään ruokavaliohoidolla olleiden 78 ihokeliakiapotilaan elämänlaatua ja koettuja vatsaoireita verrattuna 371 pitkään ruokavaliohoidolla olleeseen keliakiaverrokkiin ja 110 terveeseen verrokkiin.

Potilaiden itseilmoittamia murtumia verrattiin 222 ihokeliakiapotilaan ja 129 keliakiaverrokin välillä, ja murtumiin liittyviä tekijöitä kartoitettiin (Osatyö **III**). Isossa rekisteritutkimuksessa tutkittiin 368 pitkään hoidolla olleen ihokeliakiapotilaan ja 1 076 hoidetun keliakiaverrokin sairaalahoitoisia murtumia. Erityisesti tutkimuksessa keskityttiin lonkkamurtumiin, joiden ilmaantuvuutta verrattiin myös lonkkamurtumailmaantuvuuteen Suomen väestössä (Osatyö **IV**).

Aineistot osatöihin **I** ja **III** kerättiin tutkimuksia varten suunnitelluilla kyselyillä ja osatyöhön **II** haastattelulla. Elämänlaatua arvioitiin Psychological General Well-being (PGWB)– (Osatyöt **I**-**III**) ja Short-from 36 –kyselyiden (Osatyö **II**) avulla ja vatsaoireiden vaikeutta arvioitiin Gastrointestinal Symptoms Rating Scale – kyselylomakkeella (Osatyöt **II** ja **III**). Terveyden ja hyvinvoinnin laitoksen ylläpitämää hoitoilmoitusrekisteriä käytettiin osatyössä **IV**.

Ihokeliakiapotilaat kokivat diagnoosivaiheessa terveytensä heikentyneeksi ja he kärsivät alentuneesta elämänlaadusta kontrolleihin verrattuna. Niillä ihokeliakiapotilailla, jotka kärsivät iho-oireiden lisäksi vatsaoireista, elämänlaatu oli matalampi kuin niillä, joilla vatsaoireita ei ollut (PGWB yhteissumma, mediaani 89 vs. 100, $p = 0.003$). Vuoden kuluttua gluteenittoman ruokavaliohoidon aloituksesta elämänlaatu oli sekä vatsaoireisilla että –oireettomilla ihokeliakiapotilailla samalla tasolla kuin terveillä verrokeilla. Myös pitkään ruokavaliolla olleiden ihokeliakiapotilaiden elämänlaatu oli verrokkien tasolla (PGWB yhteissumma, mediaani 104 vs. 107, $p = 0.150$), eikä hoidetuilla ihokeliakiapotilailla todettu pitkittyneitä vatsaoireita. Itseilmoitettu elinikäinen luunmurtumariski todettiin samankaltaiseksi ihokeliakiassa ja keliakiassa, mutta keliakia- tai ihokeliakiadiagnoosin jälkeen ihokeliakiaa sairastavilla naisilla todettiin keliakiaa sairastaviin naisiin verrattuna matalampi murtumariski (riskitiheyssuhde, HR 0.473, 95% luottamusväli CI: 0.25–0.88). Ihokeliakiapotilaat, jotka raportoivat murtuman, kärsivät hankalammista refluksioireista ja käyttivät enemmän protonipumpun estäjälääkkeitä kuin ne, joilla ei ollut murtumaa. Myös sairaalahoitoisten luunmurtumien riski diagnoosin jälkeen oli pienempi ihokeliakiapotilailla kuin keliakiaverrokeilla (HR 0.620, 95% CI: 0.43–0.95). Tästä huolimatta sekä keliakiassa että ihokeliakiassa lonkkamurtumailmaantuvuudet olivat Suomen väestön tasolla.

Tämä tutkimus osoitti, että ihokeliakiaan liittyy kohonnut tautitaakka diagnoosivaiheessa, ja lisääntynyttä tautitaakkaa tavataan etenkin niillä ihokeliakiapotilailla, jotka kärsivät vatsaoireista. Lyhyt- tai pitkäaikaisesti hoidetussa ihokeliakiassa elämänlaadun ei todettu alentuneen, eikä hoidettuun ihokeliakiaan liittynyt pitkittyneitä vatsaoireita. Diagnoosin jälkeinen murtumariski todettiin ihokeliakiassa keliakiaa pienemmäksi. Lonkkamurtumariski ei ollut väestöön verrattuna lisääntynyt ihokeliakiassa, mutta ei myöskään keliakiassa, johon aiempien tutkimusten perusteella liittyy lisääntynyt lonkkamurtumariski.

TABLE OF CONTENTS

ABBREVIATIONS

BMD	bone mineral density
BMI	body-mass index
CD-QoL	Coeliac Disease Quality of Life Survey
CDQ	Coeliac disease questionnaire
CI	confidence interval
DALY	disability-adjusted life years
DH	dermatitis herpetiformis
DGP	deaminated gliadin peptide
DRQ	disease-related questionnaire
DXA	dual energy X-ray absorptiometry
EmA	endomysial antibody
GSRS	Gastrointestinal Symptoms Rating Scale
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health-related quality of life
ICD	International Statistical Classification of Diseases
Ig	immunoglobulin
IL	interleukin
IQR	interquartile range
MHC	major histocompatibility complex
NHDR	National Hospital Discharge Register
NHL	non-Hodgkin's lymphoma
TG	transglutaminase
OR	odds ratio
PGWB	Psychological General Well-Being
PPI	proton-pump inhibitor
PROM	patient-reported outcome measure
RCD	refractory coeliac disease
SF-36	Short Form 36
SSRI	selective serotonin receptor inhibitors
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals (**I**-**IV**)

I Pasternack C, Kaukinen K, Kurppa K, Mäki M, Collin P, Hervonen K, Reunala T, Huhtala H, Kekkonen L, Salmi T (2017): Gastrointestinal Symptoms Increase the Burden of Illness in Dermatitis Herpetiformis: A Prospective Study. Acta Derm Venereol. 97(1):58–62.

II Pasternack C, Kaukinen K, Kurppa K, Mäki M, Collin P, Reunala T, Huhtala H, Salmi T (2015): Quality of Life and Gastrointestinal Symptoms in Long-Term Treated Dermatitis Herpetiformis Patients: A Cross-Sectional Study in Finland. Am J Clin Dermatol. 16:545–52.

III Pasternack C, Mansikka E, Kaukinen K, Hervonen K, Reunala T, Collin P, Huhtala H, Mattila V.M., Salmi T (2018): Self-reported fractures in dermatitis herpetiformis compared to coeliac disease. Nutrients. 10:351

IV Pasternack C, Koskinen I, Hervonen K, Kaukinen K, Järvelin J, Reunala T, Collin P, Huhtala H, Mattila V.M., Salmi T: Risk of fractures in dermatitis herpetiformis and coeliac disease: a register-based study. Submitted.

INTRODUCTION

Coeliac disease is a gluten-sensitive small bowel enteropathy with a prevalence of 1–2% (Singh et al. 2018). Coeliac disease is characterized by a wide range of gastrointestinal and extraintestinal symptoms and due to the wide clinical spectrum and at times mild and vague symptoms, coeliac disease is an underdiagnosed disease with a long diagnostic delay (Bai and Ciacci 2017). Once diagnosed, gluten-free diet is the cornerstone of treatment in coeliac disease. The strict life-long diet, however, is socially restrictive, time-consuming and difficult to comply with (See et al. 2015). Prolonged gluten consumption due to diagnostic delay and poor adherence to diet predisposes coeliac disease patients to increased risk of complications and one of the most common complication related to coeliac disease is the bone fractures. Bone fracture risk has been shown to be elevated in coeliac disease and is mainly thought to be associated with small bowel mucosal villous damage affecting the absorption of nutrients (Heikkilä et al. 2015).

Due to difficult and diverse symptoms, challenging treatment and troublesome complications, an increased burden of disease has been shown to be related to coeliac disease. The burden is most prevalent in untreated coeliac disease: untreated coeliac disease patients perceive their quality of life impaired and use more health care resources and medications compared to controls (Nachman et al. 2009; Ukkola et al. 2012a). Despite the many negative aspects of gluten-free diet, the burden in coeliac disease decreases after the initiation of the treatment (Ukkola et al. 2011b; Burger et al. 2017). Nevertheless, quality of life does not normalize with the gluten-free diet and the use of health care resources remains increased compared to the general population (Violato et al. 2012; Burger et al. 2017). In addition, the burden does not only concern coeliac disease patients but also their non-coeliac partners (Roy et al. 2016b).

Dermatitis herpetiformis (DH) is a well-characterized extraintestinal manifestation of coeliac disease. In patients with DH, gluten induces an intensively itching blistering rash and in addition the coeliac-type small bowel mucosal atrophy and inflammation. DH is also treated with strict gluten-free diet and the diet heals both the mucosal villous atrophy and the rash (Reunala 2001). Despite DH being a cutaneous manifestation of coeliac disease treated with the same restrictive gluten-

free diet, and in addition a chronic itching skin disease, the burden and quality of life in DH have so far been rarely studied. Also, very little is known about the bone fracture risk in DH, although DH patients have the same small bowel mucosal villous atrophy as coeliac disease patients, although this is usually less severe.

The aim of the dissertation was to estimate the burden related to both untreated and treated DH by studying quality of life, use of heath care resources and medication and the fracture risk in DH patients.

REVIEW OF THE LITERATURE

1 DISEASE SPECTRUM OF COELIAC DISEASE

1.1 Coeliac disease

Coeliac disease is a chronic autoimmune-mediated small bowel enteropathy. In coeliac disease ingested gluten peptides trigger a small-bowel mucosal inflammation and villous atrophy in genetically susceptible individuals. Until the 1980s coeliac disease was considered a rare entity occurring mainly in children as a malabsorption disorder with overt gastrointestinal symptoms and weight loss. Since then the prevalence of the disease has increased (Singh et al. 2018) and its clinical presentation has become more diverse (Bottaro et al. 1999; Kivelä et al. 2015).

In all coeliac disease patients the gluten-dependent immune reaction affects primarily the small intestine. Therefore gastrointestinal symptoms such as bloating, loose stools and abdominal pain or discomfort are still a common nuisance for patients with coeliac disease. However, coeliac disease affects many different organs and thus a wide range of extraintestinal symptoms have become increasingly common (Volta et al. 2014; Kivelä et al. 2015). These extraintestinal symptoms are discussed in detail in Chapters 1.2 and 1.3. In addition, totally asymptomatic coeliac disease exists and is typically detected in patients belonging to coeliac disease at-risk groups, such as relatives of coeliac disease patients or in patients with other autoimmune diseases (Chapter 1.4 and Table 1) (Fasano et al. 2003).

1.2 Dermatitis herpetiformis

Dermatitis herpetiformis (DH) was first described by Louis Duhring in 1884 as a life-long violently itching skin disease (Duhring 1884). Differential diagnostics from other blistering autoimmune skin diseases became possible in 1969, when skin immunofluorescence findings typical for DH were described (Van Der Meer 1969). In the 1960s it was further observed that the majority of DH patients had gluten-reactive small-bowel mucosal villous atrophy (Marks et al. 1966; Weinstein et al. 1971) and currently DH is widely accepted as a cutaneous manifestation of coeliac disease (Reunala 2001; Collin et al. 2017).

The typical presentation of DH is an intense pruritus with a symmetric polymorphic blistering rash (Reunala 2001). The most common sites of the rash are the extensor surfaces of the elbows and knees, buttocks, back and scalp. The rash may also appear on the abdomen, groin or face; even oral lesions have been reported but these are rare (Lähteenoja et al. 1998). The DH blisters are relatively small and are frequently eroded and crusted as a result of scratching (Reunala 2001). DH is often suspected in the presence of pruritus and rash at typical DH locations but it can also be confounded with other itching skin diseases (Reunala 2001). The presence of gastrointestinal symptoms in DH has been little studied but the clinical consensus is that the gastrointestinal symptoms that may appear in association with DH are often minor (Collin et al. 2017).

Although there is no doubt that DH belongs to the coeliac disease spectrum (Collin et al. 2017), in this thesis the term coeliac disease is used to refer to all phenotypes of coeliac disease other than DH.

1.3 Other extraintestinal symptoms of coeliac disease

In addition to DH, a variety of other extraintestinal symptoms of coeliac disease are known. In childhood coeliac disease the most frequent extraintestinal manifestation is poor growth and this is associated with more severe disease (Nurminen et al. 2015). Delayed puberty and enamel defects may occur in children with coeliac disease (Aine 1994; Bottaro et al. 1999), and as the enamel defects are permanent they also persist to adulthood (Aine et al. 1990). Anaemia may occur in all age groups, is one of the most common extraintestinal presentation of coeliac disease and is also linked to more severe disease (Abu Daya et al. 2013; Saukkonen et al. 2017). Anaemia in coeliac disease is caused by malabsorption of micronutrients such as iron, and more rarely folic acid or vitamin B_{12}, but the chronic inflammation may also contribute (Bergamaschi et al. 2008). The liver enzymes are elevated in up to 20% of newly diagnosed patients and the serum transaminases often normalize with gluten-free diet (Sainsbury et al. 2011). In addition, coeliac disease related neurologic symptoms have been shown to occur, the most common of these being gluten ataxia and peripheral neuropathy (Hadjivassiliou et al. 2003; Briani et al. 2008; Thawani et al. 2015). Joint symptoms, including pain and swelling, have also been reported (Lubrano et al. 1996). Furthermore, coeliac disease is linked to problems with reproduction (Singh et al. 2016). Bone mineral density (BMD) is often decreased in untreated coeliac disease and is discussed in greater detail in Chapter 6.

1.4 Risk groups and associated conditions

The relatives of coeliac disease and DH patients are at increased risk of having both disorders (Reunala 1996). According to a recent meta-analysis, the prevalence of coeliac disease or DH in first-degree relatives of individuals with either manifestation is 7.5%, siblings being the most often affected (Hervonen et al. 2002; Singh et al. 2015).

Coeliac disease is associated with certain genetic disorders. Individuals with Down's syndrome are at 6-fold risk of coeliac disease and those with Turner's syndrome are at 3.3-fold risk for coeliac disease compared to general population (Mårild et al. 2013, 2016). Also, the prevalence of IgA deficiency is 2% in coeliac disease patients and thus higher than in general population (0.4%) (Chow et al. 2012; Pallav et al. 2016). Partial IgA deficiency has also been reported in DH, but according to current knowledge total IgA deficiency cannot emerge in DH as the presence of IgA is the pathognomonic finding in DH (Samolitis et al. 2006).

Many autoimmune conditions are known to occur in association with coeliac disease and DH. In a large study from Denmark, autoimmune comorbidities occurred in 16.4% of coeliac disease patients and 5.3% of general population (Grode et al. 2018). Common associated autoimmune diseases are type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome and autoimmune liver disease (Table 1). Furthermore, approximately 5% of patients with type 1 diabetes have been diagnosed with coeliac disease (Elfström et al. 2014), and among adult patients with autoimmune thyroid disease the prevalence of biopsy-proven coeliac disease has been 2.7% (Roy et al. 2016a). In patients with Sjögren's syndrome or Addison's disease, coeliac disease has been found in 14.7% and 8% of individuals respectively (Iltanen et al. 1999; Myhre et al. 2003). Recently, a connection between DH, and to a lesser extent coeliac disease, with another autoimmune bullous disease bullous pemphigoid was reported in a large case-control study (Varpuluoma et al. 2019). Further, other autoimmune skin diseases have been shown to sporadically co-occur with coeliac disease and DH (Rodrigo et al. 2018, Reunala and Collin 1997).

Table 1. Prevalence of autoimmune diseases in coeliac disease, dermatitis herpetiformis and general population in selected studies

Coeliac disease		Dermatitis herpetiformis		General population	
Study	Prevalence, %	Study	Prevalence, %	Study	Prevalence, %
Type 1 diabetes mellitus					
Bibbò et al. 2017	2.7	Krishnareddy et al. 2014	0	Hakkarainen et al. 2017	0.007
Kylökäs et al. 2016	3.8	Ohata et al. 2012	8.8	Bruno et al. 2016	0.001
Krishnareddy et al. 2014	1.9	Hervonen et al. 2004	2.3	Dabelea et al. 2014	0.002
Reunala and Collin 1997	5.5	Reunala and Collin 1997	1.0	Menke et al. 2013	0.003
Autoimmune thyroid diseases					
Krishnareddy et al. 2014	10.2	Handa et al. 2018	13.8	Sategna-Guidetti et al. 2001	7.6
Hakanen et al. 2001	13.9	Krishnareddy et al. 2014	12.2	Hakanen et al. 2001	2.1
Sategna-Guidetti et al. 2001	13.7	Ohata et al. 2012	1.1		
Reunala and Collin 1997	6.0	Reunala and Collin 1997	4.3		
Sjögren's syndrome					
Bibbò et al. 2017	2.7	Krishnareddy et al. 2014	1.0	Anagnostopoulos et al. 2010	0.2
Krishnareddy et al. 2014	10.5	Ohata et al. 2012	1.1	Birlik et al. 2009	0.4
Reunala and Collin 1997	2.9	Reunala and Collin 1997	1.0	Haugen et al. 2008	0.2
Autoimmune hepatitis					
Bibbò et al. 2017	0.4	Krishnareddy et al. 2014	3.1	Kim et al. 2017	0.005
Krishnareddy et al. 2014	0.3			Grønbaek et al. 2014	0.002
Addison's disease					
Krishnareddy et al. 2014	0.3	Krishnareddy et al. 2014	0	Olafsson and Sigurjonsdottir 2016	0.002
Elfström et al. 2007	0.3	Reunala and Collin 1997	0	Meyer et al. 2014	0.001
Reunala and Collin 1997	0.5				
Vitiligo					
Bibbò et al. 2017	1.2	Handa et al. 2018	1.5	Zhang et al. 2016	0.2
Krishnareddy et al. 2014	1.3	Krishnareddy et al. 2014	2.0		
Norström et al. 2012	3.8				
Alopecia					
Krishnareddy et al. 2014	0.3	Handa et al., 2018	1.5	Safavi 1992	0.2
Norström et al. 2012	1.8	Krishnareddy et al. 2014	1.0		
Reunala and Collin 1997	0.3	Reunala and Collin, 1997	0		

2 PATHOGENESIS

2.1 Genetics

Coeliac disease and DH are polygenetic diseases and the genetic predisposition is essential for disease development, although gluten is the trigger of the disease (Sollid and Jabri 2013). The most important genetic factor behind coeliac disease and DH is the gene cluster of chromosome six called the major histocompatibility complex (MHC) II (Katz et al. 1972; Stokes et al. 1972). The MHC II encodes cell surface proteins called human leukocyte antigens (HLA). These membrane-bound glycoproteins are found in antigen presenting cells and their function is to present peptides to immune cells (Sollid and Jabri 2013).

The HLA molecules are heterodimers consisting of α- and β-chains encoded by HLA-DQA1 and HLA-DQB1 genes. The HLA-DQ2 haplotype is present in more than 90% of coeliac disease and DH patients and is encoded by the HLADQA1*05:01 and HLADQB1*02:01 (also called HLA-DQ2.5) alleles. Practically all the remaining patients have the HLA-DQ8 haplotype encoded by alleles HLADQA1*03:01 and HLADQB1*03:02 (Sollid et al. 1989; Spurkland et al. 1997; Karell et al. 2003). HLA dosage may affect the risk of developing coeliac disease (Liu et al. 2014), and although HLA-DQ2 homozygosis has been associated with more severe coeliac disease (Karinen et al. 2006), other studies have failed to observe any association between the HLA-region and severity or manifestation of coeliac disease (Johnson et al. 2004; Thomas et al. 2009; Agardh et al. 2015). The matter is further emphasized in a twin study reporting monozygotic twins with one having coeliac disease and the other DH (Hervonen et al. 2000). However, while the HLA-DQ2 and DQ8 haplotypes exist in up to 50% of northern population (Kårhus et al. 2018a), they are necessary but not sufficient for the pathogenesis and thus the majority of carriers will never develop coeliac disease or DH. In addition, over 40 non-HLA regions have been found to increase the risk of coeliac disease and DH (Trynka et al. 2012).

2.2 Gluten and environment

The prolamin storage proteins in wheat, barley and rye are collectively called 'gluten'. More specifically, the proteins in wheat are called respectively gliadins and glutenins and in barley and rye hordeins and secalins (Sollid and Jabri 2013). Ingested gluten is a prerequisite for triggering coeliac disease and DH. However, it is unclear why the disease process is triggered in only a small portion of genetically susceptible individuals. The amount of dietary gluten consumed seems to be associated with the prevalence of coeliac disease at an epidemiological level (Ramakrishna et al. 2016; Singh et al. 2018). The timing of gluten introduction in childhood also has some effects as late gluten introduction increases the diagnostic age (Lionetti et al. 2014) and also seems to slightly increase the risk of generating coeliac disease (Aronsson et al. 2016; Pinto-Sánchez et al. 2016).

There is evidence that non-dietary risk factors are also involved in triggering loss of gluten tolerance (Lindfors et al. 2019). Infections and normal intestinal microbiota downregulate immunity and modulate immune tolerance. For this reason the hygiene hypothesis has been suggested to explain the increased incidence of coeliac disease and other autoimmune diseases in the developed countries (Bach 2018). A vast geographical gradient in the incidence of coeliac disease between Finland and Russia supports the hygiene hypothesis as the genetic predisposition for coeliac disease and the use of grains in these two populations is fairly similar but the socioeconomic environment differs (Kondrashova et al. 2008). In addition, many factors related to the peri- or postnatal period have been detected, such as being born during the summer season (Lebwohl et al. 2013; Tanpowpong et al. 2013) or by elective caesarean section (Decker et al. 2010; Mårild et al. 2012) have both been associated with increased risk of coeliac disease. The protective effect of breastfeeding explained by the high numbers of immunomodulating and antimicrobial molecules in breastmilk has also been proposed, but a recent meta-analysis failed to observe such a significance (Pinto-Sánchez et al. 2016). A positive association between gastrointestinal and other types of infections and development of coeliac disease has been reported in many studies (Stene et al. 2006; Mårild et al. 2015; Kemppainen et al. 2017; Kårhus et al. 2018), and altered duodenal and faecal microbiota has also been linked to coeliac disease (Girbovan et al. 2017). In addition, DH patients have been shown to have different microbiota when compared with coeliac disease patients with gastrointestinal symptoms (Wacklin et al. 2013), but other than that very little is known about the generation of different phenotypes of coeliac disease.

2.3 Small bowel pathogenesis

The ingested gluten is incompletely digested in the human gastrointestinal system, which leads to the generation of harmful gliadin peptides in the small-bowel lumen. These peptides generate an inflammatory reaction via the innate immune system in the small bowel mucosa (Sollid and Jabri 2013). The toxic gliadin peptides seem to have diverse harmful effects on the mucosa, but one of the most important is the production of interleukin (IL) 15 in mucosal cells (Maiuri et al. 2003). The IL-15 and other co-existing factors induce a stress reaction in the epithelial barrier, causing the leakage of gliadin fragments into the lamina propria (Meresse et al. 2004; Setty et al. 2015).

The enzyme called tissue transglutaminase (TG2) has a key role in the pathogenesis of coeliac disease as it has the ability to deaminate gliadin peptides in the lamina propria. This deamination increases gliadins' affinity to bind the peptide binding groove of the HLA-DQ-molecule (Molberg et al. 1998). The antigen-presenting cells with the HLA-DQ-gliadin-complexes interact with CD4 gliadin-specific T cells enhancing their activity and resulting in adaptive immune activation. Consequently high levels of proinflammatory cytokines such as interferon-γ and IL-21 are produced (Sollid and Jabri 2013). The production of proinflammatory cytokines and IL-15 produced in the mucosal cells generate an appropriate environment for the differentiation and activation of intraepithelial cytotoxic T lymphocytes. This dysregulated activation leads to the selective destruction of intestinal epithelial cells causing the initially mucosal villous atrophy and crypt hyperplasia characteristic of coeliac disease (Schuppan et al. 2009; Sollid and Jabri 2013). The other role of the gluten-reactive T cells is to activate the B cells and help them to differentiate to plasma cells producing anti-gliadin and anti-TG2 antibodies (Di Niro et al. 2012).

2.4 Skin immunopathogenesis in dermatitis herpetiformis

The pathognomonic granular IgA deposits in the papillary dermis of DH patients were identified as early as in 1969 (Van Der Meer 1969), but the target of the IgA long remained unclear. In 2002 it was shown that this target and also the autoantigen of DH is epidermal transglutaminase (TG3) (Sárdy et al. 2002). TG3 is an enzyme from the same family as TG2, but is less frequently expressed in tissues (Hitomi 2005). It is still not known why some patients with coeliac predisposition develop antibodies against TG3. However, TG3 is homologous to TG2 in its the

enzymatically active domains and for this reason intermolecular epitope spreading has been suggested as a cornerstone of TG3 antibody formation (Zone et al. 2011), and also of the development of DH. Recent evidence further suggests that TG3-antibodies are produced in the small bowel (Hietikko et al. 2018a).

TG3 is known also to exist in the skin of healthy individuals - not in the papillary dermis but in the keratinocyte layers of the epidermis (Hitomi 2005). Due to the predilection sites of skin lesions, it is hypothesized that microtrauma causes the release of TG3 from the keratinocytes in DH (Zone et al. 2011). From there, TG3 could migrate to the basement membrane to bind with the antibodies. Alternatively, TG3 may be released into the bloodstream and the immunocomplexes formed in the circulation could then be deposited on the papillary dermis. The TG3-IgA immunocomplexes have been recently found in the circulation, which lends support to the latter theory (Görög et al. 2016).

IgA and TG3 are found together in the papillary dermis in a form of insoluble, gluten-dependent aggregates and it has been shown that the TG3 co-localized with IgA in the papillary dermis maintains its enzymatic activity (Taylor et al. 2015). This activity has been suggested to lead to fibrinogen binding, and as fibrinogen is an inflammatory protein, it is postulated that it could promote the attraction of immunogenic cells. The accumulation of T cells could then lead to the production of proinflammatory cytokines attracting the neutrophils that drive blister formation (Taylor et al. 2015).

The immunopathogenesis in DH is possibly an outcome of prolonged gluten consumption in patients with latent or neglected coeliac disease (Sárdy et al. 2002). Patient series with coeliac disease evolving into DH with ongoing gluten-consumption have been described (Kurppa et al. 2008; Salmi et al. 2015), and it has also been found that age correlates with the presence of serum TG3 antibody titres in coeliac disease (Salmi et al. 2016). The epidemiological aspects of the two diseases, discussed in more detail in the next chapter, also support this hypothesis.

3 EPIDEMIOLOGY

According to a recent meta-analysis, the global prevalence of serologically diagnosed and biopsy-proven coeliac disease is 1.4% and 0.7% respectively (Singh et al. 2018). In Finland the prevalence of coeliac disease has been shown to be as high as 2% (Lohi et al. 2007; Vilppula et al. 2009; Mustalahti et al. 2010). With wider awareness and improved serological diagnostic tools, the incidence of diagnosed coeliac disease has increased worldwide (Kang et al. 2013), but the true incidence of the disease has also increased (Lohi et al. 2007; Rubio-Tapia et al. 2009; Catassi et al. 2010). In Finland the incidence of all phenotypes of coeliac disease combined, also including DH, has risen from 5 per 100,000 in the 1980s, to 39 per 100,000 in 2006 (Collin et al. 2007; Virta et al. 2009). Recently, a small decrease in the incidence of adult coeliac disease has been observed in Finland despite the increasing awareness of the disease (Virta et al. 2017), and it was conjectured that exposure to an unknown trigger factor may have plateaued.

In the 1980s the incidence of DH in Finland was on the same level as the incidence of coeliac disease (Collin et al. 2007). Unlike in coeliac disease, the incidence of DH has continuously decreased after the 1980s in Finland and in the United Kingdom (Salmi et al. 2011; West et al. 2014; Virta et al. 2017). The incidence of DH in Finland is currently 2.7/100,000, the prevalence is 75/100,000, and 13% of coeliac disease patients suffer from DH (Salmi et al. 2011).

Childhood coeliac disease is common, but a childhood diagnosis of DH is rare in Finland, where only 4% of those diagnosed with DH were children (Hervonen et al. 2014). Globally childhood diagnosis of DH seems to be more common (Dahlbom et al. 2010; Antiga et al. 2013). Both coeliac disease and DH may, however, emerge at any age and the mean age of DH and adult coeliac disease diagnosis in Finland is approximately 50 years (Mansikka et al. 2017; Virta et al. 2017). Females predominate over males in coeliac disease (Singh et al. 2018), although some screening studies show no gender differences (Fasano et al. 2003; Vilppula et al. 2009). On the contrary, previously males were predominant in DH and the gender ratio was estimated at 2:1 (Moi 1984; Smith et al. 1992). However, this has equalized in recent decades; the gender ratio is practically even with only slight male predominance (1.1:1) (Salmi et al. 2011; West et al. 2014).

4 DIAGNOSIS

4.1 Small bowel biopsies

For decades the diagnosis of coeliac disease has been based on demonstration of small bowel mucosal inflammation, villous atrophy and crypt hyperplasia from duodenal biopsies taken during gastroscopy (Ludvigsson et al. 2014). The diagnostic biopsy should be taken during a normal gluten-containing diet and multiple biopsies are recommended due to the possibility of patchy changes (Bai and Ciacci 2017).

The villous atrophy develops gradually from a normal mucosal morphology and typically a Marsh classification has been used to rate the severity of mucosal damage (Marsh 1992). In addition, reduced villous height to crypt depth ratio has been shown to be a specific measure of the damage as it considers both the atrophy and the crypt hyperplasia. The villous height to crypt depth ratio should be defined as an average of at least three separate units and ratios above two are considered normal (Kuitunen et al. 1982; Taavela et al. 2013a).

Defining intraepithelial lymphocytes from frozen small bowel biopsies may facilitate diagnosis in diagnostically challenging cases as $CD3^+$ and $\gamma\delta^+$ cells are often elevated in coeliac disease (Salmi et al. 2010) and $\gamma\delta^+$ cells are considered a typical finding in coeliac disease and DH (Savilahti et al. 1992; Järvinen et al. 2003). Small bowel mucosal antibody deposits directed against TG2 have also been detected in coeliac disease (Korponay-Szabó et al. 2004) and may be used in difficult cases as they are also present in seronegative disease (Salmi et al. 2006) and are also detectable before the villous atrophy develops (Kaukinen et al. 2005). Similar, but less prevalent, gluten-dependent TG2-specific IgA deposits are present in the small bowel mucosa of DH patients (Salmi et al. 2014) (Table 2). In Finland, according to recently published recommendations, small bowel biopsies are no longer invariably necessary for coeliac disease diagnosis. Serology-based diagnosis of coeliac disease is described in Chapter 4.3. Also, obtaining small bowel biopsies is not needed in DH diagnostics (Coeliac disease: Current Care Guidelines, 2018).

4.2 Skin biopsies

The diagnosis of DH is based on clinical suspicion followed by a skin biopsy. The diagnostic biopsy should be taken from uninvolved skin close to the active lesion. Biopsy from the erythematous skin or from uninvolved skin further from the lesion has been shown to sometimes yield false negative results (Zone et al. 1996). The biopsy should be taken during a normal gluten-containing diet to ensure the correct diagnosis although the IgA persists in the skin for a long period of time (Fry et al. 1978). The frozen skin biopsy is studied with direct immunofluorescence and demonstration of granular IgA deposits in the dermal papillae is pathognomonic for DH (Van Der Meer 1969). Histopathological analysis of lesional skin biopsy is not needed for DH diagnosis and, if taken, the findings are not totally specific for DH (Reunala 2001). DH-specific skin immunofluorescence biopsy findings with IgA have been also described in coeliac disease, but more research is needed to elucidate the matter (Cannistraci et al. 2007).

4.3 Serology

TG2 was discovered in the 1990s to be the main autoantigen of coeliac disease and DH (Dieterich et al. 1997, 1999). The TG2 antibodies from the sera can be measured with TG2 antibody testing based on immunoassay or by determining the endomysial antibodies (EmA), which also target the TG2 (Korponay-Szabó et al. 2004). In coeliac disease TG2 antibody testing is more sensitive than EmA testing (76–97% vs. 61–100%) but less specific (91–98% vs. 98–100%) (Giersiepen et al. 2012; Schyum and Rumessen 2013). EmA testing is also more laborious and subject to individual interpretation. In DH antibody testing is less accurate and the serum antibodies are negative in one third of DH patients (Mansikka et al. 2018a) (Table 2). Other antibodies detected in the sera of coeliac disease and DH patients are antireticulin and antigliadin antibodies and antibodies against deaminated gliadin peptides (DGP). The first two are no longer in use and DPG antibodies are not commonly used as primary antibodies in diagnostics. Normally the IgA class antibodies are tested but in cases where an IgA deficiency is known or suspected, the IgG counterparts can be used (Bai and Ciacci 2017).

As the quality of antibody testing has improved, serology-based diagnostics have gained ground in the diagnostics of coeliac disease. According to the guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition,, in symptomatic children the coeliac disease diagnosis can be made without biopsy if

the TG2 antibody titer is more than ten times the upper limit of normal, EmA positivity is detected in a different blood sample and the genetic predisposition (HLADQ2/DQ8 haplotypes) exists. (Husby et al. 2012). The implication of this "triple criteria" has been shown to be appropriate in diagnosing both children and adults (Werkstetter et al. 2017; Fuchs et al. 2019). The recently published Finnish current care guidelines also allow coeliac disease serology based diagnostic in adults if the TG2 antibody titer is more than ten times the upper limit of normal and EmA is positive (Coeliac disease: Current Care Guidelines, 2018). However, global coeliac disease guidelines still recommend small bowel biopsy based diagnostics in adult coeliac disease (Ludvigsson et al. 2014; Bai and Ciacci 2017).

IgA autoantibodies against TG3 have been detected in the sera of the majority of untreated DH patients and TG3 is currently considered the main autoantigen in DH (Sárdy et al. 2002). However, some coeliac disease patients also have circulatory antibodies against TG3 although they do not suffer from skin lesions (Borroni et al. 2013; Salmi et al. 2016) (Table 2). The exact role and value of TG3 antibodies have yet to be elucidated and therefore these antibodies are not currently used in clinical practice. In addition TG6 antibodies have been described in relation to gluten ataxia in coeliac disease (Hadjivassiliou et al. 2008).

Table 2. Differences in diagnostics between dermatitis herpetiformis and coeliac disease

	Dermatitis Herpetiformis	Coeliac disease
Gender distribution	Slight predominance in males	Females predominate
Age at diagnosis	Mostly adults	At any age
Serum IgA-TG2 antibodies	60–85%	95–100%
Serum IgA-TG3 antibodies	45–100%	15–53%
IgA-TG3 deposits in the skin	100%	0% [a]
IgA-TG2 deposits in small bowel	80%	95–100%
Small bowel mucosal villous atrophy	75%	95–100%

[a] some have been reported (Cannistraci et al. 2007)
References: Heil et al. 2005; Lohi et al. 2007; Hull et al. 2008; Salmi et al. 2011, 2014, 2016; Borroni et al. 2013; Reunala et al. 2015; Virta et al. 2017; Mansikka et al. 2018a

5 TREATMENT

5.1 Gluten-free diet

A strict and life-long gluten-free diet is currently the only available treatment for both coeliac disease and DH. The basis of gluten-free diet is excluding wheat, rye and barley from the diet. The incorporation of oats in the diet remains debatable. A recent meta-analysis states that oats are in general safe for patients with coeliac disease and DH (Pinto-Sánchez et al. 2017) and in Finland the majority of coeliac disease and DH patients use oats as part of their diet. However, there are also a few studies reporting adverse effects of incorporating oats into the diet of coeliac disease patients (Arentz-Hansen et al. 2004).

The gluten-free diet has many favourable effects on patients suffering from coeliac disease or DH. The diet heals gastrointestinal symptoms usually in days or weeks and this is followed by normalization of antibody titers (Bai and Ciacci 2017). Eventually the diet also heal the small bowel mucosal lesions, but this process is slow, often taking longer than one year (Rubio-Tapia et al. 2010; Sharkey et al. 2013). The skin symptoms of DH also usually recover in a few months on gluten-free diet but the histological changes in the skin persist in some cases even years after initiation of the gluten-free diet (Hietikko et al. 2018b).

5.2 Dapsone medication in dermatitis herpetiformis

The rash related to DH is often very itchy and troublesome. Although gluten-free diet is the cornerstone of treatment in DH, as mentioned previously, the rash reacts slowly to gluten-free diet. Dapsone (4,4'-diamino-diphenylsulfone) is an antibacterial agent with anti-inflammatory properties. The response for dapsone in the pruritus and the rash in DH is usually achieved in a few days after initiating therapy. Dapsone medication has no effect on the small bowel mucosal damage and thus the gluten-free diet must always be started alongside with dapsone. In DH the initial daily dose of dapsone is 25–50 mg, but it can be increased up to 100 mg /day if needed. To avoid possible side-effects, the dose is lowered to a minimum maintenance level when possible.

Dapsone has many side effects but is generally well tolerated. The most common side effect is haemolysis (Herron and Zone 2002), and other possible side effects are agranulocytosis, methaemoglobinaemia, and peripheral neuropathy. The adverse effects of dapsone increase with increasing dosage (Herron and Zone 2002). Dapsone usage must be always monitored by a dermatologist and the medication is discontinued once the disease can be controlled with gluten-free diet alone. The duration of the treatment varies from a few months to years (Reunala 2001; Herron and Zone 2002).

5.3 Follow-up

After the coeliac disease or DH diagnosis a routine follow-up is important to ensure that the clinical symptoms respond to the gluten-free diet and are alleviated and to detect possible disease complications. Coeliac disease patients are followed-up by a gastroenterologist or by a general practitioner. DH patients are normally followed-up by dermatologists until the skin lesions have disappeared and the dapsone medication can be discontinued.

In seropositive subjects TG2 and EmA serology can be used in monitoring disease activity in coeliac disease and DH but the antibodies are insensitive markers of both gluten ingestion and small bowel mucosal damage (Kumar et al. 2001; Kaukinen et al. 2002; Taavela et al. 2013b; Mansikka et al. 2017). Previously a routine follow-up biopsy in adult coeliac disease patients was recommended to ascertain histological healing and to detect refractory coeliac disease (RCD) and malignancies. However, because mucosal recovery takes more than a year in a substantial portion of patients and the complications are relatively rare (Sharkey et al. 2013; Ilus et al. 2014), follow-up biopsy is currently only recommended for seronegative patients or if the response to treatment is insufficient (Bai and Ciacci 2017; Coeliac disease: Current Care Guidelines, 2018). In DH, no follow-up biopsy, skin or small bowel, is considered necessary in DH patients who can manage the disease with gluten-free diet alone.

A long-term follow-up is also recommended for both coeliac disease and DH patients. The purpose of the follow-ups is the evaluation of the nutritional status and checking for associated conditions such as thyroid and liver diseases and preventing coeliac disease and DH related complications (Haines et al. 2008). The follow-ups are also considered to improve dietary adherence (Ludvigsson et al. 2014; Bai and Ciacci 2017).

5.4 Long-term prognosis

Coeliac disease and DH patients are at an increased risk of non-Hodgkin's lymphoma (NHL), treated coeliac disease patients being at 2- to 6 -fold risk compared to general population. (Smedby et al. 2005; Grainge et al. 2012). In DH the risk of NHL seems to be of the same magnitude as in coeliac disease (Viljamaa et al. 2006; Grainge et al. 2012), although some studies also report no increase in risk of NHL in DH (Askling et al. 2002; Lewis et al. 2008). Initiating the gluten-free diet seems to reduce the risk for both diseases (Holmes et al. 1989; Grainge et al. 2012), and in DH the risk has been shown to be increased during the first five years of dietary treatment but not thereafter (Lewis et al. 1996). Also, the risk of gastrointestinal malignancies is elevated in coeliac disease, and especially the risk of oesophageal cancer and small bowel carcinoma has been shown to be significantly increased in coeliac disease (Han et al. 2015). The overall risk of malignant diseases in coeliac disease seems to be only slightly elevated, and the latest meta-analysis suggests a pooled odds ratio (OR) of 1.25 (Han et al. 2015). In DH, the overall malignancy risk has previously been shown to be slightly increased (Sigurgeirsson et al. 1994; Askling et al. 2002), but recent studies show no increased risk of overall malignancies in DH (Viljamaa et al. 2006; Lewis et al. 2008).

RCD is a severe but rare entity in which the patient does not respond to the strict gluten-free diet and suffers from persistent villous atrophy and malabsorptive signs despite the diet. Due to persistent mucosal atrophy and increased inflammation, increased risk of malignancies is related to RCD. RCD is rare in Finland, being present in only 0.31% of coeliac disease patient (Ilus et al. 2014). However, it is more common in other countries with prevalences from 0.5–7% (Wahab et al. 2002; Eigner et al. 2017). RCD is divided into two types based on the phenotype of the intraepithelial lymphocytes. In type I RCD the prognosis is good, but type II has a poor prognosis with a five-year survival rate of 40–58% (Rubio-Tapia and Murray 2010).

Refractory DH has been investigated in only one study. The study classified DH patients as refractory when they had been on a gluten-free diet for at least three years, but still took at least 75 mg/week of dapsone to control the rash. The prevalence of refractory DH in Finland was only 1.7% and, contrary to RCD, in the Finnish study the small bowel mucosa had healed in all refractory DH patients despite ongoing skin symptoms and none of the patients had developed lymphoma. Therefore, the prognosis of refractory DH seems to be superior to that of RCD (Hervonen et al. 2016).

Coeliac disease is associated with increased mortality. However, mortality among patients with coeliac disease seems to have decreased during recent decades, and the OR of all-cause mortality in coeliac disease is currently estimated at 1.24 (Tio et al. 2012). The increase in mortality is caused by neoplasms, cardiovascular diseases and respiratory infections (Sultan et al. 2015; Holmes and Muirhead 2018). Interestingly, no such increased mortality has been demonstrated in DH. Some studies have found no difference in mortality between the DH patients and general population (Swerdlow et al. 1993; Lewis et al. 2008) and some studies have even found reduced mortality in DH (Viljamaa et al. 2006; Hervonen et al. 2012).

5.5 New treatments

As the inconvenience of the gluten-free diet has become increasingly obvious and knowledge of the pathogenesis of coeliac disease has increased, many alternative treatment options for coeliac disease have been proposed. The first-generation therapeutics are the intraluminal therapies, which are also the best studied and most promising by far. They include agents that detoxify gluten by modifying, degrading or binding gluten in the gut lumen (Gianfrani et al. 2007; Mitea et al. 2008; Pinier et al. 2009). Also, the drugs involved in the regulation of tight junctions in small bowel mucosa have been studied. Immunotherapies aimed at restoring gluten tolerance and immunosuppressants for more severe coeliac disease have also been considered. Out of these, many therapy options are still at the discovery phase, but there are also phase II drug studies on glutenases and tight junction modulator larazotide acetate (Leffler et al. 2012; Lähdeaho et al. 2014). Regardless of well-conducted studies, it has been suggested that no new treatments are foreseen in the near future (Kaukinen et al. 2014; Wungjiranirun et al. 2016).

6 BONE MINERAL DENSITY AND FRACTURES

Decreased BMD is a major risk factor of bone fractures. BMD is measured with a dual energy X-ray absorptiometry (DXA) commonly from lumbar spine, femur or wrist. The BMD predicts fracture probability well (Kanis et al. 2001). However, body-mass index (BMI), family history of fractures, smoking, prior fragility fracture and factors associated with risk of falling are also known to predict fractures (Kanis et al. 2008). Fractures are burdensome to both patients and society; they impair quality of life, cause major disability and are costly to treat (Burge et al. 2007; Adachi et al. 2010; Hopkins et al. 2016). In addition, hip fractures cause loss of independence and increase mortality (Ariza-Vega et al. 2014; Katsoulis et al. 2017).

6.1 Bone mineral density in coeliac disease

BMD has been shown to be decreased in untreated coeliac disease but after the initiation of gluten-free diet BMD increases (Table 3). Childhood coeliac diagnosis and early adoption of a gluten-free diet allow patients to regain BMD comparable to that in healthy population because peak bone mass is not achieved until puberty (Larussa et al. 2012a). However, for patients diagnosed after puberty, regaining bone mass is not always sufficient and studies concerning BMD in long-term treated coeliac disease patients show increased amount of osteoporosis and osteopenia in adult coeliac disease patients (Mcfarlane et al. 1995; Larussa et al. 2017).

Table 3. Selected* studies prospectively describing bone mineral density (BMD) at the time of coeliac disease diagnosis and after one year on a gluten-free diet (GFD).

Study	Country	Coeliac disease patients	Controls	BMD in untreated coeliac disease	BMD improvement with 1 year of GFD treatment	Comments
Valdimarsson et al., 1996	Sweden	63	25	46% decreased BMD	Significant increase	Age negatively correlated with BMD, Symptoms did not associate with BMD
Sategna-Guidetti et al., 2000	Italy	86	-	40% osteopenia, 26% osteoporosis	Significant increase	Menopausal status did not affect the change in BMD
Valdimarsson et al., 2000	Sweden	105	942	Decreased BMD compared to controls	Significant increase, 3 years of GFD	Secondary hyperparathyroidism negatively affected the BMD
Kurppa et al., 2010	Finland	27 mild enteropathy	-	11% osteopenia 47% osteoporosis	Increase	
		46 villous atrophy		21% osteopenia, 51% osteoporosis	Significant increase	
Casella et al., 2012	Italy	1,166 young patients	-	10 % osteoporosis	Significant increase	
		59 old patients		69 % osteoporosis	Significant increase	
Passananti et al., 2012	Italy	95 females	-	52% decreased BMD	Significant increase, 2 and 5 years of GFD	Small bowel damage or physical activity was not associated with BMD
Pantaleoni et al., 2014	Italy	169	-	37% osteopenia 21% osteoporosis	Significant increase	
Newnham et al., 2016	Austria	99	-	24% osteopenia 10% osteoporosis	Significant increase in those with low baseline BMD, 1 and 5 years of GFD	Biggest change during the first year but continued to change for 5 years
Zylberberg et al. 2018	USA	103	-	49 % osteopenia 33 % osteoporosis	Significant increase	Low baseline serum calcium associated with better increase of BMD

*Prospective studies involving over 60 coeliac disease patients

The pathophysiology of bone disease in coeliac disease seems to be multifactorial involving both local and systemic mechanisms (Larussa et al. 2012a). The most apparent explanation for decreased BMD in untreated coeliac disease is small bowel mucosal villous atrophy decreasing the absorption of nutrients from the gastrointestinal tract causing micronutrient deficiency impeding bone metabolism (Larussa et al. 2012a). In addition, hyperparathyroidism caused by decreased absorption of calcium in the intestines of coeliac disease patients has also been suggested to decrease BMD by stimulating bone degradation (Selby et al. 1999; Valdimarsson et al. 2000). The increased amount of proinflammatory cytokines in the sera of coeliac disease patients has also been associated with low BMD as the chronic inflammation is known to disturb the balance of bone formation and degradation (Fornari et al. 1998; Larussa et al. 2012a). In addition, bone-specific antibodies have been detected in coeliac disease, but their true presence and role in BMD is unknown (Sugai et al. 2002; Larussa et al. 2012b).

6.2 Bone fractures in coeliac disease

The risk for any-type of fractures in coeliac disease has been reported to be increased in most, but not all studies conducted (Table 4). Hip fracture risk has been studied so far in five studies, three of which found hip fracture risk to be increased in coeliac disease. The most recent meta-analysis summarises that the risk for any-type fracture is increased by 30% and the risk for hip fracture increased by 69% in coeliac disease (Heikkilä et al. 2015). Age at diagnosis, diagnostic delay, persistent mucosal atrophy and non-compliance with gluten-free diet are factors associated with increased fracture risk in coeliac disease (Vasquez et al. 2000; Pinto-Sánchez et al. 2011; Lebwohl et al. 2014). In addition, differences in body composition and problems with neuromuscular function have been proposed to increase the risk of fractures in coeliac disease, but the evidence is insufficient (Pinto-Sánchez et al. 2011).

Table 4. Studies on fracture risk in coeliac disease and dermatitis herpetiformis (DH).

Study, Country	Data source	Coeliac disease Non-coeliac	Age, years	Female, %	Results [a]	Comments
Vasquez et al., 2000 Argentina	Self-reported, Interview	165 patients 165 controls	Median 40 Median 41	87 87	Peripheral fracture OR 3.5 (1.8–7.2)	Fracture risk was associated with poor adherence to GFD, increasing diagnostic age and delayed diagnosis
Fickling et al., 2001 United Kingdom	Self-reported, Questionnaire	75 patients 75 controls	Mean 52 Matched	60/75 Matched	Increased in coeliac disease 21% vs. 3 %, p <0.001	
Vestergaard and Mosekilde, 2002 Denmark	Hospital discharge register	1,021 patients 3,063 controls	Mean 32 Matched	58 Matched	No difference in any or hip fractures before or after coeliac disease diagnosis	Fracture risk was associated with age
Thomason et al., 2003 United Kingdom	Self-reported, Questionnaire	244 patients 161 controls	Mean 60 Mean 61	70 71	No difference in any studied fractures	
West et al., 2003 [a] United Kingdom	Primary care database	4,732 patients 23,620 controls	Mean 44 [c] Matched	65 Matched	Any fracture HR 1.3 (1.16–1.46) Hip fracture HR 1.9 (1.20–3.02) Wrist fracture HR 1.77 (1.35–2.34)	Median follow-up 5.7 years
Moreno et al., 2004 Argentina	Interview, Medical records	78 classic coeliac 70 subclinical/silent 296 controls [e]	Mean 44 Mean 38 Matched	79 79 Matched	Any fracture OR 5.2 (2.8–9.8) No difference	
Davie et al., 2005 United Kingdom	Self-reported, Questionnaire	383 female patients[f] 445 controls [f]	Mean 61 Mean 63	100 100	Any fracture: OR 1.51 (1.13–2.02) Wrist fracture OR 1.65 (1.12–2.44) Non-wrist fracture OR 1.66 (1.21–2.27)	OR increases even further when fractures after age 50 were studied
Ludvigsson et al., 2007 [a] Sweden	Hospital discharge register	14,187 patients 68,952 controls	Median 2 [c] Matched	59 Matched	Any fracture HR 1.5 (1.4–1.6) Hip fracture HR 2.2 (2.0–2.5)	Fracture incidence remained stable 10 years before and after the coeliac disease diagnosis

Jafri et al., 2008 United States	Medical records	83 patients 166 controls	Median 46 Matched	70 Matched	Before coeliac disease diagnosis: Any fracture OR [d] 2.0 (1.0–3.9) Peripheral fracture OR [d] 2.0 (1.0–3.9) After coeliac disease diagnosis: Any fracture HR [d] 2.5 (1.1–5.6) Peripheral fracture HR [d] 4.2 (1.0–18)	No increased risk for axial and osteoporotic fractures No increased risk for peripheral and osteoporotic fractures
Lewis et al., 2008 United Kingdom [a]	Primary care database	**846 DH patients** 4,225 controls	Mean 46 [c] Matched	52 Matched	Any fracture HR 1.1 (0.77–1.52) Hip fracture HR 1.4 (0.52–3.83) Wrist fracture HR 1.3 (CI 0.48–3.45)	Median follow-up 3.7 years
Pinto-Sánchez et al. 2011 [a] Argentina	Interview, Medical records	265 patients 530 controls [e]	Median 42 [c] Matched	84 Matched	Before coeliac disease diagnosis: Peripheral fracture HR [d] 1.78 (1.05–2.14) After coeliac disease diagnosis: No increased HR	9,843 patient-years of follow-up Fractures were associated with classic coeliac disease and presence of GI symptoms
Vilppula et al., 2011 Finland	Self-reported, questionnaire	35 patients [f] 2,280 controls	Median 61 nd	57 nd	Increase in coeliac disease 23% vs 5%, $p < 0.01$	
Stobaugh et al., 2013 United States	National register	23,833 patients nd	Median 54 nd	71 nd	Hip fracture: OR [d] 3.83 (3.21–4.57) Vertebrae fracture: OR [d] 2.5 (2.04–3.07) Wrist fracture: OR [d] 3.84 (2.59–5.70)	
Canova et al., 2018 Italy [a]	Hospital discharge records	1,233 child patients 6,167 controls	Median 6 [c] Matched	60 Matched	HR 0.87 (0.55–1.37)	9,394 patient-years of follow-up

[a]Risk of fractures in coeliac disease compared to controls, values in parentheses show the 95% confidence intervals, [b] Prospective study, [c] At baseline [d] Adjusted, [e] Controls had functional gastrointestinal symptoms, [f] All individuals over 50 years of age
GFD: gluten-free diet, HR: hazard ratio, OR: Odds ratio Nd: no data, GI: gastrointestinal symptoms

6.3 Bone and dermatitis herpetiformis

Despite the fairly comprehensive knowledge about bone and coeliac disease, BMD and fractures are very little researched in DH. All the studies are rather small and the results are inconsistent (Table 5). It seems overall that BMD in DH is less affected than in coeliac disease. So far only one study on bone fractures in DH has been presented (Lewis et al. 2008). With a rather short follow-up time, the study found no increase in fracture risk in DH compared to general population (Table 4).

Table 5. Studies on bone mineral density (BMD) in dermatitis herpetiformis (DH)

Study, County	DH patients	Controls	BMD outcome	Comment
Valdimarsson et al., 1996 Sweden	7 untreated	25 healthy	No difference at diagnosis or after gluten-free diet	
Di Stefano et al., 1999 Italy	16 untreated	16 untreated coeliac disease 16 healthy	Higher BMD in DH Lower BMD in DH	Villous atrophy was associated with low BMD in DH
Abuzakouk et al., 2007 Ireland	25 treated	-	BMD did not differ from expected	No association between villous atrophy and low BMD was found in DH
Lorinczy et al., 2013 Hungary	53 treated	34 coeliac disease 42 healthy	Higher BMD in DH Lower BMD in DH	
Lheure et al., 2017 France	53 treated	-	BMD did not differ from expected	2% had osteoporosis 38% had osteopenia

7 DISEASE-RELATED BURDEN

The concept of burden of disease emerged in the 1990s when the World Bank and WHO sought to collaborate on providing a comprehensive assessment of the global disease burden (Murray 1994). The intention was to provide an indicator that would help to set health service and research priorities, identify disadvantaged groups and measure the output of interventions. For this purpose the concept of disability-adjusted life years (DALY) was established. DALY is a sum of two components; the years of life lost because of premature mortality and the years of healthy life lost because of disability. Quantifying disease burden and focusing on nonfatal outcomes was revolutionary. For example, the burden related to neuropsychiatric disorders and noncommunicable diseases such as hearing loss had been vastly underestimated when measured with mortality alone (Lopez et al. 2006).

The term disease-related burden generally refers to the gap between living free from disease and living with all the adverse effects the disease causes. These effects may be social, economic, physiological or emotional and may affect patients, their families and friends or society. Over the years, the patient-centred approach has gained ground and patients' perceptions of the disease burden have been considered important alongside epidemiological data.

7.1 Quality of life

Quality of life is a narrower concept than burden of disease, focusing solely on individuals' own perceptions of their satisfaction with life. Health-related quality of life (HRQoL) describes patients' perceptions and expectations of their health and experiences of being in poor health. HRQoL can be measured with disease-specific instruments or with general quality of life questionnaires. These patient-reported outcome measures (PROMs) capture patients' experiences of illness and present a unique opportunity to gain insight into patients' views. In addition, PROMs have an important role in clinical trials and research endeavours (Spiegel 2013).

7.1.1 Health-related quality of life in coeliac disease

In coeliac disease research the generic quality of life questionnaires, Psychological General Well-Being (PGWB) and the 36-item short-form (SF-36) are often used to quantify the quality of life related to the disease. However, coeliac disease-specific PROMs have also been designed (Häuser et al. 2007a; Dorn et al. 2010; Crocker et al. 2018).

Quality of life in coeliac disease has been a subject of interest for the last few decades. At the time of diagnosis patients with coeliac disease generally perceive their HRQoL to be poorer than that of healthy controls (Table 6). However, screen-detected coeliac disease patients' HRQoL does not differ from that of healthy controls at the time of the diagnosis (Table 6). HRQoL improves in most patients after the initiation of gluten-free diet, although the level of the healthy population is not always achieved during the first year of treatment (Table 6). HRQoL in long-term treated coeliac disease does not normalize in all patients even with long gluten-free diet treatment (Table 7), although a few studies have even reported improved HRQoL in treated coeliac disease patients compared to healthy controls (Hopman et al. 2009; Norström et al. 2011).

Poor adherence to gluten-free diet is associated with impaired HRQoL in coeliac disease (Burger et al. 2017). Other factors associated with impaired HRQoL are female gender, long diagnostic delay, persistent gastrointestinal symptoms and presence of comorbidities (Hallert et al. 1998; Usai et al. 2002; Norström et al. 2011; Paarlahti et al. 2013).

7.1.2 Health-related quality of life in dermatitis herpetiformis

There are only three studies on HRQoL in DH. In an Italian study with a subgroup of 10 DH patients HRQoL in DH was on the level of the healthy population at the time of the diagnosis and also after one year of gluten-free dietary treatment (Tontini et al. 2010). In another study with only three treated DH patients, HRQoL in DH did not differ statistically significantly from that of patients with other autoimmune bullous dermatosis, in which HRQoL was shown to be severely impaired (Penha et al. 2015). However, the DH patients scored better in the study questionnaire and the lack of statistical significance might be attributed to the small number of DH patients in the study. In the most recent study from Finland, no difference in HRQoL was observed between treated DH and coeliac disease patients (Mansikka et al. 2018b).

Table 6. Prospective studies on quality of life (QoL) in untreated coeliac disease and after one year on a gluten-free diet.

Study	Country	Coeliac disease patients	Non-coeliac controls	QoL measured with	QoL at diagnosis*	QoL at 1 year
Mustalahti et al., 2002	Finland	19 screen-detected 21 symptoms-detected	105	PGWB	No difference Worse	Improvement Improvement
Johnston et al., 2004	UK	14 screen-detected 17 symptoms-detected	23 26	SF-36	No difference Worse	No difference Improvement [a]
Nachman et al., 2009	Argentina	97 symptoms-detected 35 atypical coeliac disease	70	SF-36	Worse Worse [b]	Improvement Improvement
Kurppa et al., 2010	Finland	27 with mild enteropathy 46 with villous atrophy	110	PGWB	No difference No difference	No difference [c] Improvement
Tontini et al., 2010	Italy	18 typical coeliac disease 15 atypical coeliac disease 10 dermatitis herpetiformis	86	SF-36	Worse Worse No difference	Improvement Improvement No difference
Ukkola et al., 2011b	Finland	490 classic coeliac disease 62 atypical coeliac disease 146 screen-detected	110	PGWB	Worse Worse Worse	Improvement Improvement Improvement
Vilppula et al., 2011	Finland	35 screen-detected	110	PGWB	No difference [d]	No difference

*Compared with controls, [a]Not to level of controls, [b]No difference in silent disease, [c]Depression decreased, [d]General health subscore was lower in coeliac disease patients

SF-36: Short form 36, PGWB: Psychological general well-being

Table 7. Studies on quality of life (QoL) in long-term treated coeliac disease

Study	Country	Coeliac disease patients	Non-coeliac controls	QoL measured with	QoL outcome [a]	Factors associated with poorer QoL
Hallert, 1998	Sweden	89	GP	SF-36	Worse	Female gender Gastrointestinal symptoms
Lohiniemi et al., 2000	Finland	53	110	PGWB	Worse [b]	Gastrointestinal symptoms
Hallert, 2002	Sweden	68	68 DM2	SF-36	Same	Female gender
Usai et al., 2002	Italy	66	136	SF-36	Worse	Poor GFD adherence, Multiple associated diseases
Fera et al., 2003	Italy	100	100 100 DM2	SF-36	Worse Same	QoL correlated with anxiety
O'leary et al., 2004	Ireland	50	GP	SF-36	Worse	
Viljamaa et al., 2005	Finland	53 screen-detected 44 symptoms-detected	110, GP	PGWB, SF-36	Same Same	
Häuser et al. 2006 Häuser et al. 2007b	Germany	446 [c]	GP	SF-36, CDQ	Worse	Comorbidities, mental disorder, non-compliance with GFD, young age at diagnosis
Roos et al., 2006	Sweden	51	182	PGWB	Same	Female gender
Usai et al. 2007	Italy	129	1001	SF-36	Worse	Poor GFD adherence IBS symptoms
Barratt et al., 2011a Barratt et al., 2011b	United Kingdom	225 [c]	348	SF-36	Worse	Noncompliance with and difficulty in maintaining GFD Reflux symptoms
Norström et al. 2011	Sweden	1031 [c]	GP	EQ-5D	Better	Female gender, young age, long diagnostic delay, diagnosis before the year 1990
Lee et al., 2012	United States	1743 [c]	1179	SF-12, CD-QOL	Same	Worse social settings
Paavola et al., 2012	Finland	96 screen-detected 370 symptoms-detected	110	SF-36 PGWB	Same Worse	
Paarlahti et al., 2013	Finland	596	110	PGWB	Worse	Diagnostic delay, persistent symptoms, comorbidities

[a]Quality of life compared between coeliac disease patients and non-coeliac controls, [b]not tested, [c]cohort also included recently diagnosed patients GP: General population scores, DM2; individuals with type 2 diabetes mellitus, GFD; gluten-free diet, IBS; irritable bowel syndrome, SF-36: Short form 36, PGWB: Psychological general well-being, CD-QOL; Coeliac Disease Quality of Life, EQ-5D: EuroQol 5 dimensions instrument

7.1.3 Health-related quality of life in other chronic skin diseases

The burden related to skin diseases is beyond dispute (Hay et al. 2014). Patients with itching chronic skin diseases such as atopic dermatitis and psoriasis have impaired quality of life compared to healthy controls and their self-reported health and HRQoL is estimated to be comparable that in other chronic diseases such as cardiovascular disease, liver disease or even cancer (Pärna et al. 2015; Balieva et al. 2017). Pain and discomfort decrease the quality of life for patients with skin diseases and the symptoms disrupt sleeping. Numerous other areas of life are also affected as patients report feelings of stigmatization and have lower self-esteem. In addition, patients' personal relationships are affected by the disease and the skin disease impacts on the career choices and choices of leisure and sports activities (Sibbald and Drucker 2017).

7.2 Economic burden

The economic burden of coeliac disease is substantial and is related to both undiagnosed and diagnosed coeliac disease (Mearns et al. 2018). In undiagnosed coeliac disease the economic burden is caused by the vague unexplained symptoms preceding the diagnosis. The symptoms increase the amount of health care utilization and the use of symptomatic medication (Ukkola et al. 2012a; Fuchs et al. 2018). In addition, the long diagnostic delay predisposes patients to increased number of extraintestinal symptoms and complications (Fuchs et al. 2014; Holmes and Muirhead 2018) increasing the burden even further.

Society faces an economic burden from the diagnostics of coeliac disease. The use of a standardized algorithm in coeliac disease diagnostics prior to the biopsy reduces the costs (Hopper et al. 2008; González et al. 2017). Nevertheless, the small bowel biopsy-based diagnostic is overall expensive and laborious. The avoidance of biopsy in serology-based diagnosis has been shown to be cost saving in children (Paul et al. 2018), indicating that it may also be economical in adults.

The use of health care resources was shown to decrease in coeliac disease patients after the diagnosis (Norström et al. 2011; Ukkola et al. 2012a), but remained elevated when compared to general population (Roos et al. 2011; Violato et al. 2012). The costs related to health care were mostly outpatient costs. However, numbers of hospitalizations and emergency department visits were also higher for coeliac disease

patients compared to general population. The total costs related to health care utilization were 2.5-fold for coeliac disease patients in remission and 3.8-fold for patients with only partial remission compared to general population (Guandalini et al. 2016). This indicates that uncontrolled coeliac disease and poor adherence to diet increase the expenses of diagnosed coeliac disease.

Finally, the gluten-free diet adds to the economic burden of coeliac disease. The use of naturally gluten-free food such as fruit, vegetables and non-processed food is more costly than less healthy options (Cade et al. 1999). Prepacked gluten-free substitutes have also been found to be 240–518% more expensive than their gluten-containing counterparts (Lee et al. 2007; Singh and Whelan 2011; Fry et al. 2018).

The economic burden of DH has not been studied. However, it is probable that increased health care utilization before diagnosis is also related to DH. The diagnosis and follow-up of DH require expertise and are provided at tertiary centres and thus are also costly. In addition, the economic burden of gluten-free diet is similar in both DH and coeliac disease and in DH the economic burden is further increased by the usage of dapsone medication.

7.3 Burden of gluten-free diet

Despite the favourable effects of gluten-free diet, the diet is complex and hard to comply with. In fact, non-compliance with dietary treatment in coeliac disease is more affected by inconveniences caused by the strict diet than by sociodemographic or socioeconomic factors (Hall et al. 2009).

The strict life-long gluten-free diet should be started after the diagnostic investigations of coeliac disease or DH have been carried out and the diagnosis has been confirmed (Bai and Ciacci 2017). This is often hard, especially because wheat is ubiquitous in western diet and changing life-long dietary patterns is difficult. Gluten is widely used in the production of many processed and pre-packaged foods, and thus selecting food in the food shop is time-consuming. Fear of inadequate labelling and gluten contamination are common among coeliac disease patients and even patients who have been on a gluten-free diet for years report facing problems in determining whether a product is gluten-free (Sverker et al. 2009; Zarkadas et al. 2013). In addition, the palatability of gluten-free food is generally inferior to that of gluten-containing food and the nutritional value of the gluten-free food is often compromised (Fry et al. 2018). Thus, maintaining a healthy nutritionally balanced diet is difficult.

The social domain of life seems to be most affected by the restrictive nature of the gluten-free diet. Feelings of isolation and exclusion because of gluten-free diet are not uncommon and a significant reduction in eating out has been reported among patients following a gluten-free diet. The reason for this is the limited selection of suitable meals in restaurants and fear of inappropriate handling of gluten-free foods (Whitaker et al. 2009; Lee et al. 2012; Zarkadas et al. 2013). Travel is another area greatly affected by gluten-free dietary requirements. Packing gluten-free snacks is more difficult and following a gluten-free diet abroad is burdensome because of the unfamiliar food products and food labels in foreign languages (Lee et al. 2012; Zarkadas et al. 2013).

Good support from family and from coeliac disease societies has been shown to decrease the burden of living gluten-free (Leffler et al. 2013; Lee et al. 2016). In addition, using oats diversifies the diet by adding nutritional value and increasing palatability (Lee et al. 2009). Despite these, the treatment burden in coeliac disease is reported to be comparable to that in congestive heart failure and end-stage renal disease (Shah et al. 2014).

THE PRESENT STUDY

1 AIMS

The burden of coeliac disease is considerable. DH is a cutaneous manifestation of coeliac disease and also a chronic itching skin condition. Despite this, little research has addressed the burden of DH. The purpose of this study was to ascertain the extent of the burden of both untreated and treated DH and to compare the burden to that of coeliac disease.

The specific aims were:

1. To study the burden related to medication and health care utilization in untreated and treated DH (**I**).

2. To assess the quality of life in recently diagnosed, short-term and long-term gluten-free diet treated DH compared to quality of life in coeliac disease and healthy controls (**I–II**).

3. To elucidate the burden caused by gastrointestinal symptoms in DH and to assess the impact of these symptoms on the patient's own perception of the burden of the disease (**I–II**).

4. To study the incidence of bone fractures in DH compared to that in coeliac disease and in general population and to investigate factors related to increased fracture risk and the effects of fractures on quality of life in DH (**III–IV**).

2 STUDY PATIENTS AND CONTROLS

2.1 Dermatitis herpetiformis study patients (**I–IV**)

For Study **I** the data were gathered in collaboration with the Finnish Coeliac Society. A nationwide cohort of recently diagnosed coeliac disease patients was recruited by sending a study questionnaire (Appendix 1) to all new members of the Finnish Coeliac Society between February 2007 and May 2008 (in total 1,864 individuals). From the respondents all patients over 16 years of age with skin biopsy-proven DH were enrolled as study patients. After one year a follow-up questionnaire (Appendix 2) was sent to all respondents and a telephone reminder was given to those not responding to the follow-up questionnaire. Altogether 52 biopsy-proven DH patients responded to the baseline questionnaire and 48 of those to the follow-up questionnaire. For the purposes of the study patients were divided into two groups according to whether they reported suffering from gastrointestinal symptoms or not at the time of the DH diagnosis.

Between the years 2006 and 2010 a nationwide Finnish coeliac disease series was recruited by advertising in coeliac societies and using press announcements. The series included altogether 1,111 coeliac disease patients and data for Study **II** was gathered from among these. A telephone or face-to-face interview was conducted with all patient recruited and in addition, validated questionnaires assessing quality of life and gastrointestinal symptoms were sent to them by post. A total of 569 adult individuals with coeliac disease responded to the questionnaires. Of these 78 had been diagnosed with DH and were enrolled as study patients. The medical records of the DH patients were reviewed to ensure a skin biopsy-proven diagnosis.

In Studies **III** and **IV**, a prospectively collected DH series from 1970 onwards was used. All DH patients in the Tampere catchment area are diagnosed and treated at the special outpatient clinic at the Tampere University Hospital Department of Dermatology and were included in the series.

All adult DH patients alive in December 2015 and diagnosed before December 2014 at the outpatient clinic (n=413) were recruited for Study **III**. A questionnaire designed for the purposes of the study (Appendix 3) and general validated questionnaires eliciting quality of life and gastrointestinal symptoms were sent to all

DH patients. To increase the response rates, the questionnaires were re-sent to all non-respondents under 80 years of age. Altogether 237 out of 413 patients (56%) responded to the questionnaires. Of these responders, 15 were excluded for having a coeliac disease diagnosis set more than one year prior to the DH diagnosis and the remaining 222 constituted the study cohort. The patients' medical records were reviewed and the clinical, serological and histological severity of the disease and the use of dapsone were reviewed.

For Study **IV** all patients diagnosed with DH at Tampere University Hospital between 1969 and 2000 comprised the study cohort. All those DH patients whose coeliac disease diagnosis had been set more than one year before their DH diagnosis were excluded from this study. The remaining study group comprised 368 DH patients.

2.2 Coeliac disease controls (**II–IV**)

Study **II** included coeliac disease controls from the same coeliac disease series as the DH patients. All coeliac disease patients suffering from abdominal symptoms at the time of the coeliac disease diagnosis (n=371) were enrolled as coeliac disease controls. To ensure that the coeliac disease diagnosis was small bowel biopsy-proven, the controls' medical records were reviewed.

For Study **III** biopsy-proven coeliac disease patients likewise suffering from abdominal symptoms at diagnosis and diagnosed at Tampere University Hospital over the same time-period as the DH patients were recruited as controls (n=222). The coeliac disease individuals with abdominal symptoms were selected for purposes of comparison between DH and classical coeliac disease. The coeliac disease controls were sent a modified coeliac disease-specific study questionnaire and the same general questionnaires as the DH patients. The questionnaires were also re-sent to all non-respondents among the coeliac disease controls who were under 80 years of age. Out of 222 controls, 130 responded (59%). One of these was excluded due to DH diagnosis. The patients' medical records were reviewed and data about the clinical, serological and histological severity of the disease was gathered.

As coeliac disease controls Study **IV** included patients diagnosed with coeliac disease at Tampere University Hospital during the same time-period as the DH patients in Study **IV**. After excluding the coeliac disease patients with DH diagnosis, the control group consisted of 1,076 coeliac disease controls.

2.3 Healthy controls (**I**, **II**, **IV**)

The healthy controls in Studies **I** and **II** were recruited from among the friends and neighbours of the coeliac disease patients. The cohort consisted of 110 individuals who had not been diagnosed with coeliac disease or DH, who considered themselves healthy and had no first-degree relatives with coeliac disease or DH. The aim of this recruitment was to obtain individuals from a social and residential environment similar to that of the study patients.

In Study **II** the results from the Short Form 36 Health Survey (SF-36) questionnaire were compared with the age- and gender-adjusted Finnish general population reference values. These were obtained from a nationwide health survey encompassing 2,060 subjects (Aalto et al. 1999).

The hip fracture incidence rates of DH and coeliac disease patients in Study **IV** were compared with the incidence rates of the general population. The National Institute of Health and Welfare maintains a PERFECT (Performance, Effectiveness and Cost of Treatment episodes) database. In their report concerning the quality of joint replacement surgery in Finland, the age and gender distributed incidences for hip fractures were reported from 2014. Those incidences were used as general population comparison incidences in Study **IV.**

Table 8. Study designs and dermatitis herpetiformis (DH) patients and controls in Studies **I–IV**.

	Study design	Patients	Controls
Study **I**	Prospective cohort study	52 patients with recently diagnosed DH	110 healthy controls
Study **II**	Cross-sectional case-control study	78 long-term GFD-treated DH patients	371 GFD-treated coeliac disease controls 110 healthy controls General population (*n*=2,060)
Study **III**	Retrospective case-control study	222 long-term GFD-treated DH patients	129 GFD-treated coeliac disease controls
Study **IV**	Retrospective cohort study	368 long-term GFD-treated DH patients	1,076 long-term GFD-coeliac disease controls PERFECT database

GFD; gluten-free diet
PERFECT; Performance, Effectiveness and Cost of Treatment episodes

3 METHODS

3.1 Medical questionnaires (**I**, **III**)

Study **I** used questionnaires designed in co-operation with coeliac disease patients, the Finnish Coeliac Society and clinical researchers specialized in coeliac disease (Ukkola et al. 2011) (Appendix 1 and 2). The baseline questionnaire elicited sociodemographic conditions, coeliac disease-related symptoms prior to DH diagnosis (type, duration and bothersomeness) and reactions to being diagnosed. Both questionnaires elicited self-assessed personal health, concern about health, number of sick leave days away from work, and use of health care services and pharmaceutical agents during the previous year. In addition to these, the follow-up questionnaire also asked about the strictness of the gluten-free diet. The questionnaires included both questions with multiple options measured on a Likert scale and questions requiring responses in the respondents' own words.

The Disease Related Questionnaire (DRQ) was designed specifically for the purposes of Study **III** (Appendix 3). The questionnaire inquired about bone fractures during the patient's lifetime, and in more detail, the year and the type of trauma related to the fracture. The patient's sociodemographic and lifestyle characteristics were elicited, likewise past and present symptoms related to DH or coeliac disease. Patients were also asked to report their current height and weight, presence of comorbidities, use of long-term medication and to evaluate the strictness of their gluten-free diet. The DRQ included both open-ended questions and multiple-choice questions and was slightly modified for DH patients and coeliac disease controls.

3.2 Medical interview (**II**)

The patients recruited for Study **II** were interviewed either by a physician or a study nurse specialized in coeliac disease. The interviews were conducted in person or by telephone. The demographic data was recorded and patients were asked about the year of DH or coeliac disease diagnosis, family history of coeliac disease or DH and

coeliac disease-associated disorders. The duration and the strictness of the gluten-free diet was asked and assessed.

3.3 Quality of life and gastrointestinal symptoms (**I–III**)

The self-administrated Psychological General Well-Being (PGWB) questionnaire was used in Studies **I–III**. The PGWB is a validated general quality of life questionnaire and used widely in coeliac disease research (Table 6 and 7). The questionnaire evaluates the quality of life and well-being with 22 items, covering six emotional states: anxiety, depressed mood, self-control, positive well-being, general health and vitality. All the items use a 6-grade Likert scale, value 1 representing the worst and 6 the best well-being. The PGWB total score thus ranges between 22 and 132 points, the higher score indicating better quality of life (Dimenäs et al. 1996).

The short-form 36 (SF-36) questionnaire was used in Study **II**. The SF-36 questionnaire is also a general self-administrated questionnaire used to quantify the patients' health-related quality of life. The SF-36 is widely used in coeliac disease studies and uses eight subgroups: general health perception, physical functioning, mental health, social functioning, vitality, bodily pain, physical role functioning and emotional role functioning. The raw scores from each question are transformed with an algorithm into a scale ranging from 0 to 100, the higher score again indicating better quality of life (Ware and Gandek 1998).

The Gastrointestinal Symptoms Rating Scale (GSRS) was used to quantify the severity of gastrointestinal symptoms in Studies **II** and **III**. The GSRS questionnaire is a validated 15-item questionnaire assessing the severity of gastrointestinal symptoms in five groups: diarrhoea, indigestion, constipation, abdominal pain and reflux. A seven-grade Likert scale is used to assess each of the items, one symbolizing no symptoms and seven indicating the most severe symptoms. The total GSRS score is calculated as a mean of all 15 items and the sub-scores as a mean of all sub-dimensions. In the GSRS a higher score indicates more severe symptoms (Svedlund et al. 1988).

3.4 Bone fractures (**III–IV**)

Study **III** focused on self-reported bone fractures elicited in the DRQ. The fractures were categorized according to whether they had occurred before or after the DH or coeliac disease diagnosis. Trauma-energy was also evaluated on the basis of the

patients' descriptions and if the trauma was considered sufficient to cause a bone fracture in any person (traumas associated with high-energy sports injuries or traffic accidents), the fracture was excluded from further analysis. Fractures reported as stress fractures were also excluded.

Study **IV** focused on hospital-treated fractures. To obtain the data, all the inpatient hospital treatment periods of the study cohorts between 1970 and 2015 were gathered from the National Hospital Discharge Register (NHDR). The NHDR is a nationwide register that includes all hospitalization periods in Finland. The register is maintained by the National Institute of Health and Welfare and it is mandatory for all hospitals in Finland to contribute. The register contains information, for example, on admission and discharge dates, primary and secondary diagnosis codes and all surgical procedures performed during the stay. The diagnoses are recorded in the system according to the ICD-diagnosis coding. The ICD-8 was used between 1969 and 1986, the ICD-9 during the period 1987-1995 and the ICD-10 since 1996.

For the purposes of Study **IV**, all the treatment periods that included a diagnosis coding for hip fracture (N820*, 820*, S72*), proximal humerus fracture (N812.1, N812.0, 812*, S42.2), wrist fractures (N813.4, N813.5, N814.0, N814.1, 813*, S52.5, S52.6) or ankle fracture (N824*, 824*, S82.5, S82.6, S82.8) were extracted from the data. The main outcome of the study was the first hip fracture requiring hospital treatment because these fractures are practically always treated in hospital making the data deriving from the hospital register reliable. The first proximal humerus, wrist and ankle fractures necessitating hospital treatment were evaluated. The dates of emigration and deaths for DH and coeliac disease patients were obtained from the Population Register Centre of Finland, which covers practically all deaths and emigrations in our country. The patients were identified in both the NHDR and Population Register Centre by their personal identification codes.

3.5 Statistical analyses (I–IV)

Median values, interquartile ranges (IQR) and minimum and maximum values were used to describe the continuous variables. For the categorized variables numbers and percentages were used. The χ^2 test was used in cross-tabulations, the Mann-Whitney *U* test when the groups were compared and the Wilcoxon signed-rank test to evaluate the changes within groups. All testing was 2-sided and $p < 0.05$ was considered statistically significant.

In Study **III** the follow-up times were calculated for the first fracture overall and separately for the fractures occurring before and after diagnosis. DH patients and coeliac disease controls who had not reported the time of fracture were discarded from the analysis (four DH patients and six coeliac disease controls).

The follow-up in Study **IV** started from the date of DH or coeliac disease diagnosis or from 1 January 1970 if the diagnosis was made before that. The follow-up ended at the first fracture studied, the emigration date or date of death, or to the end of the follow-up, 31 December 2015, whichever occurred first. The follow-up times were calculated separately for each fracture studied and in addition for hip fractures the follow-up times were calculated separately for each decade of life. The 95% confidence intervals (CI) for fracture incidences were calculated in both assuming Poisson distribution and the Cox Proportional Hazards Model was used when analysing the risk of subsequent fracture between DH and coeliac disease patients.

All statistical analyses were performed with SPSS versions 20 and 24 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp. USA) in co-operation with a statistician.

3.6 Ethical considerations (**I–IV**)

The study protocols were approved by the Ethics Committee of Tampere University Hospital for Studies **I**, **III** and **IV**. The study protocol for Study **II** was approved by the review board of the Finnish Coeliac Society in compliance with all applicable Finnish laws for registered organizations and covering the protection of human suspects.

4 RESULTS

4.1 Patients and demographic data (**I–IV**)

The DH patients were more often male than the coeliac disease or healthy controls and median age at diagnosis was mostly lower in the DH study group than in the coeliac disease controls (Table 9). DH patients had less frequently subtotal or total villous atrophy at the time of diagnosis compared to the coeliac disease controls (Table 9). At DH diagnosis the median BMI of the study patients was 24 (range 16–40) kg/m^2 and after one year of treatment 25 (range 16–38) kg/m^2 (Study **I**). The BMI of long-term treated DH patients did not differ from that of treated coeliac disease controls (Study **III**). Of the long-term treated DH patients, 54% had family history of coeliac disease compared with 61% in the coeliac disease cohort. (Study **II**).

4.2 Patients' self-perceived experiences (**I**)

In total 96% of the DH patients found the symptoms before the DH diagnosis disturbing and 96% were pleased at being diagnosed. DH patients with gastrointestinal symptoms reported statistically significantly worse perception of their health and increased amount of the concern about health at the time of the diagnosis compared to those DH patients without gastrointestinal symptoms (Figure 1). After one year on a gluten-free diet self-perceived health improved in those with gastrointestinal symptoms and concern about health decreased in both groups; statistically significant differences between the groups were no longer detected (Figure 1).

Table 9. Demographic data, small bowel histology at diagnosis and gluten-free diet for dermatitis herpetiformis patients and controls (**I–IV**).

	Dermatitis Herpetiformis		Controls	
	Untreated [a]	Long-term treated	Long-term treated coeliac disease	Healthy controls
Number of participants	52 (**I**)	78 (**II**) 222 (**III**) 368 (**IV**)	371 (**II**) 129 (**III**) 1076 (**IV**)	110 (**I–II**)
Females, %	67	49 (**II**) 45 (**III**) 49 (**IV**)	81 (**II**) 81 (**III**) 68 (**IV**)	81 (**I–II**)
Age at diagnosis, median (range), years	52 (23–74)	38 (10–72) (**II**) 37 (5–78) (**III**) 39 (5–84) (**IV**)	44 (0–79) (**II**) 42 (7–72) (**III**) 39 (1–89) (**IV**)	-
Small bowel histology at diagnosis, %				
Normal	nd	14 (**II**) 22 (**III**) 29 (**IV**)	3 [b] (**II**) 4 [b] (**III**) 0 (**IV**)	100 (**I–II**)
PVA	nd	32 (**II**) 38 (**III**) 29 (**IV**)	35 (**II**) 38 (**III**) 25 (**IV**)	0 (**I–II**)
SVA/TVA	nd	54 (**II**) 40 (**III**) 42 (**IV**)	62 (**II**) 58 (**III**) 75 (**IV**)	0 (**I–II**)
Age at the time of the study, median (range), years	52 (23–74)	57 (28–81) (**II**) 65 (18–96) (**III**) 68 (22–96) (**IV**)	56 (19–92) (**II**) 66 (35–86) (**III**) 61 (9–97) (**IV**)	48 (23–87) (**I–II**)
Duration of GFD, median (IQR), years	0 (1[c])	18 (8–27) (**II**) 23 (12–32) (**III**) 28 (21–34) (**IV**)	9 (5–16) (**II**) 20 (16–23) (**III**) 23 (18–29) (**IV**)	0 (**I–II**)
Strict diet, %	0 (92[c])	95 (**II**) 72 (**III**)	98 (**II**) 84 (**III**)	0 (**I–II**)

[a] and short–term treated (one year on gluten-free diet), [b] mild enteropathy, [c]after one year on gluten-free diet
nd; no data, GFD: gluten-free diet, PVA; Partial villous atrophy, SVA/TVA; Subtotal or total villous atrophy, IQR; interquartile range

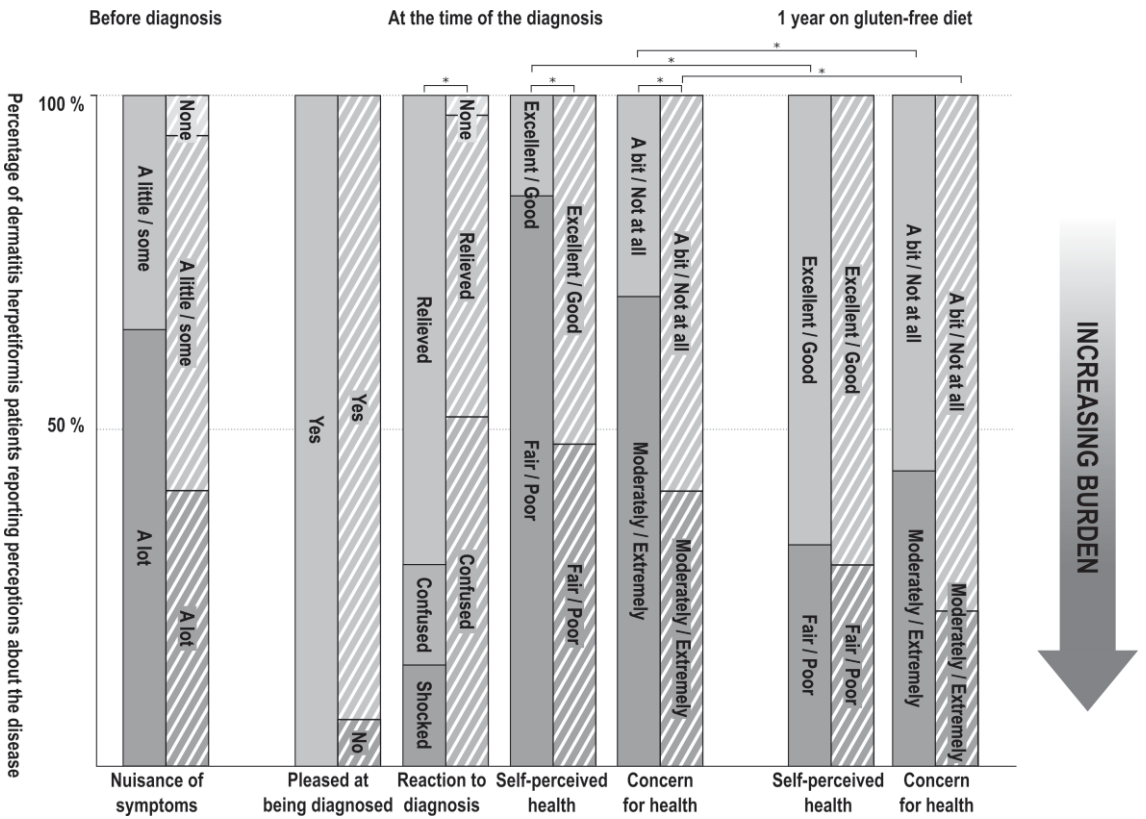

Figure 1. Self-reported perceptions of the symptoms before the dermatitis herpetiformis (DH) diagnosis, feelings about the diagnosis and perceptions of health and concern about health at the time of diagnosis and after one year of gluten-free diet for DH patients with and without gastrointestinal (GI) symptoms (**I**). The left bar in each pair of bars represents the DH patients with GI symptoms (n=20) and the striped bar on the right side represents the DH patients without GI symptoms (n=32). *p<0.05

4.3 Use of medication and health care resources (**I, III**)

The use of medication reported by the recently diagnosed DH patients remained stable when compared against the preceding and succeeding years. The DH patients with gastrointestinal symptoms at diagnosis had used more antibiotic treatments during the year before the diagnosis than had the DH patients without gastrointestinal symptoms (Table 10).

Table 10. Percentage of patients taking medications among dermatitis herpetiformis (DH) patients during the year before and the year after the diagnosis (**I**)

	Dermatitis herpetiformis		
	All (*n*=52)	With GI symptoms (*n*=20)	Without GI symptoms (*n*= 32)
Before diagnosis, %			
All painkillers	58	70	50
Painkillers for headache	31	45	22
Medicines for dyspepsia	25	35	19
Sleeping medicines	7	15	6
Antibiotic treatment	29	45 *	19
After diagnosis, %			
All painkillers	60	61	60
Painkillers for headache	31	33	30
Medicines for dyspepsia	23	28	20
Sleeping medicines	13	11	13
Antibiotic treatment	31	28	33

* $p < 0.05$ between the DH patients with and without gastrointestinal symptoms

In total, 78% of the DH patients in Study **III** had taken dapsone after the DH diagnosis and the median duration of the treatment was 24 months (IQR: 12–72). Long-term treated coeliac disease controls took vitamin D and calcium supplements and selective serotonin receptor inhibitors (SSRI) significantly more often than did long-term treated DH patients (Table 11).

Recently diagnosed DH patients reported seeking medical treatment for the same coeliac disease-related symptoms before the diagnosis a median of three times (range 0–30). The DH patients used primary health care resources significantly more during the year before than the year after the DH diagnosis (median, range, times: 3, 0–31 vs. 2, 0–8, $p < 0.001$). The outpatient visits to secondary or tertiary health care facilities did not differ, but the admissions to hospitals increased during the year after the DH diagnosis compared to the year before it (median, range, times: 0, 0–4 vs. 0,

0–40, $p = 0.004$). The presence or absence of gastrointestinal symptoms at diagnosis did not affect the use of health care resources.

Table 11. Use of long-term medication among long-term treated dermatitis herpetiformis and coeliac disease patients (**III**)

	Dermatitis herpetiformis (*n*=222)	Coeliac disease (*n*=129)
Use of medication, %		
Proton-pump inhibitors	11	15
Hormone replacement therapy	7	9
Any glucocorticoid medication	14	19
Vitamin D and calcium supplements	16*	30
Bisphosphonates	3	6
Selective serotonin receptor inhibitors	1*	7
Diuretics	11	9

$p < 0.05$ between dermatitis herpetiformis and coeliac disease

4.4 Health-related quality of life (**I–III**)

The PGWB total and the subscores were statistically significantly lower in DH patients at the time of diagnosis than in short- and long-term treated DH patients, long-term treated coeliac disease controls and healthy controls (Figure 2, Table 12). The DH patients with gastrointestinal symptoms had lower PGWB scores than the DH patients without gastrointestinal symptoms (Figure 2, Table 12).

After one year of gluten-free diet the PGWB total score for DH patients rose to the level of long-term treated DH patients, long-term treated coeliac disease controls and healthy controls. Also, the difference in PGWB scores between DH patients with and without gastrointestinal symptoms at diagnosis disappeared (Figure 2). The DH patients who reported a bone fracture had lower PGWB scores than the DH patients reporting no fractures (Figure 3 and Table 12).

Measured with the SF-36 questionnaire, the quality of life in long-term treated DH patients was on the level of the general population. The SF-36 subscores general health and role physical were significantly higher in long-term treated DH patients than in the long-term treated coeliac disease controls indicating better quality of life in DH (Figure I in original publication **II**).

In addition, newly diagnosed female DH patients had significantly lower PGWB total score, and depression and general health subscores compared to male DH patients (Table S1 in original publication **I**). Also, in long-term treated female DH patients the vitality subscores in both PGWB and SF-36 questionnaires were

significantly lower than in long-term treated male DH patients (Table 3 in original publication **II**).

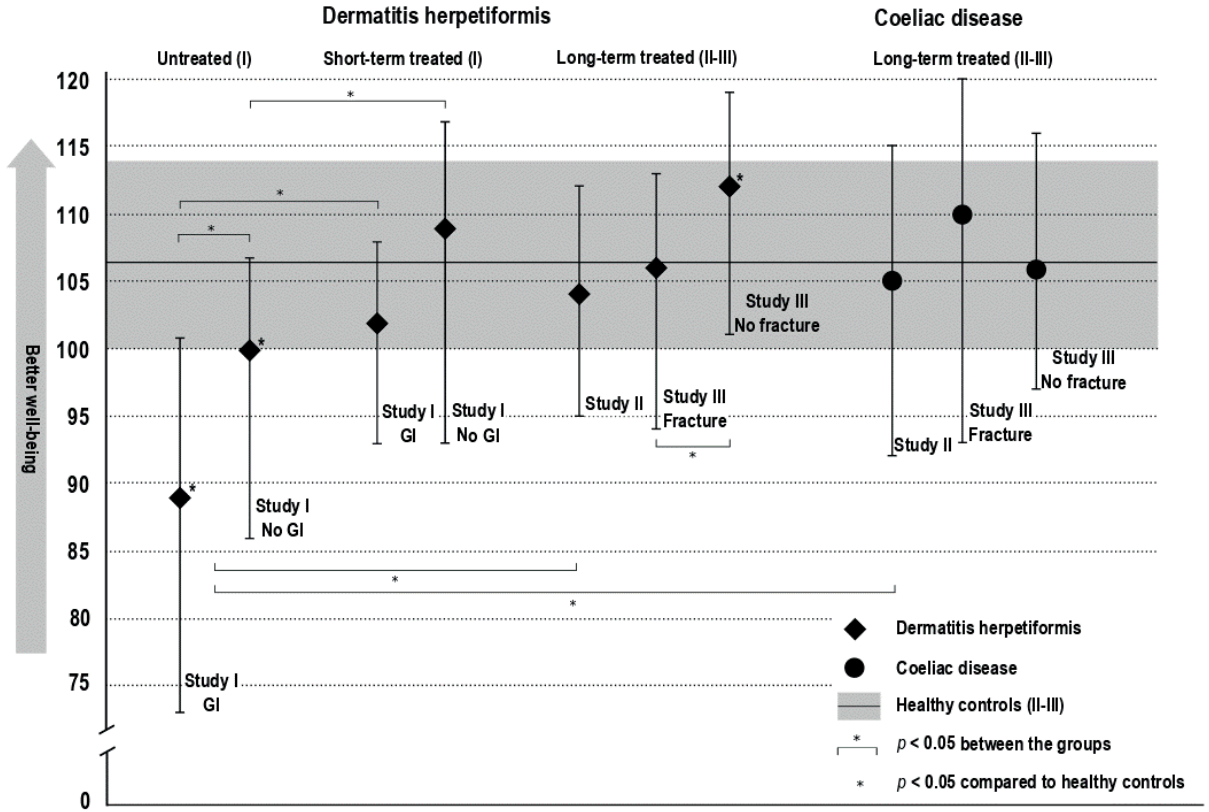

Figure 2. Median values and interquartile ranges (IQR) of Psychological General Well-being total scores for dermatitis herpetiformis (DH) patients, coeliac disease controls and healthy controls (**I–III**). The grey area presents the IQR and the black line the median values for healthy controls. The marking between the untreated DH patient groups indicates that the groups were combined for the comparison.

Table 12. Psychological General Well-Being subscores for dermatitis herpetiformis patients, coeliac disease controls and healthy controls. (**I–III**)

	Dermatitis Herpetiformis			Controls	
	Untreated	Short-term treated	Long-term treated	Long-term treated coeliac disease	Healthy
	All, *n*=52 (**I**)		Patients, *n*=78 (**II**)	Controls, *n*= 371 (**II**)	*n*=110 (**I–III**)
	With GI symptoms, *n*=20 (**I†**)		With fracture, *n*= 45 (**III†**)	With fracture, *n*=35 (**III†**)	
	Without GI symptoms, *n*=32 (**I‡**)		Without fracture, *n*=177 (**III‡**)	Without fracture, *n*=129 (**III‡**)	
Anxiety	20 (16–23) (**I†**) * c,d	24 (22–26) (**I†**)	24 (21–27) (**II**)	24 (21–27) (**II**)	25 (22–27) (**I–III**)
	23 (19–26) (**I‡**) * d	25 (23–27) (**I‡**)	25 (22–27) (**III†**)	27 (21–29) (**III†**)	
			26 (23–28) (**III‡**) *	25 (23–28) (**III‡**)	
Depression	16 (13–17) (**I†**) d	17 (15–18) (**I†**)	17 (15–18) (**II**)	17 (15–18) (**II**)	17 (15–18) (**I–III**)
	16 (14–17) (**I‡**) * d	17 (15–18) (**I‡**)	17 (16–18) (**III†**)	17 (15–18) (**III†**)	
			18 (16–18) (**III‡**) *	17 (15–18) (**III‡**)	
Well–being	16 (12–17) (**I†**) * a,c,d	17 (14–19) (**I†**)	18 (15–20) (**II**)	17 (14–20) (**II**)	17 (15–19) (**I–III**)
	17 (15–18) (**I‡**)	19 (16–20) (**I‡**)	17 (15–19) (**III†**)	18 (15–19) (**III†**)	
			18 (16–20) (**III‡**) *	17 (16–20) (**III‡**)	
Self-control	14 (11–16) (**I†**) * a,c	15 (13–17) (**I†**)	15 (14–17) (**II**)	16 (14–17) (**II**)	16 (14–17) (**I–III**)
	16 (13–17) (**I‡**)	15 (14–17) (**I‡**)	16 (15–17) (**III†**)	16 (13–17) (**III†**)	
			16 (15–17) (**III‡**) *	16 (14–17) (**III‡**)	
General health	10 (8–13) (**I†**) * c	13 (11–15) (**I†**) *	13 (11–15) (**II**) * e	13 (10–15) (**II**)	15 (13–16) (**I–III**)
	11 (9–14) (**I‡**) * c	13 (10–15) (**I‡**) *	13 (11–15) (**III†**) *	13 (11–16) (**III†**)	
			15 (13–16) (**III‡**) *	13 (11–15) (**III‡**)	
Vitality	14 (11–18) (**I†**) * a,c	18 (16–19) (**I†**) * a	18 (16–20) (**II**)	18 (16–20) (**II**)	19 (17–20) (**I–III**)
	18 (15–20) (**I‡**)	20 (17–21) (**I‡**)	18 (17–21) (**III†**)	19 (17–20) (**III†**)	
			20 (17–21) (**III‡**)	18 (16–20) (**III‡**)	

Higher score indicates better well-being. GI; gastrointestinal.

*$p < 0.05$ compared to healthy controls [a] $p < 0.05$ compared with DH patient without GI symptoms at the same time-point, [b] $p < 0.05$ compared to themselves after treatment [c] $p < 0.05$ compared to long-term treated DH (**II**) [d] $p < 0.05$ compared to long-term treated CD (**II**) [e] significance disappeared when adjusted with gender and age

4.5 Gastrointestinal and extraintestinal symptoms (**I–III**)

In Studies **I** and **III**, 38% and 49% of DH patients respectively reported suffering from gastrointestinal symptoms at the time of the diagnosis. The GSRS total scores did not differ between the long-term treated DH patients and the healthy controls, but long-term treated DH patients had statistically significantly lower GSRS total scores compared with coeliac disease controls, indicating less severe gastrointestinal symptoms (Figure 3). Whether DH patients had reported a fracture was not significantly associated with the GRSR total score (Figure 3).

The GSRS subscores of long-term treated DH patients did not differ statistically significantly from those of the healthy controls (Table 13). For long-term treated DH patients reporting a fracture the reflux subscore was statistically significantly higher than for DH patients with no fracture ($p = 0.012$) (Table 13).

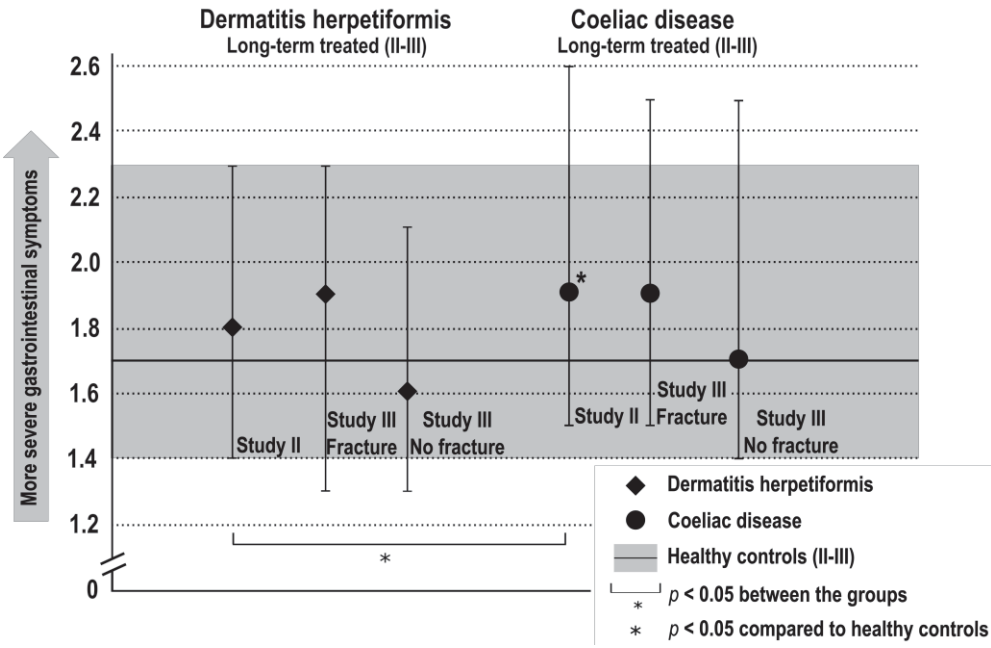

Figure 3. Median values and interquartile ranges (IQR) of Gastrointestinal Symptoms Rating Scale total scores for long-term treated dermatitis herpetiformis patients, coeliac disease controls and healthy controls (**II–III**). The grey area presents the IQR and the black line the median values for healthy controls.

Table 13. Gastrointestinal Symptoms Rating Scale subscores for long-term treated dermatitis herpetiformis patients, long-term treated coeliac disease controls and healthy controls (**II–III**)

	Dermatitis herpetiformis			Coeliac disease			Healthy controls
	Cohort, *n*=78 (**II**)	With fracture, *n*=45 (**III**)	Without fracture, *n*=177 (**III**)	Cohort, *n*=371 (**II**)	With fracture, *n*=35 (**III**)	Without fracture, *n*=94 (**III**)	*n*=110 (**II–III**)
Diarrhoea	1.3 (1.0–2.0) [a]	1.7 (1.0–2.3) *	1.3 (1.0–2.0)	1.7 (1.0–2.3)	2.0 (1.0–2.7) *	1.7 (1.0–2.5)*	1.0 (1.0–2.0)
Indigestion	2.1 (1.5–3.0)	2.0 (1.3–2.5) *	1.8 (1.5–2.5) *	2.3 (1.8–3.3)	2.4 (1.8–2.8)	2.0 (1.5–3.0)	2.3 (1.5–3.0)
Constipation	1.7 (1.0–2.0)	1.3 (1.0–2.3)	1.3 (1.0–2.3)	1.7 (1.0–2.7)	1.7 (1.3–2.5)	1.7 (1.0–2.7)	1.3 (1.0–2.3)
Pain	1.7 (1.3–2.3) [a]	1.7 (1.2–2.3)	1.3 (1.0–2.0)	2.0 (1.3–2.7)	1.7 (1.3–2.3)	1.7 (1.3–2.3)	1.7 (1.0–2.3)
Reflux	1.0 (1.0–2.0)	1.5 (1.0–2.0) *	1.0 (1.0–1.5)	1.5 (1.0–2.0)	1.5 (1.0–2.5) *	1.0 (1.0–2.0)	1.0 (1.0–1.5)

* $p < 0.05$ compared with healthy controls (**II–III**)

[a] $p < 0.05$ compared with long-term treated coeliac disease, but the significance disappeared when adjusted with gender and age (**II**)

The prevalence of additional coeliac-disease related extraintestinal symptoms was higher for the DH patients with gastrointestinal symptoms at diagnosis than for those without (Study **I**). The former reported statistically significantly more often oral symptoms (25% vs. 3%), joint symptoms (35% vs. 6%) and weight loss (25% vs. 3%). Vitamin D or iron deficiency (25% vs. 19%) and symptoms of the nervous system (15% vs. 3%) were also reported, but no statistically significant differences were detected between DH patients with and without gastrointestinal symptoms. Duration of any coeliac disease or DH related symptoms before DH diagnosis was also longer for the DH patients with gastrointestinal symptoms (median 9 years, range 0.5–45) compared to those without (median 2 years, range 0–30) (p=0.003) (Study **I**).

4.6 Bone fractures (**III–IV**)

Among the long-term treated DH patients and coeliac disease controls 45 (20%) and 35 (27%) respectively reported having a fracture during their life-time. Multiple fractures were reported by 15 DH patients and 12 coeliac disease controls. The hospital-treated hip, proximal humerus, wrist or ankle fracture had occurred in 35 (10%) of the DH patients and 105 (10%) of the coeliac disease controls after the DH or coeliac disease diagnosis. The fracture incidences are shown in Table 14 for DH patients and coeliac disease controls.

The life-time risk of self-reported fractures did not differ between DH and coeliac disease patients when adjusted by gender and age (Table 15). However, when genders were compared separately and the results were adjusted for age, the female DH patients were at significantly lower risk for self-reported fractures after the diagnosis than the female coeliac disease controls (Hazard Ratio (HR) 0.473, 95% CI: 0.25–0.88). After the diagnosis, compared with coeliac disease controls, DH patients were at significantly decreased risk of hospital-treated fractures when hip, proximal humerus, wrist and ankle fractures were studied (Table 15).

The incidence of hip fractures was compared between DH patients, coeliac disease controls and the general population. As there were so few hip fractures before the age of 70 years the fractures were studied more specifically in age groups 70–79 and 80–89 years. The hip fracture incidences did not differ between individuals with DH or coeliac disease and the general population. However, female DH patients aged 80–89 years had a higher hip fracture incidence rate than the corresponding coeliac disease controls (Figure 1 in original publication **IV**).

Table 14. Number of fractures, follow-up times and fracture incidence rates for dermatitis herpetiformis patients and coeliac disease controls (**III**–**IV**).

	Dermatitis Herpetiformis *n*=222 (**III**) *n*=368 (**IV**)			Coeliac disease *n*=129 (**III**) *n*=1,076 (**IV**)		
	Fractures, *n*	Person-years at risk	Incidence / 10^5 person-years (95% CI)	Fractures, *n*	Person-years at risk	Incidence / 10^5 person-years (95% CI)
All self-reported fractures (III)	41	12,916	317 (228–431)	29	7,479	388 (259–558)
Before diagnosis	13	8,391	155 (82–265)	3	5,080	59 (12–173)
After diagnosis [a]	31	4,929	629 (427–894)	26	2,400	1083 (707–1589)
All hospital-treated fractures after diagnosis [a, b] (IV)	35	9,728	360 (251–500)	105	24,139	435 (356–527)
Hip	14	10,003	140 (77–235)	12	25,033	72 (43–114)
Others [c]	27	9,771	276 (180–402)	89	24,178	368 (296–453)

CI; confidence intervals

[a] Diagnosis of dermatitis herpetiformis or coeliac disease, [b] Hip, proximal humerus, wrist and ankle fractures combined; [c] Proximal humerus, wrist and ankle fractures combined

Table 15. The adjusted hazard ratio (HR) and 95% confidence intervals (CI) for fractures for dermatitis herpetiformis patients compared to coeliac disease controls (**III–IV**).

	Adjusted[a] HR (95% CI)
All self-reported fractures (III)	1.031 (0.63–1.69)
Before diagnosis [b]	3.296 (0.91–11.96)
After diagnosis [b]	0.663 (0.39–1.14)
All hospital-treated fractures after diagnosis [b, c] (IV)	0.620 (0.43–0.95) *
Hip fracture	0.803 (0.38–1.68)
Other fractures [d]	0.661 (0.42–1.03)

[a]Adjusted by gender and age, [b] Diagnosis of dermatitis herpetiformis or coeliac disease, [c] Hip, proximal humerus, wrist and ankle fractures combined, [d] Proximal humerus, wrist and ankle fractures, * $p = 0.026$

DH patients and coeliac disease controls with a fracture were more often female than those without, and were also older at the time of the diagnosis (Table 16). The degree of small bowel mucosal villous atrophy at the time of the DH or coeliac disease diagnosis did not differ significantly between those with and without fractures and adherence to gluten-free diet did not differ between those with and without a fracture, either (Table 16). Both DH patients and coeliac disease controls with a fracture were more often diagnosed with osteoporosis (p=0.024 and 0.001) and had more often multiple long-term illnesses (p=0.033 and 0.057) than those without fractures. The coeliac disease patients with fracture were also significantly more often diagnosed with osteoporosis than DH patients with a fracture (p<0.001) (Table 16).

The DH patients with a fracture had been diagnosed with DH earlier than those without (median diagnostic years 1981 vs. 1985, p = 0.056) (Table 16). The severity of the skin symptoms at the time of the diagnosis did not differ between the groups, but the duration of dapsone medication after the diagnosis was longer for the DH patients with a fracture (median, IQR, months: 60, 12–171) than for those without a fracture (median, IQR, months: 24, 12–60) (p=0.031). At the time of the study, the long-term medication taken by the DH patients with a fracture was more often proton-pump inhibitors (PPI), hormone replacement therapy, vitamin D and calcium supplements and diuretics. The use of PPIs and vitamin D and calcium supplements was also significantly more common among coeliac disease patients with a fracture than among those without (Table 2 in original publication **III**).

Table 16. Demographic, clinical and small bowel histological data and adherence to gluten-free diet for dermatitis herpetiformis patients and coeliac disease controls with and without fractures (**III-IV**).

	Dermatitis herpetiformis		Coeliac disease	
	With fracture	Without fracture	With fracture	Without fracture
Number of patients	45 †	177 †	35 †	94 †
	35 ‡	333 ‡	105 ‡	971 ‡
Female, %	58 †	42 †	97 †	74 †
	63 ‡	47 ‡	75 ‡	67 ‡
Age at diagnosis, median (range)	34 (7–78) †	37 (5–78) †	45 (23–59) †	40 (7–72) †
	54 (14–81) ‡	37 (5–84) ‡	45 (34–58) ‡	37 (1–85) ‡
Year of diagnosis, median (IQR)	1990 (1976–2000) †	1991 (1982–2002) †	1994 (1989–1997) †	1996 (1991–1999) †
	1981 (1976–1989) ‡	1985 (1980–1991) ‡	1990 (1985–1996) ‡	1990 (1985–1996) ‡
Age at the time of the study, median (IQR)	68 (57–74) †	65 (54–74) †	68 (63–72) †	63 (55–71) †
	71 (56–80) ‡	67 (57–75) ‡	59 (47–70) ‡	60 (47–71) ‡
Small bowel mucosal villous atrophy [a], %				
Normal	16 †	24 †	12 [b] †	2 [b] †
	46 ‡	28 ‡	0 ‡	0 ‡
PVA	35 †	39 †	24 †	43 †
	14 ‡	30 ‡	16 ‡	26 ‡
SVA/TVA	49 †	37 †	65 †	55 †
	39 ‡	42 ‡	84 ‡	74 ‡
Gluten-free dietary adherence, %				
Strict [c]	70 †	73 †	80 †	86 †
Lapses	28 †	26 †	20 †	13 †
Normal diet	2 †	1 †	0 †	1 †
Osteoporosis, %	11 †	2 †	40 †	11 †
Multiple illnesses [d], %	33 †	19 †	43 †	26 †

PVA, Partial villous atrophy; SVA/TVA, Subtotal or total villous atrophy, † Study **III**, ‡ Study **IV**, [a] At the time of DH or coeliac disease diagnosis, [b] Mild enteropathy, [c] No dietary lapses, [d] Two or more of the following diseases: thyroid disease, diabetes, hypercholesterolemia, hypertension, rheumatoid disease, coronary artery disease.

5 DISCUSSION

The present studies ascertained the burden of disease and quality of life in DH with large well-defined cohorts. Little is so far known about the matter even though DH is a cutaneous manifestation of coeliac disease and additionally an itching chronic skin disease, both of which are known to be associated with impaired quality of life and increased burden.

5.1 Quality of life

The study established that DH is linked to poorer quality of life at the time of the diagnosis, and further, that the presence of gastrointestinal symptoms diminished quality of life and increased the perceived burden in DH. Adherence to a gluten-free diet was shown to improve quality of life in DH and after one year of dietary treatment the quality of life of DH patients equalled that of the healthy controls. Further, quality of life remained on the level of the controls even after long-term adherence to gluten-free diet in DH.

Quality of life in recently diagnosed DH patients has previously been studied only with a small subgroup of 10 DH patients, and the quality of life of the DH patients was shown to be comparable to that of the controls (Tontini et al. 2010). However, a decline in quality of life at diagnosis is well demonstrated for coeliac disease patients (Nachman et al. 2009; Ukkola et al. 2011b) and an improvement in quality of life along with gluten-free diet has also been widely observed in coeliac disease (Nachman et al. 2009; Tontini et al. 2010; Ukkola et al. 2011b). Parallel to the current DH results, the presence and severity of gastrointestinal symptoms have also been associated with poorer quality of life and increased burden in coeliac disease (Norström et al. 2011; Paarlahti et al. 2013; Fuchs et al. 2018).

The long-term treated DH patients in this study had slightly better quality of life than the long-term treated coeliac disease controls. It is known that quality of life for long-term treated coeliac disease patients does not always reach the level of healthy controls. The persistent gastrointestinal symptoms known to exist in coeliac disease have been proposed as one explanation (Laurikka et al. 2016), and in this study, too,

the long-term treated coeliac disease patients suffered from more severe gastrointestinal symptoms than did the long-term treated DH patients. The reasons why individuals with long-term treated coeliac disease suffer from persistent gastrointestinal symptoms have remained obscure. However, the differences in the degree of small bowel mucosal villous atrophy at the time of the diagnosis and differences in gut microbiota between DH and coeliac disease may partly explain the differences in the perceived gastrointestinal symptoms between these two phenotypes of the same disease (Wacklin et al. 2013).

In this study the female DH patients had lower quality of life at diagnosis than the male patients and even after long-term adherence to a gluten-free diet their vitality subscore remained impaired. An increased burden in female patients has also been observed in coeliac disease (Hallert et al. 2003; Roos et al. 2006), and has often been associated with burden of gluten-free diet as females are often the family caregivers (Sverker et al. 2009; Zarkadas et al. 2013). However, difference in quality of life between genders has also been observed in general population and thus females may be overall more susceptible than men to impairment in quality of life (Aalto et al. 1999).

The severity of skin symptoms is known to affect quality of life in other chronic itching skin diseases (Korman et al. 2016). Unfortunately, no data was available about the presence and severity of the skin symptoms at the time of diagnosis for the DH patients and therefore their effect on quality of life could not be studied. Nevertheless, skin symptoms may also contribute to the decline in quality of life in recently diagnosed DH. However, in this study the presence of skin symptoms in long-term treated DH did not affect quality of life, but this could be explained by the small number of patients suffering from skin symptoms at the time of the study.

5.2 Use of health care resources and medication

This study showed that during the year after the DH diagnosis use of primary health care resources decreased significantly from the year before the diagnosis. However, the number of hospital admissions increased in DH patients during the year after the DH diagnosis compared to the year before, which was surprising, and also difficult to explain. Use of health care resources has not so far been studied in DH. However, a similar decrease in the use of primary health care resources has also been reported after coeliac disease diagnosis (Norström et al. 2012; Ukkola et al. 2012a). This decrease in the number of visits to health care facilities during gluten-free

dietary treatment results in reduced burden for both society and patients suffering from DH or coeliac disease.

Use of medication in DH did not differ during the year before or after the DH diagnosis, but use of antibiotic treatment before the diagnosis among DH patients with gastrointestinal symptoms was more common than among those without gastrointestinal symptoms. In coeliac disease use of medication has been shown to increase before the diagnosis and to decrease thereafter (Ukkola et al. 2012a). This increased use of medications prior to the diagnosis of coeliac disease may be attributable to more vague and diverse symptoms in coeliac disease than in DH.

However, the predominance of females in coeliac disease compared to that in DH could explain the dissimilarities as in general women take more medications than men (Manteuffel et al. 2014). Nonetheless, the use of long-term medication in long term-treated DH patients was at the same level as in long-term treated coeliac disease patients, except for SSRI medication and vitamin D and calcium supplements, which coeliac disease patients used more often than did DH patients. Gender distribution differences may again explain this, but it is also possible that medical professionals are more aware of the bone complications associated with coeliac disease and therefore more often prescribe nutritional supplementation for these patients.

5.3 Bone fractures

In this study, life-time self-reported bone fractures were shown not to differ between DH patients and coeliac disease controls. However, female DH patients were at lower risk of fractures after diagnosis than diagnosed coeliac disease patients. Also, fractures necessitating hospital treatment were shown to occur less often in DH than in coeliac disease controls after diagnosis. Nevertheless, no increased hip fracture incidence was found in DH or in coeliac disease compared to general population.

Fracture risk in DH has only been explored in one study, which found no increased fracture risk in DH (Lewis et al. 2008). There, however, the follow-up time was rather short and information on adherence to diet was lacking. In another study using the same database an increased fracture risk was shown to be associated with coeliac disease (West et al. 2003). This supports our findings about a higher fracture risk in coeliac disease than in DH after diagnosis. This observed higher fracture risk in coeliac disease could be due to the to the manifestly less severe small bowel mucosal damage in DH than in coeliac disease, as severity of small bowel mucosal damage is linked to increased risk of fractures in coeliac disease (Lebwohl et al. 2014).

Contrary to our present results, hip fracture risk has previously been shown to be elevated in coeliac disease (Heikkilä et al. 2015). Fracture risk in coeliac disease has been shown to be associated with prolonged gluten exposure due to long diagnostic delay, poor adherence to gluten-free diet and persistent small bowel mucosal villous atrophy (Vasquez et al. 2000; Pinto-Sánchez et al. 2011; Lebwohl et al. 2014). In Finland diagnostic delay has decreased in both DH and coeliac disease (Fuchs et al. 2014; Mansikka et al. 2018b), strict adherence to dietary treatment is demonstrably very high (Hervonen et al. 2012; Kurppa et al. 2013), and persistent small bowel villous atrophy is moreover infrequent (Ilus et al. 2014; Hervonen et al. 2016). Also, the classic coeliac disease phenotype has been shown to be associated with increased risk of fractures (Pinto-Sánchez et al. 2011). As the rate of cases diagnosed with coeliac disease in Finland is among the highest in the world (Bai and Ciacci 2017), diversity of coeliac disease phenotypes is likely to be high in our cohort. This may affect the risk of fractures in the present study compared to cohorts with more severe forms of coeliac disease. In addition, health care is free in Finland, as in most of the western European countries, which may improve the overall health status of residents. Moreover, the general health status, especially among the elderly, has improved in Finland in recent decades, which also has a protective effect against fractures (Aromaa and Koskinen 2004).

Surprisingly, an increased hip fracture incidence rate was observed among female DH patients aged 80-89 years compared to female coeliac disease patient aged 80-89 years. Some decades ago the importance of a strict gluten-free diet in DH was less clear, DH patients were occasionally treated with dapsone and gluten-free diet was not rigorously adhered to, if indeed at all. In this study DH patients with fractures were diagnosed earlier than those without and were also diagnosed at an older age than those without fractures. Less strict adherence to gluten-free diet and delayed diagnosis may have prolonged exposure to gluten and hence predisposed these patients to fractures, which many in turn explain the increased hip fracture incidence in female DH patients aged 80–89 years. Additionally, the DH study cohort was older than the coeliac disease study cohort. Despite efforts to adjust for this effect, the finding could possibly be attributed to differences in the study populations.

DH patients and coeliac disease controls with fracture reported more severe reflux symptoms and increased use of PPI than did patients and controls without fracture. Use of PPIs has been associated with increased fracture risk in a meta-analysis (Zhou et al. 2016), thus when prescribing these medications to DH or coeliac disease patients it is advisable to weigh up the indications for PPI medication against

possible adverse effects to bone health. DH and coeliac disease patients with fractures also more often had multiple long-term illnesses and were more often diagnosed with osteoporosis than were those without fracture. However, osteoporosis is often diagnosed after fracture, leading to an underestimated prevalence among patients without fracture. Nevertheless, coeliac disease patients with fractures were more often diagnosed with osteoporosis than were DH patients with fractures. As previously noted, this may indicate that physicians are more acutely aware of the bone complications linked to coeliac disease than to DH.

5.4 Strengths and limitations of the study

The strengths of this study are the large and well-defined series of biopsy proven DH patients and coeliac controls with strict criteria for inclusion and exclusion minimizing the misclassification bias. Most DH patients had a routinely performed endoscopy and thus data about small bowel mucosal histology at the time of the diagnosis were available for the majority of DH patients. In addition, in Studies **I** and **II** the cohorts were recruited nationwide and in Study **I** prospective data were available. The cohorts in Studies **III** and **IV** were diagnosed and treated by specialists during the same time period and they included patients with varying severities of the disease. Well-defined and validated questionnaires were used to assess quality of life and severity of gastrointestinal symptoms and although these are not coeliac disease specific, they are widely used in coeliac disease studies. Furthermore, a large reliable nationwide hospital discharge register was used and its quality and accuracy have been well demonstrated, especially for hip fractures (Sund 2012; Huttunen et al. 2014).

Some limitations of the studies should nevertheless be discussed. The questionnaire-based studies used volunteers, which may have caused estimated quality of life to be superior to what it actually is among all DH patients. The questionnaire-based design also led to overrepresentation of women in the cohorts as women tend to be more likely to respond to questionnaires. In addition, the cohorts in Studies **I** and **II** were partly recruited through a coeliac disease society and although approximately 70% of coeliac disease patients are members, this may have caused selection bias as being part of a support group has been observed to diminish the burden (Lee et al. 2016). In Study **III** the design was retrospective and thus the self-reported data susceptible to recall bias. In addition, studying fractures in a self-reported design is not ideal but the results should nevertheless be comparable between the study cohorts. Also, the site of the fracture was not

addressed in Study **III**. Furthermore, as Study **IV** was a register-based study, the energies causing the fractures could not be evaluated and the data on confounding factors such as comorbidities, use of medication and, importantly, adherence to gluten-free diet, was limited. However, these aspects were covered in Study **III**.

The study used a cohort of healthy controls recruited among friends and neighbours of coeliac disease patients and being acquainted with the patient may have biased the controls' responses. Moreover, the lack of non-coeliac controls was a notable shortcoming in the fracture studies. However, the population reference values were used as a substitute for comparing the hospital-treated fractures with general population.

6 SUMMARY AND CONCLUSIONS

The present study revealed for the first time the disease burden related to untreated DH and also the alleviating effect of gluten-free diet on that burden.

Firstly, the study established that the use of primary health care resources decreases during the year after DH diagnosis compared to the year preceding the diagnosis. However, being diagnosed with DH does not seem to have an effect on use of medications.

Secondly, the study revealed the impaired quality of life associated with untreated DH. However, gluten-free diet was shown to have a favourable effect on quality of life in DH patients as this improved to the level of controls after one year of dietary treatment and remained unaltered even after long-term adherence to gluten-free diet. Moreover, quality of life in long-term treated DH patients seems to be slightly higher than in long-term treated coeliac disease patients.

Thirdly, the gastrointestinal symptoms experienced were shown to be associated with a worse quality of life and to have a negative effect on self-perceived health at DH diagnosis. Interestingly, the diagnostic delay was shown to be longer in DH patients with gastrointestinal symptoms and these patients also had a higher prevalence of additional extraintestinal symptoms than did DH patients without gastrointestinal symptoms.

Finally, the life-time bone fracture risk does not seem to differ between DH and coeliac disease. Also, the hip fracture incidence rates in both DH and coeliac disease were comparable to those in general population in an area with a high prevalence of clinically diagnosed cases and good dietary adherence rates. However, in the present study the self-reported and any-type hospital treated fracture risk after the diagnosis was lower in DH than in coeliac disease. The DH patients with fractures had lower quality of life, more severe reflux symptoms, more often took PPI medication and had a higher prevalence of multiple chronic illnesses than those DH patients without fractures.

7 CLINICAL IMPLICATIONS AND FUTURE PROSPECTS

This study elucidated the benefits of being diagnosed and initiating gluten-free diet in individuals suffering from DH. Further, the importance to society of DH diagnostics and treatment was also established. The notable burden related to DH at the time of the diagnosis should be acknowledged by physicians treating DH patients and the need for emotional support should be assessed, especially in females with DH. Also, in addition to skin symptoms, dermatologists should pay attention to the possible presence of gastrointestinal symptoms as these symptoms impair the quality of life and the self-perceived health of DH patients. The beneficial effects of gluten-free diet should be emphasized to individuals with DH: gluten-free diet was not only shown to improve quality of life, but the current study indicated that gluten-free diet has beneficial effects on bone complications. However, the need for PPI medication should be critically evaluated in DH patients as this medication was associated with increased risk of fractures. Recognition of the bone fracture risk seems to be more important in coeliac disease than in DH, but even in coeliac disease routine bone mineral density measurements are not necessary. Instead, the need for bone density measurements should be evaluated individually for each patient considering all the apparent risk factors of osteoporosis.

In the future, more needs to be known about the factors, besides gender and gastrointestinal symptoms, which impair quality of life in DH. More studies are also needed to discover why coeliac disease patients rate their quality of life lower than do DH patients in spite of the same restrictive dietary treatment. In addition, the factors associated with bone fractures in DH need further research.

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APPENDIX 1 : STUDY QUESTIONNAIRE, BASELINE

KELIAKIAN HOIDON VAIKUTTAVUUSTUTKIMUS (aikuiset)

1. Sukupuoli ☐ nainen ☐ mies

2. Syntymävuosi_____

3. Siviilisääty
☐ naimisissa tai avoliitossa
☐ naimaton
☐ asumuserossa tai eronnut
☐ leski

4. Oletteko tällä hetkellä pääasiassa:
☐ työssä
☐ osin työssä /osin eläkkeellä
☐ lomautettu
☐ työtön
☐ opiskelija
☐ kotiäiti tai -isä (myös äitiysloma, hoitovapaa)
☐ pitkäaikaisella (yli 6 kk) sairaslomalla
☐ eläkkeellä
☐ muutoin poissa työelämästä
☐ muu, mikä? _____

5. Mikä on tai oli viimeksi asemanne työyhteisössä kodin ulkopuolella?
☐ työnantaja/yksityisyrittäjä
☐ maanviljelijä/maatalon emäntä
☐ johtavassa asemassa oleva
☐ ylempi toimihenkilö
☐ alempi toimihenkilö
☐ ammattikoulutettu työntekijä
☐ työntekijä ilman ammattikoulutusta
☐ ei työssäoloa kodin ulkopuolella
☐ muu, mikä? _____

6. Onko työnne tällä hetkellä
☐ kokoaikaista
☐ osa-aikaista
☐ en ole työssä

7. Sairastatteko ☐ keliakiaa ☐ ihokeliakiaa ☐ en sairasta keliakiaa tai ihokeliakiaa
(jatkokysymyksiin ei tarvitse vastata, mutta palautattehan silti kyselyn)

8. Milloin keliakia-/ihokeliakiadiagnoosinne on tehty?

kk_____vuosi_____

9. Milloin aloititte gluteenittoman ruokavaliohoitonne?

kk_____vuosi_____ ☐ En ole vielä aloittanut gluteenitonta ruokavaliohoitoa

10. Mitkä oireet johtivat keliakiadiagnoosiinne?

- ☐ vatsavaiva (ripuli, ummetus, ilmavaivat, vatsakipu, turvotus)
- ☐ laihtuminen
- ☐ anemia, vitamiinin tai raudan puutos
- ☐ iho-oire (kutina, rakkulat)
- ☐ niveloire
- ☐ ääreis- tai keskushermosto-oireet, kuten raajojen tuntohäiriö, ataksia, epilepsia
- ☐ lapsettomuus tai raskausongelma
- ☐ suun oireet (haavaumat, pysyvien hampaiden kiillevauriot)
- ☐ luukato, murtumat
- ☐ oireeton, keliakiaseulonta riskiryhmässä;
  - ☐ suku ☐ tyyppi 1 diabetes ☐ kilpirauhastauti
  - ☐ Sjögrenin syndroma ☐ IgA- puutos ☐ muu, _____
- ☐ muu oire, _____
- ☐ sattumalöydös (mitä epäiltiin)_____

11. Kuinka kauan teillä oli mielestänne keliakiaan viittaavia oireita **ennen diagnosointia?**

_____vuotta

12. Kuinka paljon oireet haittasivat elämäänne **ennen diagnosointia?**

- ☐ erittäin paljon
- ☐ paljon
- ☐ jonkin verran
- ☐ vähän
- ☐ ei yhtään
- ☐ en osaa sanoa

13. Kuka epäili keliakiaa ensimmäisenä?

- ☐ itse epäilin, ☐ tein keliakia-pikatestin
- ☐ ystävä, sukulainen
- ☐ terveyskeskus
- ☐ työterveyshuolto
- ☐ yksityislääkäri
- ☐ aluesairaala
- ☐ keskussairaala
- ☐ yliopistollinen sairaala
- ☐ muu, kuka_____

14. Missä keliakia-/ihokeliakiadiagnoosinne tehtiin?
- ☐ terveyskeskus
- ☐ työterveyshuolto
- ☐ aluesairaala
- ☐ keskussairaala
- ☐ yliopistollinen sairaala
- ☐ yksityislääkäri
- ☐ muu, mikä_____

15. Onko teille tehty mahantähystystä ennen sitä tähystystä, jossa keliakia diagnosoitiin?
- ☐ kyllä, _____ kertaa
- ☐ ei

16. Millainen oli mielestänne terveydentilanteenne **ennen keliakian diagnosointia?**
☐ erinomainen ☐ hyvä ☐ tyydyttävä ☐ huono

17. Olitteko **ennen keliakian diagnosointia** huolestunut terveydentilastanne?
☐ paljon ☐ kohtalaisesti ☐ vähän ☐ en yhtään

18. Arvioikaa terveyspalvelujenne käyttö **keliakiadiagnoosia edeltävän vuoden ajalta?**
- ☐ en ole käyttänyt lainkaan
- ☐ terveyskeskuslääkärikäyntejä _____ kertaa
- ☐ työterveyslääkärikäyntejä _____ kertaa
- ☐ yksityislääkärikäyntejä _____ kertaa
- ☐ hammaslääkärikäyntejä _____kertaa
- ☐ sairaalan poliklinikkakäyntejä _____ kertaa
- ☐ kotisairaanhoitajakäyntejä kotonani_____ kertaa
- ☐ terveyden-/sairaanhoitajan vastaanottokäyntejä_____ kertaa
- ☐ fysioterapiakäyntejä _____ kertaa
- ☐ laboratoriokäyntejä _____ kertaa
- ☐ röntgen käyntejä _____ kertaa
- ☐ muu, mikä_____, _____ kertaa

19. Satunnaisten lääkkeiden käyttö **keliakiadiagnoosia edeltävän vuoden ajalta?**

päänsärkylääkkeitä	_____ pilleriä kuukaudessa
muita särkylääkkeitä	_____ pilleriä kuukaudessa
mahahappolääkkeitä	_____ pilleriä kuukaudessa
unilääkkeitä	_____ pilleriä kuukaudessa
mielialalääkkeitä	_____ pilleriä kuukaudessa
vitamiineja, rauta- ja luontaislääkkeitä kaikkiaan	_____ pilleriä kuukaudessa
antibioottikuureja	_____kertaa

20. Oletteko ollut sairaalahoidossa **keliakiadiagnoosia edeltävän vuoden aikana?**
☐ kyllä,_____kertaa, miksi?_____
_____
_____
☐ en

21. Kuinka monta kertaa **viimeisen 10 vuoden aikana** olette joutunut käymään lääkärissä oireiden takia, joiden takaa paljastui lopulta keliakia? _____ kertaa (arvio riittää, jos ette muista tarkkaan).

22. Kuinka monta kokonaista päivää olitte **diagnoosia edeltävän vuoden aikana** poissa työstä sairauden takia? (raskautta ei lasketa) _____ päivää (arvio riittää, jos ette muista tarkkaan).

23. Pituutenne diagnoosi hetkellä _____cm
Painonne diagnoosi hetkellä _____ kg

24. Miten reagoitte saadessanne tietää sairastavanne keliakiaa?
☐ elämäni meni täysin sekaisin
☐ hämmennyin, mutta ajattelin, että pärjään
☐ se oli helpotus
☐ ei ollut vaikutusta
☐ en osaa sanoa

25. Keneltä saitte terveydenhuollossa tietoa keliakian hoidosta? (voitte ruksata useammankin vaihtoehdon)
☐ lääkäriltä
☐ terveyden-/sairaanhoitajalta
☐ ravitsemusterapeutilta
☐ sosiaalityöntekijältä
☐ psykologilta
☐ muualta, keneltä_____

26. Saitteko lääkäriltänne tietoa keliakiasta: ☐ suullisesti ☐ kirjallisesti
☐ en suullisesti enkä kirjallisesti

27. Oliko lääkärin tai hoitajan **alussa** antama ohjaus ja tieto keliakiasta mielestänne riittävää ja selkeää?
☐ kyllä ☐ ei, miksi ei_____
☐ en saanut ohjausta

28. Oliko ravitsemusterapeutin **alussa** antama gluteenittoman ruokavaliohoidon ohjaus ja tieto keliakiasta mielestänne riittävää ja selkeää?

☐ kyllä ☐ ei, miksi ei_____

☐ en päässyt ravitsemusterapeutille

29. Mistä muualta saitte **alkuvaiheessa** tietoa keliakiasta ja sen ruokavaliohoidosta?

☐ Keliakialiitosta
☐ uudesta Keliakia-kirjasta
☐ kirjallisuudesta yleensä
☐ Keliakialiiton internet-sivuilta
☐ paikalliselta keliakiayhdistykseltä
☐ tukihenkilöltä
☐ omaiselta, ystävältä
☐ muualta, mistä_____

Toiveenne ja odotuksenne Keliakialiitolle?

_____
_____
_____
_____
_____

Toiveenne ja odotuksenne Keliakiatutkimukselle?

_____
_____
_____
_____
_____

Olettehan vastanneet jokaiseen kysymykseen!

KIITOS VASTAUKSESTANNE!

APPENDIX 2 : STUDY QUESTIONNAIRE, FOLLOW-UP

KELIAKIAN HOIDON VAIKUTTAVUUSTUTKIMUS (aikuiset, seuranta)

1. Sukupuoli ☐ nainen ☐ mies

2. Syntymävuosi _____

3. Siviilisääty
☐ naimisissa tai avoliitossa
☐ naimaton
☐ asumuserossa tai eronnut
☐ leski

4. Oletteko tällä hetkellä pääasiassa:
☐ työssä
☐ osin työssä /osin eläkkeellä
☐ lomautettu
☐ työtön
☐ opiskelija
☐ kotiäiti tai -isä (myös äitiysloma, hoitovapaa)
☐ pitkäaikaisella (yli 6 kk) sairaslomalla
☐ eläkkeellä
☐ muutoin poissa työelämästä
☐ muu, mikä _____

5. Mikä on tai oli viimeksi asemanne työyhteisössä kodin ulkopuolella?
☐ työnantaja/yksityisyrittäjä
☐ maanviljelijä/maatalon emäntä
☐ johtavassa asemassa oleva
☐ ylempi toimihenkilö
☐ alempi toimihenkilö
☐ ammattikoulutettu työntekijä
☐ työntekijä ilman ammattikoulutusta
☐ ei työssäoloa kodin ulkopuolella
☐ muu, mikä _____

6. Onko työnne tällä hetkellä
☐ kokoaikaista
☐ osa-aikaista
☐ en ole työssä

7. Mitkä ovat ruokavaliohoitonne periaatteet tällä hetkellä?
☐ käytän vain luontaisesti gluteenittomia tuotteita
☐ käytän sekä vehnätärkkelyspitoisia että luontaisesti gluteenittomia tuotteita
☐ käytän kauraa

8. Koetteko osaavanne gluteenittoman ruokavaliohoidon?
☐ kyllä ☐ en, miksi? _____

9. Koetteko gluteenittoman ruokavaliohoidon noudattamisen?
☐ helpoksi ☐ menee 'omalla painollaan' ☐ vaikeaksi

10. Millainen on gluteeniton ruokavaliohoitonne tällä hetkellä?
☐ tarkka, 100 % ☐ 'lipsun' silloin tällöin, miksi? _____
☐ en noudata ruokavaliota

11. Miten gluteeniton ruokavaliohoito on vaikuttanut elämäänne?
☐ myönteisesti ☐ kielteisesti ☐ ei vaikuta mitenkään ☐ en noudata ruokavaliota

12. Ovatko keliakiaan liittyvät oireenne **viimeisen vuoden aikana diagnoosin jälkeen?**
☐ hävinneet kokonaan
☐ vähentyneet selvästi
☐ vähentyneet hieman
☐ pysyneet ennallaan
☐ lisääntyneet
☐ minulla ei ollutkaan oireita
☐ en osaa sanoa

13. Arvioikaa terveyspalvelujenne käyttö **keliakiadiagnoosin ja ruokavaliohoidon aloittamisen jälkeen viimeisen vuoden aikana?**
☐ en ole käyttänyt lainkaan
☐ terveyskeskuslääkärikäyntejä _____ kertaa
☐ työterveyslääkärikäyntejä _____ kertaa
☐ yksityislääkärikäyntejä _____ kertaa
☐ hammaslääkärikäyntejä _____kertaa
☐ sairaalan poliklinikkakäyntejä _____ kertaa
☐ kotisairaanhoitajakäyntejä kotonani _____ kertaa
☐ terveyden-/sairaanhoitajan vastaanottokäyntejä_____ kertaa
☐ fysioterapiakäyntejä _____ kertaa
☐ laboratoriokäyntejä _____ kertaa
☐ röntgen käyntejä _____ kertaa
☐ muu, mikä_____, _____kertaa

14. Satunnaisten lääkkeiden käyttö **keliakiadiagnoosin ja ruovaliohoidon aloittamisen jälkeen viimeisen vuoden aikana?**

päänsärkylääkkeitä	_____ pilleriä kuukaudessa
muita särkylääkkeitä	_____ pilleriä kuukaudessa
mahahappolääkkeitä	_____ pilleriä kuukaudessa
unilääkkeitä	_____ pilleriä kuukaudessa
mielialalääkkeitä	_____ pilleriä kuukaudessa
vitamiineja, rauta- ja luontaislääkkeitä kaikkiaan	_____ pilleriä kuukaudessa
antibioottikuureja	_____ kertaa

15. Oletteko ollut sairaalahoidossa **viimeisen vuoden aikana diagnoosin jälkeen?**
☐ kyllä, _____kertaa, miksi? _____
_____
_____
☐ en

16. Kuinka monta kokonaista päivää olette ollut **sairastumisenne jälkeen viimeisen vuoden aikana** poissa työstä sairauden takia? (raskautta ei lasketa) _____ päivää (arvio riittää, jos ette muista tarkkaan)

17. Pituutenne tällä hetkellä _____cm
Painonne tällä hetkellä _____kg

18. Oletteko käynyt keliakian seurantavastaanotolla **vuosi diagnoosin jälkeen?**
☐ lääkärillä ☐ ravitsemusterapeutilla ☐ muualla, missä _____
☐ en missään, miksi en _____

19. Oletteko käynyt keliakian verikoeseurannassa **diagnoosin jälkeen viimeisen vuoden aikana?**
☐ kyllä, _____ kertaa ☐ en

20. Oletteko käynyt ohutsuolitähystyksen ja ohutsuolikoepalan vuosikontrollissa?
☐ kyllä, mikä on tilanteenne sen perusteella? ☐ parempi
☐ ei muutosta
☐ en osaa sanoa
☐ olen menossa tähystykseen
☐ en ole käynyt, miksi?_____

21. Millainen on mielestänne terveydentilanteenne **tällä hetkellä?**
☐ erinomainen ☐ hyvä ☐ tyydyttävä ☐ huono

22. Oletteko **tällä hetkellä** huolestunut terveydentilastanne?
☐ paljon ☐ kohtalaisesti ☐ vähän ☐ en yhtään

23. Millainen on suhtautumisenne keliakiaan **tällä hetkellä?**
☐ myönteinen ☐ kielteinen ☐ välinpitämätön ☐ en osaa sanoa

24. Oletteko tyytyväinen, että keliakianne vuosi sitten diagnosoitiin?
☐ kyllä ☐ en, miksi_____ ☐ en osaa sanoa

25. Mistä olette **viimeisen vuoden aikana** saanut keliakiaan liittyvää tietoa, ohjausta, apua ja tukea sitä tarvitessanne? (voitte ruksata useammankin vaihtoehdon)

- ☐ lääkäriltä
- ☐ terveyden-/sairaanhoitajalta
- ☐ ravitsemusterapeutilta
- ☐ sosiaalityöntekijältä
- ☐ psykologilta
- ☐ omaiselta, ystävältä
- ☐ Keliakialiitosta
- ☐ Keliakialiiton internet -sivuilta
- ☐ uudesta Keliakia-kirjasta
- ☐ paikalliselta keliakiayhdistykseltä
- ☐ tukihenkilöltä
- ☐ muualta?_____

26. Koetteko, että keliakiatietoutenne on riittävää **tällä hetkellä?**

☐ kyllä ☐ ei, mitä kaipaatte? _____

27. Oletteko osallistunut terveydenhuollon tai paikallisyhdistyksen järjestämille ensitietokursseille **viimeisen vuoden aikana?**

☐ kyllä ☐ en ☐ ei ole järjestetty ☐ en ole ollut tietoinen asiasta

28. Oletteko osallistunut Keliakialiiton sopeutumisvalmennuskurssille **viimeisen vuoden aikana**?

☐ kyllä ☐ en ☐ ei ole valittu ☐ en ole ollut tietoinen asiasta

29. Oletteko osallistunut paikallisyhdistysten toimintaan **viimeisen vuoden aikana?**

☐ kyllä ☐ en ☐ en ole ollut tietoinen asiasta

Toiveenne ja odotuksenne Keliakialiitolle?

_____
_____
_____
_____

Toiveenne ja odotuksenne Keliakiatutkimukselle?

_____
_____
_____
_____

Olettehan vastannut jokaiseen kysymykseen!

KIITOS VASTAUKSESTANNE

APPENDIX 3: DISEASE RELATED QUESTIONNAIRE, DH

KYSELYKAAVAKE IHOKELIAKIAPOTILAILLE

(Rastita oikea vaihtoehto tai kirjoita vastauksesi tyhjille viivoille)

Nimi_____ Henkilötunnus_____

Puhelinnumero_____ Sähköposti_____

Olen työssä kokopäiväisesti ☐ osapäiväisesti ☐ Ammatti_____

Olen eläkkeellä ☐ vuodesta_____ Olen koululainen/opiskelija ☐

Olen ☐ En ole ☐ Keliakiayhdistyksen jäsen

IHOKELIAKIA

1. Minä vuonna Teillä todettiin ihokeliakia eli dermatitis herpetiformis? _____

2. Kuinka kauan Teillä oli iho-oireita ennen diagnoosin tekoa?
   alle 3kk ☐ 3-6kk ☐ 6-12 kk ☐ 1-2v ☐ yli 2 v☐ en osaa sanoa ☐

3. Oliko Teillä suolisto-oireita (vatsakipua, ripulia, yms.) ennen diagnoosin tekoa?
   Ei ☐ Kyllä ☐ alle 3kk ☐ 3-6kk ☐ yli 6 kk ☐ en osaa sanoa ☐

4. Minulle ei ole ☐ on☐ tehty ohutsuolen tähystystutkimus vuonna_____

IHOKELIAKIAN RUOKAVALIOHOITO

	Kyllä	En
5. Noudatatteko tällä hetkellä gluteenitonta ruokavaliota? (jos vastaatte tähän en, siirtykää kysymykseen 9)	☐	☐

6. Minä vuonna aloititte noudattamaan gluteenitonta ruokavaliota?
   _____

7. Oma näkemykseni tämän hetkisestä gluteenittoman ruokavaliohoidon toteutumisesta
   - Noudatan gluteenitonta ruokavaliota hyvin tiukasti (en lipsu koskaan) ☐
   - Gluteeniton ruokavalioni lipsuu harvemmin kuin kerran kuukaudessa ☐
   - Gluteeniton ruokavalioni lipsuu 1-5 kertaa kuukaudessa ☐
   - Gluteeniton ruokavalioni lipsuu vähintään kerran viikossa ☐
   - En noudata gluteenitonta ruokavaliohoitoa tällä hetkellä ☐

	Kyllä	Ei
8. Onko ihokeliakiadiagnoosin jälkeen ollut ajanjaksoja, jolloin gluteeniton ruokavaliohoito on jäänyt noudattamatta	☐	☐

-jos kyllä, niin minä vuosina_____ ja kuinka kauan_____

	Kyllä	En
9. Jos ette tällä hetkellä noudata gluteenitonta ruokavaliota, oletteko joskus aikaisemmin noudattaneet sitä	☐	☐

-jos kyllä, niin minä vuosina_____ja kuinka kauan_____

	Kyllä	En
10. Käytättekö ruokavaliossanne kauraa	☐	☐

-jos kyllä, päivittäin ☐ 2-3 kertaa viikossa ☐ tätä harvemmin ☐

IHOKELIAKIAN LÄÄKEHOITO (DAPSONI / AVLOSULFON)

	Kyllä	Ei
11. Oletteko koskaan käyttäneet Dapsonia (tai Avlosulfonia)	☐	☐

-jos, niin mistä vuodesta _____

12. Käytättekö edelleen Dapsonia	☐	☐

- nykyannos_____tbl / päivä

13. Minä vuonna Dapsonin (tai Avlosulfonin) käyttö loppui? _____

IHOKELIAKIAIHOTTUMAN JA SUOLISTO-OIREIDEN PARANEMINEN

	Kyllä	Ei
14. Oireileeko ihokeliakiaihottumanne edelleen?	☐	☐

-jos kyllä, kuinka usein suunnilleen?

viikottain ☐ 1-2 kertaa kuukaudessa ☐ 1-2 kertaa puolessa vuodessa ☐

1-2 kertaa vuodessa ☐ harvemmin kuin kerran vuodessa ☐

15. Kuinka kauan gluteenittoman ruokavaliohoidon aloittamisen jälkeen kesti ennen kuin ihokeliakiaihottumanne rauhoittui?

alle 1 kk ☐ 1-3kk ☐ 3-6 kk ☐ 6-12kk ☐ 1-2 v ☐ 2-5v ☐ yli 5 v ☐

ei ole vieläkään rauhoittunut ☐ en osaa sanoa ☐

16. Kuinka kauan gluteenittoman ruokavaliohoidon aloittamisen jälkeen kesti ennen kuin suolisto-oireet rauhoittuivat?

Niitä ei ollut ☐ alle 1 kk ☐ 1-3kk ☐ 3-6 kk ☐ 6-12kk ☐ 1-2 v ☐ 2-5v ☐

yli 5 v ☐ eivät ole vieläkään rauhoittuneet v ☐ en osaa sanoa ☐

MUUT SAIRAUDET

17. Sairastatteko ihokeliakian lisäksi seuraavia lääkärin toteamia sairauksia:

	Kyllä	Ei
17.1 **Diabetes (eli sokeritauti)**	☐	☐
Vuodesta_____		
Hoitona: tablettihoito ☐ insuliinihoito ☐		
17.2 **Kilpirauhassairaus**	☐	☐
Vuodesta_____		
Liikatoiminta ☐ Vajaatoiminta ☐		
17.3 **Aivohalvaus / muu aivoverenkiertohäiriö**	☐	☐
Vuodesta_____		
Tarkempi diagnoosi_____		
17.4 **Kohonnut veren kolesteroli**	☐	☐
Vuodesta_____		
17.5 **Sepelvaltimotauti**	☐	☐
Vuodesta_____		
17.6 **Sydänveritulppa**	☐	☐
Vuonna_____		
17.7 **Muu suolistosairaus (haavainen paksusuolentulehdus, Crohnin tauti, mahahaava tms.)**	☐	☐
Vuodesta_____		
Tarkempi diagnoosi_____		
17.8 **Syöpäsairaus**	☐	☐
Vuodesta_____		
Missä elimessä_____		
17.9 **Luun murtumat**	☐	☐

Mitä murtumia ja minä vuosina_____

_____

_____

Miten aiheutuneet? (esim. kaatuessa, auto-onnettomuudessa jne.)

_____

_____

17.10 **Muita pitkäaikaisia sairauksia (verenpainetauti, sydänsairaus, astma, luuston haurastumien eli osteoporoosi, reumasairaudet yms.)** **Kyllä** ☐ **Ei** ☐

Sairaudet:

_____
_____
_____
_____

18. Käytän säännöllisesti seuraavia lääkärin määräämiä **lääkkeitä:**

_____
_____
_____
_____

19. Käytän säännöllisesti seuraavia itsehoito**lääkkeitä (särkylääkkeet, D-vitamiini, yms):**

_____
_____
_____
_____

	Kyllä	**Ei**
20. Tupakoitteko tällä hetkellä päivittäin	☐	☐
-jos, niin kuinka monta vuotta olette tupakoinut_____		
Oletteko aiemmin tupakoinut päivittäin	☐	☐
-jos, niin kuinka monta vuotta yhteensä_____		
Kuinka monta savuketta poltatte tai poltitte päivittäin ennen lopettamista?		
_____		
	Kyllä	**Ei**
21. Onko Teiltä mitattu kolesterolia viimeksi kuluneen vuoden aikana	☐	☐
-jos kyllä, mikä oli kolesteroliarvonne_____		
-oliko Teillä kolesterolilääke käytössä kun kolesteroliarvonne mitattiin	☐	☐

	Kyllä	**Ei**
22. Harrastatteko säännöllisesti vapaa-ajan liikuntaa vähintään puoli tuntia kerralla niin, että ainakin lievästi hengästytte ja hikoilette?	☐	☐

- jos kyllä, niin päivittäin ☐ 4-6 kertaa viikossa ☐ 3 kertaa viikossa ☐ 1-2 kertaa viikossa ☐ harvemmin ☐

23. Mikä on tämän hetkinen pituutenne_____cm ja painonne_____kg

LÄHISUKULAISET

24. Isäni on elossa ☐, ikä_____
kuollut ☐, ikä kuollessa _____

25. Äitini on elossa ☐, ikä_____
kuollut ☐, ikä kuollessa_____

	Kyllä	Ei
26. Minulla on lapsia	☐	☐

Lasten lukumäärät: tyttöjä_____, joista elossa _____
poikia_____, joista elossa_____

27. Minulla on sisaruksia	☐	☐

Sisarusten lukumäärät: siskoja_____, joista elossa_____
veljiä _____, joista elossa_____

LÄHISUKULAISTEN KELIAKIA TAI IHOKELIAKIA

	Kyllä	Ei
28. Yhdellä tai useammalla lähisukulaisellani on **keliakia**	☐	☐

(ilmoita sukulaisuussuhde, sairastumisikä ja onko hän elossa vai jo kuollut)
_____
_____

29. Yhdellä tai useammalla lähisukulaisellani on **ihokeliakia**	☐	☐

(ilmoita sukulaisuussuhde, sairastumisikä ja onko hän elossa vai jo kuollut)
_____
_____

	Kyllä	Ei
30. Mahdollisten lisätietojen saamiseksi minuun saa ottaa yhteyttä	☐	☐

-jos, niin puhelimitse ☐ sähköpostilla ☐

Jos teillä on erityistä kysyttävää tai kommentoitavaa, voitte kirjoittaa ne tähän
_____
_____
_____

Kiitokset vastauksestanne

APPENDIX 4: DISEASE RELATED QUESTIONNAIRE, COELIAC DISEASE

KYSELYKAAVAKE KELIAKIAPOTILAILLE

(Rastita oikea vaihtoehto tai kirjoita vastauksesi tyhjille viivoille)

Nimi_____ Henkilötunnus_____

Puhelinnumero_____ Sähköposti_____

Olen työssä kokopäiväisesti ☐ osapäiväisesti ☐ Ammatti_____

Olen eläkkeellä ☐ vuodesta_____ Olen koululainen/opiskelija ☐

Olen ☐ En ole ☐ Keliakiayhdistyksen jäsen

KELIAKIA

1. Minä vuonna Teillä todettiin keliakia _____

2. Oliko Teillä suolisto-oireita (vatsakipua, ripulia tms.) ennen keliakiadiagnoosin tekoa?

   Ei ☐ Kyllä ☐

   alle 3kk☐ 3-6kk☐ 6-12 kk☐ 1-2v☐ 2-5 v☐ 5-10 v☐ 10-20 v☐ en osaa sanoa☐

   Minkälaisia suolisto-oireita?_____

3. Oliko Teillä seuraavia muita keliakiaan viittaavia oireita ennen diagnoosin tekoa?

	Kyllä	**Ei**
3.1 Anemia	☐	☐
3.2 Painon lasku	☐	☐
3.3 Niveloireet (esim. nivelten turvottelu, nivelkipu)	☐	☐
3.4 Hermosto-oireet		
(esim. raajojen puutumista, epilepsiaa, tasapainovaikeuksia)	☐	☐
3.5 Aftat eli pienet haavaumat suussa	☐	☐
3.6 Hampaiden kiillevaurio	☐	☐

   Muu oire, mikä?_____

4. Onko Teillä todettu myös ihokeliakia Ei ☐ Kyllä ☐ vuonna_____

KELIAKIAN RUOKAVALIOHOITO

	Kyllä	En
5. Noudatatteko tällä hetkellä gluteenitonta ruokavaliota? (jos vastaatte tähän en, siirtykää kysymykseen 9)	☐	☐

6. Minä vuonna aloititte noudattamaan gluteenitonta ruokavaliota?
_____

7. Oma näkemykseni tämän hetkisestä gluteenittoman ruokavaliohoidon toteutumisesta
   - Noudatan gluteenitonta ruokavaliota hyvin tiukasti (en lipsu koskaan) ☐
   - Gluteeniton ruokavalioni lipsuu harvemmin kuin kerran kuukaudessa ☐
   - Gluteeniton ruokavalioni lipsuu 1-5 kertaa kuukaudessa ☐
   - Gluteeniton ruokavalioni lipsuu vähintään kerran viikossa ☐
   - En noudata gluteenitonta ruokavaliohoitoa tällä hetkellä ☐

	Kyllä	Ei
8. Onko keliakiadiagnoosin jälkeen ollut ajanjaksoja, jolloin gluteeniton ruokavaliohoito on jäänyt noudattamatta -jos kyllä, niin minä vuosina_____ ja kuinka kauan_____	☐	☐

	Kyllä	En
9. Jos ette tällä hetkellä noudata gluteenitonta ruokavaliota, oletteko joskus aikaisemmin noudattaneet sitä -jos kyllä, niin minä vuosina_____ja kuinka kauan_____	☐	☐

	Kyllä	En
10. Käytättekö ruokavaliossanne kauraa -jos kyllä, päivittäin ☐ 2-3 kertaa viikossa ☐ tätä harvemmin ☐	☐	☐

SUOLISTO-OIREIDEN PARANEMINEN

	Kyllä	Ei
11. Onko Teillä edelleen keliakiaan liittyviä suoloireita -jos kyllä, kuinka usein suunnilleen? viikottain ☐ 1-2 kertaa kuukaudessa ☐ 1-2 kertaa puolessa vuodessa ☐ 1-2 kertaa vuodessa ☐ harvemmin kuin kerran vuodessa ☐	☐	☐

12. Kuinka kauan gluteenittoman ruokavaliohoidon aloittamisen jälkeen kesti ennen kuin suolisto-oireet rauhoittuivat?
    Niitä ei ollut ☐ alle 1 kk ☐ 1-3kk ☐ 3-6 kk ☐ 6-12kk ☐ 1-2 v ☐ 2-5v ☐
    yli 5 v ☐ eivät ole vieläkään rauhoittuneet v ☐ en osaa sanoa ☐

MUUT SAIRAUDET

13. Sairastatteko keliakian lisäksi seuraavia lääkärin toteamia sairauksia:

	Kyllä	Ei
13.1 **Diabetes (eli sokeritauti)**	☐	☐

Vuodesta_____

Hoitona: tablettihoito ☐ insuliinihoito ☐

	Kyllä	Ei
13.2 **Kilpirauhassairaus**	☐	☐

Vuodesta_____

Liikatoiminta ☐ Vajaatoiminta ☐

	Kyllä	Ei
13.3 **Aivohalvaus / muu aivoverenkiertohäiriö**	☐	☐

Vuodesta_____

Tarkempi diagnoosi_____

	Kyllä	Ei
13.4 **Kohonnut veren kolesteroli**	☐	☐

Vuodesta_____

	Kyllä	Ei
13.5 **Sepelvaltimotauti**	☐	☐

Vuodesta_____

	Kyllä	Ei
13.6 **Sydänveritulppa**	☐	☐

Vuonna_____

	Kyllä	Ei
13.7 **Muu suolistosairaus (haavainen paksusuolentulehdus, Crohnin tauti, mahahaava tms.)**	☐	☐

Vuodesta_____

Tarkempi diagnoosi_____

	Kyllä	Ei
13.8 **Syöpäsairaus**	☐	☐

Vuodesta_____

Missä elimessä_____

	Kyllä	Ei
13.9 **Luun murtumat**	☐	☐

Mitä murtumia ja minä vuosina_____

_____

_____

Miten aiheutuneet? (esim. kaatuessa, auto-onnettomuudessa jne.)

_____

_____

13.10 **Muita pitkäaikaisia sairauksia (verenpainetauti, sydänsairaus, astma, luuston haurastumien eli osteoporoosi, reumasairaudet yms.)** **Kyllä** ☐ **Ei** ☐

Sairaudet:

_____
_____
_____
_____

14. Käytän säännöllisesti seuraavia lääkärin määräämiä **lääkkeitä:**

_____
_____
_____
_____

15. Käytän säännöllisesti seuraavia itsehoito**lääkkeitä (särkylääkkeet, D-vitamiini, yms):**

_____
_____
_____
_____

	Kyllä	**Ei**
16. Tupakoitteko tällä hetkellä päivittäin	☐	☐
-jos, niin kuinka monta vuotta olette tupakoinut_____		
Oletteko aiemmin tupakoinut päivittäin	☐	☐
-jos, niin kuinka monta vuotta yhteensä_____		
Kuinka monta savuketta poltatte tai poltitte päivittäin ennen lopettamista?		
_____		
	Kyllä	**Ei**
17. Onko Teiltä mitattu kolesterolia viimeksi kuluneen vuoden aikana	☐	☐
-jos kyllä, mikä oli kolesteroliarvonne_____		
-oliko Teillä kolesterolilääke käytössä kun kolesteroliarvonne mitattiin	☐	☐

	Kyllä	**Ei**
18. Harrastatteko säännöllisesti vapaa-ajan liikuntaa vähintään puoli tuntia kerralla niin, että ainakin lievästi hengästytte ja hikoilette?	☐	☐

- jos kyllä, niin päivittäin ☐ 4-6 kertaa viikossa ☐ 3 kertaa viikossa ☐ 1-2 kertaa viikossa ☐ harvemmin ☐

19. Mikä on tämän hetkinen pituutenne_____cm ja painonne_____kg

LÄHISUKULAISET

20. Isäni on elossa ☐, ikä_____
kuollut ☐, ikä kuollessa _____

21. Äitini on elossa ☐, ikä_____
kuollut ☐, ikä kuollessa_____

	Kyllä	Ei
22. Minulla on lapsia	☐	☐

Lasten lukumäärät: tyttöjä_____, joista elossa _____
poikia_____, joista elossa_____

23. Minulla on sisaruksia	☐	☐

Sisarusten lukumäärät: siskoja_____, joista elossa_____
veljiä _____, joista elossa_____

LÄHISUKULAISTEN KELIAKIA TAI IHOKELIAKIA

	Kyllä	Ei
24. Yhdellä tai useammalla lähisukulaisellani on **keliakia**	☐	☐

(ilmoita sukulaisuussuhde, sairastumisikä ja onko hän elossa vai jo kuollut)
_____
_____

25. Yhdellä tai useammalla lähisukulaisellani on **ihokeliakia**	☐	☐

(ilmoita sukulaisuussuhde, sairastumisikä ja onko hän elossa vai jo kuollut)
_____
_____

	Kyllä	Ei
26. Mahdollisten lisätietojen saamiseksi minuun saa ottaa yhteyttä	☐	☐

-jos, niin puhelimitse ☐ sähköpostilla ☐

Jos teillä on erityistä kysyttävää tai kommentoitavaa, voitte kirjoittaa ne tähän
_____
_____
_____

Kiitokset vastauksestanne

ORIGINAL PUBLICATIONS

PUBLICATION I

Gastrointestinal Symptoms Increase the Burden of Illness in Dermatitis Herpetiformis: A Prospective Study

Pasternack C, Kaukinen K, Kurppa K, Mäki M, Collin P, Hervonen K, Reunala T, Huhtala H, Kekkonen L, Salmi T

Acta Derm Venereol. 2017 97(1):58–62
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CLINICAL REPORT

Gastrointestinal Symptoms Increase the Burden of Illness in Dermatitis Herpetiformis: A Prospective Study

Camilla PASTERNACK[1], Katri KAUKINEN[1,2], Kalle KURPPA[3], Markku MÄKI[3], Pekka COLLIN[4], Kaisa HERVONEN[1,5], Timo REUNALA[1,5], Heini HUHTALA[6], Leila KEKKONEN[7] and Teea SALMI[1,5]

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Dermatitis herpetiformis (DH) is an extraintestinal manifestation of coeliac disease. The burden of illness in untreated coeliac disease is known to be considerable, but corresponding evidence for DH is lacking. In this study the burden of DH was evaluated prospectively in 52 patients newly diagnosed with DH using a study questionnaire and a validated Psychological General Well-Being (PGWB) questionnaire. The PGWB scores were compared with those of 110 healthy controls. Quality of life was significantly ($p < 0.001$) lower among patients with DH at the time of diagnosis, but after one year on a gluten-free diet their quality of life was at same level as that of the controls. The presence of gastrointestinal symptoms was shown to significantly increase the burden of untreated DH. We conclude that there is a significant burden related to untreated, but not to treated, DH, and the burden is even greater among DH patients with gastrointestinal symptoms.

Key words: dermatitis herpetiformis; burden of illness; quality of life; gastrointestinal symptoms; coeliac disease; gluten-free diet.

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Dermatitis herpetiformis (DH) is an extraintestinal manifestation of coeliac disease. The predominant symptom in DH is an itching blistering rash, which is triggered by ingestion of gluten (1). Diagnosis of DH is based on typical cutaneous symptoms and demonstration of granular immunoglobulin A (IgA) deposits in a skin biopsy (2). In addition to the skin manifestations, patients with DH also evince a coeliac-type gluten-sensitive small-bowel enteropathy, the majority having some degree of small-bowel mucosal villous atrophy (3). However, according to the present understanding, DH patients rarely experience gastrointestinal (GI) symptoms, although the evidence is scant. DH and coeliac disease also share the same immunogenic background, as both groups of patients have circulating immunoglobulin A (IgA) antibodies against endomysium (EmA) and tissue transglutaminase (TG2) auto-antigens. There is also a similar genetic background between the 2 diseases, with a strong association with human leukocyte antigen (HLA)-DQ2, and the disorders often occur in families (1). Consistently with coeliac disease, the treatment of choice in DH is a life-long gluten-free diet (GFD), which ameliorates both the rash and the small-bowel mucosal changes (4).

The disease burden is known to be considerable in coeliac disease; the diagnostic delay is frequently long, resulting in a burden of ongoing symptoms, a decrease in quality of life, increased use of on-demand medication, and the economic burden of healthcare utilization for society (5–7). Most patients with coeliac disease benefit from a GFD; their well-being increases and symptoms are alleviated (6, 8). However, dieting is troublesome and compliance difficult (9, 10). A substantial burden of illness is also related to a number of itching chronic skin diseases, such as psoriasis and atopic dermatitis (11, 12). Although DH is an itching chronic skin disease and an extraintestinal manifestation of coeliac disease, knowledge of its detriments is scarce. The aim of this prospective study was to assess the burden of illness during the year prior to DH diagnosis and one year after initiation of GFD treatment, and to determine whether GI complaints contribute to the burden of DH.

MATERIALS AND METHODS

Study design and participants

The data used in this study were obtained from a nationwide cohort of patients newly diagnosed with coeliac disease. Information was gathered in collaboration with the Finnish Coeliac Society, which currently has over 20,000 members. In Finland, approximately 70% of all patients with coeliac disease join the Finnish Coeliac Society shortly after being diagnosed. Between February 2007 and May 2008, a study questionnaire (see below in detail) was posted to all new members of the Finnish Coeliac Society. From among the respondents, patients over 16 years of age with skin biopsy-proven DH were enrolled as study patients. A follow-up questionnaire was sent to all respondents after one year. At follow-up, a telephone reminder was given to all non-respondents. For the present purpose, the DH patients were divided into 2 groups based on the presence or absence of self-reported GI symptoms at the time of diagnosis.

The control group comprised 110 adults who considered themselves healthy and had no first-degree relatives with coeliac

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disease. They were recruited from the close neighbourhood and from among friends of the patients with coeliac disease, the aim being to obtain a control group from a social and residential environment similar to that of the study patients.

The study protocol was approved by the review board of the Finnish Coeliac Society in compliance with all applicable Finnish laws for registered organizations, and covering the protection of human suspects. Informed consent was obtained from all study subjects after a full written explanation of the aims of the study, including considerations regarding ethics, data protection and the anonymous deposition of the questionnaires. Furthermore, all control patients gave their written informed consent and the study protocol involving the control patients was approved by the Regional Ethics Committee of Tampere University Hospital.

Questionnaires

The baseline and follow-up study questionnaires were designed in co-operation with the Finnish Coeliac Society, patients with coeliac disease, and clinical researchers specialized in coeliac disease. The questionnaires included both free-text questions and questions with multiple options measured on a Likert scale. The baseline questionnaire comprised questions on sociodemographic conditions, duration, type and nuisance of coeliac disease-related symptoms prior to DH diagnosis and reactions to the diagnosis. In the case of coeliac disease-related symptoms, any symptom belonging to the wide symptom spectrum (GI and non-GI manifestations), was considered. The nuisance of symptoms was recorded with alternatives "a lot", "a little", "some", "none" or "cannot tell". The reaction to the diagnosis was assessed with alternatives "it was a shock", "confused but confident", "it was a relief" and "no effect". Both questionnaires inquired into self-assessed personal health, concern for health, and use of healthcare services and pharmaceutical agents during the previous year. Self-assessed personal health was recorded on a 4-point scale with the alternatives "excellent", "good", "fair" and "poor", and concern for health with the alternatives "extremely", "moderately", "a bit" and "not at all". The follow-up questionnaire also asked about the strictness of the diet. Strictness of diet was recorded with 2 options: "strict diet" and "dietary lapses".

Quality of life was evaluated with a self-administrated Psychological General Well-Being (PGWB) questionnaire. PGWB is a 22-item questionnaire, which has been validated and widely applied in coeliac disease research to assess quality of life and well-being (13–16). PGWB covers 6 emotional states: anxiety, depressed mood, self-control, positive well-being, general health, and vitality. All of the items use a 6-grade Likert scale, where value 1 represents the poorest and value 6 the best possible well-being. The total score of PGWB thus ranges between 22 and 132 points, a higher score indicating better quality of life.

Statistical analysis

The feasibility of the study questionnaires designed in co-operation with the Finnish Coeliac Society was pre-tested with a group of patients with coeliac disease who are members of the Society. Test-retest reliability was confirmed by having 11 treated patients with coeliac disease complete the same questionnaire one week after initial contact. The intraclass correlation coefficient was measured and the kappa values ranged from 0.84 to 1.00 (values above 0.70 are excellent). Cronbach's α was not calculated as the test items were separated. All data were blindly coded before analysis.

All statistical analyses were performed with the IBM SPSS software, version 20 (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY, USA) in co-operation with a statistician. As the data were non-normally distributed, median values, minimum and maximum values and interquartile ranges were used to describe the continuous variables. All testing was 2-sided and $p<0.05$ was considered statistically significant. A χ^2 test was used in cross-tabulations, Wilcoxon signed-rank test for evaluating changes within groups and Mann-Whitney U test for assessing changes between groups.

RESULTS

The questionnaire was sent to 1,864 new members of the Finnish Coeliac Society, of whom 1,062 responded. At baseline 52 biopsy-proven newly diagnosed DH patients were enrolled, and 48 out of these 52 responded to the follow-up questionnaires after one year. The median age of the patients with DH at time of diagnosis was 52 years (range 23–74 years) and 35 patients were female (67%). The median age of the control group was 48 years (range 23–87 years) and 81% were female.

At diagnosis, the PGWB total score was significantly lower in DH patients (median 97, interquartile range (IQR) 83–107) compared with healthy controls (median 107, IQR 100–114) ($p<0.001$), as were all PGWB subscores (data not shown). After one year on a GFD the DH patients' PGWB total score increased significantly (median 106, IQR 94–113) and a statistically significant difference was no longer detected between treated DH patients and controls ($p=0.49$); the only subscore that remained inferior for DH patients was general health (median 13, IQR 10–15 vs. median 15, IQR 13–16, $p=0.001$).

When female and male DH patients were compared, the median duration of coeliac disease-related symptoms prior to diagnosis was significantly longer in females (4.5 vs. 2 years, $p=0.049$). Female DH patients also had lower PGWB scores in total, depression and general health scores compared with male patients at time of diagnosis. However, after one year on a GFD, there was only a non-significant trend in vitality subscore towards decreased vitality in females (Table SI[1]).

At time of diagnosis, 20 patients with DH (38%) reported having GI symptoms and 32 patients (62%) had no such symptoms. There were no differences in age, gender, body mass index (BMI) and occupational status between these 2 groups, but the median duration of coeliac disease-related symptoms was significantly longer in patients with DH with GI symptoms (9 vs. 2 years, $p=0.003$) (**Table I**). One year after diagnosis, 94% of the DH patients with, and 90% of those without, GI symptoms were on a strict GFD.

At diagnosis, the PGWB total score was significantly inferior in patients with DH with GI symptoms than among those with no such symptoms (Fig. S1[1]). Also the well-being, self-control and vitality subscores were significantly lower in patients with GI symptoms (**Table II**). After one year of diet, the PGWB total scores had

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-2471

Table I. Sociodemographic data and duration of symptoms prior to diagnosis in dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms

	DH with GI symptoms ($n = 20$)	DH without GI symptoms ($n = 32$)	p-value
Male, n (%)	6 (30)	11 (34)	0.744
Age at diagnosis, years, median (range)	49 (26–73)	55 (23–74)	0.353
Duration[a], years, median (range)	9 (0.5–45)	2 (0–30)	0.003
Body mass index, kg/m^2, median (interquartile range)			
At diagnosis	22.6 (21.7–26.6)	25.0 (23.0–29.4)	0.077
After one year	23.7 (20.9–26.6)	25.6 (22.3–27.4)	0.317
Occupational status, n (%)			0.403
Employed	13 (65)	20 (62.5)	
Student	1 (5)	0 (0)	
Retired	6 (30)	12 (37.5)	

[a]Duration of overall symptoms prior to diagnosis. Any coeliac disease-related symptoms.

increased significantly in both groups and were at the same level as in healthy controls (Fig. S1[1]). In PGWB subscores vitality and general health remained inferior in treated DH patients with GI symptoms compared with controls (Table II).

At diagnosis DH patients with GI symptoms significantly more frequently reported oral symptoms (25% vs. 3%), joint symptoms (35% vs. 3%) and weight loss (25% vs. 3%) compared with those free of such symptoms. The DH patients with GI symptoms were significantly more concerned about their health and reported inferior self-perceived health compared with those without GI symptoms (**Table III**) at time of diagnosis, while no significant differences between the groups were detected after one year on a GFD (Table III). Almost all DH patients found their symptoms disturbing at least to some degree at diagnosis, and all DH patients with GI symptoms and 93% of those without such symptoms were pleased to be diagnosed (Table III).

DH patients with GI symptoms used, in general, more painkillers, medication for dyspepsia, sleeping medication and antibiotics than those without such symptoms within one year prior to, but not after, the diagnosis (**Fig. 1**). A significant difference was observed only in the use of antibiotics during the year prior to diagnosis. The use of healthcare services as all-cause consultations did not vary between the DH groups and the number of days of sickness absences from work were equal between groups both during the year prior to and after the diagnosis (Table SII[1]).

Table III. Subjective perceptions of symptoms, diagnosis, and health at time of diagnosis and after one year on a gluten-free diet (GFD) in dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms

	DH with GI symptoms ($n = 20$)	DH without GI symptoms ($n = 32$)	p-value
Nuisance of symptoms before diagnosis, %[a]			0.238
A lot	65	41	
A little or some	35	53	
None or cannot tell	0	6	
Reaction to diagnosis, %			0.013
It was a shock	15	0	
Confused but confident	15	52	
It was a relief	70	45	
No effect	0	3	
Pleased at being diagnosed, %	100	93	0.263
Self-perceived health, %			
At diagnosis			0.018
Poor or fair	85	52	
Good or excellent	15	48	
After 1 year on GFD			0.809
Poor or fair	33	30	
Good or excellent	67	70	
Concern for health, %			
At diagnosis			0.039
Extremely or moderately	70	41	
A bit or not at all	30	59	
After one year on GFD			0.127
Extremely or moderately	44	23	
A bit or not at all	56	77	

[a]Any coeliac disease-related symptoms.

DISCUSSION

DH is an extraintestinal manifestation of coeliac disease presenting with troublesome, itching skin symptoms. A considerable burden of illness is related to itching chronic skin diseases (11, 12), but research on the burden of illness in DH is scant. Previously, a small study ($n = 10$) showed that DH patients' quality of life did not differ from that of healthy controls at the time of diagnosis, nor after one year of diet (17). In the present prospective study, we showed that DH patients' quality of life at the time of diagnosis was inferior compared with that of the healthy subjects. However, if patients with DH were compared with the classical coeliac disease patients from the same series (6), the DH patients had better quality of life at diagnosis. We further detected an improvement in DH patients' life quality after one year of GFD treatment, reaching the level of healthy controls in most values measured, and being superior to

Table II. Median values and interquartile ranges for Psychological General Well-Being (PGWB) subscores in dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms at diagnosis and after one year on a gluten-free diet (GFD), and in healthy controls. A higher score indicates better quality of life

	DH patients						Healthy controls ($n = 110$)
	With GI symptoms ($n = 20$)			Without GI symptoms ($n = 32$)			
Symptom	At diagnosis	On GFD	p-value	At diagnosis	On GFD	p-value	
Anxiety	20 (16–23)[b]	24 (22–26)	0.006	23 (19–26)[a]	25 (23–27)	0.003	25 (22–27)
Depression	16 (13–17)	17 (15–18)	0.054	16 (14–17)[a]	17 (15–18)	0.013	17 (15–18)
Well-being	16 (12–17)[a,c]	17 (14–19)	0.064	17 (15–18)	19 (16–20)	0.014	17 (15–19)
Self-control	14 (11–16)[b,c]	15 (13–17)	0.045	16 (13–17)	15 (14–17)	0.667	16 (14–17)
General health	10 (8–13)[b]	13 (11–15)[a]	0.003	11 (9–14)[b]	13 (10–15)[a]	0.008	15 (13–16)
Vitality	14 (11–18)[b,c]	18 (16–19)[a,c]	0.003	18 (15–20)[a]	20 (17–21)	0.006	19 (17–20)

[a]$p < 0.05$ compared with controls. [b]$p \leq 0.001$ compared with controls. [c]$p < 0.05$ compared with DH patient without GI symptoms at the same time-point.

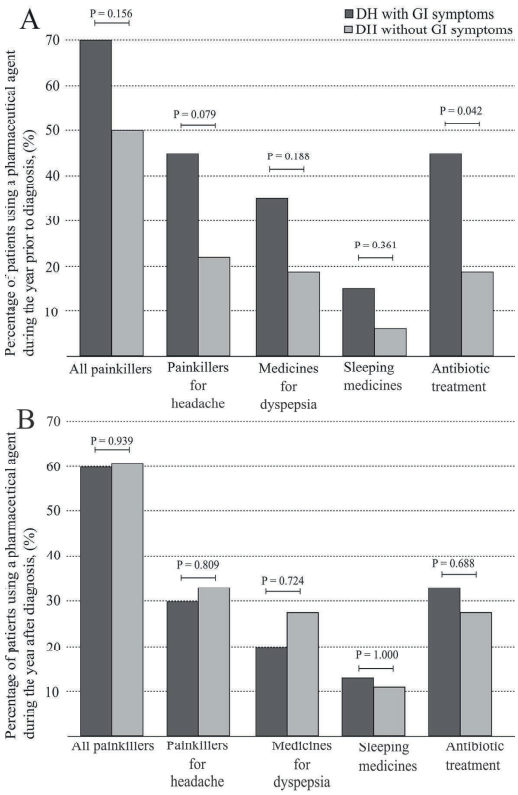

Fig. 1. The percentage of dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms using pharmaceutical agents (A) during the year prior to diagnosis and (B) during the year after diagnosis on a gluten-free diet.

that in the classical coeliac disease patients from the same series (6). We have previously shown in a different series that DH patients' quality of life is comparable to that of the healthy population even in the long term (18), which supports our present results.

In this study female patients with DH were found to have a poorer quality of life than male patients with DH. In our previous work, a similar decreased vitality was observed in long-term GFD-treated female patients with DH compared with male patients with DH (18). The same difference has been seen in classical coeliac disease: women have been shown to have a deteriorated quality of life compared with men (19, 20). The reasons for this gender difference in DH and coeliac disease are, thus far, unclear, but might be associated for example with challenges in everyday life, since women are, for example, more likely to be responsible for the planning and preparation of meals for the family (21). Female patients had a longer diagnostic delay in the current study compared with male patients, again as has been shown in coeliac disease (22). Furthermore, female DH and coeliac disease patients have been shown to have more severe GI symptoms than males (18, 23). The above-mentioned factors are also both linked to diminished quality of life in coeliac disease (5, 19, 24), and thus might offer other explanations for the gender differences in quality of life.

In addition to the skin symptoms, 38% of all patients with DH reported having GI symptoms at the time of diagnosis. In previous studies the prevalence of GI symptoms in DH cohorts has varied from 30% to none (3, 25–27). Since both patients' and dermatologists' primary focus is on the troublesome skin symptoms, there is a possibility that, especially milder, GI symptoms are ignored or not fully addressed. We showed that the presence of GI symptoms had a significant effect on the burden related to DH, as has been shown in coeliac disease (5, 19). DH patients with GI symptoms were more concerned about their health, perceived their health to be more deteriorated, and obtained lower scores in the PGWB questionnaire. DH patients with GI symptoms had also had longer diagnostic delay than DH patients without such symptoms. In addition, DH patients with GI symptoms presented overall a more heterogeneous clinical picture, demonstrated by the higher prevalence of additional oral and joint symptoms, and weight loss compared with DH patients without GI symptoms, this probably complicating the diagnostics and resulting in increased diagnostic delay. Interestingly, at diagnosis DH patients with GI symptoms had also used significantly more antibiotic treatments during the previous year than the DH patient without such symptoms.

Some limitations to the present study need to be discussed. In DH, the skin symptoms react slowly to GFD treatment alone, and therefore dapsone medication is often used in combination with dietary treatment to alleviate the skin symptoms more quickly (4). We had no data on the use of dapsone in our study population, and thus cannot verify the improved well-being in DH patients to be due solely to the GFD. We also used a generic quality of life questionnaire, which, although validated and widely used, is not designed specifically for coeliac disease or DH. In addition, by collaborating with the Finnish Coeliac Society we were able to recruit a fairly large and nationwide study cohort, although this might have caused selection bias. Also, in contrast to the known slight male predominance in DH (1), only 33% of the patients in this study were men. This may also have caused bias, since female patients with DH more readily perceive their quality of life to be poor compared with male patients. However, this does not explain the difference in quality of life between the DH patients with and those without GI symptoms, because the gender distributions were similar between the groups.

This study showed an impaired quality of life in DH at diagnosis and an improvement in the level of the healthy cohort after the first year on a GFD. At diagnosis, the

presence of GI symptoms affected patients' subjective perceptions of their well-being and was associated with an increased diagnostic delay and increased presence of other coeliac disease-related symptoms. In conclusion, closer attention should be paid to GI symptoms in DH.

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Supplementary material to article by C. Pasternack et al. "Gastrointestinal Symptoms Increase the Burden of Illness in Dermatitis Herpetiformis: A Prospective Study"

Table SI. *Median values and interquartile ranges for Psychological General Well-Being (PGWB) total score and subscores in female and male dermatitis herpetiformis (DH) patients at diagnosis and after one year on a gluten-free diet (GFD). A higher score indicates better quality of life*

	DH patients at diagnosis			DH patients on GFD		
Symptom	Female ($n=35$)	Male ($n=17$)	p-value	Female ($n=33$)	Male ($n=15$)	p-value
Total	90 (80–101)	104 (95–109)	0.034	102 (91–111)	112 (102–117)	0.089
Anxiety	20 (18–23)	23 (19–26)	0.145	24 (22–26)	26 (24–28)	0.092
Depression	15 (13–16)	17 (16–18)	0.027	16 (15–18)	18 (16–18)	0.119
Well-being	16 (13–18)	17 (16–18)	0.284	18 (14–20)	18 (17–21)	0.162
Self-control	14 (13–16)	16 (14–17)	0.113	15 (14–17)	16 (13–17)	0.492
General health	10 (8–12)	13 (10–15)	0.021	12 (10–15)	15 (11–16)	0.342
Vitality	16 (12–19)	18 (16–20)	0.155	18 (16–20)	20 (17–21)	0.075

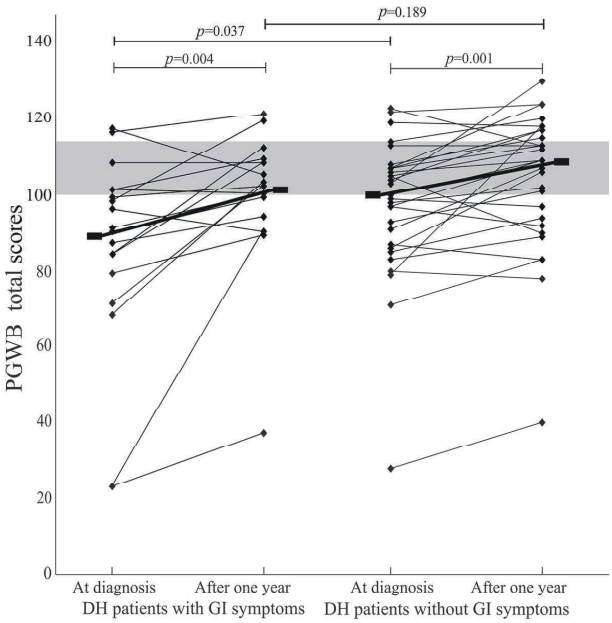

Fig. S1. Psychological General Well-Being (PGWB) total scores in dermatitis herpetiformis (DH) patients with and without gastrointestinal (GI) symptoms at diagnosis and one year after starting the gluten-free diet treatment. The *wider black lines* represent the median values for DH patient scores and the *grey area* represents the interquartile range for PGWB total scores of control population ($n = 110$).

Table SII. Median values and ranges for the number of doctor visits before diagnosis, use of healthcare services and days of absence from work during the year prior to diagnosis and during the year after diagnosis on a gluten-free diet for dermatitis herpetiformis (DH) patients

	DH patients with gastrointestinal symptoms ($n = 20$)	DH patients without gastrointestinal symptoms ($n = 32$)	p-value
Number of doctor visits before diagnosis[a]	4 (0–30)	3 (0–20)	0.076
Outpatient visits in primary healthcare			
Year prior to diagnosis	2 (0–31)	3 (0–30)	0.929
Year after diagnosis	2 (0–6)	2 (0–8)	0.594
Outpatient visits in secondary and tertiary healthcare			
Year prior to diagnosis	0 (0–4)	0 (0–10)	0.945
Year after diagnosis	0 (0–4)	0.5 (0–13)	0.644
Admissions to hospital			
Year prior to diagnosis	0 (0–2)	0 (0–4)	0.552
Year after diagnosis	0 (0–30)	0 (0–40)	1.00
Days of absence from work			
Year prior to diagnosis	0 (0–100)	0 (0–365)	0.721
Year after diagnosis	0 (0–30)	0 (0–40)	0.879

[a]Patients seeking help for the same coeliac disease-related symptom overall.

PUBLICATION II

Quality of Life and Gastrointestinal Symptoms in Long-Term Treated Dermatitis Herpetiformis Patients: A Cross-Sectional Study in Finland

Pasternack C, Kaukinen K, Kurppa K, Mäki M, Collin P, Reunala T, Huhtala H, Salmi T

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Quality of life and gastrointestinal symptoms in long-term treated dermatitis herpetiformis patients: a cross-sectional study in Finland

Running head: Quality of life in dermatitis herpetiformis

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Abstract

Background: Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease. Both conditions are treated with a restrictive life-long gluten-free diet (GFD). Treated coeliac disease patients have been shown to have more gastrointestinal symptoms and inferior quality of life compared to healthy controls, but evidence regarding quality of life in DH is lacking. Objective: The aim was to evaluate whether long-term GFD-treated DH patients suffer from persistent gastrointestinal symptoms and if they experience a drawdown in quality of life. Methods: Gastrointestinal symptoms and quality of life were assessed in 78 long-term GFD-treated DH patients using validated "Gastrointestinal Symptom Rating Scale", "Psychological General Well-Being" and "Short Form 36" questionnaires. The findings were compared to 110 healthy controls, population-based reference values and 371 treated coeliac disease-controls. Results: The median age of the DH patients at the time of the study was 57 years, and 51% were male. Significant differences in gastrointestinal symptoms or quality of life were not detected when treated DH patients were compared to healthy controls, but treated DH patients had less gastrointestinal symptoms and increased quality of life compared to coeliac disease-controls. Female DH patients had more gastrointestinal symptoms and reduced vitality compared to male DH patients. The presence of skin symptoms nor the adherence or duration of GFD did not have any influence on gastrointestinal symptoms or quality of life.
Conclusion: We conclude that long-term GFD-treated DH patients do not suffer from the burden of dietary treatment and have a quality of life comparable to that of controls.

Key points:

- Long-term gluten-free diet treated DH patients did not experience more gastrointestinal symptoms nor had a decline in the quality of life compared to healthy controls.
- Gluten-free diet treated DH women had more gastrointestinal symptoms and decline in vitality compared to DH men

1 Introduction

Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease, occurring in approximately 12% of coeliac disease patients. [1] DH manifests as an itchy, blistering rash predominantly on the extensor surfaces of elbows and knees, and on the buttocks and scalp. [2] The diagnosis of DH is based on typical clinical manifestation and the demonstration of granular immunoglobulin (Ig) A deposits in the papillary dermis. [3] The majority of DH patients evince small-bowel mucosal villous atrophy characteristic of coeliac disease, and the remainder have coeliac-type inflammation in the gut. Regardless of the mucosal damage, DH patients are thought to suffer only rarely from gastrointestinal symptoms or have signs of malabsorption. [4, 5]

The treatment of choice for coeliac disease and DH is a strict life-long gluten-free diet (GFD). The diet has a positive effect on the small-bowel mucosal villous atrophy and it also alleviates gastrointestinal complaints and malabsorption and the DH rash. [6, 7] A long-lasting strict GFD has also been shown to reduce the risk of malignant diseases such as lymphoma associated with DH and coeliac disease. [8] However, the diet is hard to comply with and

it causes drawdown in life quality because of its life-long restrictive nature, which interferes with everyday life. [9-11] Furthermore, the diet is more expensive than the normal gluten-containing diet.

Coeliac disease patients have been found to have a quality of life inferior to that in general population at the time of diagnosis. [12, 13] Even though health-related quality of life (HRQoL) has been shown to improve concomitant with treatment, [12, 14] in most studies the HRQoL of long-term GFD-treated coeliac disease patients does not reach the level of the normal population. [14-17] Furthermore, coeliac disease patients have been shown to suffer from persistent gastrointestinal complaints even after a long-term GFD. [18, 19] DH is a chronic itching skin disease and patients adhere to the same burdensome GFD as coeliac disease patients, but little is known about HRQoL in DH. The aim of this study was to establish whether the burden of restrictive GFD causes a drawdown in DH patients' HRQoL or do the benefits of decreased symptoms overcome the negative effects of GFD. Further, we aimed to find out whether treated DH patients suffer from persistent gastrointestinal symptoms. The results were compared to healthy controls and treated coeliac disease-controls.

2 Materials and Methods

2.1 Patients and controls

This was a cross-sectional study on the Finnish DH population. The cohort was derived from an adult coeliac disease series, including altogether 1111 patients. The series was recruited nationwide between the years 2006 and 2010 by advertising in national and local coeliac disease societies and using newspaper advertisement. Personal or telephone interviews were conducted to

the recruited either by a physician or a study nurse specialized in coeliac disease. The interviews included questions about demographic data, the year of DH or coeliac disease diagnosis, skin symptoms, coeliac disease-associated disorders, family history of coeliac disease or DH, duration of the diet and strictness of GFD at the time of the study. The strictness of the diet was assessed based on the interviews and patients were distributed into four groups: 1. strict diet, no dietary lapses, 2. dietary lapses less than once a week, 3. dietary lapses more than once a week and 4. unrestricted gluten-containing diet (Table 1). In addition, validated questionnaires about gastrointestinal symptoms, HRQoL and psychological general well-being were mailed to those enrolled.

Out of the 1111 recruited patients, 569 patients over 18 years answered to the validated questionnaires. Out of these 569, 78 patients had been diagnosed with DH and they were enrolled as cases in the study group. The medical records of the DH patients were reviewed to verify that all had had skin symptoms compatible with DH at the time of diagnosis, and that the presence of skin immunoglobulin A (IgA) deposits in the papillary dermis was confirmed by direct immunofluorescence. [3]

DH patients' gastrointestinal symptoms and quality of life as measured by the Psychological General Well-Being (PGWB) questionnaire were compared to 110 healthy controls, who considered themselves healthy and had no first-degree relatives with coeliac disease. These healthy controls were recruited from the immediate neighbourhood and among friends of the coeliac disease patients. The aim was to obtain a control group from a social and residential environment similar to that of the study patients. The median age of the healthy control group was 48 years (range 23-87) and 19% were male (Table 1). The results of the Short Form SF-36 (SF-36) questionnaire were compared to the age- and gender-adjusted Finnish general population reference values obtained

from a nationwide health survey involving 2060 subjects: 45% were male and the mean age was 49 years (standard deviation 17), median not known. [20] Furthermore, 371 GFD-treated coeliac disease patients suffering from abdominal symptoms at the time of the diagnosis, were selected as a coeliac disease-controls from the same series where DH patients were chosen. The biopsy-proven coeliac disease diagnoses were verified from the medical records. In the coeliac disease control group, 19% of patients were male and the median age at the time of the study was 56 years (range 19-92) (Table 1).

All participants gave their written informed consent. The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital.

2.2 Methods

Gastrointestinal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS), which is a 15-item questionnaire used to evaluate common gastrointestinal symptoms in five different groups: diarrhoea, indigestion, constipation, abdominal pain and reflux. The questionnaire uses a seven-grade Likert scale for each item, one symbolizing no symptoms and seven indicating the most severe symptoms. A higher score thus indicates more symptoms. The final scores are calculated as a mean for each sub-dimension and the total GSRS score as the mean of all 15 items. [21]

The quality of life was assessed with PGWB and SF-36 questionnaires. The PGWB is a questionnaire used to assess health-related quality of life and well-being. This is a 22-item questionnaire which includes six emotional states: anxiety, depressed mood, self-control, positive well-being, general health and vitality. All of the items use a six-grade Likert scale, where a value of one represents the poorest and value six the best possible well-being. The total score

ranges therefore between 22 and 132 points, a higher score indicating better quality of life. [22] The SF-36 is a generic HRQoL questionnaire, which uses eight parameters to quantify the quality of life. These are: general health perceptions, physical functioning, mental health, social functioning, vitality, bodily pain, physical role functioning and emotional role functioning. A scoring algorithm is used to transform the raw scores on each question into a scale ranging from 0-100, higher scores indicating better quality of life. [23] All of the questionnaires have been widely used in coeliac disease research and were chosen in view of their comparability with previous research and their good validity and reproducibility. [14, 24, 25]

2.3 Statistics

The data were analysed with the IBM SPSS Statistics 20 software package (International Business Machines Corp., New York, USA) in cooperation with a statistician. Since the data were not normally distributed, median values and interquartile ranges were calculated for all GSRS and PGWB parameters. Statistical significances were tested by Mann-Whitney U-test. *P* values <0.05 were considered statistically significant. The data with significance were further adjusted by gender and age. In order to make the values comparable with the reference, in SF-36 the means and standard deviations were used to describe the results. Significances between DH patients and the Finnish reference values were evaluated by estimating the confidence intervals for the differences in means.

3 Results

Forty (51%) of the 78 DH patients were male (Table 1). The median age of the DH patients at the time of the diagnosis was 38 years and at the time of the current study 57 years. At the time of the diagnosis all DH patients were shown to have IgA deposits detected by direct immunofluorescence in skin biopsies. Twenty-two out of the 41 (54%) DH patients with available small-bowel biopsy result at the time of the diagnosis had subtotal villous atrophy, 13 (32%) had partial villous atrophy, and 6 (14%) evinced normal villous architecture. At the time of the study, 95% of the DH patients were on a strict GFD, and the median duration of the diet was 18 years. None of the DH patients was consuming a normal gluten-containing diet (Table 1). At the time of the study 73 out of 78 (94%) DH patients had negative endomysial antibodies.

When the GFD-treated DH patients were compared to healthy controls, a non-significant trend emerged in GSRS reflux score, DH patients having more symptoms than healthy controls. However, this significance disappeared when adjusted for gender and age (Table 2). No other differences between DH patients and healthy controls were found in GSRS scores (Table 2). DH patients did not differ from healthy controls in the PGWB total or any sub-dimension scores. Only the unadjusted general health score was inferior in DH patients compared to healthy controls, but again the divergency disappeared when adjusted for gender and age (Table 2). Significant differences were not detected between DH study patients and healthy controls when the different aspects of quality of life were measured by SF-36 questionnaire (Fig. 1).

At the time of the diagnosis, 191 out of 309 (62%) coeliac disease patients with available data had subtotal villous atrophy in the small bowel mucosa, 109

(35%) had partial villous atrophy and 9 (3%) minor coeliac enteropathy. At the time of the study endomysial antibodies were negative in 350 out of 369 (95%) coeliac disease patients. When the GFD-treated DH patients were compared to treated coeliac disease-controls, DH patients had statistically significantly less symptoms in GSRS total and GSRS sub-dimension scores diarrhoea and pain. When data was adjusted for gender and age, only the difference in GSRS total score remained significant (Table 2). No differences were found in PGWB scores between treated DH patients and coeliac disease-controls. (Table 2) However, in SF-36 questionnaire coeliac disease-controls had significantly lower scores compared to DH patients in physical function, role physical and general health sub-dimension scores. There was also a non-significant trend in bodily pain. When the results were adjusted by gender and age, significance remained in general health and role physical sub-dimensions (Fig. 1).

When DH women were compared to DH men, a statistically significant difference was found in the GSRS parameters 'total' and 'constipation', DH women having more symptoms than DH men. A similar trend for women to experience more symptoms than men was also seen in other parameters of the GSRS questionnaire (Table 3). In PGWB and SF-36, a significant difference between the genders was found in vitality, which was inferior in DH women in both questionnaires (Table 3). In SF-36, there was also a borderline significant difference (P= 0.061) in mental health, showing poorer mental health in DH women compared to DH men (Table 3). No gender differences were found in coeliac disease-control group (data not shown).

Seventeen per cent of DH patients (13 out of 78) reported having visible skin symptoms compatible with DH or pruritus at the time of the study (Table 1), but the presence or absence of skin symptoms had no influence on GSRS,

PGWB or SF-36 scores (data not shown). Similarly, neither adherence to nor duration of GFD had any effect on the presence of persistent skin symptoms or on the questionnaire scores when the results were compared within the DH cohort.

4 Discussion

This is the first large study focusing on gastrointestinal symptoms and quality of life in a long-term GFD-treated cohort of DH patients. We found that long-term GFD-treated DH patients do not suffer from the burden of a GFD nor from the burden of the disease itself, as their quality of life was found to be comparable to that of the general population. Since HRQoL is known to be reduced in other comparable chronic itching skin diseases such as psoriasis and atopic dermatitis [26-28] the fact that our DH patients well-being is comparable to controls could be due to the very specific and curative treatment of GFD.

GFD-treated DH patients did not suffer from gastrointestinal complaints unlike coeliac disease patients who have been shown to suffer from persistent gastrointestinal complaints even when maintaining a strict GFD. [18, 19, 29] In Finland after long-term GFD 96% of coeliac disease patients have shown to evince normal villous architecture in small bowel biopsies. [30] In this study 95% and 98% of DH and coeliac disease patients followed a strict GFD and 94% and 95% of DH and coeliac disease patients were seronegative supporting excellent clinical and histological recovery on GFD in both groups. It has been suggested that the explanation for the persistent gastrointestinal symptoms in GFD-treated coeliac disease patients lies in the low amount of fibre in the diet [29, 31] or in trace amounts of gluten. [32] However, DH patients follow

exactly the same strict GFD as coeliac disease patients. Diagnostic delay and severity of gastrointestinal symptoms prior to diagnosis are known to be factors increasing the risk of prolonged gastrointestinal symptoms in coeliac disease. [19] DH patients are thought to suffer from milder gastrointestinal symptoms before the diagnosis but research has been unable to show a difference in the duration of symptoms prior to diagnosis between DH and coeliac disease. [33] Also the composition and diversity of the duodenal microbiota have been shown to vary between untreated classical coeliac disease and DH. [34] Although it has not been studied how GFD-treatment changes the duodenal microbiota, the difference in duodenal microbiota might have a role in explaining the difference in gastrointestinal symptoms between treated DH and coeliac disease patients. Moreover, the prevalence of irritable bowel syndrome-type symptoms has been found to be significantly higher in patients with coeliac disease compared to the normal population, [15, 35] while there is no evidence of this in DH. Thus coexisting undiagnosed gastrointestinal disorders might also influence the incidence of gastrointestinal symptoms in coeliac disease patients.

DH skin symptoms are known to alleviate comparatively slowly with GFD-treatment only, [4] and hence dapsone is a medication that is often used for a few months to a few years in combination with dietary treatment to reduce the skin symptoms more quickly. [4] We did not have data about the use of dapsone in our study population and therefore in patients with ongoing skin symptoms dapsone usage cannot be excluded even though dapsone is not commonly used in DH patients with a long duration of GFD. Although not scientifically studied in DH, the presence of skin symptoms are known to affect poorly the patients' quality of life. In our data only 13 DH patients were suffering from skin symptoms at the time of the study, and therefore it is possible that we were

unable to show the effect of the skin symptoms to the quality of life due to the small cohort size. In addition, instead of using dermatological questionnaires, we used generic quality of life questionnaires, which might have limited accuracy to show the effect of skin symptoms on HRQoL.

In our study cohort we found DH women to have more gastrointestinal complaints, especially constipation, compared to DH men. Coeliac disease women are also known to suffer from increased gastrointestinal symptoms compared to men, [18, 29] although our data showed no gender difference in coeliac-disease control group. In addition, more women than men are known to suffer from irritable bowel syndrome and especially constipation-predominant condition. [36] In this study DH women showed also lower vitality compared to DH men, which would imply that women with DH feel more tired and worn out compared to DH men. A similar distinction between the genders in HRQoL parameters has been widely observed previously in coeliac disease, [24, 25, 29] even though not evident in this current study. Interestingly this gender distinction in HRQoL is not found in all chronic diseases such as type-2 diabetes patients. [37]

In contrast to previous coeliac disease research, we focused here solely on DH patients and our DH cohort size was large. Previous research on HRQoL in DH has been scant; to our knowledge, only Tontini et al. [38] have focused on this aspect. In their coeliac disease study, they assessed the HRQoL of a small subcohort of 10 DH patients with the Italian version of the SF-36 questionnaire. Similarly to ourselves, they found no differences in the HRQoL of treated DH patients when compared to a control group. In addition to cohort size, other strengths of our study were the nationwide approach and the well-verified skin biopsy-proven DH diagnosis. Control patients did not undergo gastroscopy and small bowel biopsy to exclude coeliac disease, but even if there were a few

asymptomatic coeliac disease patients among controls this would not have influenced the results. In addition, we used well validated questionnaires, and while they are not coeliac disease- or DH-specific, they are widely used in coeliac disease studies. One limitation in our study is that we used volunteers, which might cause selection bias and possibly mislead the life quality being superior than it actually is. It must also be conceded that since the availability of gluten-free food is relatively good in Finland and adherence to the GFD is very high, our results may not be directly generalizable to different cultures or to countries with poorer dietary adherence.

5 Conclusions

The aim of this cross-sectional study was to evaluate whether long-term GFD-treated DH patients suffer from persistent gastrointestinal symptoms and if they experience a drawdown in quality of life. The conclusion was that the gastrointestinal symptoms and the quality of life of long-term GFD-treated DH patients are comparable to those in the general population. However, women with DH suffer from more severe gastrointestinal complaints and inferior vitality compared to DH men, which should be recognized during the follow-up.

6 Compliance with Ethical Standards

The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital and has therefore been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Camilla Pasternack, Katri Kaukinen, Kalle Kurppa, Markku Mäki, Pekka Collin, Timo Reunala, Heini Huhtala, and Teea Salmi have no conflicts of interest to declare.

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Table 1 Demographic data, associated disorders and gluten-free diet of treated dermatitis herpetiformis (DH) study patients, healthy controls and treated coeliac disease-controls.

	Study patients	Control patients (n=481)	
	DH patients (n=78)	Healthy controls (n=110)	Coeliac disease controls (n=371)
Male, n (%)	40 (51)	21 (19)	69 (19)
Age at diagnosis, median (range), years	38 (10-72)	-	44 (0-79)
Age at time of study, median (range), years	57 (28-81)	48 (23-87)	56 (19-92)
Family history of coeliac disease, n (%)	42 (54)	0	227 (61)
Coeliac disease-associated autoimmune disorders, n (%)			
Thyroid disease	13 (17)	0	67 (18)
Type 1 diabetes mellitus	2 (3)	0	7 (2)
Sjögren's syndrome	2 (3)	0	6 (2)
Duration of gluten-free diet, median (range), years	18 (1-47)	0	9 (0.5-53)
Strictness of gluten-free diet, n (%)			
Strict[a]	74 (95)	0	363 (98)
Dietary lapses 2-3 times/month	3 (4)	0	6 (2)
Dietary lapses more than 1/week	1 (1)	0	0

Normal gluten-containing diet	0	110 (100)	0
Skin symptoms at time of study, n (%)	13 (17)	nd	0

[a]No dietary lapses; nd, no data

Table 2 Unadjusted median values and interquartile ranges for Gastrointestinal Symptoms Rating Scale (GSRS) and Psychological General Well-Being (PGWB) scores for study patients with treated dermatitis herpetiformis (DH), healthy controls and treated coeliac disease-controls. In GSRS higher score indicates more symptoms and in PGWB higher score indicates better quality of life.

		Study patients	Control patients (n=481)			
	Symptom	DH patients (n=78)	Healthy controls (n=110)	Coeliac disease-controls (n=371)	P value[a]	P value[b]
GSRS	Total	1.8 (1.4-2.3)	1.7 (1.4-2.3)	1.9 (1.5-2.6)	0.804	0.014
	Diarrhoea	1.3 (1.0-2.0)	1.0 (1.0-2.0)	1.7 (1.0-2.3)	0.462	0.020*
	Indigestion	2.1 (1.5-3.0)	2.3 (1.5-3.0)	2.3 (1.8-3.3)	0.701	0.142
	Constipation	1.7 (1.0-2.0)	1.3 (1.0-2.3)	1.7 (1.0-2.7)	0.716	0.082
	Pain	1.7 (1.3-2.3)	1.7 (1.0-2.3)	2.0 (1.3-2.7)	0.714	0.012*
	Reflux	1.0 (1.0-2.0)	1.0 (1.0-1.5)	1.5 (1.0-2.0)	0.054*	0.544
PGWB	Total	104 (95-112)	107 (100-114)	105 (92-115)	0.150	0.746
	Anxiety	24 (21-27)	25 (22-27)	24 (21-27)	0.184	0.481
	Depression	17 (15-18)	17 (15-18)	17 (15-18)	0.841	0.836
	Well-being	18 (15-20)	17 (15-19)	17 (14-20)	0.382	0.494
	Self-control	15 (14-17)	16 (14-17)	16 (14-17)	0.582	0.535

General health	13 (11-15)	15 (13-16)	13 (10-15)	0.001*	0.426
Vitality	18 (16-20)	19 (17-20)	18 (16-20)	0.095	0.770

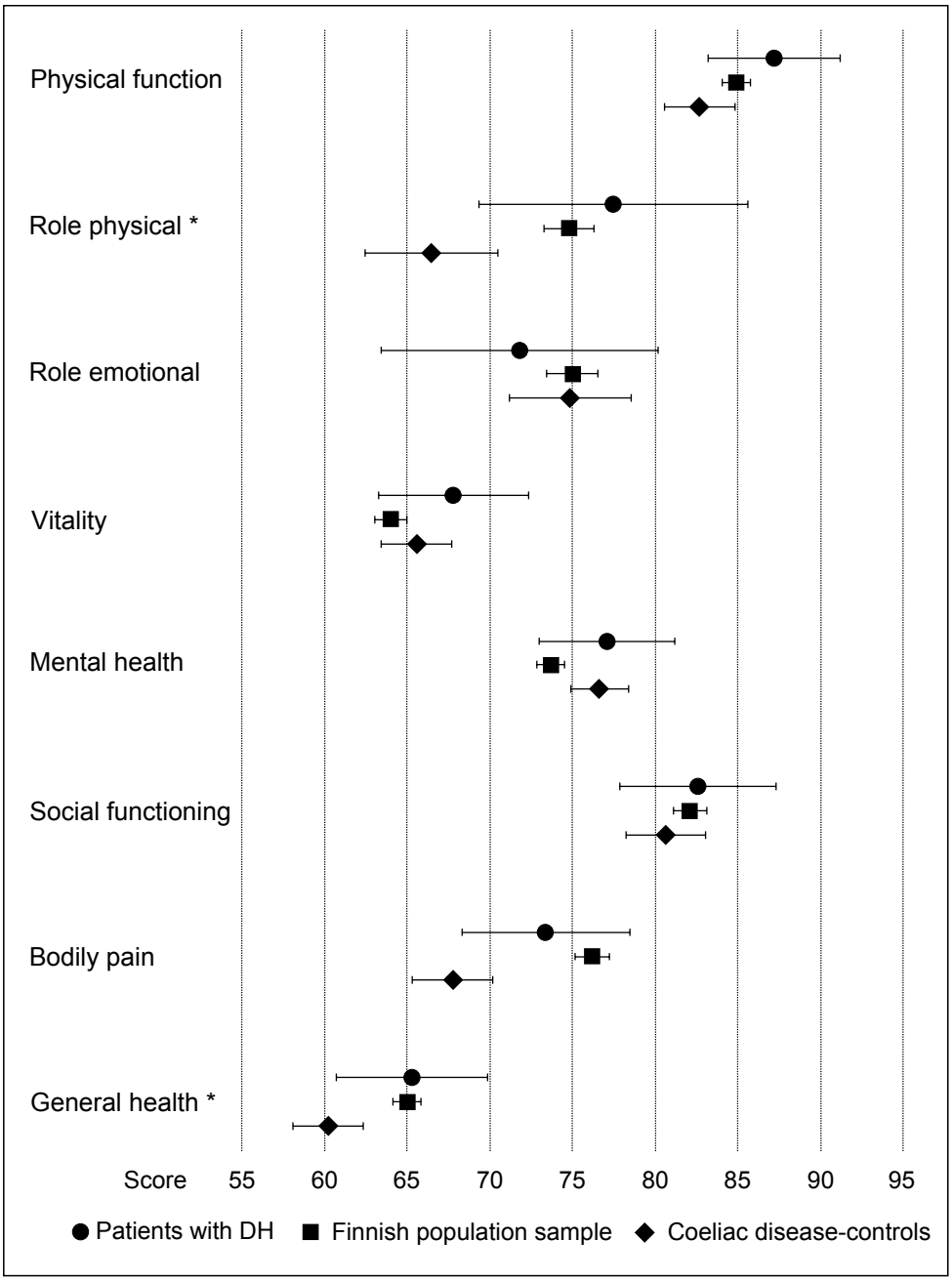
[a]Difference between DH patients and healthy controls; [b]Difference between DH patients and coeliac disease-controls;

*Significance disappears when adjusted by gender and age

Table 3 Median scores and interquartile ranges for Gastrointestinal Symptoms Rating Scale (GSRS), Psychological General Well-Being (PGWB), and Short Form 36 Health Survey (SF-36) questionnaires for treated male and female dermatitis herpetiformis (DH) patients. In GSRS higher score indicates more symptoms and in PGWB and SF-36 higher score indicates better quality of life.

	Parameter	DH men (n=40)	DH women (n=38)	P value
GSRS	Total value	1.6 (1.3-2.1)	2.1 (1.5-2.5)	0.006
	Diarrhoea	1.3 (1.0-1.9)	1.3 (1.0-2.1)	0.328
	Indigestion	2.0 (1.5-2.8)	2.4 (1.8-3.3)	0.101
	Constipation	1.3 (1.0-1.7)	1.7 (1.3-2.7)	0.007
	Pain	1.7 (1.0-2.0)	1.8 (1.3-2.3)	0.077
	Reflux	1.0 (1.0-2.0)	1.5 (1.0-2.0)	0.199
PGWB	Total score	107 (96-117)	101 (95-109)	0.135
	Anxiety	24 (21-27)	24 (22-26)	0.717
	Depression	17 (15-18)	16 (14-18)	0.163
	Well-being	18 (15-20)	18 (16-19)	0.771
	Self-control	16 (14-17)	15 (13-17)	0.117
	General health	13 (12-16)	13 (11-15)	0.160
	Vitality	19 (17-21)	17 (15-20)	0.052
SF-36	Physical function	95 (86-100)	93 (75-100)	0.183
	Role physical	100 (75-100)	100 (73-100)	0.940
	Role emotional	100 (41.65-100)	100 (33-100)	0.531
	Vitality	75 (65-85)	70 (49-80)	0.022
	Mental health	86 (73-91)	80 (68-85)	0.061
	Social functioning	88 (75-100)	88 (75-100)	0.588
	Bodily pain	78 (68-90)	78 (54-90)	0.558
	General health	70 (51-84)	65 (55-80)	0.250

Figure 1 Short Form 36 Health Survey (SF-36) mean scores and 95% confidence intervals for long-term gluten-free diet-treated dermatitis herpetiformis (DH) patients (n=78), Finnish general population reference values (n=2060) and treated coeliac disease-controls (n=371). (*Significant difference between DH patients and coeliac disease-controls)


Physical function
Role physical *
Role emotional
Vitality
Mental health
Social functioning
Bodily pain
General health *
Score
55
60
65
70
75
80
85
90
95
Patients with DH
Finnish population sample
Coeliac disease-controls

PUBLICATION III

Self-reported fractures in dermatitis herpetiformis compared to coeliac disease

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Article

Self-Reported Fractures in Dermatitis Herpetiformis Compared to Coeliac Disease

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Abstract: Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease. Increased bone fracture risk is known to associate with coeliac disease, but this has been only scantly studied in DH. In this study, self-reported fractures and fracture-associated factors in DH were investigated and compared to coeliac disease. Altogether, 222 DH patients and 129 coeliac disease-suffering controls were enrolled in this study. The Disease Related Questionnaire and the Gastrointestinal Symptom Rating Scale and Psychological General Well-Being questionnaires were mailed to participants; 45 out of 222 (20%) DH patients and 35 out of 129 (27%) of the coeliac disease controls had experienced at least one fracture ($p = 0.140$). The cumulative lifetime fracture incidence did not differ between DH and coeliac disease patients, but the cumulative incidence of fractures after diagnosis was statistically significantly higher in females with coeliac disease compared to females with DH. The DH patients and the coeliac disease controls with fractures reported more severe reflux symptoms compared to those without, and they also more frequently used proton-pump inhibitor medication. To conclude, the self-reported lifetime bone fracture risk is equal for DH and coeliac disease. After diagnosis, females with coeliac disease have a higher fracture risk than females with DH.

Keywords: dermatitis herpetiformis; coeliac disease; fracture; bone health; quality of life

1. Introduction

Coeliac disease is a systemic autoimmune disorder triggered by gluten and characterized by small-bowel mucosal villous atrophy. It has a highly heterogeneous clinical picture including intestinal, extraintestinal, and asymptomatic manifestations [1]. A number of comorbidities are associated with coeliac disease, one of which is metabolic bone disease predisposing to bone fractures [2]. At the time of diagnosis, coeliac disease patients frequently suffer from decreased bone mineral density (BMD) [2,3], which in turn may be a risk factor for fractures. Decreased BMD is not limited to only patients with severe gastrointestinal symptoms; it also occurs in subclinical and asymptomatic coeliac disease patients [4–6]. Once diagnosed, coeliac disease is treated with a life-long gluten-free diet (GFD). Strict adherence to a GFD typically improves bone health in coeliac disease, but full bone recovery is often not reached in adult coeliac disease patients [7]. Fracture risk in coeliac disease has been studied

extensively, and based on a recent meta-analysis, it can be concluded that the risk of fractures in coeliac disease is increased by 30% for any fractures and by 69% for hip fractures [8].

Dermatitis herpetiformis (DH) is one of the well-established extraintestinal manifestations of coeliac disease [9]. In DH, dietary gluten induces an itchy, blistering rash, which responds to a GFD [10]. Since a GFD often alleviates the intensively itching rash fairly slowly, patients with severe symptoms are additionally treated with dapsone medication at the beginning of the dietary treatment to alleviate the skin symptoms more quickly [11]. At diagnosis, DH patients also suffer from coeliac disease-type small-bowel mucosal villous atrophy or inflammation. Occasionally gastrointestinal symptoms also occur, but they are often minor [9,12]. It seems presumable that the increased risk of bone fractures would also be associated with DH, but bone complications in DH have been studied scantily and the results are thus far conflicting [13–17]. The only study focusing on the fracture risk in DH found no increase in risk [13]. The aim of the current study was to discover whether DH patients have an increased bone fracture risk similar to the one known to exist in coeliac disease. A further objective was to study the factors associated with increased bone fracture risk in DH, and to assess the burden related to fractures.

2. Materials and Methods

2.1. Patients, Controls, and Study Design

All patients with DH within the catchment area of the city of Tampere are diagnosed and treated at a special outpatient clinic at Tampere University Hospital's Department of Dermatology. The diagnosis of DH is based on clinical symptoms and the demonstration of granular immunoglobulin A deposits in perilesional skin biopsies studied with direct immunofluorescence [18]. From 1970 onwards, data have been prospectively collected from all patients diagnosed with DH. All adult DH patients alive in December 2015 and diagnosed before December 2014 (n = 413) were recruited to the study. The control group comprised 222 biopsy-proven coeliac disease patients diagnosed at Tampere University Hospital over the same time period who were suffering from abdominal symptoms at the time of diagnosis.

Self-administered study questionnaires (see below for more detail) were mailed to the patients and controls. A second round of questionnaires were sent to all non-respondent patients and controls under 80 years old. For the DH patients, the total response rate was 56% (237 out of 413). Of these responders, 15 patients were excluded for having a coeliac disease diagnosis made more than one year prior to the DH diagnosis. The remaining 222 DH patients constituted the study cohort. For the coeliac disease controls, the final response rate was 59% (130 out of 222), and one patient was excluded because of a DH diagnosis. The patients' medical records were reviewed and the clinical, serological, and histological severity of the disease and the use of dapsone were recorded.

The DH patients and coeliac disease controls received a full written explanation of the aims of the study and they gave their written informed consent. The Regional Ethics Committee of Tampere University Hospital approved the study protocol.

2.2. Questionnaires

Three self-administrated questionnaires were used in this study: the Disease Related Questionnaire (DRQ), which was specifically designed for this study, and the general Psychological General Well-Being (PGWB) and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires, which have been widely used in coeliac disease studies. The DRQ includes both open questions and multiple-choice questions. Patients were asked to report all experienced bone fractures during their lifetime, the year of each fracture, and the type of trauma causing the fracture. The DRQ also includes questions about the respondent's sociodemographic and lifestyle characteristics, presence of comorbidities, use of long-term medication, and current weight and height. In addition, the questionnaire also enquires about previous and current clinical symptoms related to coeliac disease and DH and the strictness of the respondent's GFD.

The PGWB is a 22-item questionnaire used to evaluate quality of life and well-being [19,20]. It covers six emotional states: anxiety, depressed mood, self-control, positive well-being, general health, and vitality. All of the items use a six-grade Likert scale, where value one represents the poorest and value six the best possible well-being. The total PGWB score thus ranges from 22 to 132 points, with a higher score indicating a better quality of life.

The GSRS is a 15-item questionnaire used to assess the severity of five groups of gastrointestinal symptoms: diarrhoea, indigestion, constipation, abdominal pain, and reflux [21]. The questionnaire uses a seven-grade Likert scale for each item, one symbolizing no symptoms and seven indicating the most severe symptoms. The final scores are calculated as a mean for each sub-dimension and the total GSRS score as the mean of all 15 items. A higher score indicates more severe symptoms.

2.3. Fractures

The self-reported fractures were categorized based on whether they had occurred before or after the DH or coeliac disease diagnosis. The traumas causing the fractures were evaluated, and if the trauma was considered sufficient to cause a bone fracture in any person (traffic accidents, high-energy sports fractures), the fracture was excluded from further analysis. Fractures diagnosed as stress fractures were also excluded from all further analysis.

2.4. Statistical Analysis

Median values, minimum and maximum values, and interquartile ranges (IQR) were used to describe the continuous variables. All testing was two-sided and $p < 0.05$ was considered statistically significant. The chi-squared test was used in cross-tabulations and the Mann–Whitney *U* test was used for assessing changes between groups. Kaplan–Meier survival analysis was used to compare the cumulative incidence of fractures between the groups. The odds ratios (OR) and 95% confidence intervals (CI) were calculated by using binary logistic regression analysis. For fracture incidence rates, 95% CI were calculated assuming the number of fractures to have a Poisson distribution. All of the statistical analyses were performed with SPSS version 20 (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY, USA) in cooperation with a statistician.

3. Results

In total, 101 of the 222 DH patients (45%) and 104 of the 129 coeliac disease controls (81%) were female. The DH patients were younger at the time of diagnosis than the coeliac disease controls (Table 1). At the time of the study, there were no differences in age or body mass index between the groups. The median follow-up time after diagnosis was 23 years (range 2–53) for the DH patients and 20 years (range 1–43) for the coeliac disease controls. The DH patients and the coeliac disease controls reported a total of 128 fractures, of which 9 excess-trauma fractures and 5 stress fractures were excluded from further analysis. There were no statistical differences between the groups in terms of the number of study participants who reported a fracture (Table 1).

The fracture incidence rate per 10^5 person-years for the first fracture was 317 (95% CI 228–431) for the DH patients and 388 (95% CI 259–558) for the coeliac disease controls. For the first fracture after DH or coeliac disease diagnosis, the fracture incidence rates per 10^5 person-years were 629 (95% CI 427–894) for the DH patients and 1083 (95% CI 707–1589) for the coeliac disease controls. In the binary logistic regression analysis, the risk of fracture for the coeliac disease group did not statistically significantly differ from the DH group before (OR 1.47, 95% CI 0.88–2.43, $p = 0.141$) or after adjustment for gender and age at the time of the study (adjusted OR 1.04, 95% CI 0.60–1.79, $p = 0.891$). In the Kaplan–Meier analysis, neither the cumulative lifetime fracture incidence (Figure 1A) nor the incidence before diagnosis ($p = 0.127$) significantly differed between the groups. The cumulative incidence of fractures after the diagnosis was statistically significantly higher in the coeliac disease group than in the DH group (Figure 1B). When the genders were analysed separately the difference was observed for female ($p = 0.021$) but not for male patients ($p = 0.291$).

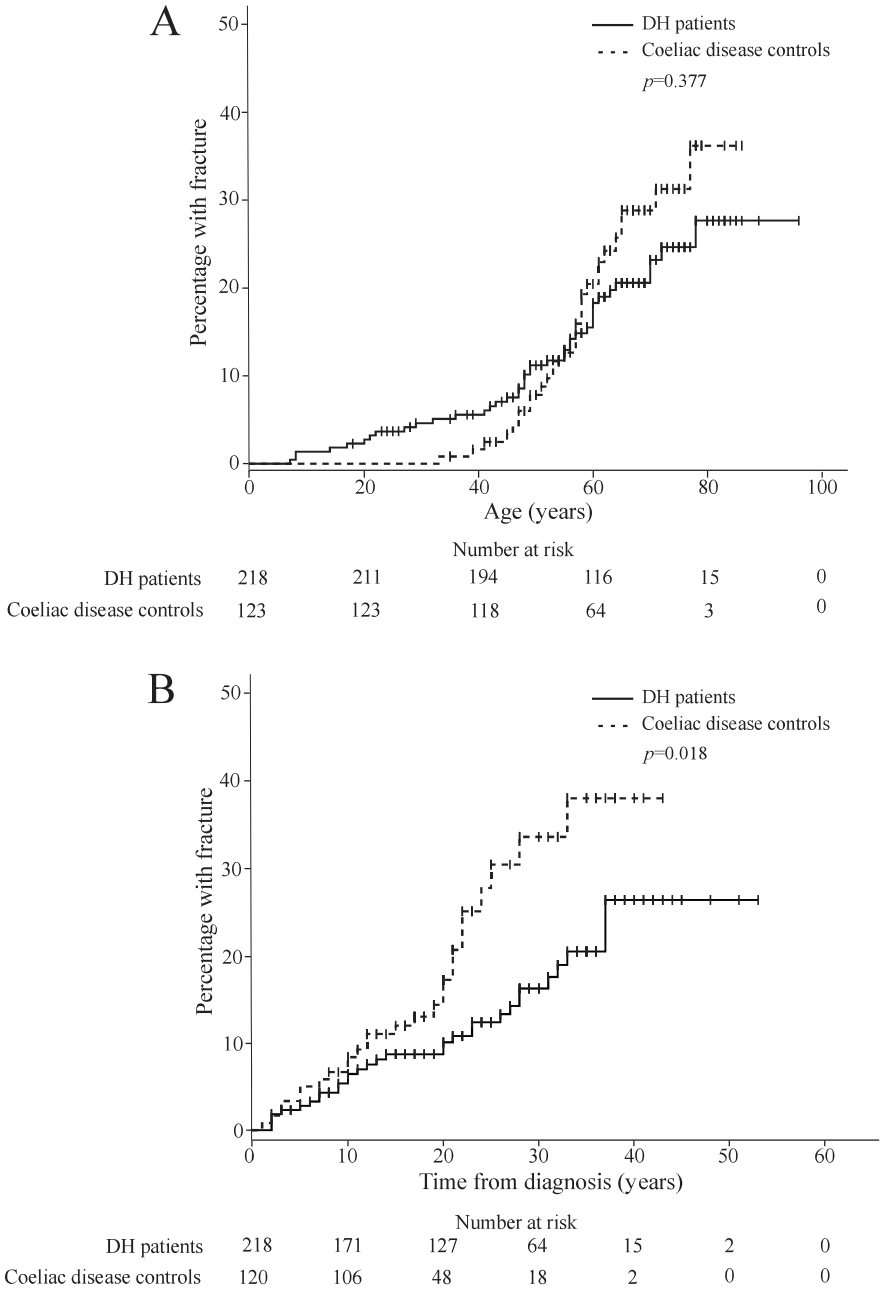

Figure 1. Kaplan–Meier cumulative incidence of the first fracture (**A**) and for first fracture after diagnosis (**B**) for the dermatitis herpetiformis (DH) patients and the coeliac disease controls.

In both study groups, patients with fractures were more often female, had more often been diagnosed with osteoporosis, and more often had multiple long-term illnesses (Table 2). At the time of the study, those with fractures were more often using proton-pump inhibitors (PPI) and vitamin D

and calcium supplementation than those with no reported fractures (Table 2). The current usage of hormone replacement therapy and diuretics was more common among the DH patients with reported fractures than those without, but this was not seen in the coeliac disease controls. There were no differences in the smoking habits or current adherence to a GFD, the amount of weekly exercise, or the use of glucocorticoids or bisphosphonates between those with and without fractures in either groups (Table 2). Compared to coeliac disease controls with fractures, DH patients with fractures were statistically significantly more often male, and they were younger at the time of the diagnosis (Table 2) and at the time of the first fracture (median 48 years vs. 57 years, $p = 0.048$).

The DH patients with fractures more frequently had severe villous atrophy in the small bowel at the time of the diagnosis than those without fractures, but the difference in the histological severity of the disease did not reach statistical difference (Table 3). There were no differences in the duration of skin symptoms before DH diagnosis, the severity of skin symptoms, or the presence of gastrointestinal symptoms at diagnosis between DH patients with fractures and those without, but DH patients with fractures had used dapsone medication statistically significantly longer after diagnosis than those without fractures (Table 3).

The severity of the gastrointestinal symptoms as measured with the GSRS total score did not differ between DH patients or coeliac disease controls with and without fractures (Table A1). However, DH patients with fractures reported higher GSRS reflux subscores than those without fractures (median 1.5 vs. 1.0, $p = 0.012$). This was also seen in the coeliac disease controls, although without reaching statistical significance (median 1.5 vs. 1.0, $p = 0.083$). The quality of life measured with the PGWB questionnaire was decreased in DH patients with fractures compared to those without in total score (median 106 vs. 112, $p = 0.006$) and in all other subscores except depression (Table A1). This same phenomenon was not observed in the coeliac disease controls (Table A1).

Table 1. Demographic data and reported fractures among 222 dermatitis herpetiformis (DH) patients and the 129 coeliac disease controls.

	DH Patients (n = 222)		Coeliac Disease Controls (n = 129)		p-Value
	n	%	n	%	
Female	101	45	104	81	<0.001
Age at diagnosis, median (range), years	37 (5–78)		42 (7–72)		0.027
Age at the time of the study, median (range), years	65 (18–96)		66 (35–86)		0.654
BMI [1] at the time of the study, median (range), kg/m^2	26 (17–40)		26 (15–46)		0.714
Reported fractures	45	20	35	27	0.140
Before diagnosis	13	6	3	3	0.143
After diagnosis	31	14	26	22	0.080
Reported multiple fractures	15	7	12	9	0.388

[1] BMI, Body mass index.

Table 2. Demographic data, strictness of gluten-free diet (GFD), and clinical data for the dermatitis herpetiformis (DH) patients and the coeliac disease controls with and without fractures.

	DH Patients (n = 222)			Coeliac Disease Controls (n = 129)		
	With Fracture (n = 45)	**Without Fracture (n = 177)**	**p-Value**	**With Fracture (n = 35)**	**Without Fracture (n = 94)**	**p-Value**
Female, %	58 *	42	0.064	97	74	0.002
Age at diagnosis, median (range), years	34 (7–78) *	37 (5–78)	0.652	45 (23–59)	40 (7–72)	0.428
Age at the time of the study, median (range), years	68 (22–85)	65 (18–96)	0.343	68 (51–82)	63 (35–86)	0.020
Smoking at the time of the study, %			0.581			0.218
Non-smoker	69	68		66	70	
Ex-smoker	17	22		31	20	
Current smoker	14	10		3	10	
Exercise at the time of the study, %			0.341			0.396
Not at all	11	11		6	10	
1 to 3 times per week	55	43		57	44	
4 to 7 times per week	34	46		37	46	
Dietary adherence to GFD at the time of the study, %			0.858			0.646
Strict [1]	70	73		80	86	
Dietary lapses less than once a month	21	18		17	10	
Dietary lapses more than once a month	7	8		3	3	
Normal diet	2	1		0	1	
Diagnosed with osteoporosis, %	11 *	2	0.024	40	11	0.001
Multiple long-term illnesses [2], %	33	19	0.033	43	26	0.057
Use of long-term medication at the time of the study, %						
Proton-pump inhibitor	21	9	0.029	26	11	0.034
Hormone replacement therapy	14	4	0.008	3	11	0.155
Any glucocorticoid medication	18	12	0.349	26	16	0.205
Vitamin D and calcium supplementation	39	10	<0.001	43	25	0.045
Bisphosphonates	5	3	0.545	9	6	0.506
Diuretics	21	9	0.028	11	8	0.491

[1] No dietary lapses, [2] Two or more of the following diseases: thyroid disease, diabetes, hypercholesterolaemia, hypertension, rheumatoid disease, coronary artery disease. * $p < 0.05$ when the DH patients with fractures were compared to the coeliac disease patients with fractures.

Table 3. Disease-related characteristics presented as percentages, median values, and interquartile ranges (IQR) for the dermatitis herpetiformis (DH) patients with fractures and those without fractures.

	DH Patients		*p*-Value
	With Fracture (*n* = 45)	**Without Fracture (*n* = 177)**	
Year of DH diagnosis, median (IQR)	1990 (1976–2000)	1991 (1982–2002)	0.076
Duration of skin symptoms prior to DH diagnosis, median (IQR), months	12 (6–60)	10 (5–24)	0.183
Severity of skin symptom at diagnosis, %			0.818
Mild	19	15	
Moderate	46	50	
Severe	35	35	
Presence of gastrointestinal symptoms at the time of diagnosis, %	47	49	0.886
Small-bowel histology at diagnosis, %			0.405
Normal	16	24	
PVA [1]	35	39	
SVA/TVA [2]	49	37	
Use of dapsone after diagnosis, %	79	77	0.854
Duration of dapsone, median (IQR), months	60 (12–171)	24 (12–60)	0.031

[1] PVA, Partial villous atrophy; [2] SVA/TVA, Subtotal or total villous atrophy.

4. Discussion

In the current study, the lifetime fracture risk in DH was found not to differ from that in coeliac disease, which is well known to be linked to increased bone fracture risk [8]. However, it was found that females with coeliac disease had more fractures after coeliac disease was diagnosed than females with DH after DH diagnosis. The sole previous study addressing bone fracture risk in DH, with a respectable 846 DH patients from the United Kingdom, found no increased fracture risk in DH compared to the general population (hazard ratio 1.1) [13]. However, the study had limitations, as their observation period was rather short (median 3.7 years, 3496 person-years) and the data collected regarding adherence to GFD treatment was scanty. In the current study, the fracture incidence was smaller than in the work by Lewis et al. but the results are not comparable, as different study methods and follow-up times were used. In addition, our study groups had good adherence to a GFD, which is likely to decrease the fracture incidence. Other than the study by Lewis et al., bone health in DH has been investigated in four small studies focusing on the DH patients' BMD. Two studies found that DH patients have a decreased BMD compared to non-DH controls but better BMD than coeliac disease controls [14,15], and two studies found that the BMD in DH patients did not differ from that expected [16,17].

It is acknowledged that strict adherence to a GFD increases BMD in coeliac disease patients [2,7], and thus probably decreases the risk of bone fractures in the long term. In the current study, there were no differences in the strictness of GFD at the time of the study in the DH patients and the coeliac disease controls with and without fractures (Table 2). Overall, the GFD in this study cohort was strict, showing that bone fractures also tend to occur when the patients adhere to the diet well. However, we do not have short-term data about the strictness of the diet after the diagnosis. The duration of dapsone use after diagnosis was longer for DH patients reporting fractures compared to those who did not (Table 3). Longer requirement of dapsone usage suggests more active and prolonged rash, which might be a consequence of ongoing gluten consumption from dietary lapses on GFD. Less strict GFD after diagnosis in turn would be a logical cause for increased risk of fractures.

Bone deterioration in coeliac disease is considered a consequence of autoimmune reaction. The autoimmune reaction causes local and systemic chronic inflammation, which in turn causes

micronutrient deficiency and activates a network of cytokines that have deleterious consequences for bone remodeling [22]. As DH and coeliac disease principally share the same pathogenetic mechanisms, it is accurate to assume that the same mechanisms explain the increased fracture risk also observed in DH. However, our study showed that after diagnosis, the female coeliac disease controls experienced more fractures than the female DH patients. This difference could be caused by the on-going small-bowel inflammation that remains in coeliac disease even after the recovery of the mucosal architecture [23]. In addition, the age at diagnosis was higher for the coeliac disease controls compared to the DH patients. The higher age at diagnosis has been linked to less complete bone recovery following GFD, and it seems that the ability to bone recovery is the least satisfactory for peri- and post-menopausal women [3,24]. The higher age at diagnosis might also indicate that coeliac disease patients have suffered from the untreated disease longer than DH patients, and untreated disease particularly before puberty would have unfavorable effects on bone health.

The prevalence of gastrointestinal symptoms at the time of diagnosis was not linked to reported fractures, nor was any symptom other than reflux in the GSRS questionnaire at the time of the study. Consistently with more severe reflux symptoms detected, both the DH patients and the coeliac disease controls with fractures reported using PPI as a long-term medication more often than those without fractures. The usage of PPI medication has been reported to increase the risk of fractures at any site in a recent meta-analysis [25]. Thus, caution with PPI medications should be advised, although based on the experienced reflux symptoms, there is a clear need for PPI medication in certain individuals with DH and coeliac disease.

This study showed that the DH patients who reported fractures had a decreased quality of life compared to those with no fractures. Although we do not know if this decrease in life quality is caused by the burden of fractures or simply explained by a higher rate of multiple long-term illnesses detected in patients with fractures, we think that more attention should be directed to fractures in DH. In this study cohort, very few of the DH patients with fractures had been diagnosed with osteoporosis, which suggests that BMD measurements may not have been carried out systematically in the presence of fractures. This limits the awareness and motivation to adequately treat patients suffering from low BMD, and thus it also limits the prevention of additional fractures.

The strengths of this study are the large cohorts of patients with biopsy-proven DH and coeliac disease with strict inclusion and exclusion criteria, and thus a minimal possibility for misclassification bias. The cohorts were diagnosed and treated by specialists during the same time period, and they included patients with different severities of the disease from the same geographic area. The limitations of this study should be recognized, however. The fractures in this study were self-reported, which is not ideal. Nevertheless, questionnaire studies have in fact proven to be rather reliable [26], and although we know that the results are underestimations of the true occurrence due to recall bias [27], the groups in this study are comparable because they were both studied in a similar manner. Another limitation is that we have not taken the site of the fracture into account in our analysis, so we do not know how this would have differed between the groups. The study also compared only the fractures between DH and coeliac disease, and we did not enrol healthy controls. The gender distributions between our cohorts were unequal, but they correspond to the true distributions in both diseases and therefore the cohorts cannot be considered unrepresentative.

5. Conclusions

In conclusion, the fracture risk in DH is analogous to that in coeliac disease, which is a disease widely documented to be associated with increased bone fracture risk. However, after the diagnosis, the fracture risk was higher in coeliac disease than in DH for female patients. The severity of the skin disease did not correlate with the fracture risk in DH, but the reflux symptom and usage of PPI medication were linked to an increased fracture risk. The quality of life was shown to be decreased in DH patients with a history of fractures, which indicates that more attention should be directed to the fracture risk in DH, and BMD measurements should not be overlooked.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Median values and interquartile ranges for the Psychological General Well-Being (PGWB) and Gastrointestinal Symptoms Rating Scale (GSRS) totals and subscores for the dermatitis herpetiformis (DH) patients and the coeliac disease controls with and without fractures. In the PGWB, a higher score indicates a better quality of life, and in the GSRS, a higher score indicates more severe symptoms.

	DH Patients (n = 222)			Coeliac Disease Controls (n = 129)		
	With Fracture (n = 45)	Without Fracture (n = 177)	p-Value	With Fracture (n = 35)	Without Fracture (n = 94)	p-Value
GSRS						
Total	1.9 (1.3–2.3)	1.6 (1.3–2.1)	0.191	1.9 (1.5–2.5)	1.7 (1.4–2.5)	0.472
Diarrhoea	1.7 (1.0–2.3)	1.3 (1.0–2.0)	0.116	2.0 (1.0–2.7)	1.7 (1.0–2.5)	0.635
Indigestion	2.0 (1.3–2.5) *	1.8 (1.5–2.5)	0.630	2.4 (1.8–2.8)	2.0 (1.5–3.0)	0.343
Constipation	1.3 (1.0–2.3)	1.3 (1.0–2.3)	0.568	1.7 (1.3–2.5)	1.7 (1.0–2.7)	0.572
Pain	1.7 (1.2–2.3)	1.3 (1.0–2.0)	0.130	1.7 (1.3–2.3)	1.7 (1.3–2.3)	0.517
Reflux	1.5 (1.0–2.0)	1.0 (1.0–1.5)	0.012	1.5 (1.0–2.5)	1.0 (1.0–2.0)	0.083
PGWB						
Total	106 (94–113)	112 (101–119)	0.006	110 (93–120)	106 (97–116)	0.629
Anxiety	25 (22–27)	26 (23–28)	0.020	27 (21–29)	25 (23–28)	0.757
Depression	17 (16–18)	18 (16–18)	0.311	17 (15–18)	17 (15–18)	0.948
Well-being	17 (15–19)	18 (16–20)	0.007	18 (15–19)	17 (16–20)	0.941
Self control	16 (15–17)	16 (15–17)	0.052	16 (13–17)	16 (14–17)	0.888
General health	13 (11–15)	15 (13–16	0.012	13 (11–16)	13 (11–15)	0.712
Vitality	18 (17–21)	20 (17–21)	0.029	19 (17–20)	18 (16–20)	0.665

* $p < 0.05$ when the DH patients with fractures were compared to the coeliac disease patients with fractures.

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PUBLICATION IV

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

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