Tampere University

ANNA ALAKOSKI

Dermatitis Herpetiformis

Gastrointestinal findings, anaemia and effects of gluten-free dietary treatment

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ACADEMIC DISSERTATION
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Lempäälä, September 2021

Anna Alakoski

ABSTRACT

Dermatitis herpetiformis (DH) is an itchy, blistering cutaneous disease and an extraintestinal manifestation of coeliac disease. In DH, dietary gluten evokes an autoimmune process in genetically predisposed individuals, which leads to the development of DH rash and coeliac-type small bowel mucosal damage. The diagnosis of DH is based on a demonstration of granular immunoglobulin A deposits in papillary dermis in direct immunofluorescence examination. The treatment for DH and coeliac disease is life-long gluten-free diet (GFD), where wheat, rye and barley are strictly avoided, but there has been some uncertainty about the safety of oats. Strict adherence to GFD eventually heals skin symptoms and small bowel mucosa, but risk of lymphoma is known to be elevated in DH.

The aims of this dissertation were to investigate gastric findings and anaemia in DH, as well as the long-term prognosis of DH, in terms of the safety of oat consumption, morbidity, mortality and causes of deaths. The study cohorts for all studies were gathered from prospectively collected series of DH patients diagnosed in Tampere University Hospital, Department of Dermatology, between 1970 and 2019. Additionally, a sub-cohort of DH patients recruited by a nationwide search were included (III). In Study I, the prevalence of chronic atrophic gastritis (CAG) and *Helicobacter pylori* (*H. pylori*) infection was measured in 93 DH patients who had undergone gastroscopy at the time of DH diagnosis and had a classification of gastritis according to the Sydney system. The control group included 186 adults undergoing gastroscopy because of dyspepsia symptoms. In Study II, the prevalence of anaemia at diagnosis and one year thereafter and factors associated with anaemia were investigated in 250 DH patients who had available blood haemoglobin (Hb) level at diagnosis. As controls, 139 patients with classic coeliac disease were chosen. In Study III, the prevalence of oat consumption in 312 long-term GFD-treated DH patients was measured, and further, health and quality of life were compared between those consuming and not consuming oats. In Study IV, mortality and causes of death of 476 DH patients were compared to age- and sex-matched general population, and further, health behaviour was investigated in 179 working-aged DH patients compared to 895 working-age controls from general population. In all studies, the demographic and baseline data were gathered from the medical records and by

interviews (III: sub-cohort 2), and the follow-up data from medical records, questionnaires and interviews. Two DH-specific questionnaires designed for the purposes of the study were used and elicited information on clinical symptoms, GFD and dapsone treatments, long-term illnesses and complications of DH. Additionally, in Study III, the Gastrointestinal Symptoms Rating Scale questionnaire was used to assess gastrointestinal symptoms and Psychological General Well-being and Dermatology Life Quality Index questionnaires were used to assess quality of life. Health behaviour in Study IV was measured with the Finnish Adult Health Behaviour Survey.

This dissertation showed that both CAG and *H. pylori* infection were more common in DH than in controls with dyspepsia (16% vs. 3%, p<0.001, and 18% vs. 9%, p=0.028, respectively). Furthermore, *H. pylori* infection was more frequent in DH patients with CAG than in those without CAG (44% vs. 14%, p 0.012). The prevalence of anaemia was 12% in untreated DH, and no significant difference was seen compared to the prevalence of anaemia in coeliac disease (17%, p=0.257). Anaemia in untreated DH was not associated with the severity of skin symptoms or small bowel villous atrophy and clinical recovery did not differ between DH patients with and without anaemia. Prevalence of anaemia at one-year follow-up was 19% in DH and it was mainly associated with dapsone treatment. According to the health behaviour analysis, DH patients were less often smokers and also had less frequently hypercholesterolaemia than general population. At long-term follow-up 82% of DH patients were consuming oats and had fewer gastrointestinal symptoms, less dapsone usage and better quality of life than those not consuming oats. Finally, it was established that overall standardized mortality ratio (SMR) was reduced in DH (0.72, 95% confidence intervals CI 0.55-0.87), and further, cause-specific SMR was reduced for cerebrovascular (0.38, 95% CI 0.10-0.97) and alcohol-related diseases (0.00, 95% CI 0.00-0.88). Instead, SMR for lymphoproliferative diseases increased during five years after diagnosis (2.49, 95% CI 0.91-5.40), but not thereafter.

This dissertation demonstrated that CAG and *H. pylori* infections were more common in DH than in controls, however, the clinical relevance and association with gastric carcinoma remains obscure and needs further research. Anaemia was fairly uncommon in untreated DH and not associated with the severity of the disease. Anaemia in treated DH, however, is mostly related to dapsone treatment. Long-term consumption of oats is safe in DH and the overall prognosis of DH patients adhering to GFD is good. All-cause and cerebrovascular mortality risks were decreased, and elevated mortality risk for lymphoproliferative diseases decreased after five years of GFD adherence.

TIIVISTELMÄ

Ihokeliakia on keliakian ilmenemismuoto, jossa oireena on ihon voimakkaasti kutiseva, rakkuloiva ihottuma. Ihokeliakiassa ravinnon gluteeni laukaisee geneettisesti alttiilla henkilöillä autoimmuuniprosessin, joka johtaa keliakiatyyppiseen ohutsuolen limakalvovaurioon ja ihokeliakiaihottumaan. Ihokeliakian diagnoosi varmistetaan ihon immunofluoresenssitutkimuksella, jossa havaitaan rakeinen IgA-kertymä verinahassa. Ihokeliakian hoitona on elinikäinen gluteeniton ruokavalio, jossa vältetään vehnää, ohraa ja ruista, mutta kauran soveltuvuus ruokavalioon on ollut kiistanalaista. Gluteeniton ruokavalio parantaa iho-oireet ja ohutsuolimuutokset, mutta lymfoomariskin tiedetään olevan suurentunut ihokeliakiassa.

Väitöskirjan tavoitteena oli tutkia mahalöydöksiä ja anemiaa ihokeliakiassa sekä ihokeliakian pitkäaikaisennustetta kaurankäyttöön, sairastavuuteen, kuolleisuuteen ja kuolinsyihin liittyen. Tutkimuskohortit kaikkiin osatöihin (I-IV) kerättiin Tampereen yliopistollisen sairaalan ihotautiklinikassa vuosina 1970-2019 prospektiivisesti kerätyistä ihokeliakiapotilaista. Mukana oli myös ryhmä ihokeliakiapotilaita, jotka oli rekrytoitu kansallisesti (III). Osatyössä I tutkittiin kroonisen atrofisen gastriitin ja helikobakteeri-infektion yleisyyttä 93 ihokeliakiapotilaalla, joille oli tehty gastroskopia diagnoosivaiheessa ja mahalöydöksiin oli käytetty Sydneyn luokitusta. Verrokkeina oli 186 aikuista, joille oli tehty ylävatsavaivojen vuoksi gastroskopia. Osatyössä II tutkittiin anemian yleisyyttä diagnoosivaiheessa ja vuoden kuluttua diagnoosista sekä anemiaan liittyviä tekijöitä 250 ihokeliakiapotilaalla, joilta oli tutkittu veren hemoglobiini (Hb) diagnoosivaiheessa. Verrokkeina oli 139 klassista keliakiapotilasta. Osatyössä III tutkittiin kaurankäytön yleisyyttä 312 pitkäaikaisesti gluteenitonta ruokavaliota noudattaneella ihokeliakiapotilaalla ja lisäksi tutkittiin kaurankäytön vaikutuksia terveyteen sekä elämänlaatuun. Osatyössä IV tutkittiin kuolleisuutta ja kuolinsyitä 476 ihokeliakiapotilaalla ja näitä verrattiin ikä- ja sukupuolivakioituun normaaliväestöön. Lisäksi 179 työikäisen ihokeliakiapotilaan terveyskäyttäytymistä verrattiin 895 työikäiseen henkilöön. Osatöiden diagnoosivaiheen tiedot kerätiin sairaskertomuksista ja osin haastatteluilla (III: ryhmä 2). Seurantatiedot kerättiin kyselykaavakkeista, sairaskertomuksista ja haastatteluista. Osatöissä käytettiin kahta ihokeliakiapotilaille suunniteltua kyselykaavaketta, jotka

sisälsivät kysymyksiä ihokeliakian oireista, ruokavaliosta ja dapsoni-lääkityksestä sekä pitkäaikaissairauksista ja ihokeliakian komplikaatioista. Lisäksi osatyössä III vatsaoireita kartoitettiin Gastrointestinal Symptoms Rating Scale -kyselylomakkeella ja elämänlaatua Psychological General Well-being - ja Dermatology Life Quality Index -kyselykaavakkeilla sekä osatyössä IV terveyskäyttäytymistä Suomalaisen aikuisväestön terveyskäyttäyminen ja terveys -kyselyllä.

Tutkimus osoitti, että krooninen atrofinen gastriitti ja helikobakteeri-infektio olivat yleisempiä ihokeliakiapotilailla kuin ylävatsavaivoista kärsivillä verrokeilla (16% vs 3%, $p<0.001$, ja 18% vs 9%, $p=0.028$, vastaavasti). Helikobakteeri-infektio oli yleisempi ihokeliakiapotilailla, joilla oli krooninen atrofinen gastriitti verrattuna niihin, joilla ei ollut gastriittia (44% vs 14%, $p=0.012$). Ihokeliakiapotilaista 12%:lla esiintyi anemiaa diagnoosivaiheessa ja anemian esiintyvyys ei eronnut merkittävästi keliakiasta (17%, $p=0.257$). Ihokeliakiassa diagnoosivaiheen anemia ei assosioitunut iho-oireiden tai ohutsuolen villusatrofian vaikeusasteeseen eikä sillä ollut vaikutusta kliinisten oireiden parantumiseen ruokavaliohoidolla. Vuoden kuluttua diagnoosista anemiaa oli 19%:lla ihokeliakiaa sairastavista, mutta anemia liittyi pääasiallisesti dapsoni-lääkitykseen. Terveyskäyttäytymisanalyysin perusteella ihokeliakiapotilailla oli vähemmän hyperkolesterolemiaa kuin normaaliväestöllä ja he myös tupakoivat vähemmän. Ihokeliakiapotilaista 82% käytti kauraa ruokavaliossaan, ja kauraa käyttävillä oli parempi elämänlaatu ja vähemmän suolioireita kuin kauraa käyttämättömillä. Ihokeliakiapotilailla oli normaaliväestöä pienempi kokonaiskuolleisuus (vakioitu kuolleisuussuhde SMR 0.72, 95% luottamusväli CI 0.55-0.87) ja lisäksi alentunut kuolleisuus aivoverenkierron häiriöihin (SMR 0.38, 95% CI 0.10-0.97) ja alkoholiin liittyviin sairauksiin (SMR 0.00, 95% CI 0.00-0.88). Sen sijaan kuolleisuus lymfoomiin oli lisääntynyt ensimmäiset viisi vuotta diagnoosista (SMR 2.49, 95% CI 0.91-5.40), mutta ei enää sen jälkeen.

Tämä väitöskirjatutkimus osoitti, että anemia on melko harvinaista hoitamattomassa ihokeliakiassa, eikä anemian esiintyvyys liity taudin vaikeusasteeseen. Hoidetussa ihokeliakiassa anemia on pääosin dapsonista johtuvaa. Kroonista atrofista gastriittia sekä helikobakteeri-infektiota esiintyy enemmän ihokeliakiassa kuin kontrolleilla, mutta näiden löydösten kliininen merkitys ja yhteys mahasyöpään on epävarmaa ja vaatii lisää tutkimuksia. Kaurankäyttö on turvallista ihokeliakiassa ja ihokeliakian kokonaisennuste on hyvä erityisesti niillä, jotka noudattavat gluteenitonta ruokavaliota. Kokonaiskuolleisuus sekä aivoverenkiertohäiriöiden aiheuttama kuolleisuus todettiin pienentyneeksi ja lisäksi riski lymfoomaakuolleisuuteen pienenee normaaliksi 5 vuoden kuluttua ihokeliakian diagnoosista gluteenittoman ruokavalion myötä.

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ABBREVIATIONS

Ab	Antibody
ARA	Anti-reticulin antibody
BMD	Bone mineral density
CAG	Chronic atrophic gastritis
CI	Confidence interval
DGP	Deamidated gliadin peptide
DH	Dermatitis herpetiformis
DLQI	Dermatology Life Quality Index
ELISA	Enzyme-linked immunosorbent assay
GFD	Gluten-free diet
GI	Gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
Hb	Haemoglobin
HLA	Human leukocyte antigen
HR	Hazard ratio
ICD-10	International Classification of Diseases
IEL	Intraepithelial lymphocyte
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
IQR	Interquartile range
MHC	Major histocompatibility complex
NHL	Non-Hodgkin's lymphoma
OR	Odds ratio
PGWB	Psychological General Well-being
RR	Risk ratio
SMR	Standardized mortality ratio
T1DM	Type 1 diabetes mellitus
TG3	Epidermal transglutaminase

TG2	Tissue transglutaminase
TG6	Transglutaminase 6
UK	United Kingdom
US	United States

ORIGINAL PUBLICATIONS

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

Publication I Alakoski A, Salmi T, Hervonen K, Kautiainen H, Salo M, Kaukinen K, Reunala T, Collin P (2012). Chronic Gastritis in Dermatitis Herpetiformis: A Controlled Study. Clin Dev Immunol 2012: 1–5.

Publication II Alakoski A, Pasternack C, Reunala T, Kaukinen K, Huhtala H, Mansikka E, Jernman J, Hervonen K, Salmi T (2021). Anaemia in dermatitis herpetiformis: Prevalence and associated factors at diagnosis and one-year follow-up. Acta Derm Venereol. 101: adv00443.

Publication III Alakoski A, Hervonen K, Mansikka E, Reunala T, Kaukinen K, Kivelä L, Laurikka P, Huhtala H, Kurppa K, Salmi T (2020). Long-term safety and quality of life effects of oats in dermatitis herpetiformis. Nutrients 12:1060.

Publication IV Hervonen K*, Alakoski A*, Salmi T, Helakorpi S, Kautiainen H, Kaukinen K, Pukkala E, Collin P, Reunala T (2012). Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients. Br J Dermatol 67:1331-1337.

* equal contribution

AUTHOR'S CONTRIBUTIONS

I: A.A. was responsible for the collection and editing of the study material, interpretation and evaluation of the results, as well as writing and editing of the article. A.A. also contributed to the planning of the study protocol and statistical analyses.

II. A.A. was responsible for the editing of the study material, interpretation and evaluation of the results as well as writing and editing of the article. A.A. also contributed to the planning of the study protocol and statistical analyses.

III: A.A. was responsible for the editing of the study material, interpretation and evaluation of the results as well as writing and editing of the article. A.A. also contributed to the planning of the study protocol and statistical analyses.

IV: A.A. contributed to planning of the study protocol, collection of the study material as well as interpretation and evaluation of the results writing and editing of the article.

1 INTRODUCTION

Dermatitis herpetiformis (DH), a cutaneous manifestation of coeliac disease, is an autoimmune disease characterized by itching and blistering rash typically on the elbows, knees and buttocks triggered by dietary gluten (Bolotin and Petronic-Rosic, 2011a). Additionally, DH patients have coeliac type enteropathy with small bowel mucosal inflammation and in the majority of cases also villous atrophy (Mansikka et al., 2017). In coeliac disease, one of the most common findings at diagnosis is anaemia, presenting in 20-30% of patients with coeliac disease in Western countries (Balaban et al., 2019; Laurikka et al., 2018). Instead, anaemia has been far less studied in DH, since there is only one study examining anaemia in untreated DH in India, reporting a 23% anaemia prevalence (Handa et al., 2018).

The diagnosis of DH is confirmed by the demonstration of granular IgA in papillary dermis with direct immunofluorescence examination from perilesional skin biopsy (Zone et al., 1996). Instead, gastroscopy is no longer routinely needed at diagnosis. According to preliminary evidence, there is some indication that the risk for autoimmune based chronic atrophic gastritis (CAG) might be increased in DH. (Gillberg et al., 1985; Lancaster-Smith et al., 1974; O'Donoghue et al., 1976; Primignani et al., 1990; Stockbrügger et a, 1976). Generally, CAG has suggested to be a precursor lesion of gastric cancer (Adamu et al., 2010; Correa, 1992), particularly when *Helicobacter pylori (H. pylori)* infection is involved (Thomas et al., 2019). However, the frequency of CAG and *H. pylori* infection in Finnish DH population remains obscure.

After the diagnosis, a strict gluten-free diet (GFD), avoiding wheat, rye and barley is initiated. However, while the DH and coeliac disease guidelines have generally accepted oats as part of the GFD (Al-Toma et al., 2019; Caproni et al., 2009), there has been still some debate about the possible toxicity of oats for some patients (Ciacci et al., 2015), and moreover, studies on long-term consumption of oats in DH are lacking. Even with a strict GFD, the clearance of the skin symptoms may take months or even a few years, and therefore for DH patients with severe skin symptoms, dapsone (diamino-diphenyl sulphone) medication is additionally instituted and continued until the skin symptoms are controlled with GFD alone (Salmi and Hervonen, 2020). In DH strict adherence to GFD seems to decrease the

risk for complications, such as lymphoma, since lymphoma occurs especially in those not adhering to GFD (Hervonen et al., 2005; Lewis et al., 1996; Viljamaa et al., 2006). In coeliac disease, overall mortality has been shown to be increased (Corrao et al., 2001; Grainge et al., 2011; Holmes et al., 2018), while there are two previous studies according to which mortality in DH seems not to be increased (Swerdlow et al., 1993; Viljamaa et al., 2006)., However, there is also a contrasting study demonstrating increased mortality in DH (Peters et al., 2003).

The aim of this dissertation was to study gastric findings in DH at diagnosis, as well as the prevalence of anaemia in untreated and treated DH and factors associated with anaemia. A further aim was to examine the prevalence and safety of oat consumption and the long-term prognosis of DH in terms of morbidity and mortality.

2 REVIEW OF THE LITERATURE

2.1 Overview and clinical features of dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a highly pruritic and blistering autoimmune skin disease, which was originally described by Louis Duhring in 1884 (Duhring, 1884). In the 1950s, dapsone was introduced as a treatment for DH rash (Kruizinga and Hamminga, 1953) and moreover, in 1969, the discovery of granular immunoglobulin A (IgA) deposits in the dermis of DH patients enabled the precise diagnosis of the disease (Van der Meer, 1969). In 1966, the majority of DH patients were found to have enteropathy indistinguishable from that detected in coeliac disease patients (Marks et al., 1966). Soon thereafter it was demonstrated that cutaneous symptoms and enteropathy of DH were caused by dietary gluten and that both responded to gluten-free diet (GFD) (Fry et al., 1969; Fry et al., 1973; Reunala et al., 1977). Since then, DH has been considered to be a cutaneous manifestation of coeliac disease (Collin et al., 2017; Reunala, 1978).

DH is characterized by a polymorphic skin eruption with vesicles and papules located symmetrically on elbows, knees and buttocks. Sometimes other skin areas such as scalp, face and upper back are additionally affected (Bolotin and Petronic-Rosic, 2011a). Moreover, purpura in the hands and feet as the only or concomitant symptom of DH has been described as a possible, albeit rare, manifestation (López Aventín et al., 2013; Tu et al., 2013). In milder forms of DH, symptomatic and asymptomatic periods may alternate, whereas in more severe disease itching and blistering are continuous (Reunala et al., 2018). However, itching is commonly intense and scratching of the vesicles results in erosions and crust in typical DH, predilection sites being a common clinical finding (Kárpáti, 2012; Reunala et al., 2018). The most relevant conditions to consider in differential diagnosis of DH include other bullous skin diseases, particularly linear IgA dermatosis and bullous pemphigoid, but other pruritic skin disorders such as atopic dermatitis, discoid eczema and scabies should also be taken into account (Collin and Reunala, 2003). At diagnosis, up to 40% of DH patients suffer from gastroenterological symptoms, such as diarrhoea, bloating or abdominal pain, but the symptoms are usually mild (Pasternack et al., 2017; Reunala et al., 1984).

2.2 Clinical features of coeliac disease

In coeliac disease ingestion of gluten causes a wide spectrum of clinical manifestations, including diverse gastrointestinal, as well as extraintestinal symptoms and findings. Moreover, coeliac disease may also remain totally asymptomatic. (Fasano and Catassi, 2001). According to recent recommendations, coeliac disease should be classified as classical, non-classical or asymptomatic disease (Ludvigsson et al., 2013).

In classical coeliac disease, the affected individual has gastrointestinal symptoms or signs of malabsorption, such as diarrhoea, steatorrhoea or weight loss. In children with classical coeliac disease growth failure may also be present. (Green et al., 2015; Lebwohl et al., 2018; Ludvigsson et al., 2013)

In non-classical coeliac disease symptoms and signs of malabsorption are absent, but patients may have gastrointestinal symptoms not included as presentations of classical coeliac disease, such as constipation or dyspepsia (Ludvigsson et al., 2013; Singh and Makharia, 2014a). In addition, non-classical coeliac disease patients may have various symptoms deriving from any extraintestinal organ, and due to the availability of reliable coeliac autoantibody tests, highly variable non-classical symptoms have become increasingly common (Garampazzi et al., 2007; Volta et al., 2014). One extraintestinal and non-classical manifestation of coeliac disease is DH, where symptoms derive from the skin. Other well-known extraintestinal manifestations are neurological symptoms including cerebellar ataxia, peripheral neuropathy and epilepsy (Bushara, 2005; Luostarinen et al., 1999), joint problems such as arthritis and arthralgia (Daron et al., 2017; Therrien et al., 2020), infertility (Singh et al., 2016) or miscarriage (Castaño et al., 2019), aphtous stomatitis (Nemțeanu et al., 2020; Nieri et al., 2017) and liver dysfunction (Abdo et al., 2004; Rubio-Tapia et al., 2019). In childhood, dental enamel defects may also develop (Aine et al., 1990; Nieri et al., 2017) or puberty may be delayed (Bona et al., 2002; Smecuol et al., 1996). In addition, there are numerous relatively common and non-specific symptoms that have been described as non-classical manifestations of coeliac disease such as fatigue, headache, myalgia and various neuropsychiatric symptoms (Jericho et al., 2017; Laurikka et al., 2018; Leffler et al., 2015), but no definite associations with coeliac disease have so far been established (Laurikka et al., 2018). Further, one challenge is to distinguish between the symptoms and the complications of coeliac disease, and also to identify independently associated diseases; overlapping and variability in classification of terms occur. However, one proposed classification is that coeliac disease symptoms should be reversible with a

GFD, whereas complications may be permanent and irreversible, especially if the initiation of GFD is delayed. (Laurikka et al., 2018)

Asymptomatic coeliac disease refers to coeliac disease patients who do not suffer from any symptoms commonly related to untreated coeliac disease. These patients are generally found in screening of individuals with high risk for coeliac disease. (Ludvigsson et al., 2013) Asymptomatic coeliac disease is fairly common, as a large Italian multicentre study has previously demonstrated that 23% of all coeliac disease patients may be asymptomatic (Bottaro et al., 1999).

2.3 Anaemia in dermatitis herpetiformis and coeliac disease

Anaemia has been shown to be a common finding in coeliac disease (Berry et al., 2018; Harper et al., 2007), and anaemia is classified variously as either a symptom of classical coeliac disease (Ludvigsson et al., 2013) or as an extraintestinal manifestation of coeliac disease (Abu Daya et al., 2013; Laurikka et al., 2018; Leffler et al., 2015). In DH, there are only a few studies addressing anaemia (Table 1). Gawkrodger and colleagues (1988) reported an 8% prevalence of macrocytic anaemia in 86 DH patients, while the frequency of total anaemia was not reported. In that study, altogether 45 out of 86 (52%) of the DH study patients were on dapsone or sulphapyridine treatment and 63 out of 86 (73%) were already on GFD. However, in addition to overall anaemia prevalence, it remained unclear how many of the study patients with anaemia were on dapsone or sulphapyridine treatment or on GFD. Instead, in the study by Fry and associates (1967) all but one of the 12 DH study patients were on dapsone treatment and four out of 12 patients (30%) were adhering to GFD, and altogether 42% of the patients had anaemia. However, when anaemia is investigated in DH, it is essential to take into account dapsone usage, since anaemia is one of the most common side effects of dapsone treatment. Only one study has so far studied the prevalence of anaemia in untreated DH (Handa et al., 2018). In that study, the frequency of anaemia was 23% at the time of DH diagnosis in Indian population (Table 1).

In untreated coeliac disease, anaemia has been shown to occur in approximately 20-30% of coeliac disease patients in Western countries (Balaban et al., 2019; Halfdanarson et al., 2007; Laurikka et al., 2018) (Table 1). Anaemia may present as the sole finding of otherwise asymptomatic coeliac disease (Bottaro et al., 1999) and even though the main mechanism is considered to be malabsorption of nutrients due to damaged small bowel mucosa, the aetiology is multifactorial (Balaban et al.,

2019; Berry et al., 2018; Harper et al., 2007). The most frequent form of anaemia in coeliac disease is iron deficiency anaemia, but other forms, such as vitamin B_{12} and folate deficiency anaemia and anaemia of chronic disease may also occur (Berry et al., 2018; Harper et al., 2007; Martín-Masot et al., 2019). In coeliac disease, anaemia has been associated with higher coeliac autoantibody levels and more severe villous atrophy (Abu Daya et al., 2013; Saukkonen et al., 2016; Taavela et al., 2013; Zanini et al., 2013), but opposite results have also been reported (Brar et al., 2006a).

Table 1. Studies investigating the prevalence of anaemia at the time of the diagnosis in dermatitis herpetiformis (DH) and coeliac disease (CD)

Study	Country	Patients	Prevalence of anaemia
Handa et al., 2018	India	65 DH patients	23%
Nurminen et al., 2019	Finland	511 CD patients, children	18%
Unal and Bekdas, 2018	Turkey	117 CD patients, children	61%
Harper et al., 2007	US	405 CD patients, adults	20%
Rajalahti et al., 2017	Finland	455 CD patients, children	18%
Saukkonen et al., 2016	Finland	163 CD patients, adults	23%
Schøsler et al., 2015	Denmark	90 CD and 3 DH patients, adults	30%
Singh and Makharia, 2014b	India	338 CD patients, adults and adolescents	85%
Abu Daya et al., 2013	US	727 CD patients, adults	23%
Ehsani-Ardakani et al., 2013	Iran, Romania, Italy (multi-center study)	450 CD patients, adults and children	21%
Zanini et al., 2013	Italy	1245 CD and 163 DH patients, adults (age >14 years)	40%
Bodé and Gudmand-høyer, 1996	Denmark	45 CD and 5 DH patients, adults	22%

US=United States

2.4 At-risk groups and associated diseases of dermatitis herpetiformis and coeliac disease

Since coeliac disease may be totally asymptomatic, screening with coeliac autoantibody tests among individuals known to be at an increased risk of coeliac disease is currently widely advised (Coeliac disease: Current care guidelines, 2018; Rubio-Tapia et al., 2013). At-risk groups recommended for screening are first-degree relatives of DH and coeliac disease patients, among whom the prevalence of coeliac disease has been reported to be as high as 7.5% (Singh et al., 2015). Screening is also recommended for patients with autoimmune diseases, especially type 1 diabetes mellitus (T1DM), autoimmune thyroid disease, autoimmune hepatitis or Sjögren's syndrome and additionally for individuals with Down's syndrome, selective IgA deficiency, IgA nephropathy and those with unexplained increase of liver transaminases (Coeliac disease: Current care guidelines, 2018; Rubio-Tapia et al., 2013). The respective prevalences of coeliac disease among patients with T1DM and autoimmune thyroid disease are 6% and 2-4% in literature (Elfström et al., 2014; Collin et al., 2002). Fifteen percent of patients with Sjögren's syndrome (Iltanen et al., 1999) and 7-10% with Down's syndrome have been shown to have coeliac disease (Alsaffar et al., 2017; Book et al., 2001).

Consistently, the prevalence of various autoimmune diseases is known to be increased in patients with DH and coeliac disease (Cosnes et al., 2008; Grode et al., 2018; Neuhausen et al., 2008; Reunala and Collin, 1997). In DH, the most commonly associated autoimmune diseases are T1DM, autoimmune thyroid diseases, autoimmune hepatitis and Sjögren's syndrome (Krishnareddy et al., 2014; Reunala and Collin, 1997). The prevalence of T1DM in DH has been shown to be 1-9% (Hervonen et al., 2004; Ohata et al., 2012; Reunala and Collin, 1997) and 1-14% of DH patients have autoimmune thyroid diseases (Handa et al., 2018; Krishnareddy et al., 2014; Ohata et al., 2012; Reunala and Collin, 1997). The frequency of autoimmune hepatitis has been reported to be 3% in DH (Krishnareddy et al., 2014) and Sjögren's syndrome around 1% (Krishnareddy et al., 2014; Ohata et al., 2012; Reunala and Collin, 1997). Moreover, according to a recent study, the risk for bullous pemphigoid has been shown to be 22-fold in DH compared to controls (Varpuluoma et al., 2019). Associations between DH and various other diseases such as sarcoidosis, lupus erythematosus, vitiligo, alopecia areata have also been documented (Reunala and Collin, 1997), but the evidence is rather scarce.

Similarly to DH, coeliac disease is most frequently associated with T1DM, autoimmune thyroid diseases, autoimmune hepatitis and Sjögren's syndrome.

Associations between coeliac disease and Addison's disease, alopecia areata and vitiligo have also been reported. (Bibbò et al., 2017; Collin et al., 2002; Krishnareddy et al., 2014)

2.5 Epidemiology of dermatitis herpetiformis and coeliac disease

The highest DH prevalence reported has been 0.08% in a Finnish DH cohort study (Salmi et al., 2011). In the United Kingdom (UK), DH prevalence has been reported to be 0.03% (West et al., 2014), and in the United States (US) 0.01% (Smith et al., 1992). The incidence of DH has decreased over time: in Finland the annual incidence has been shown to decrease from 5.2/100,000 detected between the years 1980 and 1989, to 2.7/100,000 between the years 2000 and 2009 (Salmi et al., 2011). Similarly, in the UK the incidence has been shown to drop from 1.82/100,000 to 0.8/100,000 between the years 1990 and 2011 (West et al., 2014).

DH is diagnosed most commonly in the fifth decade, and diagnostic age has been shown to increase over time (Salmi et al., 2011). Even though DH may occur at any age, it seems to be rare among children in Finland since less than 4% (18 out of 477) of the DH patients diagnosed between 1970 and 2009 in Finland were children (Hervonen et al., 2014; Salmi et al., 2011). In childhood DH, females seem to predominate, which is opposite to the situation in adulthood DH (Hervonen et al., 2014) where a slight male preponderance exists (Alonso-llamazares et al., 2007; Salmi et al., 2011).

In coeliac disease, the global prevalence of small bowel biopsy-proven disease has been 0.7% according to a recent meta-analysis (Singh et al., 2018) and 0.5-0.7% in Finland (Ilus et al., 2014a; Lohi et al., 2007). Instead, the global prevalence of serologic screening-based coeliac disease, reflecting the real prevalence of coeliac disease, has been 1.4% (Singh et al., 2018) and in Finland, 2%, (Lohi et al., 2007; Mustalahti et al., 2010; Vilppula et al., 2009). In contrast to DH, the incidence of coeliac disease is increasing over time and may be partly, but not solely, due to improved diagnostics as the true prevalence and incidence seem to be increasing as well (Lohi et al., 2007). Unlike in DH, there is a female preponderance in coeliac disease and coeliac disease diagnosis is much more common during childhood (Singh et al., 2018).

2.6 Genetic background and familial occurrence of dermatitis herpetiformis

DH and coeliac disease are both considered to have multifactorial aetiology requiring several genetic and environmental factors for the onset of the disease. The main genetic predisposing factor is located on chromosome six in the major histocompatibility complex (MHC) II region (Mowat, 2003). The role of MHC II is to encode human leukocyte antigens (HLA), which are found on the cell surface of antigen presenting cells and their function is to present short peptide-antigens (epitopes) to CD4+ T lymphocytes (Alonso-llamazares et al., 2007). Virtually all patients with DH and coeliac disease carry either haplotype HLA-DQ2 or HLA-DQ8 or both (Kaukinen et al., 2002; Sollid et al., 1989; Spurkland et al., 1997). Although either HLA-DQ2 or HLA-DQ8 is necessary for the pathogenesis of coeliac disease and DH, these alleles do not totally explain susceptibility since they are common in Western population, occurring in up to half of them (DiGiacomo, 2013; Kårhus et al., 2018). In addition, in recent decades, genome-wide association studies have enabled the identification of several non-MHC genes, which may be implicated in the development of DH and coeliac disease (Dieli-Crimi et al., 2015; Sollid and Jabri, 2013).

Due to the genetic background, family members of DH and coeliac disease patients are at an increased risk of developing the disease. The familial occurrence of DH has been little studied. However, among first-degree relatives of Finnish DH patients, the prevalence of DH or coeliac disease was shown to be 5.4 %, and the existing disease was more frequently coeliac disease than DH. (Hervonen et al., 2002) Moreover, 18% of the DH patients had at least one affected first-degree relative (Hervonen et al., 2002). Interestingly, in studies with monozygotic twins with DH, it has been demonstrated that even genetically identical twins may have disparate clinical pictures of the disease: one twin may have DH and the other coeliac disease. This suggests that the exact phenotype of the disease may be attributable to environmental factors. (Hervonen et al., 2000)

2.7 Pathogenesis of dermatitis herpetiformis: coeliac-type enteropathy and rash

Small bowel changes in DH and coeliac disease and DH rash develop as a result of a complex interaction between genetic and environmental factors (Dieli-Crimi et al.,

2015). Dietary gluten, a complex mixture of seed proteins found in cereal such as wheat, rye and barley (Balakireva and Zamyatnin, 2016), is the most important predisposing environmental factor. However, since DH and coeliac disease develop in only a minority of genetically predisposed individuals, some other triggers such as bacterial or viral infections may also contribute (Plot and Amital, 2008; Sollid and Jabri, 2013). Additionally, dysregulation of gut microbiota may play an important role in the pathogenesis, and it is even possible that the composition and diversity of the intestinal microbiota partly explain different manifestations of coeliac disease (Wacklin et al., 2013).

After ingestion, gluten is partly hydrolyzed by proteases of the gastrointestinal tract and transported across the intestinal epithelium to the lamina propria (Balakireva and Zamyatnin, 2016). There tissue transglutaminase (TG2) modifies gluten peptides, which are then presented by dendritic cell-bound specific HLA molecules to CD4+ T lymphocytes (Balakireva and Zamyatnin, 2016). Activated gluten-reactive CD4+ T cells produce high levels of cytokines, such as interferon (IFN) γ and interleukin (IL)-21 (Di Sabatino et al., 2012; Nilsen et al., 1998). IL-15 produced by stressed mucosal epithelial cells enhances an inflammatory process which leads to increased cytotoxicity of intraepithelial lymphocytes (IEL)s against enterocytes. This consequently results in epithelial apoptosis and eventually the development of the typical coeliac lesions; villous atrophy, crypt hyperplasia and increased IEL count. Additionally, activation of CD4+ lymphocytes also leads to the clonal expansion of B lymphocytes, which, after differentiation to plasma cells, start to produce antibodies against gliadin and TG2. (Di Sabatino et al., 2006; Sollid and Jabri, 2013)

TG2 is widely known to be the major autoantigen in coeliac disease (Dieterich et al., 1997) and TG2 targeted antibodies have been found in the sera as well as in the duodenum of patients with both DH and coeliac disease (Dieterich et al., 1997; Dieterich et al., 1999; Koskinen et al., 2008; Salmi et al., 2014). However, in DH, epidermal transglutaminase (TG3), has been identified as the main autoantigen and the target of IgA deposits in the papillary dermis (Sárdy et al., 2002). TG3 is closely related, but not identical to TG2 (Bolotin and Petronic-Rosic, 2011a). Plasma cells producing TG3 antibodies have been identified in the small bowel (Sankari et al., 2020) and TG3 antibodies are known to circulate in the serum of DH patients (Reunala et al., 2015b). However, it remains unproven whether TG3-IgA immunocomplexes typical for DH are transported to skin via circulation (Görög et al., 2016) or whether TG3, which is normally primarily present in the epidermis (Bolotin and Petronic-Rosic, 2011a), diffuses from the epidermis into the papillary

dermis to form complexes with IgA-type antibodies (Zone et al., 2011). It has been suggested that stretching or pressure of the skin activates the TG3 enzyme, which leads to the accumulation of inflammatory cells, such as T-lymphocytes and neutrophils, in papillary dermis. Consequently, inflammatory cells secrete inflammatory cytokines and other inflammatory mediators, which, in turn, leads to neutrophilic micro-abscesses and further to blister formation. (Reunala et al., 2015)

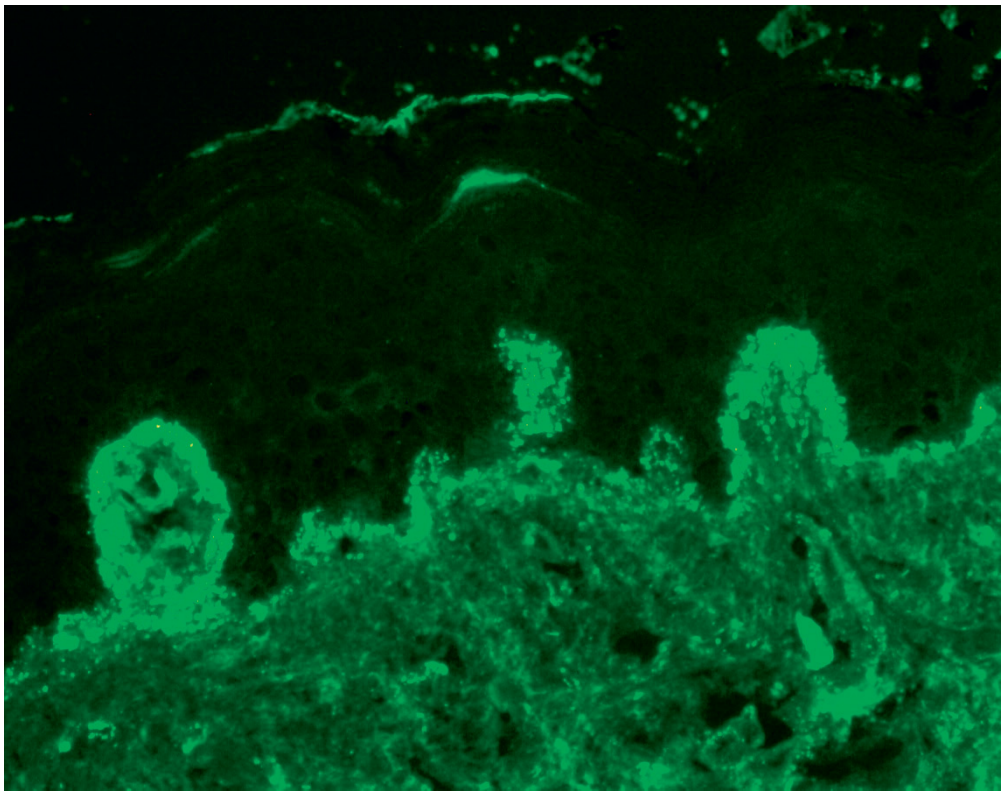
It has been suggested that DH evolvement initiates from the small bowel as subclinical coeliac disease (Reunala et al., 2015a), and further, that coeliac disease patients with long diagnostic delay may develop DH with TG3 antibody response. The proposed mechanism is an epitope spreading phenomenon and antibody response initially directed against TG2, but eventually the development of antibodies also targeting TG3. (Sárdy et al., 2002) However, the possibility of a direct gluten induced TG3 autoimmune process cannot be excluded (Kárpáti et al., 2018).

2.8 Skin biopsy findings in dermatitis herpetiformis

A pathognomonic finding in DH is granular IgA deposition on the dermal papillae or basement membrane or both in skin biopsy specimens investigated with direct immunofluorescence (Antiga and Caproni, 2015; Seah and Fry, 1975) (Figure 1). In linear IgA disease and bullous pemphigoid, important differential diagnoses to consider, immunoglobulins are also present at the basement membrane, but in linear IgA disease the pattern is linear and in bullous pemphigoid immunoglobulin G (IgG) is detected instead of IgA (Caproni et al., 2009).

For immunofluorescence investigation, skin biopsy should be taken from uninvolved, normal appearing skin near the rash, since even though IgA is relatively widespread in the skin of DH individuals, it is not evenly distributed, and IgA is less common in erythematous lesional skin and in skin areas never affected by rash (Zone, 1996). IgA is known to target TG3, the main autoantigen in DH (Sárdy et al., 2002), and disappearance of IgA and TG3 has been shown to be concomitant after GFD is initiated (Hietikko et al., 2018). However, disappearance of IgA happens slowly and may even take several years (Bardella et al., 2003).

Figure 1. Granular immunoglobulin A deposits in papillary dermis of dermatitis herpetiformis patient detected with direct immunofluorescence



When skin biopsy is taken for histological examination, it should be taken from the lesional skin, preferably from intact vesicle or erythematous skin (Bolotin and Petronic-Rosic, 2011b). Typical histological findings for DH are subepidermal blister formation and neutrophilic infiltrate in the dermal papillae forming micro-abscesses (Warren and Cockerell, 2002). However, this histological skin finding is not totally specific for DH, and further, non-specific perivascular lymphocytic infiltrate and inflammation in dermal papillae are often also detected (Reunala et al., 2018).

2.9 Serological findings in dermatitis herpetiformis and coeliac disease

Anti-gliadin and anti-reticulin antibody (ARA) tests were formerly used to detect coeliac disease and DH. However, the anti-gliadin antibody test was abandoned

because of low specificity (Caio et al., 2019) and the ARA test because of variable sensitivity compared to currently used tests (Hällström, 1989; Volta et al., 1991). The deamidated gliadin peptide (DGP) antibody test is more reliable than the traditional anti-gliadin antibody test in the diagnosis of coeliac disease (Lewis and Scott, 2010), but only a few studies on DGP antibodies in DH have been presented (Hull et al., 2008; Sugai et al., 2006). According to the current understanding, DGP antibodies do not provide any additional advantages compared to currently used tests investigating antibodies against TG2 (Antiga and Caproni, 2015).

EmA and TG2 antibodies are both directed against TG2 (Korponay-Szabó et al., 2000), but the TG2 antibody test is an enzyme-linked immunosorbent assay (ELISA) based test, whereas the EmA test is performed using indirect immunofluorescence technique and therefore is quite laborious and subjective in the interpretation (Caproni et al., 2001). EmA and TG2 antibody levels have been shown to correlate with each other in DH as well as in coeliac disease (Kumar et al., 2001). IgA-type antibodies are normally investigated, but, in the case of IgA deficiency and coeliac disease suspicion, IgG antibodies may be used (Bai et al., 2017).

The majority of untreated DH patients, 74-80%, have been demonstrated to have circulating EmA and TG2 antibodies (Dieterich et al., 1999; Kumar et al., 2001; Porter et al., 1999), whereas the specificity for DH of serum TG2 antibodies has been shown to be 92-98% (Caproni et al., 2001; Dieterich et al., 1999), and 98-100% for EmA, respectively (Kumar et al., 2001; Peters and McEvoy, 1989). The TG2 autoantibody levels have been shown to correlate with the severity of small bowel villous atrophy in DH (Dahlbom et al., 2010; Mansikka et al., 2017), regardless of which, normal TG2 antibody finding does not exclude villous atrophy (Mansikka et al., 2017). In coeliac disease, a meta-analysis reported equal sensitivity for EmA and TG2 antibody tests (93%), but slightly higher specificity (>99%) for EmA test compared with TG2 antibody test (>98%) (Lewis and Scott, 2006). As in DH, the levels of EmA and TG2 antibodies have been shown to correlate with the severity of small bowel damage also in coeliac disease (Tortora et al., 2014; Tursi et al., 2003).

The majority of DH patients also have circulating antibodies against TG3 at the time of the diagnosis (Hull et al., 2008; Jaskowski et al., 2010; Reunala et al., 2015b; Rose et al., 2009). However, 24-53% of coeliac disease patients without skin symptoms also have serum TG3 autoantibodies (Hull et al., 2008; Reunala et al., 2015b), which have been shown to correlate with age at coeliac disease diagnosis (Salmi et al., 2016). Previous evidence suggests that there may be two different antibody populations targeting TG3: one group, seen only in DH, is exclusively against TG3, whereas the other, seen in DH and coeliac disease, has cross-reactivity

against both TG2 and TG3 and also lower avidity to bind TG3 than the first population (Sárdy et al., 2002). Also, TG3 antibody levels have been shown to be higher in DH than in coeliac disease (Reunala et al., 2015b; Sárdy et al., 2002). In DH, TG3 antibodies have been shown to be gluten-dependent and their levels decrease parallel with TG2 and EmA antibodies on GFD (Borroni et al., 2013; Reunala et al., 2015b). However, TG3 antibodies are not yet routinely used in DH diagnostics since more knowledge is needed about the sensitivity and specificity of these antibodies as well as antibody kits and cut-off levels (Ziberna et al., 2021).

In addition to TG3 antibodies, antibodies targeted against transglutaminase 6 (TG6) have been reported in coeliac disease and connected to neurological presentation, especially to gluten ataxia (Hadjivassiliou et al., 2013). Among Finnish patients, serum TG6 antibodies have been found in 39% of untreated DH patients (Hadjivassiliou, 2020) compared to only 14% of untreated coeliac disease patients (Hadjivassiliou et al., 2013). In DH, however, the relation of TG6 antibody positivity and clinical presentation remains obscure (Hadjivassiliou et al., 2020).

2.10 Gastrointestinal findings in dermatitis herpetiformis and coeliac disease

2.10.1 Gastric findings: Chronic atrophic gastritis, *Helicobacter pylori* infection and cancer

Chronic atrophic gastritis (CAG) is known to be a precursor of gastric carcinoma (Adamu et al., 2010; Correa, 1992), especially when associated with *Helicobacter pylori (H. pylori)* infection (Thomas et al., 2019). Additionally, chronic *H. pylor*i infection may also predispose to gastrointestinal lymphoma (Thomas et al., 2019). In the majority of cases, CAG is solely caused by *H. pylori* infection, but CAG may also be of autoimmune origin, especially when limited to the fundus and corpus part of the stomach (Minalyan et al., 2017; Toh, 2014). However, according to current knowledge, *H. pylori* may also be involved in the development of autoimmune based CAG (Annibale et al., 2001a; Veijola et al., 2010).

The Sydney classification was developed in 1990 for the histopathological grading of gastritis. It combines aetiological, topographical and morphological information, which is helpful in generating a clinical diagnosis of gastritis. (Dixon et al., 1996) The Sydney classification has not previously been used in DH studies. Overall, there are

only a few, rather old, studies investigating CAG in DH, and the numbers of DH patients investigated in these studies were small and a control group was included only in one study (Table 2). In those studies, CAG seemed to be a fairly common finding in DH presenting in up to 50% of patients. Only one study has so far investigated the prevalence of *H. pylori* infection in DH, and did not disclose any increased prevalence of *H. pylori* infection in DH or coeliac disease compared to general population (Crabtree et al., 1992). Therefore, *H. pylori* infection may not be the only explanation for higher prevalence of CAG in DH. In coeliac disease, chronic gastritis has been reported to be more common than among non-coeliac patients undergoing gastroscopy (Gabrieli et al., 2017; Lebwohl et al., 2015). Moreover, in coeliac disease, gastritis has been shown to correlate with more severe villous atrophy (Lebwohl et al., 2015).

Table 2. Studies investigating atrophic gastritis in dermatitis herpetiformis (DH)

Author	Country	Patients	Prevalence of atrophic gastritis	Comments
Primignani et al., 1990	Italy	57 DH patients, 149 dyspepsia controls	30% in DH patients, 15% in controls	Gastroscopy was performed in all DH patients and controls
Gillberg et al., 1985	Sweden	90 DH patients	27%	Gastroscopy was performed in all and all of the patients were on a normal diet.
O'Donoghue et al., 1976	UK	16 DH patients	50%	Gastroscopy was performed in 15 out of 16 DH patients
Stockbrügger et al., 1976	Sweden	17 DH patients	35%	Gastroscopy was performed only in 7 out of 17 DH patients with achlorhydria
Lancaster-Smith et al., 1974	UK	32 DH patients	6%	Gastroscopy was performed only in five out of 32 DH patients positive for serum parietal cell antibodies

UK=United Kingdom

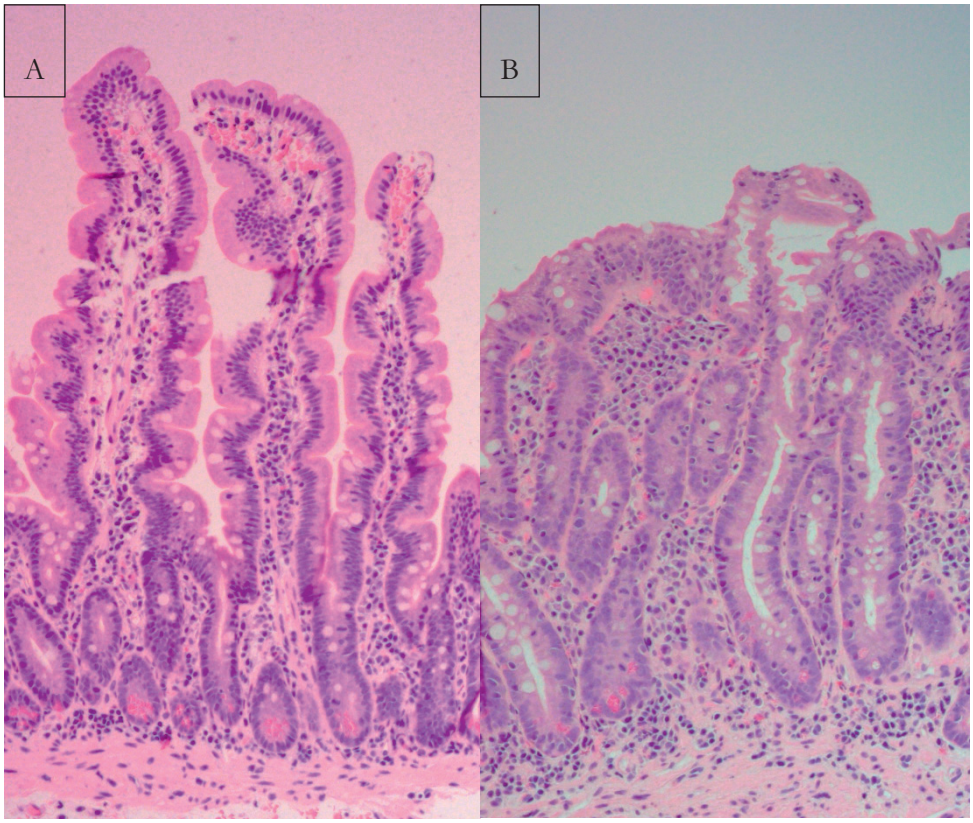
2.10.2 Small bowel findings in dermatitis herpetiformis and coeliac disease

In DH and coeliac disease, small bowel biopsies for histological examination should be taken from the distal part of the duodenum (Bai et al., 2017). Characteristic

findings for coeliac disease in biopsy specimens are villous atrophy, crypt hyperplasia and inflammation with increased densities of IELs (Oberhuber et al., 2000) (Figure 2). The development of small bowel mucosal damage is gradual starting from inflammation and resulting in overt villous atrophy. The Marsh classification has been developed to describe different stages of disease development: Marsh I signifies intestinal inflammation (>30 IELs per 100 epithelial cells) but normal villous and crypt architectures. In Marsh II enlarged crypts and in Marsh III villous atrophy are present (Marsh, 1992). In addition, Marsh III lesion and villous atrophy can further be classified into three sub-categories; partial (Marsh 3a), subtotal (Marsh 3b) and total villous atrophy (Marsh 3c). (Dickson et al., 2006; Oberhuber et al., 2000)

Approximately three quarters of patients with DH have villous atrophy at diagnosis and the remainder have normal villous architecture (Gawkrodger et al., 1984; Marks et al., 1966). In Finland there has been a trend towards milder villous atrophy in DH during the last 40 years since severe villous atrophy has been shown to become more rare (Mansikka et al., 2017). However, even those DH patients without villous atrophy have coeliac-type small bowel mucosal inflammation and increased densities of IELs (Järvinen et al., 2004). Characteristic for DH, as also for coeliac disease, is increased densities of γδ+ IELs (Järvinen et al., 2003; Savilahti et al., 1992). Additionally, TG2-targeted IgA autoantibody deposits have been shown to be present in the small bowel mucosa of the majority of DH patients (Salmi et al., 2014), even though the prevalence of the deposits is lower than in coeliac disease (Koskinen et al., 2008). Both TG2- and TG3-secreting plasma cells have been identified in the intestines of DH patients, and TG3-secreting plasma cells seem to be rather DH-specific and generally mostly absent from patients with coeliac disease (Sankari et al., 2020).

Figure 2. Histological picture of normal duodenum (A) and coeliac type villous atrophy (B)



2.11 Diagnostic criteria for dermatitis herpetiformis and coeliac disease

The diagnostic examinations for DH and coeliac disease should be performed while the patient is adhering to gluten-containing diet in order to avoid false-negative results. In DH the diagnosis is based on the typical clinical picture and the demonstration of distinctive granular IgA deposits in the papillary dermis in perilesional skin biopsy investigated with direct immunofluorescence (Seah and Fry, 1975; Van der Meer, 1969). If the result of immunofluorescence skin biopsy is negative but the suspicion of DH is strong, another skin biopsy should be considered: false-negative results are possible especially if the biopsy is taken from a suboptimal site. For example, a biopsy from inflamed skin may lead to false-negative

results as intense inflammation may secondarily lead to the destruction of immunoreactants. (Görög et al., 2021; Zone et al., 1996; Zone, 2005)

Lesional skin biopsy for histological examination is not required for DH diagnosis, but if taken, histological findings consistent with DH can support the diagnosis in problematic cases and may be helpful especially in differential diagnostics (Bolotin and Petronic-Rosic, 2011b). Likewise, a positive serum coeliac autoantibody result has a supportive role in the diagnosis, and it has been proposed to investigate preferably at least TG2 antibodies when DH is suspected (Coeliac disease: Current care guidelines, 2018; Görög et al., 2021). However, seronegativity does not exclude DH as coeliac autoantibodies are more prevalent in cases where villous atrophy is present (Mansikka et al., 2017). According to the Finnish national guidelines on coeliac disease and DH updated in 2018, small bowel biopsy is no longer needed in DH diagnostics (Coeliac disease: Current care guidelines, 2018). The severity of small bowel mucosal damage varies between DH patients, but clinical recovery and long-term prognosis are similar for DH patients with and without villous atrophy at diagnosis (Mansikka et al., 2018). However, in the European guidelines for DH, gastroscopy and small bowel biopsy are still recommended when DH is diagnosed, except in children with very high levels (≥10 times above the upper limit of normal) of serum TG2 antibodies (Görög et al., 2021).

In coeliac disease, small bowel villous atrophy detected from duodenal biopsy was previously regarded as the gold standard for diagnosis. However, in 2012 the European guidelines recommended serology-based diagnosis for children when the TG2 antibody test result is ≥10 times the upper normal limit and as a confirmatory test the EmA is also positive. Otherwise, gastroscopy and small bowel biopsies continue to be required (Husby et al., 2020). In Finland, serology-based diagnosis with the same criteria has also been applied in adults since 2018 (Coeliac disease: Current care guidelines, 2018). It has been estimated that at least one third of coeliac disease patients could be diagnosed based on serological findings (Fuchs et al., 2019; Werkstetter et al., 2017).

HLA-DQ2/8 typing is not routinely applied in DH diagnostics. Genotyping should be considered only in selected and obscure cases, and a mainly negative result has diagnostic value as it virtually excludes DH as well as coeliac disease. (Al-Toma et al., 2019; Görög et al., 2021)

2.12 Treatment of dermatitis herpetiformis and coeliac disease

2.12.1 Gluten-free diet

The treatment of choice for DH and coeliac disease is a strict life-long GFD (Al-Toma et al., 2019; Caproni et al., 2009; Rubio-Tapia et al., 2013). Gluten is a complex mixture of seed storage proteins belonging to the prolamin superfamily, since they carry significant amounts of proline and glutamin amino acids in their structures. Prolamins are a group of alcohol soluble storage proteins found mainly in seeds and cereals, such as wheat (gliadin), barley (hordein), rye (secalin) and oats (avenin) (Balakireva and Zamyatnin, 2016; Biesiekierski, 2017). The prolamins of wheat, rye and barley are known to be toxic in DH and coeliac disease, but the role of oats is less straightforward (Ciacci et al., 2015).

After the diagnosis is confirmed, DH and coeliac disease patients commence GFD under the guidance of a doctor and a dietician. Even though the diet should be strict, total avoidance of gluten is not feasible. The exact level below of which gluten is harmless is not known. However, the evidence suggests that less than 10mg per day is unlikely to cause harm in most patients (Al-Toma et al., 2019; Rubio-Tapia et al., 2013).

In DH, adherence to GFD heals the skin symptoms eventually, although total clearing of the rash may take from several months to a few years (Fry et al., 1973; Reunala et al., 1977). Gastrointestinal symptoms in coeliac disease, on the other hand, usually heal within weeks after initiating the diet but persistent gastrointestinal symptoms are also possible (Murray et al., 2004; Paarlahti et al., 2013). Moreover, GFD may also have a positive impact on extraintestinal symptoms and findings such as anaemia (Annibale et al., 2001b; Jericho et al., 2017), hypertransaminasemia (Jericho et al., 2017), stomatitis (Bardella et al., 1995), neurological symptoms, decreased bone mineral density and poor growth (Laurikka et al., 2018). Eventually, GFD leads to healing of the small bowel mucosal changes and normalization of serum autoantibodies (Dipper et al., 2009; Galli et al., 2014; Reunala, 1978; Reunala et al., 2015). According to current knowledge, adherence to GFD does not seem to reduce the risk of developing autoimmune diseases (Ouaka-Kchaou et al., 2008; Sategna et al., 2001; Viljamaa et al., 2005), even though opposite results have also been reported (Cosnes et al., 2008; Mones, 2009; Ventura et al., 1999).

Despite the clear advantages of GFD, there are also disadvantages affecting dietary compliance: GFD is socially restrictive (White et al., 2016), as well as

expensive to maintain (Lee et al., 2019; Panagiotou and Kontogianni, 2017). Non-compliance and inadvertent gluten consumption are the main reasons for non-responsive symptoms in coeliac disease (Abdulkarim et al., 2001; Dewar et al., 2012). Furthermore, since the diet is not easy to follow, GFD may cause frustration and anxiety about health. GFD adherence among Finnish DH patients has nevertheless been shown to be high, as in Finnish studies 72-95% of DH patients followed a strict GFD (Mansikka et al., 2018; Pasternack et al., 2015). Likewise, in Finnish coeliac disease studies, strict adherence to GFD in coeliac disease has been 88-97% (Aaltonen et al., 2017; Kurppa et al., 2013), but overall, according to a systematic review, strict adherence rates in coeliac disease are highly variable, ranging from 42% to 91% (Hall et al., 2009).

2.12.2 Oats

Oats have similar prolamin fraction as wheat, rye and barley. However, the prolamin of oats is structurally different and therefore, uncontaminated (=not including traces of other cereals) oats have been considered to be probably safe in GFD (Al-Toma et al., 2019; Caproni et al., 2009; La Vieille et al., 2016; Rubio-Tapia et al., 2013). However, the issue has been somewhat controversial worldwide.

Oats have several health effects related to their being rich in fibre, minerals and vitamins. Soluble fibres in oats slow glucose and cholesterol absorption in the intestine (Butt et al., 2008), which, in turn, has been shown to lower blood sugar and cholesterol levels (Bao et al., 2014; Hou et al., 2015; Whitehead el al, 2014). Additionally, oats contain twice as much protein as rice and include oil with a high percentage of unsaturated fatty acids (Fric et al., 2011). Conventional GFD without oats has been shown to cause nutritional deficiency in fibre and micronutrients in coeliac disease (Kemppainen et al., 1995; Thompson et al., 2005; Vici et al., 2016). Additionally, GFD products have also been demonstrated to have higher glycaemic index than corresponding gluten-based products, which is related to increased obesity risk in coeliac disease (Vici et al., 2016). Adding oats to GFD improves the nutritional value of the diet by increasing the intake of fibre, vitamin B, magnesium and iron (Kemppainen et al., 2010). Additionally, oats improve the variety and taste of the food in GFD (Peräaho et al., 2004a) and consuming oats may even improve the quality of life in coeliac disease (Aaltonen et al., 2017).

While in coeliac disease the majority of studies conducted have demonstrated oats to be safe (Table 3), in some studies, the consumption of oats has caused

gastrointestinal symptoms, intestinal inflammation and even villous atrophy (Ilus et al., 2012; Lundin et al., 2003; Peräaho et al., 2004b). Furthermore, there is only limited knowledge about the safety of oats in DH and long-term follow-up studies are lacking. In two oats-challenge studies with GFD-treated DH patients and with 3-6 months follow-up, oats seemed to be harmless (Hardman et al., 1997; Reunala et al., 1998) (Table 3). However, according to an earlier Finnish questionnaire study, almost one fifth of the DH patients had stopped using oats because of skin or gastrointestinal symptoms (Peräaho et al., 2004a).

In Finland, coeliac disease and DH patients have been allowed to consume oats since 1997 and 1998, respectively. It is similarly stated in a recent European DH guideline that ingesting uncontaminated oats is safe in DH (Görög et al., 2021). However, guidelines debating that there may be a risk that some DH and coeliac disease patients are intolerant of oats exist (Al-Toma et al., 2019; Bai et al., 2017; Rubio-Tapia et al., 2013).

Table 3. Safety of oats in gluten-free diet (GFD) in dermatitis herpetiformis (DH) and selected* coeliac disease (CD) studies

Study, country	Study patients	Controls	Study design	Follow-up	Outcomes
Reunala et al., 1998, Finland	11 GFD-treated DH patients	12 GFD-treated DH patients without oats	Prospective challenge study with 50g oats daily	6 months	No changes in the small bowel histology or CD serology 3 study patients and 3 controls developed transient rash
Hardman et al., 1997, UK	10 GFD-treated DH patients	-	Prospective challenge study with 50-70g oats daily	3 months	No changes in the small bowel histology or CD serology
Kaukinen et al., 2013, Finland	70 GFD-treated CD patients consuming oats	36 GFD-treated CD patients without oats	Cross-sectional study, median daily usage of oats 20g	Median duration of oats consumpti on 5 years	No differences in the small bowel histology, CD serology, GI symptoms or quality of life between groups
Cooper et al., 2013, UK	46 GFD-treated CD patients	-	Prospective challenge study with mean usage of 286g oats weekly	1 year	No changes in the small bowel histology or coeliac serology. Two patients developed villous atrophy, which was caused by incomplete adherence to GFD, several patients had mild GI symptoms
Peräaho et al., 2004, Finland	23 GFD-treated CD patients	16 GFD-treated CD patients without oats	Prospective challenge study with 50g oats daily	1 year	Small bowel IEL density was higher and GI symptoms more frequent in oats group No differences in CD serology or in the small bowel villous atrophy
Janatuinen et al., 2002, Finland	46 GFD-treated CD patients	46 GFD-treated CD patients without oats	5 years prospective follow-up, 50-70g oats daily	5 years	No differences between groups in small bowel inflammation or villous atrophy or CD serology
Janatuinen, E. et al., 1995, Finland	26 GFD treated and 19 new CD patients	26 GFD treated and 21 new CD patients without oats	Prospective challenge study with 50g oats daily	6 months for GFD treated and 12 months for new CD patients	No differences between groups in small bowel inflammation or villous atrophy, CD serology or symptoms

*coeliac disease studies with over 30 adult patients and including small bowel biopsies and coeliac serology

GI=gastrointestinal, IEL=intraepithelial lymphocyte, UK=United Kingdom

2.12.3 Dapsone

After the diagnosis of DH, pruritus and the DH rash may last for several months or even a few years even with a strict GFD. Therefore, for patients with severe skin symptoms, dapsone medication is initiated (Caproni et al., 2009). Dapsone treatment relieves pruritus in days but does not have any effect on enteropathy (Salmi and Hervonen, 2020).

Dapsone belongs to a sulfone group of drugs and has antimicrobial and anti-inflammatory properties (Wozel et al., 2014). In Finland, the starting dose for adults is usually 25-50mg/day and this can be increased up to 100mg/day if needed. When the skin symptoms disappear, the dose must be tapered slowly and dapsone is discontinued when the GFD alone finally controls the cutaneous symptoms (Salmi and Hervonen, 2020). In Finland, dapsone is initiated in about 70% of DH patients and the treatment is usually required for two to three years (Mansikka et al., 2018; Salmi and Hervonen, 2020). Dapsone is generally well-tolerated by DH patients, but there are certain side-effects, dose-dependent haemolysis being the most common. Additionally, methemoglobinemia, agranulocytosis or even hepatitis may occur, but these are rare. A dermatologist is responsible for dapsone initiation and dosing, and regular follow-up of blood count and liver function tests during dapsone treatment is needed. (Salmi and Hervonen, 2020; Garioch et al., 2006; Ciacci et al., 2015)

2.13 Prognosis of dermatitis herpetiformis and coeliac disease

2.13.1 Refractory disease

On rare occasions, the DH rash does not respond to strict long-term GFD, and dapsone is needed continuously (Garioch et al., 1994; Hervonen et al., 2016). Only one study on refractory DH has been presented, and there the definition of refractory DH was that despite strict adherence to GFD for at least three years, regular dapsone treatment was needed to control the rash. The study demonstrated that less than 2% of Finnish DH patients had refractory DH and needed dapsone treatment despite a median of 16 years of GFD adherence. However, serum coeliac autoantibodies were negative, and the small bowel mucosa had healed in refractory DH patients and none had developed lymphoma or other long-term complications.

Refractory DH seems, thus, to have a better prognosis than refractory coeliac disease. (Hervonen et al., 2016)

In refractory coeliac disease persistent malabsorptive symptoms and small bowel villous atrophy do not respond to a GFD (Rubio-Tapia et al., 2010). In refractory coeliac disease the risk for lymphoma is increased (Al-toma et al., 2007; Rubio-Tapia et al., 2010). However, refractory coeliac disease is divided into two subtypes depending on the presence of normal IELs (type I) or abnormal IELs (type II) in the small bowel mucosa. Type I has a better prognosis than type II (Al-toma et al., 2007; Rubio-Tapia et al., 2010). The frequency of refractory coeliac has been reported to be 0.31% in Finland (Ilus et al., 2014), while the prevalence in other countries has been 0.7-1.5% (Malamut and Cellier, 2019).

2.13.2 Bone mineral density and fractures

The mineral density of the bone is decreased in osteoporosis and its precursor osteopenia. Low bone mineral density (BMD), in turn, increases the risk of bone fractures. Due to malabsorption caused by small intestinal enteropathy, patients with DH and coeliac disease are potentially at risk of having decreased BMD and fractures. (Zanchetta et al., 2016)

BMD in DH has been little studied and the results are discrepant. According to fairly small studies, BMD in DH may be decreased or equal to that of healthy controls, but somewhat higher than in coeliac disease (Abuzakouk et al., 2007; Di Stefano, 1999; Lheure et al., 2017; Lorinczy et al., 2013). In coeliac disease, the prevalence of low BMD has ranged from 38 to 72% at the time of diagnosis (Zanchetta et al., 2016). Adherence to a GFD may result in partial recovery or sometimes even full recovery of BMD (Grace-Farfaglia, 2015). According to a recent meta-analysis, coeliac disease patients have increased risk for fractures as in coeliac disease any fractures were twice as common as in general population (Heikkilä et al., 2015). However, only three studies have investigated the risk of bone fractures in DH (Lewis et al., 2008; Pasternack et al., 2018; Pasternack et al., 2019). Lewis and colleagues (2008) found no increased risk of fractures in DH compared to general population and in a Finnish study the self-reported incidence of fractures was similar between DH and coeliac disease patients (Pasternack et al., 2018). Further, Pasternack et al. (2019) studied the incidence rate of hospital-treated fractures in long-term GFD-treated DH and coeliac disease and found no increased risk for hip

fractures in DH compared to general population and slightly lower risk for any hospital-treated fractures in DH than in coeliac disease.

2.13.3 Malignancies

No overall increase in the risk of malignancy has been increased in the majority of studies investigating the risk of malignancies in DH, (Collin et al., 1996; Grainge et al., 2012; Lewis et al., 2008; Viljamaa et al., 2006), although contrary results have also been reported (Leonard et al., 1983; Swerdlow et al., 1993). However, the risk for lymphomas has been shown fairly consistently to be increased in DH, and the risk has been up to 6-fold that of general population (Askling et al., 2002; Collin et al., 1996; Grainge et al., 2012; Leonard et al., 1983; Lewis et al., 1996; Sigurgeisson et al., 1994; Viljamaa et al., 2006). Moreover, the risk of lymphoma has been shown to be especially high in those DH patients not adhering to a GDF (Hervonen et al., 2005; Leonard et al., 1983; Lewis et al., 1996), and the risk for lymphoma seems to decrease to the same level as in general population after GFD adherence for five years in DH (Lewis et al., 1996). By contrast, the risk for breast cancer may be even lower in DH than in general population (Lewis et al., 2008).

The overall risk for malignancies in coeliac disease has been shown in numerous studies to be increased (Grainge et al., 2012; Holmes et al., 1989; West et al., 2004). However, opposite results have also been reported, in which the overall cancer risk in coeliac disease has been equal to that in general population (Card et al., 2004; Ilus et al., 2014b; Lohi et al., 2009a). The cancers related to coeliac disease are mainly gastrointestinal lymphomas, particularly non-Hodgkin's lymphomas (NHL) (Catassi et al., 2002; Grainge et al., 2012; West et al., 2004), but other gastrointestinal malignancies have also been reported (Askling et al., 2002; Card et al., 2004; Green et al., 2003; Ilus et al., 2014b). Delayed diagnosis may increase the malignancy risk in coeliac disease (Silano et al., 2007), and strict GFD of five to 15 years' duration may decrease the malignancy risk in coeliac disease to reference level (Grainge et al., 2012; Holmes et al., 1989).

2.13.4 Mortality

Despite the risk for lymphomas, the overall mortality rate seems not to be increased in DH(Collin et al., 1996; Lewis et al., 2008; Viljamaa et al., 2006) and conversely may even be slightly lower than mortality in general population (Swerdlow et al.,

1993; Viljamaa et al., 2006). In the study by Swerdlow et al. (Table 4) all-cause mortality and cancer mortality in DH were slightly, but not significantly, lower than expected. Instead, mortality from ischaemic heart diseases was significantly lower than expected, and equal in GFD adherent and GFD non-adherent DH patients. In the study by Viljamaa and colleagues, the mortality rate in DH at diagnosis was significantly lower than expected and also lower than in coeliac disease (Table 4), and the mortality rate in DH even continued to decline over time after GFD initiation (Viljamaa et al., 2006). However, opposite findings have also been reported, as a Swedish study with a sub-group of DH patients among hospitalized coeliac disease patients reported increased mortality rate in DH (Peters et al., 2003) (Table 4).

In coeliac disease, several studies have reported increased mortality rates (Corrao et al., 2001; Holmes and Muirhead, 2018; Ludvigsson et al., 2009; Rubio-Tapia et al., 2009; West et al., 2004) (Table 4). However, opposite results have also been reported as in previous studies with screen-detected patients (Canavan et al., 2011; Lohi et al., 2009) and in biopsy-based coeliac disease (Koskinen et al., 2020; Sultan et al., 2014) mortality rate was similar to that in general population (Table 4). The greater number of deaths in coeliac disease have been mainly caused by lymphoproliferative diseases (Corrao et al., 2001; Holmes and Muirhead, 2018; West et al., 2004). The severity of the disease may be associated with increased mortality risk in coeliac disease (Corrao et al., 2001; Ludvigsson et al., 2009), and adherence to GFD also seems to reduce the mortality risk (Corrao et al., 2001; Ludvigsson et al., 2009).

Table 4. Mortality in dermatitis herpetiformis (DH) and selected* coeliac disease (CD) studies

Study, country	Study patients	Control patients	Follow-up	Relative mortality risk
Lewis et al., 2008, UK	846 DH patients	4225, age- and sex-matched	3496 person years	Overall HR 0.93 HR for any malignancy 1.0, for lymphoproliferative diseases 1.7
Swerdlow et al., 1993	152 DH patients	General population	5-39 years	Overall SMR 0.87 SMR for any malignancy 0.72, for ischaemic heart disease 0.37
Koskinen et al., 2020, Finland	99094 DH or CD patients	38384, age- and sex-matched	99094 person years, mean 7.7 years	Overall HR 1.01
Holmes and Muirhead, 2018, UK	2515 CD patients	General population	23955 person years, median 9.3 years	Overall SMR 1.57 SMR for any malignancy 2.25, for cardiovascular diseases 2.17, for NHL 6.32
Sultan et al., 2014, UK	10825 CD patients	107096, age-matched	60225 person years, median 5 years	Overall HR 0.94
Canavan et al., 2011), UK	87 screen-detected CD patients at diagnosis	7440 with negative coeliac serology	117914 person years, median 16.8 years	Overall HR 0.98

Godfrey et al., 2010, US	126 screen-detected CD patients (age >50) at diagnosis	254 age- and sex-matched with negative coeliac serology	Median 10.3 years	Overall HR 0.8 HR for any malignancy 0.63
Lohi et al., 2009, Finland	74 screen-detected CD patients	296 with negative coeliac serology	147646 person years	Overall RR 1.19 in TG2 Ab positive and 0.78, in EmA-positive group 0.78 RR for any malignancy 0.87 in TG2 Ab positive and 0.73, in EmA positive group for lymphoma 2.69 in TG2 Ab positive and 9.51 in EmA positive group for ischaemic heart disease 0.90 in TG2 Ab positive and 0.49 in in EmA positive group
Ludvigsson et al., 2009, Sweden	CD: 29096 patients with villous atrophy, inflammation: 13096 patients with intestinal inflammation, latent: 3791 patients with only positive CD serology	229800 age- and sex-matched	Median 8.8 years, mean 10.1 years	Overall HR 1.39 in all, 1.39 in CD group, 1.72 in inflammation group, 1.35 in latent CD group RR for any malignancy 1.55 in CD group, 2.32 in inflammation group, 1.41 in latent group
Rubio-Tapia et al., 2009), US	14 screened CD patients from US Air Force	9119 with negative CD serology from US Air Force	45 years	Overall HR 3.9
Viljamaa et al., 2006, Finland	366 DH and 781 CD patients	General population	17245 person years	Overall SMR 0.52 in DH,1.26 in CD SMR for ischaemic heart disease 0.72 in DH, 1.59 in CD for any malignancy 0.62 iin DH and 0.96 in CD for lymphoproliferative diseases 2.18 in DH and 4.12 in CD
West et al., 2004, UK	4732 CD patients	23680 age- and sex-matched from the General Practice Research Database	18923 person years, median 3.4 years	Overall HR 1.31 HR for any malignancy 1.29, for lymphoproliferative diseases 4.80

Peters et al., 2003, Sweden	221 DH and 10032 CD patients	General population	81182 person years, mean 8.1 years	Overall SMR 2.0 in all, 1.4 in DH SMR for any malignancy 1.7, for NHL 11.4, for ischaemic heart disease 1.5 in all
Corrao et al., 2001, Italy	1072 CD patients	General population	Mean 6 years	Overall SMR 2.0 in all, 10.7 in those without GFD, 2.5 in those with severe clinical symptoms, 1.2 in asymptomatic patients SMR for any malignancy 2.6, for NHL 69.3

Ab=antibody, EmA=endomysium antibody, GFD=gluten-free diet, NHL=non-Hodgkin's lymphoma UK=United Kingdom, US= United States, RR=Risk ratio, SMR=Standardised mortality ratio, HR= hazard ratio, TG2=transglutaminase 2, * overall mortality risk measured

2.13.5 Quality of life

Health-related quality of life assessments have become important tools in measuring the burden of disease in clinical studies. Health-related quality of life can be measured either with general quality of life questionnaires or disease-specific tools and they can describe physical, mental and social dimensions of well-being from a patient's own perspective (Burger et al., 2016; Häuser et al., 2007).

Only limited data exists on quality of life in DH. In a recent Finnish study, the quality of life in DH patients at diagnosis was reported to be significantly lower than that of healthy controls and especially among those having gastrointestinal symptoms (Pasternack et al., 2017). However, in the same study, quality of life improved with GFD, and was at the same level as that of healthy individuals after one year (Pasternack et al., 2017). According to another Finnish study, the quality of life in long-term treated DH was found to be at the same level as that of healthy controls and even higher than in long-term treated coeliac disease controls (Pasternack et al., 2015). However, a third DH study from Finland found no difference in quality of life between DH and coeliac disease in long-term follow-up (Mansikka et al., 2018).

In classical coeliac disease, quality of life is reported to be inferior at diagnosis compared to both general population and to screen-detected coeliac disease (Johnston et al., 2002; Nachman et al., 2009). Adhering to a GFD improves quality of life in classical coeliac disease, even to the same level as in healthy individuals (Casellas et al., 2008; Johnston et al., 2004; Nachman et al., 2009; Rustagi et al., 2020). However, in some studies, quality of life has remained inferior during follow-up despite GFD (Hallert, 1998; Usai et al., 2002). In screen-detected coeliac disease the quality of life seemed to be at the same level as in healthy controls at diagnosis (Johnston et al., 2004; Mustalahti et al., 2002). After GFD initiation, quality of life in screen-detected coeliac disease either stays at the same level (Nachman et al., 2009) or may even improve (Mustalahti et al., 2002).

3 THE PRESENT STUDY

3.1 Aims

The main aims of the present study were to investigate gastric findings and malabsorption in DH, and to study prognosis of GFD-treated DH patients

The specific aims were:

1. To study the prevalence of chronic atrophic gastritis and *H. pylori* infection in untreated DH (I)
2. To evaluate the prevalence of anaemia and factors associated with anaemia at DH diagnosis and one year thereafter (II)
3. To study the prevalence, health and quality of life effects of consuming oats in long-term GFD-treated DH patients (III)
4. To study the mortality and causes of death in DH patients (IV)

3.2 Patients and controls

3.2.1 Dermatitis herpetiformis study patients (I-IV)

Table 5. Study design, dermatitis herpetiformis (DH) patients and controls in Studies I-IV

	Study design	Study patients	Females (%)	Mean age at DH diagnosis, years (range)	Controls
Study I	Retrospective cohort study	93 DH patients	43	47 (16-76)	186 dyspeptic controls
	Follow-up questionnaire				
Study II	Retrospective cohort study	250 DH patients	48	42 (18-84)	139 coeliac disease controls
	Follow-up questionnaire/interview				
Study III	Retrospective cohort study	312 DH patients	49	39 (1-81)	-
	Follow-up questionnaire				
Study IV	Retrospective cohort study	476 DH patients	48	43 (3-84)	Age- and sex-matched Finnish population
	Follow-up questionnaire				895 controls from Finnish Adult Health Behavior Survey

Tampere University Hospital's Department of Dermatology operates a special outpatient clinic for DH patients, where all DH patients in the hospital catchment area are diagnosed and treated by DH-specialized dermatologists. DH patients diagnosed at this clinic were prospectively collected from 1970 onwards, and this single-centre cohort consists of over 500 patients with DH. DH cohorts used in all studies (I, II, III: sub-cohort 1, IV) were gathered from this cohort, and in all DH patients studied (I-IV), the diagnosis of DH was based on a typical clinical picture and demonstration of granular IgA in perilesional immunofluorescence skin

biopsies. According to the national guidelines at the time, the majority of patients underwent gastroscopy with small bowel biopsies at diagnosis. After DH was diagnosed and gastroscopy performed, all DH patients were advised as a routine policy to initiate a strict life-long GFD with the help of a dietician. Additionally, for those with severe symptoms, dapsone medication was initiated to alleviate the itching and rash. DH patients were followed-up routinely by a dermatologist in the outpatient clinic for at least one to two years or until the rash had disappeared and the dapsone medication could be discontinued.

Study I included DH patients diagnosed at Tampere University Hospital between 1990 and 2009 who had undergone gastroscopy with biopsies from the duodenum and stomach at the time of DH diagnosis (Table 5), and had gastritis classified according to the Sydney system available. Four patients under 16 years of age and one 100-year-old female were excluded due to the lack of controls. Study II included adult DH patients (≥18 years of age) from a Tampere University Hospital cohort diagnosed between 1970-2019 who had blood haemoglobin (Hb) level available at the time of DH diagnosis. For the follow-up data analysis, only patients having Hb level available one year after diagnosis were included. Study III included two cohorts: sub-cohort 1 included 224 DH patients diagnosed between 1970 and 2014 from the Tampere University Hospital DH cohort, and sub-cohort 2 included 88 DH patients recruited via a nationwide search by newspaper announcement between 2006 and 2010 with the help of the respective coeliac disease societies. Only GFD-adherent DH patients with data available on oat consumption who had responded to follow-up investigations were included in Study III. Further, 11 patients were excluded from sub-cohort 2, since they were already included in cohort 1. Study IV comprised all DH patients diagnosed at Tampere University Hospital between 1970 and 2014. For the health behaviour analysis, only 179 DH patients aged 15-64 at the time of the follow-up were included because the control group consisted of working-aged population.

3.2.2 Control subjects

For Study II, 139 coeliac disease patients with biopsy proven diagnosis at the age of 18 or over and with Hb level available at the time of diagnosis were chosen as control patients (Table 5). All coeliac disease control patients were diagnosed at Tampere University Hospital, Department of Gastroenterology and Alimentary Tract Surgery,

during the same time period as the DH patients, and only patients with classical presentation of coeliac disease were selected.

Study I included 186 non-coeliac controls undergoing gastroscopy at Valkeakoski Regional Hospital between 2009 and 2011 because of dyspepsia symptoms with gastritis classified according to the Sydney system (Table 5). Two control patients of similar sex and age (±5years), without small bowel villous atrophy were selected for each DH patient.

In Study IV, age- and sex-matched Finnish general population during the same calendar period was used as a reference for the mortality analysis. For the health behaviour analysis, five age and sex-matched controls from the latest Finnish Adult Health Behaviour Survey at the time of the study were chosen as controls for every DH patient, and hence a total of 895 controls were included. (Table 5)

3.3 Methods

3.3.1 Demographic data and clinical symptoms

Demographic characteristics and baseline data including severity and duration of clinical symptoms, initiation of dapsone treatment, results of gastric and small bowel biopsies, coeliac disease serology and other laboratory results of the DH study patients and controls were reviewed from medical records (I-IV) and in sub-cohort 2 (III) also by structured telephone interviews.

Severity of skin symptoms (II, III), and the presence of gastrointestinal symptoms at diagnosis (I, II, III), as well as duration of skin and gastrointestinal symptoms before diagnosis (II) in DH were gathered from the medical records. The severity of skin symptoms at diagnosis was further graded as mild, moderate or severe by a dermatologist. The grading was based on the presence of a few, several, or many blisters, macular eruptions, and erosions on the knees, elbows, buttocks, scalp, or elsewhere on the body.

Duration of dapsone treatment was elicited with DH-specific questionnaires (II, III). When the duration of skin symptoms after diagnosis was studied (II), in those who had started dapsone after being diagnosed, the duration of dapsone treatment was interpreted as the duration of skin symptoms, since dapsone is routinely discontinued as soon as the skin symptoms are controlled with GFD alone. Instead, in those not starting dapsone at diagnosis, duration of skin symptoms after diagnosis

was gathered from the questionnaires described in detail below. Duration of skin symptoms after diagnosis was further classified into three categories: less than one year, one to two years and longer than two years.

The duration of gastrointestinal symptoms after diagnosis (II) and the presence of gastrointestinal symptoms at one-year (II) and long-term follow-up (III) as well as severity of gastrointestinal symptoms at long-term follow-up (III) were also elicited with questionnaires or interviews (Study II, sub-cohort 2). Duration of gastrointestinal symptoms after diagnosis was further classified as no symptoms, or symptom duration less than three months, three to twelve months and over twelve months.

3.3.2 Gastric (I) and duodenal (I-IV) biopsy samples

At the time of DH diagnosis, the majority of the patients underwent gastroscopy and the taking of gastric and duodenal biopsies before GFD was initiated. The histological findings were interpreted by experienced pathologists, and for this study, histological gastric and duodenal reports were reviewed from the medical records.

Gastric samples were interpreted according to the Sydney classification, where five parameters are evaluated from the antrum and corpus part of the stomach: inflammation, activity, atrophy, metaplasia and *H. pylori*. Scale is from 0-3, where 0 indicates normal finding and 3 the most severe finding. For the present study, atrophy, metaplasia and *H. pylori* were recorded, and atrophic gastritis was defined as atrophy in the antrum, corpus or both (pangastritis). Instead, *H. pylori* finding was regarded as positive if *H. pylori* infection was detected anywhere in the stomach and no grade was set. In order to analyse small bowel mucosal morphology, the small bowel mucosal biopsies were graded as subtotal or total villous atrophy, partial villous atrophy or normal mucosa.

3.3.3 Laboratory parameters (II, III)

The results of coeliac disease autoantibody tests were gathered at diagnosis from DH patients (II, III) and coeliac disease controls (II) and also at one-year follow-up in DH (II). The serum coeliac disease autoantibody tests gathered were ARA, EmA or TG2 antibody tests, depending on the time of the testing. Titers 1:≥5 were considered positive in the ARA and EmA tests, and in the TG2 antibody tests, the reference value was 20 or 5 U/ml, depending on whether an INOVA (INOVA

Diagnostics, San Diego, CA, USA) or Celikey (CelikeyPharmacia, Uppsala, Sweden) test was used. The ARA, EmA and TG2 antibody tests were collectively referred to as serum coeliac autoantibodies.

For Study II, the levels of Hb in DH and coeliac disease controls at diagnosis were gathered. Serum vitamin B_{12} or transcobalamin II-bound vitamin B_{12} (B12-TC2), erythrocyte folate (E-folate) or serum folate (S-folate) and serum ferritin and transferrin receptor at the time of the diagnosis were also collected from the DH patients. However, the serum ferritin and transferrin receptor test results were excluded from further analysis since their availability from the medical records was low. Additionally, Hb levels at one-year follow-up were recorded from DH patients. Laboratory values were measured by standard laboratory methods: Hb (reference values: 117–155 g/l for women and 134–167g/l for men), serum vitamin B_{12} or B12-TC2 (reference values 145–570 pmol/l and >35 pmol/l) and E- or S-folate (reference values 1187–2854 nmol/l and 8.8–42.4 nmol/l). Anaemia was defined as Hb level under the reference value given for the respective gender.

3.3.4 Adherence to a gluten-free diet and consumption of oats

DH patients' GFD adherence at one year (II) or at long-term follow-up (III, IV) and consumption of oats (III) was elicited from DH-specific questionnaires (II, III: sub-cohort 1) or by interviews conducted by a study physician or nurse (III: sub-cohort 2). In Study II, DH patients were interpreted as adherent or non-adherent to GFD one year after being diagnosed. When long-term GFD adherence was investigated (III, IV), it was further classified as strict, with no dietary lapses, dietary lapses less often than once a month or dietary lapses once a month or more often. Consumption of oats at long-term follow-up was classified as at least twice a week, less than twice a week or none at all (III).

3.3.5 Questionnaires (I-IV)

The questionnaires used to gather the follow-up data for the present study were sent in 2011 (I, IV) to those DH patients diagnosed between 1970 and 2009 in Tampere University Hospital and in 2015 (II, III) to the DH patients diagnosed between 1970 and 2014 in Tampere University Hospital. Thus, there were two different DH-specific questionnaires, which were designed for study purposes by our research group. Both questionnaires included open and multiple-choice questions and

inquired about the initiation and adherence of GFD, use of dapsone treatment, consumption of oats and the presence of long-term illnesses and malignancies. The later questionnaire additionally included questions about the presence and duration of cutaneous and gastrointestinal symptoms, occurrence of bone fractures, regular use of prescribed as well as over-the-counter medications and about smoking and amount of weekly physical exercise. For further analysis (III), fractures caused by excessive trauma and non-melanoma skin cancers were excluded.

Health behaviour of DH patients diagnosed 1970-2009 at Tampere University Hospital was measured with the special Finnish Adult Health Behaviour Survey (Tolonen et al., 2006) enclosed with the DH-specific questionnaire (IV) in 2011. The Adult Health behaviour Survey questionnaire has been sent annually since 1978 by the Finnish Institute for Health and Welfare to Finnish working-aged population to study the health behaviour of the general population. The questionnaire includes over 100 questions about eating habits, smoking, alcohol consumption and physical activity.

Additionally, the DH patients diagnosed in Tampere University Hospital between 1970 and 2014 as well as sub-cohort 2 in Study III were sent validated questionnaires in 2015 and between 2006 and 2010 respectively in order to gather follow-up data on quality of life and gastrointestinal symptoms (III). Health-related quality of life was measured with the Psychological General Well-being (PGWB) and Dermatology Life Quality Index (DLQI) questionnaires and gastrointestinal symptoms with the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire (III). PGWB is a general health-related quality of life questionnaire including 22 questions (Grossi et al., 2006; McDowell, 2010). It contains six sub-divisions: anxiety, depressed mood, positive well-being, self-control, vitality and general health. The scores on all segments are summed and the total score ranges from 22 to 132, with higher scores indicating better quality of life. The DLQI is a 10-item quality of life measuring tool, designed specifically for dermatological patients (Finlay and Khan, 1994; Lewis and Finlay, 2004). The DLQI questionnaire includes six different segments: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. The scores on ten questions are summed for the total score, which varies between 0 and 30, higher score indicating poorer quality of life. The GSRS is a validated 15-item questionnaire measuring the severity and occurrence of gastrointestinal symptoms in five categories: diarrhoea, indigestion, constipation, abdominal pain and reflux. There is a seven-point Likert scale for each question, and one means no symptoms and seven the most severe symptoms. Sub-scores for each of the five categories are calculated as the average of relevant items and the total

score is calculated as the average of all items. (Parijs et al., 2008; Svedlund et al., 1988)

3.3.6 Mortality analysis (IV)

Practically all causes of death in Finland are recorded by Statistics Finland, and for this study, all the dates and causes of death of the DH patients between 1971-2010 were identified by linking the personal identification codes with the death certificate files held by Statistics Finland. The causes of death were coded according to ICD-10 (International Classification of Diseases).

When mortality was analysed, the number of person-years of follow-up was measured starting on 1 January in the year following the DH diagnosis and ending on the date of death or on 31 December 2010. For comparison, sex-, age- and calendar-period-specific mortality rates in the Finnish population were used to calculate the expected number of deaths. The expected number of deaths was calculated separately for the 53 specific cause-of-death sub-categories included in the selection of categories of the longitudinal time series of Statistics Finland.

3.3.7 Statistical analyses

For the descriptive statistics and further analysis, DH patients and controls, as well as DH patients with and without CAG were compared in Study I. In Study II the groups compared were DH and coeliac disease controls at the time of diagnosis and DH patients with and without anaemia at diagnosis and at one-year follow-up. Additionally, DH patients were divided into three groups depending on whether the Hb value had decreased, remained constant, or increased during the first year from diagnosis and the groups were compared. A change in Hb level ≥10 g/l during the first year of treatment was considered clinically relevant. In Study III, comparisons were made between the baseline and long-term follow-up data of DH patients consuming and not consuming oats. In Study IV, mortality rates and health behaviour were compared between DH patients and general population.

In all studies (I-IV), categorical variables were presented as numbers and percentages, and continuous variables as means or medians with interquartile ranges (IQR) or ranges (min–max). Cross-tabulation with a two-sided chi-squared test or Fisher's exact test were used to compare the categorial variables and the Mann–Whitney U or Kruskal-Wallis H tests were used for comparing the continuous

variables. Statistical significance was set at $p<0.05$. Odds ratios (OR)s were presented with 95% confidence intervals (CI) (I).

In Study IV, the standardized mortality ratios (SMR), i.e. the ratio of observed and expected number of deaths, were calculated for all-cause mortality of the whole DH cohort and separately for men and women. SMRs for the different causes of death were calculated for the whole period and separately for the first five years of follow-up after DH diagnosis and then for follow-up after five years. Additionally, all-cause SMRs were calculated separately for the DH patients with and without small bowel villous atrophy at diagnosis. The corresponding 95% CI were defined assuming Poisson distribution of the observed number of deaths.

3.4 Ethical considerations

The provisions of the Declaration of Helsinki (1975) were followed in all studies. The Regional Ethics Committee of Tampere University Hospital approved the protocols of the studies and the use of register-based data. All subjects responding to the questionnaires gave their written informed consent.

3.5 Results

3.5.1 Gastric findings and villous atrophy in dermatitis herpetiformis (I, II, III)

Sixteen out of the 93 (17%) patients with untreated DH had atrophic gastritis in the antrum, corpus or both segments of the stomach compared to six out of 186 (3%) controls with dyspepsia ($p<0.001$). Moreover, DH patients had more frequently intestinal metaplasia than did control subjects (14% vs. 7%, $p=0.038$). In the corpus segment of the stomach, both atrophy and metaplasia were significantly more common in DH patients than among controls (16% vs. 3%, $p<0.001$, and 9% vs. 3%, $p=0.027$, respectively), but no differences were detected between the groups in the frequencies of antrum atrophy or metaplasia (Table 6). Additionally, *H. pylori* infection was significantly more common in DH than among the controls (18% vs. 9%, $p=0.028$). (Table 6)

Table 6. Demographic data and gastrointestinal findings of 93 patients with untreated dermatitis herpetiformis (DH) and 186 controls with dyspepsia

	DH patients (n=93)	Controls (n=186)
Females; n (%)	40 (42)	80 (43)
Mean age; years (range)	47 (16-76)	55 (18-86)
Gastric findings		
Corpus atrophy; n (%)	15 (16)*	5 (3)*
Corpus metaplasia; n (%)	8 (9)**	5 (3)**
Antrum atrophy; n (%)	3 (3)	2 (1)
Antrum metaplasia; n (%)	8 (9)	8 (4)
H. pylori infection; n (%)	17 (18)***	17 (9)***
Small bowel mucosa		
Normal; n (%)	22 (24)	186 (100)
Partial villous atrophy; n (%)	37 (40)	0
Subtotal or total villous atrophy; n (%)	34 (37)	0

H. pylori = *Helicobacter pylori*, *p<0.001, **p=0.027, ***p=0.028

Of the 16 DH patients with CAG, 13 (81%) had atrophy only in the corpus, 2 (13%) had pangastric atrophy, i.e. atrophy in both corpus and antrum, and one (6%) had atrophy only in the antrum. Seven out of 16 (44%) DH patients with CAG had concurrent intestinal metaplasia in the corpus, and of those, two had concurrent metaplasia in the antrum, i.e. pangastric metaplasia. One of the two patients with pangastric metaplasia had simultaneous pangastric atrophy. *H. pylori* infection in the gastric mucosa was detected in 44% of the DH patients with CAG compared to 14% of the DH patients without CAG (p=0.012). Small bowel villous atrophy was detected at diagnosis in 69% of the patients with CAG and in 78% of the patients without CAG, but the difference was not statistically significant (p=0.52). Compared to the DH patients with CAG, a slightly higher prevalence of villous atrophy was also detected in Studies II-IV, where the prevalence of villous atrophy in DH ranged from 74 to 80% (Table 7). To be more specific, 40% of all DH patients in Studies I-III were found to have subtotal or total villous atrophy, 37% partial villous atrophy and 23% normal villous architecture. Further, when gastrointestinal symptoms were compared between DH patients with and without CAG, no statistically significant difference was detected as 33% of the DH patients with CAG and 40% of those without CAG with available data were suffering from gastrointestinal symptoms (p=0.36). However, patients with CAG were found to be significantly older than those without CAG (mean age 63, range 47-76 and mean age 44, range 7-76, respectively), but the gender distribution was equal in the two groups.

The median follow-up in 16 patients with CAG was 6.8 (range 1-15) years. At follow-up, all the 16 DH patients with CAG adhered strictly to GFD and none of the patients needed dapsone treatment. Of the 16 patients with CAG, four out of the 11 patients having partial or subtotal villous in the small bowel at diagnosis had had undergone follow-up gastroscopy, where all were found to have normal villous architecture in the small bowel. Additionally, one out of five patients with CAG having normal villous atrophy at diagnosis had undergone follow-up gastroscopy and still had normal villous atrophy. However, CAG was persistent in the stomach in all four DH patients for whom biopsies had also been taken from the stomach during the follow-up gastroscopy. When development of malignancies was investigated in the DH patients with CAG, one DH patient having pangastritis and intestinal metaplasia at the time of DH diagnosis was found to have been diagnosed with gastric cancer one year after DH diagnosis. Development of prostate cancer was also detected in one DH patient with CAG after DH diagnosis. Two patients had had breast cancer before the DH diagnosis. Associated autoimmune diseases were found in three patients with CAG; one had hypothyreosis, one pernicious anaemia as well as hyperthyreosis, and one was suffering from vitiligo.

Table 7. Gastrointestinal symptoms, coeliac disease serology, small bowel villous atrophy and gluten-free diet (GFD) adherence as well as usage of dapsone treatment in dermatitis herpetiformis study patients (I-IV)

	At diagnosis	At one-year follow-up	At long-term follow-up
Frequency of gastrointestinal symptoms; n (%)	28/93 (30) (I) 97/202 (48) (II) 133/277 (51) (III)	14/88 (16) (II)	17/243 (7) (III)
Positive coeliac disease serology*; n (%)	142/222 (64) (II) 140/194 (72) (III)	27/93 (29) (II)	ND
Prevalence of small bowel villous atrophy; n (%)	71/93 (76) (I) 182/246 (74) (II) 195/243 (80) (III) 281/369 (76) (IV)	ND	ND
Adherence on GFD, n (%)	ND	141/180 (78) (II)	310/310 (100**) (III) 304/311 (98) (IV)
Dapsone initiated at diagnosis/used at follow-up, n (%)	181/238 (76) (II) 129/161 (80) (III) 203/312 (65) (IV)	69/120 (58) (II)	13/216 (6) (III) 25/312 (8) (IV)

*IgA-class anti-reticulin, endomysium, or tissue transglutaminase antibody test, **by definition, study only included patients adhering to GFD, ND=no data

3.5.2 Anaemia in dermatitis herpetiformis at diagnosis (II)

When 250 DH and 139 classical coeliac disease patients were compared, DH patients were more often males than were coeliac disease patients (52% vs. 23%, p<0.001), but median ages at time of diagnosis did not differ significantly between the groups (44, range 32-59, and 40, range 32-52 respectively, p=0.057). At diagnosis, 12% (31 out of 250) of the DH patients and 17% (23 out of 139) of the coeliac disease patients had anaemia and the difference was not statistically significant (p=0.257). Median Hb levels at diagnosis did not differ significantly between the genders in DH and coeliac disease either (median values in DH females 131g/l and 146g/l in DH males and in coeliac disease 128g/l and 146g/l respectively). In DH, anaemia was slightly more frequent in males than in females, but the difference did not reach statistical significance (15% vs. 9%, p=0.136). Additionally, DH males had more often severe skin symptoms at diagnosis than did females (38% vs. 25%, p=0.022), and consequently, dapsone usage was more common in males than in females after diagnosis (84% vs. 68%, p=0.004). However, the frequency of small bowel villous

atrophy was similar in DH males and females (74% vs. 73%, p=0.924). Seven percent (7 out of 100) of the DH patients with available data were shown to have vitamin B_{12} deficiency and 73% (55 out of 75) folate deficiency at diagnosis.

When comparing DH patients with and without anaemia at diagnosis, those without anaemia had more frequently gastrointestinal symptoms at diagnosis (52% vs. 18%, p=0.003), and also suffered from longer duration of gastrointestinal symptoms after diagnosis than did DH patients without anaemia (p=0.004). Age, gender, severity and duration of skin symptoms before or after diagnosis, small bowel histology and coeliac seropositivity at diagnosis were not related to anaemia in DH. Additionally, the frequency of vitamin B_{12} and folate deficiencies did not differ significantly between DH patients with and without anaemia (Table II in the publication for Study II).

3.5.3 Anaemia in dermatitis herpetiformis at one-year follow-up (II)

At one-year follow-up, 19% (31 out of 160) of the DH patients had anaemia. Anaemia was slightly more common in DH males than in DH females (25% vs. 14%), but the difference was not statistically significant (p=0.085). Additionally, the median Hb level decreased significantly during the first year after diagnosis in DH males from 146 to 141g/l (p<0.001) and in females non-significantly from 131 to 128 g/l (p=0.490).

Altogether 78% of the DH patients were adhering to GFD at the time of the follow-up. When all 160 DH patients with and without anaemia were further compared at one-year follow-up, the prevalence of anaemia was higher among those who still needed dapsone at one-year follow-up than among those who were not taking dapsone (80% vs. 53%, p=0.026) (Table 8). Also, when the patients adhering to GFD with available data were analysed, prevalence of anaemia was more common in those who had ongoing dapsone treatment at one-year follow-up than in those without dapsone treatment (28% vs. 0%, p<0.001). Dapsone was also more frequently taken by male DH patients than by females at one-year follow-up (66% vs. 47%, p=0.015), but the duration of skin symptoms after diagnosis did not differ between the genders. Instead, the DH study patients having anaemia at follow-up had significantly (p=0.006) longer duration of skin symptoms after diagnosis than those without anaemia (Table 8). Adherence to GFD, duration or severity of skin symptoms at diagnosis, frequency or duration of gastrointestinal symptoms before or after diagnosis, small bowel histology at diagnosis, positivity of coeliac serology

either at diagnosis or at one-year follow-up or presence of folate or vitamin B12 deficiency at diagnosis were not related to presence of anaemia at one-year follow-up (Table 8).

When DH patients were divided into three groups according to Hb changes during the one-year follow-up, 16% of the patients had decreased, 76% constant, and 8% increased Hb levels. The group with decreased Hb levels was found to have the highest Hb levels at diagnosis (median Hb levels at diagnosis 135 g/l in females and 155 g/l in males, $p<0.001$ in both genders), and the group with increased Hb level initially had the lowest Hb levels (median Hb levels at diagnosis 117 g/l in females and 125 g/l in males, $p=0.001$ in both genders). Additionally, DH patients having decreased Hb level at follow-up had more frequently ongoing dapsone treatment at one-year follow-up ($p=0.015$) and also had a longer duration of skin symptoms after diagnosis ($p=0.005$) than those with constant or increased Hb levels. No other significant differences between the groups were detected in the demographic data, clinical symptoms at diagnosis or at follow-up, small bowel villous atrophy at diagnosis or coeliac disease serology at diagnosis or at follow-up.

Table 8. Demographic, clinical, histological and laboratory data of 160 dermatitis herpetiformis (DH) patients with anaemia[1] and without anaemia one year after DH diagnosis

	DH patients with anaemia[1] one year after diagnosis, n=31 (19%)		DH patients without anaemia[1] one year after diagnosis, n=129 (80%)		
	n/median	%/range	n/median	%/range	p-value
At diagnosis					
Females	11	36	68	53	0.085
Age (years)	51	19-83	49	18-83	0.931
Duration of skin symptoms (months)	11	3-360	10	0-480	0.269
Severity of skin symptoms[2]					0.114
Mild	3/30	10	26/124	21	
Moderate	20/30	67	57/124	46	
Severe	7/30	23	41/124	33	
Initiation of dapsone	26/30	87	91/125	73	0.113
Positive coeliac serology[3]	15/28	54	77/116	66	0.205
Gastrointestinal symptoms	8/24	33	57/109	52	0.093
Small bowel histology					0.885
Normal	9/31	29	34/127	27	
Partial villous atrophy	12/31	39	46/127	36	
Subtotal or total villous atrophy	10/31	32	47/127	37	
Vitamin B_{12} deficiency[4]	3/13	18	4/53	8	0.349
Folate deficiency[5]	5/17	30	18/38	47	0.212
After diagnosis					
Duration of skin symptoms					0.006
< 1 year	1/17	6	35/92	38	
1-2 years	5/17	29	31/92	34	
> 2 years	11/17	65	26/92	28	
Ongoing dapsone treatment at one year	16/20	80	53/100	53	0.026
Positive coeliac serology[3] at one year	8/18	44	19/75	25	0.109
Duration of gastrointestinal symptoms					0.178
No symptoms after diagnosis	6/9	67	27/55	49	
< 3 months	3/9	33	8/55	15	
3-12 months	0	0	11/55	20	
> 12 months	0	0	9/55	16	
Adherence to gluten-free diet at 1 year	18/21	86	82/94	87	1.000

[1]Blood Hb level <117 g/l for women and <134 g/l for men; [2]Graded according to the presence of a few, several or many blisters, macular eruptions and erosions; [3]IgA-class anti-reticulin, endomysium or tissue transglutaminase antibody test; [4]Serum vitamin B_{12} value <145 pmol/l or transcobalamin II bound vitamin B_{12} value <35 pmol/l, [5]Erythrocyte folate value < 1,187 nmol/l or serum folate value < 8.8 nmol/l.

3.5.4 Prognosis of dermatitis herpetiformis on gluten-free diet

3.5.4.1 Adherence to gluten-free diet and factors related to consumption of oats (II, III, IV)

Adherence to GFD was 78% one year after DH diagnosis (II) and 98% at long-term follow-up (IV) (Table 7). Further, 72-80% of the DH patients were adhering strictly to GFD and had no dietary lapses (III, IV). By definition, all 312 DH patients in Study III were on GFD, and of these, 256 (82%) were consuming oats at the time of follow-up and consumption of oats did not differ significantly between the two sub-cohorts of the study. Of the patients consuming oats, 72% were eating oats at least two times a week and 28% less than two times a week. No significant differences in GFD adherence were detected between those consuming and those not consuming oats. The frequency of strict adherence was 79% in those consuming and 88% in those not consuming oats, while the percentage of patients with dietary lapses less than once a month and dietary lapses once a month or more often were in 14% and 7% in the oats group and 7% and 2% in the no-oats group respectively (p=0.229).

Gender and age at diagnosis did not differ between those consuming and those not consuming oats: 49% of those consuming and 46% of those not consuming oats were females (p=0.745) and median ages were 37 (IQR 27-50) years and 39 (IQR 27-50) years respectively (p=0.481). Nor did the year of diagnosis differ between the two groups as regards consumption of oats as the median year of diagnosis in those consuming oats was 1993 (IQR 1982-2002) and 1998 (IQR 1982-2000) in those not consuming oats (p=0.184). Median duration of skin symptoms before diagnosis was 11 (IQR 6-36) months among those consuming and 10 (IQR 5-60) months among those not consuming oats (p=0.671). However, patients who were not consuming oats at follow-up had slightly more frequently severe skin symptoms at diagnosis than did those who were consuming oats, but the difference did not reach statistical significance (48% vs. 31%, p=0.076). A non-significant difference was likewise detected in the initiation of dapsone after diagnosis between those not consuming and consuming oats (86% vs. 73%, respectively, p=0.119). Gastrointestinal symptoms were present at diagnosis in 48% of those consuming and in 50% of those not consuming oats at follow-up (p=0.756). The severity of villous atrophy did not differ between the groups (p=0.530) nor did the prevalence of positive coeliac disease serology (74% vs. 61%, p=0.156)

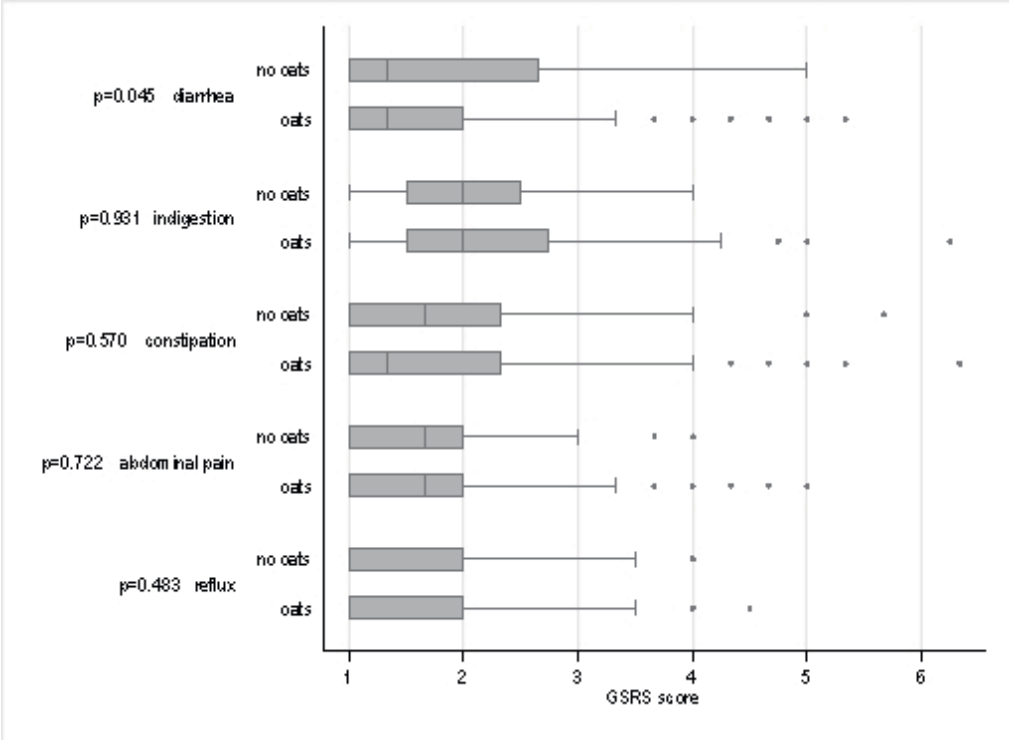
3.5.4.2 Morbidity, quality of life and effects of consuming oats (III, IV)

The follow-up data of 179 working-aged DH patients in the Adult Health Behaviour Survey (IV) revealed that the DH patients had significantly less often hypercholesterolaemia than matched controls (15 % vs. 24 % p=0.008), even though DH patients reported using animal fats more frequently in cooking (32% vs. 17%, p<0.001). Instead, no significant differences were detected in the occurrence of ischaemic heart disease or high blood pressure nor in the use of anti-hypertensive drugs (Table 4 in the publication for Study IV). DH patients reported less frequently present (7% vs. 16%, p=0.003) or past (48% vs. 64%, p<0.001) smoking than did the controls. Physical activity, height and weight or alcohol consumption, except abstinence from beer (50% vs. 24%, p<0.001), did not differ between the DH patients and controls.

When the follow-up data of 256 DH patients consuming oats and 56 DH patients not consuming oats were compared, no differences were seen in the median age at follow-up (62, IQR: 18-96 years vs. 62, IQR: 32-85 years, p=0.963) or median duration of GFD (21, IQR: 1–47 years vs. 24, IQR: 2–41 years, p=0.161). The number of long-term illnesses and the prevalence of coronary heart disease, cerebrovascular disease, osteopenia or osteoporosis, bone fractures and malignancies did not differ between DH patients consuming and not consuming oats at follow-up (Table 2 in the publication for Study III). Additionally, the number of regularly used prescription and over-the-count medications was not related to consumption of oats. Body-mass index was 25 kg/m^2 (range 17-40) among oats consumers and 26 kg/m^2 (range 20-33) among those not consuming oats (p=0.242). The amount of physical exercise taken was not related to consumption of oats, but those not consuming oats, were more often current smokers than were those consuming oats (16% vs. 7%, p=0.032).

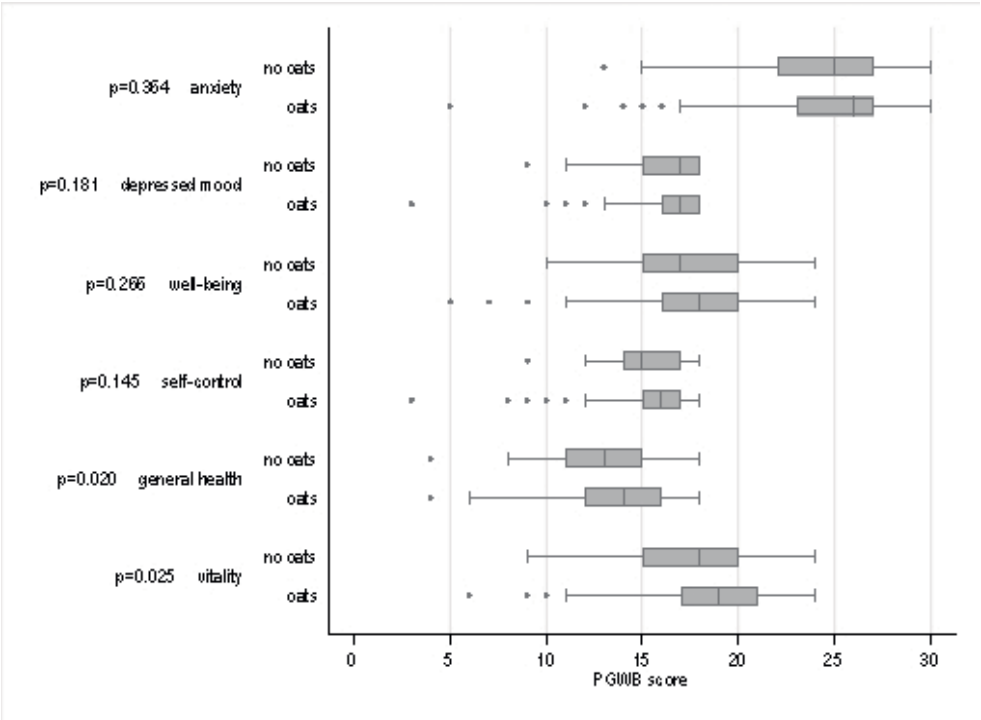
When the presence and severity of gastrointestinal symptoms were analysed, the DH patients not consuming oats were found to have current gastrointestinal symptoms significantly more frequently than those consuming oats (19% vs. 4%, p=0.04). Moreover, in the GSRS sub-score analysis the diarrhoea score was significantly lower in those consuming oats (p=0.045), but other sub-scores did not differ (Figure 3). Likewise, GSRS total score did not differ between those consuming and not consuming oats (1.7, IQR: 1.3-2.2 and 1.7, IQR: 1.4-2.2, p=0.322).

Figure 3. Median values and interquartile ranges for Gastrointestinal Symptom Rating Scale (GSRS) questionnaires' sub-scores for the 312 dermatitis herpetiformis patients on a gluten-free diet with or without oats



Additionally, those not consuming oats had more often ongoing dapsone treatment than did patients who were consuming oats at follow-up (14% vs. 4%, p=0.040), although the prevalence of reported current skin symptoms did not differ significantly in these groups (16% vs. 28%, p=0.090). When quality of life was measured with the DLQI questionnaire, the dermatology quality of life scores were higher in the oats group (0, IQR: 0–0 and 0, IQR: 0–1, p=0.028). Also, in the PGWB questionnaire, the median values for general health and the vitality sub-scores were significantly higher in the oats group (p=0.020 and p=0.025, respectively), while total score (110 vs. 103, p=0.083) as well as other sub-scores were equal in the groups (Figure 4).

Figure 4. Median values and interquartile ranges for Psychological General Well-being (PGWB) questionnaires' sub-scores for the 312 dermatitis herpetiformis patients on a gluten-free diet with or without oats



3.5.4.3 Mortality (IV)

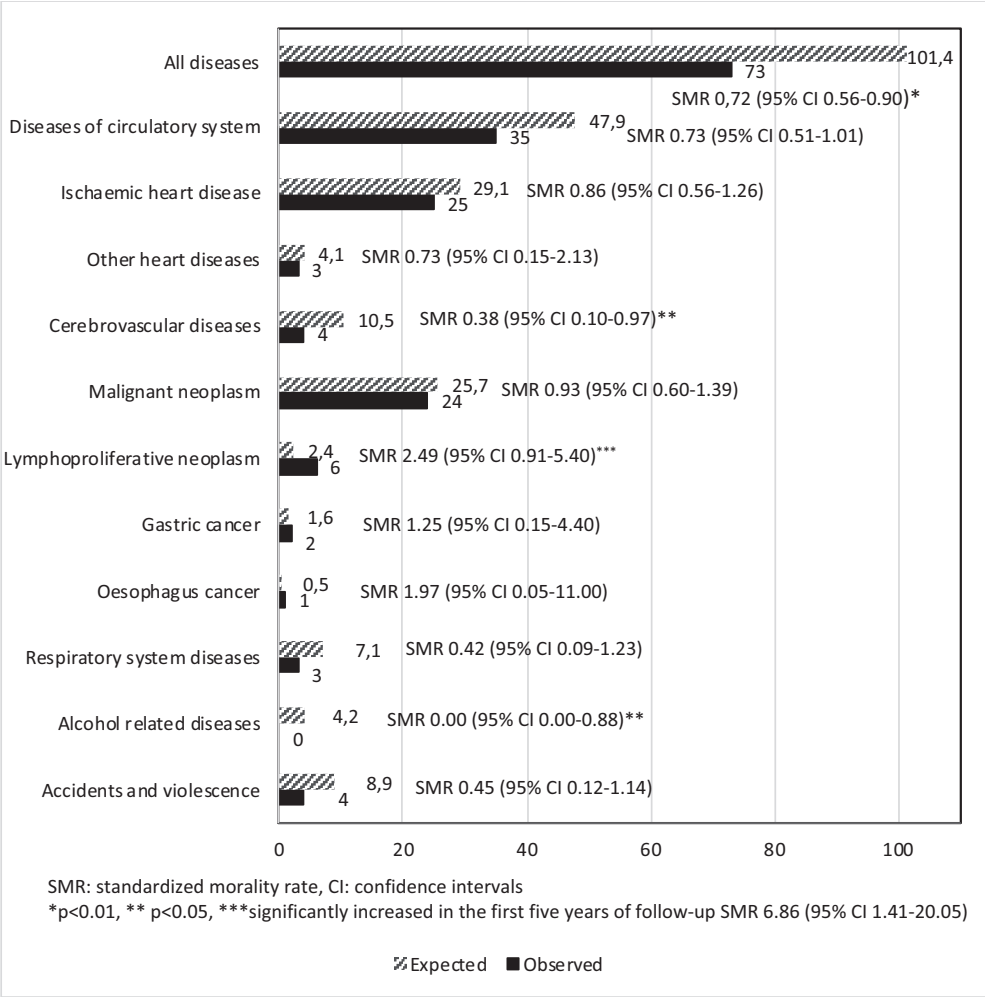
In the 476 DH study patients followed up for a total of 9,079 person-years, the number of observed deaths was 77, while the number of expected deaths was 110. Consequently, the all-cause SMR was significantly reduced, 0.70 (95% CI 0.55–0.87, p<0.001). All-cause SMR was also significantly reduced in 249 males (0.68, 95% CI 0.49–0.91, p<0.01), but no statistically significant level was reached in females (0.72, 95% CI 0.50–1.00). Moreover, the all-cause SMR for all DH patients during the first five years of follow-up after diagnosis was significantly reduced (0.50, 95% CI 0.24–0.92 p<0.05), and this was also seen in males (0.40, 95% CI 0.13-0.92, p<0.05), but not in females (0.69, 95% CI 0.22-1.60). After five years of follow-up, all-cause SMR was still significantly reduced in all patients (0.74, 95% CI 0.57-0.93, p<0.05), but not separately in males (0.75, 95% CI 0.53-1.02) or females (0.73, 95% CI 0.49-1.04).

When mortality was analysed according to specific causes of death, a significantly reduced mortality rate was seen in cerebrovascular (SMR 0.38, 95% CI 0.10–0.97)

and alcohol-related diseases (SMR 0, 95% CI 0.00–0.88) (Figure 5). Instead, the mortality rate for lymphoproliferative malignancies was significantly increased during the first five years of follow-up after diagnosis (SMR 6.86, $p<0.05$, 95% CI 1.41–20.05), but not in the whole follow-up period (SMR 2.49; 95% CI 0.91–5.40). No significant differences were detected in mortality rates related to diseases of the circulatory system, ischaemic or other heart diseases, all malignant neoplasms, gastric or oesophageal cancers, respiratory system diseases or accidents and violence.

When mortality rates were counted only for those 369 DH patients who had undergone gastroscopy with small bowel biopsy before starting GFD, all-cause SMR was reduced (0.75, 95% CI 0.56-0.96, $p<0.05$). The all-cause SMR was similarly decreased in patients with normal mucosa (0.77, 95% CI 0.48-1.16) and in patients with villous atrophy at diagnosis (0.73, 95% CI 0.50-1.01). The SMR for lymphoproliferative malignancies was similar in those with normal mucosa (3.41 95% CI 0.41-12.33) and in those with villous atrophy at diagnosis (2.85 95% CI 0.58-8.27).

Figure 5. Standardized mortality ratios (SMR) and corresponding numbers of observed and expected deaths for different causes of deaths in 476 patients with dermatitis herpetiformis



SMR: standardized morality rate, CI: confidence intervals
*p<0.01, ** p<0.05, ***significantly increased in the first five years of follow-up SMR 6.86 (95% CI 1.41-20.05)

3.6 Discussion

3.6.1 Gastric findings in dermatitis herpetiformis

The present study showed that CAG in the corpus or multifocal CAG was more frequent in DH than in controls with dyspepsia, but the prevalence of CAG in the antrum did not differ between the groups. Additionally, it was established that *H. pylori* infection was more common in DH than in dyspepsia patients, and further, DH patients with CAG had more frequently *H. pylori* infection than did those without CAG.

The findings of this study are in line with those of Primignani et al. (1990) reporting a similarly higher frequency of CAG in DH (30%) in Italy than in controls suffering from dyspepsia (15%). However, the percentages of CAG in both study patients and controls were higher than in the present study, and since *H. pylori* infection is known to be commonly involved in the development of CAG, one explanation for the higher percentages of CAG may be higher frequency of *H. pylori* infection in Italy than in northern countries (O'Connor and O'Moráin, 2013). Mean age, instead, was lower in the study by Primignani and colleagues than in our study and thus does not explain the differences in CAG prevalences, while the prevalence of *H. pylori* infection is usually higher in older individuals (O'Connor and O'Moráin, 2013). Other studies have reported the prevalence of CAG to be 6-50% in DH (Gillberg et al., 1985; Lancaster-Smith et al., 1974; O'Donoghue et al., 1976; Stockbrügger et al., 1976) (Table 2). However, in those studies control groups were lacking and the numbers of DH patients were quite small, and, in addition, in two studies gastroscopy was performed selectively on those screened to be positive for parietal cell antibodies or with achlorhydria. Endoscopy-based studies investigating the prevalence of atrophic gastritis in general population are scarce, but in a Swedish study with 1,000 individuals, prevalence of CAG in the corpus or multifocal CAG was 6% (Storskrubb et al., 2008), which also suggests that atrophic gastritis is more common in DH than in general population.

The association between *H. pylori* infection and CAG is well established (Weck and Brenner, 2006) and this also emerged in our study, as 44% of DH patents with CAG had concurrent *H. pylori* infection compared to 14% in those without CAG. *H. pylori* infection was also more common in DH than in controls, whereas, the study by Crabtree et al. (1992) found a similar prevalence of *H. pylori* infection in DH, coeliac disease and controls. Consequently, while it is probable that *H. pylori* infection

contributes to the development of CAG in DH, an autoimmune mechanism may also be involved. However, while the exact mechanism of autoimmune-based gastritis is still unclear, it is known to develop either without *H. pylori* infection located solely in the corpus or with the help of *H. pylori* infection and typically with a multifocal CAG distribution (Neumann et al., 2013).

Our study also showed that CAG in DH is persistent and unresponsive to GFD, since in all CAG patients undergoing follow-up gastroscopy, small bowel villous atrophy had recovered with GFD, while CAG was still present. Our results corroborate earlier studies demonstrating that GFD does not have an effect on CAG or other gastric morphological findings in DH (Andersson et al., 1984; Kastrup et al., 1985). In addition to CAG with or without *H. pylori* infection being resistent to GFD and irrespective of villous atrophy, it is known to be frequently asymptomatic and cannot be recognized on the basis of symptoms (Minalyan et al., 2017; Neumann et al., 2013). This was also seen in this study, as the presence of gastrointestinal symptoms was shown not to differ between DH patients with CAG and those without CAG. Moreover, it is known that CAG, especially with *H. pylori* infection, may be a precursor of gastric cancer (Adamu et al., 2010; Correa, 1992), and eradication of *H. pylori* seems to decrease the malignancy risk according to recent meta-analysis (Rokkas et al., 2017). In the present study development of gastric cancer was detected in one DH patient with CAG at diagnosis, but while an increased malignancy risk in DH patients with persistent CAG is possible, more research and evidence are needed to confirm the association. Likewise, whether autoimmune CAG increases the risk of concomitant autoimmune diseases needs to be explored further in the future.

3.6.2 Anaemia in dermatitis herpetiformis

This study demonstrated that anaemia is a fairly uncommon finding in untreated DH, occurring in 12% of patients at diagnosis, and the presence of anaemia seemed not to be associated with the severity of the disease in terms of small bowel villous atrophy or the severity of skin symptoms. Moreover, the 17% anaemia prevalence detected in untreated classical coeliac disease was slightly, but not significantly, higher than in untreated DH, thereby supporting the claim that villous atrophy is not the sole aetiology of anaemia in DH or coeliac disease.

The only study so far to investigate anaemia in untreated DH found the prevalence of anaemia in DH to be 23% in India (Handa et al., 2018), which is slightly

higher than in our study. However, this difference may be explained by the different geographical location, since studies predicting anaemia in coeliac disease have also reported much higher prevalences of anaemia in India, 93% (Berry et al., 2018) than in European countries, where the prevalence of anaemia in untreated coeliac disease has been reported to be 23-40% (Bergamaschi et al., 2008; Saukkonen et al., 2017; Schøsler et al., 2015; Zanini et al., 2013) (Table 1). The prevalence of anaemia in coeliac disease in the present study was thus somewhat lower than previously reported.

The presence of anaemia in untreated DH in the present study was irrespective of the severity or duration of skin symptoms at diagnosis and, moreover, the patients without anaemia had gastrointestinal symptoms even more frequently than did those with anaemia. In studies with coeliac disease, the association of gastrointestinal symptoms with anaemia has been inconsistent (Rajalahti et al., 2017; Saukkonen et al., 2017; Singh et al., 2014). It seems that in DH and coeliac disease, the likelihood of anaemia cannot be predicted by the clinical symptoms. Additionally, in the present study, anaemia in untreated DH was not associated with other factors indicating disease severity such as degree of villous atrophy or positivity of coeliac disease serology. In coeliac disease studies, claims about an association with anaemia and severity of villous atrophy or coeliac disease serology have been inconsistent, as in some studies, anaemia has been reported to be associated with higher TG2 antibody levels and more severe villous atrophy (Abu Daya et al., 2013; Berry et al., 2018; Zanini et al., 2013). Opposite results have also been reported (Brar et al., 2006). This reflects the prevailing perception that the aetiology of anaemia in DH, as in coeliac disease, may be multifactorial, meaning that in addition to malabsorption of iron and other nutrients caused by small bowel villous atrophy, other mechanisms such as systemic inflammation caused by cytokine activation may be implicated (Harper et al., 2007). The folate or vitamin B_{12} deficiencies reported in our study also support the multifactorial aetiology of anaemia in DH, regardless of the fact that folate or vitamin B_{12} deficiencies were not associated with anaemia.

According to the present study, clinical symptoms resolved similarly in the DH patients presenting with and without anaemia at diagnosis; the duration of skin symptoms after diagnosis was equal between the groups and gastrointestinal symptoms diminished even more rapidly in those with anaemia at diagnosis. Even though the frequency of anaemia was higher at one-year follow-up in DH than at the time of diagnosis, it seemed to be mainly caused by the well-known side-effect of dapsone treatment, since the only factors associated with anaemia at follow-up were being on dapsone treatment and longer duration of skin symptoms. The role

of dapsone in the prevalence of anaemia at follow-up was also supported by the fact that males had anaemia at follow-up slightly more often than females, and even though duration of skin symptoms was not found to be longer in males than in females, males still used dapsone treatment more often than females. Furthermore, those who had decreased Hb level during the first year after diagnosis used dapsone more often at follow-up and had a longer duration of skin symptoms after diagnosis than those with increased or constant Hb level. This indicates that anaemia at follow-up was not caused by the same factors as anaemia at diagnosis.

Comparing the results of the present study regarding the 19% anaemia prevalence at one-year follow-up with the two earlier studies reporting anaemia in treated DH (Fry et al., 1967; Gawkrodger et al., 1988) is difficult. The study by Fry and associates reported a 42% anaemia prevalence, but 11 out of 12 study patients were on dapsone treatment and only 30% were on GFD, while in the study by Gawkrodger and colleagues, only 8% prevalence of macrocytic anaemia was reported, and it remained unclear whether or not this was also the total frequency of anaemia. Moreover, it remained obscure which percentage of the patients with anaemia were treated with GFD or dapsone. An explanation for the rather low anaemia frequency during GFD treatment in the present study may be the good GFD adherence rates in Finland (Pasternack et al., 2015). It is also possible that GFD adherence in DH has improved with time, and hence may be better nowadays than over thirty years ago, when the other studies were conducted. Additionally, the current recommendations of dapsone dosage in Finland may be lower since dapsone is usually initiated at a dosage of 25–50 mg daily.

3.6.3 Long-term prognosis of dermatitis herpetiformis

3.6.3.1 Morbidity, consumption of oats and quality of life

The present study established that patients with DH reported hypercholesterolemia at follow-up less often than controls from general population despite the more frequent use of animal fats in cooking. Additionally, compared to controls, DH patients were less often present or past smokers. Our findings are thus in line with those of a study from the UK reporting a more advantageous lipid profile and less smoking in treated DH than in the healthy controls (Lear et al., 1997). Supporting findings have also been reported in coeliac disease, since total cholesterol levels have been shown to be low in untreated disease and remain low even during GFD (Brar

et al., 2006b; Lewis et al., 2009), and further, coeliac disease patients have been shown to smoke less than general population (Austin et al., 2002; Snook et al., 1996). Furthermore, in an earlier study comparing ischaemic heart disease patients with and without coeliac disease, those with coeliac disease had lower cholesterol levels, were less commonly active smokers and had slightly less frequently hypertension and less severe coronary artery disease (Emilsson et al., 2013). In the present DH study, the frequencies of ischaemic heart disease or hypertonia were not found to differ significantly from those of controls, and nor did body mass index. Unlike DH, the association between coeliac disease and atherosclerotic disease has been widely studied with inconsistent findings. However, a recent meta-analysis summarized that there may be even a slightly increased risk for cerebrovascular and coronary heart disease in coeliac disease (Heikkilä et al. 2015).

Low cholesterol levels at the time of DH and coeliac disease diagnosis may be, at least partly, explained by reduced cholesterol synthesis and absorption in the gut due to intestinal malabsorption (Lewis et al., 2009; Vuoristo & Miettinen, 1982). However, the reasons for more favourable lipid profile during GFD are more obscure, but an inverse association with high-density lipoprotein cholesterol and systemic inflammation has been demonstrated (Lee et al., 2000; Lewis et al., 2009). Anti-inflammatory treatment of active rheumatoid arthritis, a chronic autoimmune disease like DH and coeliac disease, has been shown to lead to an increase in high-density lipoprotein cholesterol, which, in turn, has many antioxidative, antithrombotic and anti-inflammatory effects (Lewis et al., 2009; Birjmohum et al.,2007). Smoking, although being one of the most important risk factors for cerebrovascular and ischaemic heart disease, may be a protective factor against the development of coeliac disease. Similarly, an inverse association between smoking and ulcerative colitis has been demonstrated (Birrenbach et al., 2004). The pathomechanism of preventive effect of smoking against some gastrointestinal diseases may be the various immunomodulatory effects of smoking (Wijarnpreecha et al., 2018). Smoking has also been shown to reduce intestinal permeability, which may be an important counteracting factor in the development of celiac disease, as intestinal permeability of immunogenic gluten particles is considered to be one of the early events in the pathogenesis of celiac disease (Wijarnpreecha et al., 2018; Cukrowska et al., 2017).

When studying morbidity in DH, it is essential to consider whether patients are adhering to GFD, since the dietary treatment may affect the prognosis. In the present study 98% of DH patients adhered to a GFD, 78-80% of them strictly. Oats may also have health effects, and in our study 82% of DH patients were consuming

oats as a part of their GFD. The frequency of oat consumption in our study was markedly higher than in a previous Finnish questionnaire study reporting only 55% of DH patients consuming oats (Peräaho et al., 2004a). In the present study, we also tried to ascertain the factors predicting oat consumption in DH and found that consumption of oats was slightly more common in those having less severe skin symptoms at diagnosis, even though the difference was not statistically significant. Therefore, it is possible that patients with more severe symptoms are reluctant to try oats due to the fear of exacerbating the troublesome skin symptoms. A parallel finding has also been reported in coeliac disease, as in a previous Finnish study, coeliac disease patients initially suffering from milder symptoms were more likely to consume oats (Aaltonen et al., 2017).

An important observation of the present study was that long-term consumption of oats seems to be safe in DH. Consumption of oats did not cause increased occurrence of long-term illnesses or DH related complications. In fact, long-term consumption of oats seemed to have beneficial effects on the symptoms deriving from the gastrointestinal tract, since those not using oats seemed more often to have diarrhoea at follow-up than those eating oats. In coeliac disease, instead, some studies have reported gastrointestinal symptoms when adding oats to GFD (Lundin et al., 2003; Peräaho et al., 2004b), but these symptoms may be caused by rapidly increased intake of fibre (Mälkki., 2004) since several studies have shown that long-term consumption of oats in coeliac disease does not cause gastrointestinal symptoms or complications (Aaltonen et al., 2017; Janatuinen et al., 2002; Kaukinen et al., 2013). Moreover, DH patients not consuming oats at follow-up had more often ongoing dapsone treatment and slightly more frequently skin symptoms than did those not consuming oats, which may indicate that they may have had some dietary lapses. On the other hand, there were no differences in strictness of GFD between those consuming and not consuming oats according to the questionnaire. It is also possible, that those with prolonged skin symptoms symptoms may have stopped eating oats or were not initially willing to start eating oats, because of fear of exacerbating their skin and/or gastrointestinal symptoms.

The findings of this long-term follow-up study support the results of short-term oats challenge studies in DH, in which oats were considered safe, even though some patients, but also controls, were having transient skin symptoms (Hardman et al., 1997; Reunala et al., 1998) (Table 3). Instead, a previous Finnish questionnaire study reported that almost one fifth of DH patients had stopped eating oats because of skin symptoms (Peräaho et al., 2004a). It therefore seems possible that some of the DH patients suffered from transient skin symptoms when initiating consumption of

oats, while it remains unclear whether those skin symptoms are oats related or caused by accidental dietary lapses on GFD or even other skin diseases.

Our study also demonstrated that consumption of oats is associated with improved quality of life in DH. Earlier studies on the quality of life effects of oats in DH are lacking, but in coeliac disease, patients consuming oats have similarly reported somewhat better quality of life and general health than patients not consuming oats. This better quality of life among oats users in DH and coeliac disease may be due to the properties of oats, namely good taste, ease of use, low cost and diversification of GFD, as was reported by the DH and coeliac disease patients in a Finnish questionnaire study (Peräaho et al., 2004a).

3.6.3.2 Mortality

This study, including a large cohort of biopsy-confirmed DH patients with long follow-up, demonstrated that the all-cause mortality risk in DH was lower than in general population. Further, mortality risk in DH was reduced specifically for cerebrovascular and alcohol-related diseases, even though the reported consumption of alcohol did not differ between DH patients and controls. One reason for the slightly discrepant results concerning alcohol consumption and alcohol-related mortality may be selection bias: it is probable that heavy alcohol users with and without DH are less likely to participate in questionnaire studies, whereas mortality was analysed from the whole DH cohort and compared to matched general population thus most likely yielding more reliable results. Conversely, the mortality rate for lymphoproliferative malignancies in DH was significantly increased during the first five years after DH diagnosis, but not thereafter. It was also shown in our present study, as also in another coeliac disease study (Ludvigsson et al., 2009), that mortality rate in DH is irrespective of severity of small bowel damage at diagnosis.

A similarly decreased overall mortality rate in DH was found in a previous study by our group, although the number of patients in that study was smaller and the follow-up time more limited (Viljamaa et al., 2006). A study by Lewis and colleagues (2008) with 846 DH patients from the UK and with a follow-up of 3,496 person-years, demonstrated slightly, but not significantly, decreased mortality compared to general population. Likewise borderline decreased mortality risk was seen in another study from the UK (Swerdlow et al., 1993) investigating 152 DH patients diagnosed 1950-1985 in one hospital and followed up for 5-39 years (Table 4). Moreover, in two studies investigating mortality risk in both DH and coeliac disease (Peters et al., 2003; Viljamaa et al., 2006), the mortality risk in DH was found to be lower than in

coeliac disease, even though in the study by Peters and colleagues, the overall mortality risk in DH was found to be slightly increased (Table 4). Even though DH is one manifestation of coeliac disease, increased overall mortality risk in coeliac disease compared to that in general population has been reported in several studies (Corrao et al., 2001; Holmes and Muirhead, 2018; Ludvigsson et al., 2009; Peters et al., 2003; Rubio-Tapia et al., 2009; Viljamaa et al., 2006; West et al., 2004) (Table 4). Interestingly, there thus seems to be actual difference in the mortality risks between DH and coeliac disease.

In previous studies investigating causes of death in DH, two studies have reported slightly decreased mortality risk from ischaemic heart disease (Swerdlow et al., 1993; Viljamaa et al., 2006)(Table 4). Contrary to that in DH, in coeliac disease, the mortality risk from ischaemic heart disease and cardiovascular disease has been reported to be increased in two studies (Holmes and Muirhead, 2018; Viljamaa et al., 2006) and decreased in one study with screened coeliac disease (Lohi et al., 2009) (Table 4). In our study, mortality risk from ischaemic heart disease was similar to that in general population, but the mortality risk from cerebrovascular disease was, instead, decreased. The main risk factors of cerebrovascular disease are hypertension, diabetes mellitus, hypercholesterolaemia, obesity, smoking and excessive alcohol consumption (Seshadri and Debette, 2016). Two of those, smoking and hypercholesterolaemia, were shown to be less frequent in DH in our study, which may contribute to lower mortality risk from cerebrovascular disease in DH. Additionally, DH patients had lower risk of mortality from alcohol-related diseases, which may indicate less frequent excessive alcohol consumption in DH than in general population, even though alcohol consumption was reported to be at the same level according to the questionnaires in our study. However, although there seem to be no previous studies examining mortality risk specifically from cerebrovascular disease in DH, the risk factors for both cerebrovascular and ischaemic heart diseases are quite similar, reflecting that according to present and previous studies, mortality risk in DH from atherosclerotic diseases seems to be either at the same level as in general population or possibly even lower.

In DH, many studies have reported increased risk for developing NHL (Askling et al., 2002; Collin et al., 1996; Grainge et al., 2012; Leonard et al., 1983; Sigurgeisson et al., 1994). Moreover, the risk for lymphoma in DH is increased, especially in patients not compliant with GFD, and further, GFD seems to have a protective effect against developing NHL after five years of strict adherence (Lewis et al., 1996). This was also shown in our study, since mortality risk for lymphoma was increased during the first five years of follow-up, but not thereafter.

It is hard to find any explanation for the lower mortality risk in DH than in coeliac disease. However, it seems, that inadequate GFD adherence plays a major role in the occurrence of malignant diseases in DH and coeliac diseases, which, may consequently lead to higher mortality rates. Thus, one possible explanation for the lower mortality in DH may be in GFD; while patients with DH usually adhere strictly to DH as our study showed, strictness of GFD in coeliac disease is more variable (Hall et al., 2009), although no differences in adherence to GFD have been reported in Finland (Pasternack et al., 2018). However, compliance with GFD in DH may be better because DH patients usually suffer severe itching and rash quite quickly when consuming gluten, while most patients with coeliac disease seem not to suffer from severe gastrointestinal symptoms after occasional gluten intake (Lähdeaho et al., 2011). Additionally, the variable mortality rates in DH studies may also be due to incomplete adherence to GFD, since in a study by Peters et al. (2003) demonstrating slightly higher mortality rate in DH, data on GFD adherence was lacking. Another explanation for higher mortality rates in coeliac disease could be more severe villous atrophy in coeliac disease leading to more severe systemic inflammation, even though this was not shown in present study. Finally, one explanation may be the more careful follow-up in specialized clinics in DH in Finland due the centralized diagnostics and follow-up requirements of dapsone medication.

3.6.4 Strengths and limitations of the study

The main strength of the present study was the large and prospectively gathered series of DH patients diagnosed in our catchment area, where DH prevalence has been shown to be the highest in the world (Salmi et al., 2011). Moreover, DH diagnosis was clinically and skin-biopsy confirmed in each patient, and the majority of the patients underwent gastroscopy as routine policy at the time of the diagnosis and had biopsy results available from the small bowel. After the diagnosis was confirmed, all the patients were advised by the dermatologist and the dietician to initiate a strict life-long GFD. Further, the patients were carefully followed-up by DH-specialized dermatologist until the symptoms abated and dapsone was no longer needed. Thereafter, follow-up data was collected via structured and also validated questionnaires. In addition, it is of importance that GFD adherence rates have been shown to be high among Finnish DH and coeliac disease patients (Pasternack et al., 2015).

There were also some limitations in the dissertation, such as retrospective study design in all studies. This led to non-systematic collection of laboratory test results, especially before 1990. The follow-up information was mainly based on questionnaires and interviews gathered retrospectively, which may have caused selection or re-call bias. In Study I, DH patients had undergone gastroscopy between 1990 and 2009, and the controls between 2009 and 2011, and since the prevalence of *H. pylori* infection has decreased in Finland in recent decades (Kosunen et al., 1997; Renhnberg-Laiho et al., 2001), this may have had an effect on the results. Additionally, activity of gastritis was not analysed, because it was considered unreliable to do this retrospectively from histological reviews. Moreover, we did not use any serological tests to measure *H. pylori* infection or gastritis. In Study II, a limitation was the lack of healthy controls, however, the prevalence of anaemia in DH was, instead, compared with that in coeliac disease, where the prevalence of anaemia is known to have increased (Balaban et al., 2019; Halfdanarson et al., 2007). Data on iron status, complete blood count and body mass index were unfortunately not available, and thus thorough investigation into the aetiology of anaemia was not possible. In Study III, recruitment of the DH patients via coeliac disease societies may have caused selection bias, however, the two sub-cohorts included in the study were shown not to differ. Additionally, knowledge of the duration of oat consumption in those consuming oats, the reasons for not eating oats and whether some patients previously eating oats had stopped due to symptoms were not available. In Study IV, one limitation could be that while being single-centre study, the results of this study may not be generalized to all DH populations. Another limitation was that health behaviour was studied only in individuals of working-age.

3.7 Conclusions and future prospects

This study showed that the risks for CAG and *H. pylori* infection in patients with DH are increased and that *H. pylori* infection is more prevalent in DH patients with CAG than in those without. Gastritis in DH is located mainly in the corpus and may thus be of autoimmune origin. CAG was shown not to be associated with gastrointestinal symptoms or severity of villous atrophy, and it seemed resistent to GFD treatment. Further studies are needed to ascertain the risk of cancer development in DH patients with CAG. However, this study demonstrated that mortality due to gastric carcinoma is not increased in DH, and therefore, our findings do not contradict the current recommendations not to perform gastroscopy at diagnosis in DH. However,

if gastroscopy is for some reason performed, biopsies should be taken from the stomach in addition to the duodenum.

It was also demonstrated that anaemia is a rather rare finding in DH at diagnosis, and clinical symptoms are not a reliable marker of anaemia in DH. Further studies are needed to evaluate the aetiology of anaemia in DH in more detail. However, recovery from gastrointestinal and skin symptoms in DH is fortunately not poorer in those having anaemia at diagnosis than in those with normal Hb. Anaemia at one year after diagnosis seems mainly to be related to the well-known side effects of dapsone treatment used by those with prolonged skin symptoms.

The present study confirmed an excellent long-term prognosis in DH and strengthened the previous knowledge of high GFD adherence rates in DH. The long-term consumption of oats was shown to be safe and seemed to even decrease gastrointestinal symptoms and to improve quality of life. However, it remains obscure whether there is a small minority of DH patients intolerant of oats, and more research should be directed towards those DH patients who have abandoned oats. In general, there does not seem to be increased morbidity related to treated DH in the long term, as the mortality rate seems to be even lower than in general population. Even mortality risk for lymphoproliferative diseases, well-known complications for DH, was only increased during the first five years after diagnosis, but not in the whole DH cohort. The fundamental reasons for lowered mortality in DH and discrepant mortalities between DH and coeliac disease, different manifestations of the same disease treated with the same GFD, needs to be further scrutinized.

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PUBLICATIONS

PUBLICATION I

Chronic Gastritis in Dermatitis Herpetiformis: A Controlled Study

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Clinical Study

Chronic Gastritis in Dermatitis Herpetiformis: A Controlled Study

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Background and Objective. Previous small studies suggest that chronic atrophic gastritis is common in dermatitis herpetiformis (DH). We here examined the frequency and topography of chronic gastritis in 93 untreated DH subjects and in 186 controls with dyspepsia. *Methods*. Specimens were drawn from the gastric corpus and antrum and examined for atrophy, intestinal metaplasia, and *Helicobacter pylori*. Duodenal biopsies were taken. *Results*. Atrophic corpus gastritis was more frequent in DH than in controls (16.0% and 2.7%, resp., $P < 0.001$); atrophy in the antrum was rare in both groups (3.2% and 1.1%, $P = 0.34$). Intestinal metaplasia was present in 13 (14.0%) DH and 12 (6.5%) control patients ($P = 0.038$) and *H. pylori* in 17 (18.3%) and 17 (9.3%) ($P = 0.028$), respectively. Small-bowel villous atrophy was seen in 76% of the DH patients, equally in patients with and without chronic gastritis. One DH patient with atrophic gastritis developed gastric cancer. *Conclusion*. In DH, chronic atrophic gastritis was common in the corpus, but not in the antrum. *H. pylori* will partly explain this, but corpus atrophy is suggestive of an autoimmune etiology. Atrophic gastritis may increase the risk of gastric cancer. We advocate performing upper endoscopy with sufficient histologic samples in DH.

1. Introduction

The majority of patients with dermatitis herpetiformis (DH) evince small-bowel mucosal damage or inflammation similar to that in classic or early-stage celiac disease [1, 2]. Patients rarely suffer from abdominal symptoms, and irrespective of small-bowel mucosal morphology, the rash in DH responds to a gluten-free diet, the treatment of choice for the condition [3, 4]. Coeliac disease and DH share a similar genetic background and occur frequently in the same families; even identical twins may have different phenotypes [5, 6]. Tissue-type transglutaminase is the major autoantigen in coeliac disease, but an immune response to epidermal transglutaminase is probably essential for the development of DH, although this is not fully proven [7, 8]. Altogether, DH is indisputably an extraintestinal manifestation of coeliac disease.

Again similarly to coeliac disease, autoimmune conditions occur together with DH [9]. Earlier studies indicate that chronic atrophic gastritis (CAG) is common in DH and may be of autoimmune origin, but the data are based on a limited number of patients only [10–12]. *Helicobacter pylori* infection is the main agent causing chronic gastritis [13, 14], but autoimmune gastritis may also occur. *H. pylori* gastritis is often patchy and affects the antral mucosa, whereas autoimmune gastritis occurs typically in the corpus of the stomach.

The Sydney System is a systematic approach to determine the topography, morphology, etiology, and severity of gastritis [15]. It has not previously been applied in DH. Small-intestinal biopsy helps to estimate the severity of villous atrophy but is not necessary for the ultimate diagnosis of DH. Provided that CAG is common in patients with DH, this

Table 1: Gastric findings in the 93 patients with dermatitis herpetiformis (female 40, median age 48 years; range 7–76) and 186 control patients with dyspepsia (female 80, median age 56 years; range 18–86).

	Dermatitis herpetiformis $n = 93$	Control patients $n = 186$	Odds ratio	P-value
Corpus atrophy	15 (16.0%)	5 (2.7%)	6.96 (CI 2.29–25.16)	<0.001
Antrum atrophy	3 (3.2%)	2 (1.1%)	3.07 (CI 0.34–37.16)	0.34
Intestinal metaplasia[1]	13 (14.0%)[2]	12 (6.5%)[3]	2.36 (CI 1.05–5.30)	0.038
Helicobacter pylori[1]	17 (18.3%)	17 (9.1%)	2.22 (CI 1.09–4.54)	0.028

[1]in corpus or antrum.
[2]antrum 8, corpus 8.
[3]antrum 8, corpus 5.

would constitute a further indication for endoscopy. In the present study we examined the occurrence of CAG and *H. pylori*, as classified by the Sydney System, in a large series of DH patients sampled over the past 20 years. The histologic data were compared to those from patients of similar sex and age who were suffering from dyspepsia.

2. Material and Methods

The study was carried out over the period 1990–2009 at the Department of Dermatology, Tampere University Hospital. The cohort comprised 93 patients with DH, from whom biopsy samples had been taken from duodenum and from stomach for the classification of gastritis according to the Sydney System. The diagnosis of DH was based on the typical clinical picture and direct immunofluorescence showing granular IgA deposits in the papillary dermis in the uninvolved skin [16]. Patients' medical records were examined. Duodenal biopsy specimens were graded as subtotal villous atrophy, partial villous atrophy, and normal mucosa. Gastric mucosal atrophy was graded from 0 to 3, grade 0 indicating normal morphology and 3 the most severe involvement, in line with the Sydney System [15]. *H. pylori* was not graded, since a positive finding anywhere in the stomach was considered diagnostic for the infection. The patients with DH were regularly followed up in the special outpatient clinic for 1-2 years [17]. A questionnaire was sent to all DH patients who were alive in 2011, and it included questions on adherence to the gluten-free diet, the use of dapsone, and the occurrence of associated diseases and malignancies.

The control group comprised patients suffering from dyspepsia and undergoing upper gastrointestinal endoscopy at the Regional Hospital of our catchment area in 2009–2011. Two control patients of similar sex and age (±5 years) and no small-bowel mucosal villous atrophy were chosen for each DH case, the final series thus consisting of 186 control subjects.

The statistical differences between DH and control patients and DH patients with and without CAG were calculated by chi-square test or Fisher's exact test when appropriate. Odds ratios were given with 95% confidence intervals.

The study was based on the case records, and permission to read these was obtained. A statement of the Ethical Committee was not considered obligatory.

3. Results

Atrophy of the corpus and intestinal metaplasia were significantly more common in DH than in the control subjects (Table 1). By contrast, there was no significant difference between the groups in the occurrence of antral atrophy, which was altogether a relatively uncommon finding. The mean score for atrophy in the corpus was 1.6 in DH patients and 2.3 in control subjects.

Seven (44%) DH patients with CAG had associated intestinal metaplasia in the body of the stomach and additional two patients in the antrum (Table 2). *H. pylori* infection was significantly more frequent in DH than in controls (18% and 9%, resp., Table 1). One patient (no. 3, Table 2) with pangastritis and intestinal metaplasia in the initial biopsy developed gastric cancer one year later. Forty-four percent of DH patients with CAG showed *H. pylori* in the gastric mucosa, compared to 14% without CAG (Table 3).

Table 3 shows the 16 DH patients with CAG to be older (mean 63 years) than the 78 without (mean 44 years). Small-intestinal villous atrophy was found in 76.6% of patients with DH and was equally common in patients with and without CAG. Thirty percent of patients with DH reported abdominal complaints; again, there was no significant difference between patients with or without CAG (Table 3).

All 16 DH patients with CAG started a gluten-free diet after the diagnosis of DH, nine in addition using daily 25 mg to 50 mg of dapsone to control the rash. All maintained a strict diet and no longer needed dapsone at the end of the followup.

Associated autoimmune diseases were found in three DH patients with CAG; one had hypothyroidism, one pernicious anaemia and Graves' disease, and one vitiligo (Table 2). One DH patient with CAG developed prostate cancer, and two patients had had breast cancer before the diagnosis of DH.

4. Discussion

The frequency of CAG in the corpus was significantly more common in the DH patients than in the control subjects suffering from dyspepsia. No such a difference was seen in the antrum of the stomach. Previously, Primignani et al. [12] conducted a study in 57 Italian patients with DH and found a prevalence of CAG of 30%, compared to 15% in non-DH

Table 2: Gastric and duodenal findings, dapsone, and gluten-free diet (GFD) treatment, and associated diseases and malignancies in 16 dermatitis herpetiformis (DH) patients with chronic atrophic gastritis.

Patient no.	Sex/age (years)	Year of DH diagnosis	Gastric findings			Duodenal histology at diagnosis/on GFD	Associated autoimmune diseases and malignancies
			Corpus atrophy/metaplasia[1]	Antrum atrophy/metaplasia[1]	*Helicobacter pylori*		
1	F/53	1996	1/1	0/0	−	PVA	Breast cancer 1992
2	F/69	1999	1/0	0/0	−	PVA	—
3	M/68	2000	1/2	2/2	−	PVA/N	Gastric cancer 2001
4	M/64	2001	3/2	0/0	−	PVA/N	Hypothyreosis >10 yrs before DH diagnosis Prostate cancer 2010
5	M/61	2001	1/0	0/1	−	N/N	—
6	F/58	2001	1/0	0/0	+	PVA/N	—
7	F/62	2001	2/0	0/0	−	PVA	Breast cancer 1992
8	M/57	2001	1/0	0/0	+	PVA	—
9	M/48	2002	1/0	0/0	+	N	—
10	M/71	2003	2/1	0/0	−	N	Vitiligo 2003
11	F/56	2003	3/1	0/0	−	PVA/N	Pernicious anemia 2004 Graves' disease 2005
12	M/71	2004	2/1	0/2	+	N	—
13	M/76	2006	3/2	0/1	−	N	—
14	F/74	2007	1/0	1/0	+	PVA	—
15	F/63	2007	1/0	0/0	+	SVA	—
16	M/69	2008	0/0	2/2	+	SVA	—

SVA: subtotal villous atrophy, PVA: partial villous atrophy, N: normal mucosa at diagnosis and on a gluten-free diet (GFD).
[1]score 0–3 according to the Sydney System.

Table 3: Data on 94 patients with dermatitis herpetiformis. Comparison between cases with and without chronic atrophic gastritis (CAG).

	DH patients with CAG $n = 16$	DH patients without CAG $n = 78$	P-value
Mean age at diagnosis years (range)	63.0 (47–76)	43.9 (7–76)	
Men	9 (56.3%)	45 (57.7%)	
Duodenal histology			
(i) partial or subtotal villous atrophy	11 (68.8%)	61 (78.2%)	0.52
(ii) normal mucosa	5 (31.2%)[1]	17 (21.8%)	
Helicobacter pylori	7 (44.0%)	11 (14.1%)	0.012
Abdominal complaints	5 (31.2%)	23 (40.4%)[1]	0.36

DH: dermatitis herpetiformis.
[1]Data available on 57 patients.

control subjects with dyspepsia ($P < 0.05$). Patients with DH do not usually suffer from dyspepsia, and therefore the control group was not analogous to the study group. Storskrubb et al. [18] carried out esophago-gastroduodenoscopy at random for 1000 Swedish adults. The overall frequency of corpus atrophy was 5% and antrum atrophy 2%. Our data thus indicate that atrophic corpus gastritis is more common in patients with DH than in the population in general.

H. pylori infection is common in CAG [13, 14, 19]. In line with this, the present DH patients with CAG had *H. pylori* significantly more often than those without CAG. This may be partly explained by the age difference; *H. pylori* is more common in older people, and our patients with GAG were older that those without (Table 3). However, the presence of *H. pylori* in all DH patients (18.3%) was significantly higher than among dyspeptic control subjects with a similar age distribution (9.1%, Table 1). By comparison, Crabtree et al. [20] examined 58 DH patients in Britain and by serological methods found *H. pylori* IgG antibodies in 63% of patients, this frequency being however only slightly higher than in other dermatological patients.

There are some limitations to the present study. It was based on the case records, and it was not possible to re-read the biopsy samples. Nevertheless, we considered that the activity of gastritis, as defined by the Sydney System, [15] would have been unreliable to analyze here. Circulating parietal cell and intrinsic factor antibodies could not be determined. Our DH patients were recruited during the years 1990–2009, whereas the controls were enrolled later, in 2009–2011. This may have affected the results in that during the last decades, the prevalence of *H. pylori* has decreased in Finland and elsewhere [21]. However, all but two DH patients with CAG and also patients with *H. pylori* were diagnosed in 2000–2009.

Previous studies have shown that patients with DH similar to those with celiac disease frequently have associated autoimmune conditions such as thyroid diseases and insulin-dependent diabetes mellitus [9, 22, 23]. In the present study two DH patients with CAG had thyroid disease, one of them also pernicious anemia and one patient vitiligo. Due to the limitations of the study, we cannot be sure whether the CAG in the present DH patients was of autoimmune origin. However, this is quite possible judging from the topography of CAG, that is antrum-sparing gastritis [15], and the overall autoimmune nature of DH [23].

CAG is known to be associated with an increased risk of gastric cancers, which seems to decrease after eradication of *H. pylori* [24, 25]. One of our DH patients with CAG developed gastric cancer one year after the diagnosis of DH. Prior to this, he had shown pangastric atrophy and moderate intestinal metaplasia without *H. pylori* infection. The patient had adhered strictly to a gluten-free diet since the diagnosis; the small-bowel mucosa showed no atrophy, and the rash was controlled without dapsone. Similarly, the small-bowel mucosa and the rash in the other DH patients with CAG responded well to GFD treatment. In contrast, CAG persisted in all 4 patients subjected to control biopsies, indicating that CAG in DH does not respond to gluten withdrawal, as also previously documented [26, 27]. Patients with DH run an increased risk of lymphoma [28, 29], but previous large DH studies have not shown any increased risk of gastric or other cancers [28, 30]. Whether persisting CAG in DH involves a risk of gastric cancer is a possibility which should be examined in further studies.

5. Conclusion

The present controlled study showed that patients with DH have at the time of the diagnosis a significantly increased frequency of CAG in the corpus but not in the antrum. In addition to *H. pylori* infection, autoimmune mechanisms may be implicated in the development of gastritis. The DH patients here did not present with any specific gastrointestinal symptoms. One DH patient with CAG developed gastric cancer. In untreated DH we recommend upper gastrointestinal endoscopy, upon which biopsy specimens should be taken not only from the duodenum but also from the gastric corpus and antrum.

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PUBLICATION II

Anaemia in dermatitis herpetiformis: Prevalence and associated factors at diagnosis and one-year follow-up

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CLINICAL REPORT

Anaemia in Dermatitis Herpetiformis: Prevalence and Associated Factors at Diagnosis and One-year Follow-up

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Dermatitis herpetiformis is a cutaneous manifestation of coeliac disease. Anaemia is a common finding in patients with untreated coeliac disease, but little is known about the occurrence of anaemia in those with dermatitis herpetiformis. This study investigated the prevalence of anaemia and factors associated with anaemia in 250 patients with dermatitis herpetiformis, at diagnosis and one year after diagnosis. As controls, 139 patients with coeliac disease were included. Patient records were reviewed to gather baseline clinical, histological, and laboratory data. Follow-up data for patients with dermatitis herpetiformis were collected from patient records and via questionnaires or at follow-up visits. The prevalence of anaemia was 12% in patients with dermatitis herpetiformis and 17% in patients with coeliac disease at diagnosis ($p = 0.257$). Anaemia in patients with dermatitis herpetiformis was not associated with the severity of skin symptoms or small bowel damage. The prevalence of anaemia at a 1-year follow-up had increased to 19%, but it was associated mainly with dapsone treatment.

Key words: coeliac disease; dapsone; gluten-free diet; villous atrophy.

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SIGNIFICANCE

Dermatitis herpetiformis is a cutaneous manifestation of coeliac disease. Anaemia is a relatively common finding in patients with untreated coeliac disease, but little is known about the prevalence of anaemia in patients with dermatitis herpetiformis. This study showed that the prevalence of anaemia at diagnosis did not differ significantly between 250 patients with dermatitis herpetiformis and 139 patients with coeliac disease. Anaemia at diagnosis in dermatitis herpetiformis was not associated with the severity of skin symptoms or small bowel damage. The prevalence of anaemia at a 1-year follow-up had increased slightly, but it was associated mainly with dapsone treatment, which is generally known to have potential haematological side-effects.

Dermatitis herpetiformis (DH) is a blistering and itching skin disease and a cutaneous manifestation of coeliac disease (1). In DH and coeliac disease, digested gluten provokes a wide spectrum of clinical symptoms in genetically susceptible individuals (2). Although patients with DH rarely develop prominent gastrointestinal symptoms, three-quarters of them have a variable degree of small bowel mucosal villous atrophy (3, 4), and those with normal villous architecture evince intestinal coeliac-type inflammation (5, 6). Furthermore, characteristic of both DH and coeliac disease, is an autoantibody response targeted against tissue transglutaminase (TG2) (7, 8). A pathognomonic feature of DH, however, is the presence of granular IgA deposits in the dermis, directed against epidermal transglutaminase (TG3) (9).

Strict lifelong adherence to a gluten-free diet (GFD) is an effective treatment for DH and coeliac disease. The diet alleviates the gastrointestinal and, also eventually, cutaneous symptoms, and results in normalization of the small bowel mucosal architecture (10, 11). In addition, dapsone medication is initiated for most patients with DH to quickly alleviate the troublesome skin symptoms (12).

The clinical picture of coeliac disease has changed over time, and the frequency of classical coeliac disease symptoms, such as chronic diarrhoea and weight loss, has decreased, while, concomitantly, non-classical manifestations have become more common (13). Anaemia is one of the most common presentations of coeliac disease (13, 14), occurring even as the only manifestation of an otherwise silent coeliac disease (15). In studies performed in Western countries, the prevalence of anaemia among people with untreated coeliac disease is in the region of 20–30% (16–19). Iron deficiency anaemia seems to be the most common form of anaemia in coeliac disease, but vitamin B_{12} and folate deficiencies, as well as anaemia of chronic disease, also occur (17, 20). The main, but not the sole, mechanism for anaemia in coeliac disease is thought to be malabsorption caused by the damaged small bowel mucosa (14, 17, 20), and in the majority of studies, anaemia has been associated with more severe villous atrophy and higher autoantibody levels at diagnosis (18, 19, 21, 22).

There is scant knowledge regarding anaemia in patients with DH. A few earlier studies have shown that the prevalence of anaemia may be as high as 42% among patients with treated DH (23, 24). However, even though it is frequently used in the initial treatment in addition to a GFD, dapsone has a well-known adverse effect of dose-

dependent haemolysis (25). To our knowledge, only one study has investigated the frequency of anaemia among patients with untreated DH, finding the prevalence of anaemia to be 23% (26).

The aim of the current study was to examine the prevalence of anaemia in a large well-defined cohort of patients with untreated DH and to compare it to anaemia in patients with coeliac disease. A further aim was to identify the factors associated with anaemia at diagnosis of DH and after adherence for one year to dapsone and/or GFD treatment.

MATERIALS AND METHODS

Patients and controls

This study included 250 adult patients with DH (≥18 years of age) with an available blood haemoglobin (Hb) value investigated at the time of diagnosis of DH. The patients had been diagnosed in 1970–2019 at a special outpatient clinic for patients with DH at the Department of Dermatology, Tampere University Hospital, Tampere, Finland, and for each patient, the diagnosis of DH was based on the typical clinical picture and the demonstration of dermal granular IgA deposits in perilesional skin immunofluorescence biopsies. After diagnosis, all patients were routinely referred to undergo gastroscopy with small bowel biopsies, and were further advised to adhere to a strict, lifelong GFD.

Dapsone medication was initiated, according to routine practice, for patients with DH who had severe skin symptoms. All patients were followed-up at a special DH outpatient clinic until the DH rash had resolved and the dapsone medication could be discontinued.

As a control group, 139 patients with coeliac disease diagnosed at ≥18 years of age and with an available diagnostic Hb value were included. All patients had a small bowel biopsy-confirmed diagnosis of coeliac disease performed at Tampere University Hospital during the same time period as the patients with DH, and all were considered to have the classical presentation of coeliac disease.

Study protocol

The medical records of all participating patients with DH and with coeliac disease, from the time of the diagnosis, were reviewed. Data on demographic characteristics, presence of gastrointestinal symptoms, small bowel mucosal findings, serum coeliac autoantibody tests, and Hb levels were gathered. The small bowel mucosal histology was interpreted by an experienced pathologist, and the result was graded as subtotal or total villous atrophy, partial villous atrophy, or normal mucosa, as described previously (3). The serum IgA class coeliac disease autoantibody tests were anti-reticulin antibody (ARA), endomysium antibody (EmA), or TG2 antibody tests, depending on the time of testing.

In addition, data on the duration of skin symptoms before diagnosis, severity of skin symptoms at diagnosis, initiation of dapsone treatment, and levels of serum vitamin B_{12} or transcobalamin II-bound vitamin B_{12} (B12-TC2), as well as erythrocyte folate (E-folate) or serum folate (S-folate) were collected from the medical records of all study patients with DH. Serum ferritin and transferrin receptor test results were also recorded, but since they are only sparsely investigated in DH, their availability from medical records was very low, and these parameters were excluded from further analysis. The skin symptoms were graded as mild, moderate, or severe by a dermatologist, and the grading was based on the presence of a few, several, or many blisters, macular eruptions, and erosions on the knees, elbows, buttocks, scalp, or elsewhere on the body

For patients with DH, the 1-year follow-up data on the positivity of serum coeliac autoantibody tests and Hb levels were recorded from the patient records. Follow-up data on the duration of skin and gastrointestinal symptoms, as well as the duration of dapsone treatment, were gathered from DH-specific questionnaires sent to all patients with DH diagnosed between 1970 and 2014, as described previously (27), and from the remainder at follow-up visits to the DH outpatient clinic. The DH-specific questionnaire included both open and multiple-choice questions, and even though it is not validated, it has been used previously in several studies on DH (27, 28). The duration of skin symptoms after diagnosis was further classified into 3 groups: less than one year, 1–2 years, and longer than 2 years. For those receiving dapsone after diagnosis, the duration of dapsone treatment was interpreted as the duration of skin symptoms, since dapsone is routinely discontinued as soon as the skin symptoms are controlled with a GFD alone. For those not using dapsone, the duration of skin symptoms was recorded from the questionnaire. Moreover, the duration of gastrointestinal symptoms after diagnosis was classified as: no symptoms, less than 3 months, 3–12 months, and over 12 months.

The Regional Ethics Committee of Tampere University approved the study protocol and usage of the register-based data. All subjects provided written informed consent.

Laboratory parameters

The following laboratory values were measured by standard laboratory methods: blood Hb (reference values: 117–155 g/l for women and 134–167g/l for men), serum vitamin B_{12} or B12-TC2 (reference values 145–570 pmol/l and >35 pmol/l, respectively) and E- or S-folate (reference values 1,187–2,854 nmol/l and 8.8–42.4 nmol/l, respectively).

In the ARA and EmA tests, titres 1:≥5 were considered positive. In the TG2 antibody tests, the reference value was 20 or 5 U/ml, depending on whether an INOVA (INOVA Diagnostics, San Diego, CA, USA) or Celikey (Celikey Pharmacia, Uppsala, Sweden) test was used. The ARA, EmA, and TG2 antibody tests are all directed against TG2 (29), and in this study, a positive result in any of these tests was interpreted as positive coeliac disease serology.

Statistical analysis

The patients with DH were divided into 2 groups based on whether they had anaemia or normal Hb, according to the reference values at the time of the diagnosis or at the 1-year follow-up. A change in Hb value ≥10 g/l during the first year of treatment was considered clinically relevant, and patients with DH were divided into 3 groups depending whether the Hb value had decreased, remained constant, or increased during the first year of treatment according to the clinically relevant criteria. Categorical variables were presented as numbers and percentages, and continuous variables as medians with quartiles (Q_1–Q_3) or ranges (min–max), as the majority of the data were skewed. A χ^2 test or Fisher's exact test was used in cross-tabulations, and the Mann–Whitney *U* test or Kruskal–Wallis H test was used for comparing continuous variables. All statistical analyses were performed using SPSS version 26. Statistical significance was set at $p<0.05$ and testing was two-sided.

RESULTS

At the time of diagnosis

The median age of the 250 patients with DH at diagnosis was 44 years (range 18–84 years) (**Table I**). Compared with the controls with coeliac disease, the patients with DH were more often male, and, in DH, the serum coeliac

Table I. Demographic, clinical, and histological data and laboratory values of 250 patients with dermatitis herpetiformis (DH) and 139 control patients with coeliac disease (CD) at the time of diagnosis

	Patients with DH $n=250$		Patients with CD $n=139$		
	n/median	%/ Q_1–Q_3	*n*/median	%/ Q_1–Q_3	*p*-value
Females	120	48	107	77	<0.001
Age, years	44	32–59	40	32–52	0.057
Anaemia[a]	31	12	23	17	0.257
Haemoglobin, g/l	138	129–147	130	122–143	<0.001
Females	131	123–137	128	120–136	0.089
Males	146	138–153	146	140–153	0.738
Positive coeliac serology[b]	142/222	64	92/111	83	<0.001
Gastrointestinal symptoms	97/201	48	128/133	96	<0.001

[a]Blood haemoglobin value <117 g/l for females and <134 g/l for males. [b]IgA-class anti-reticulin, endomysium, or tissue transglutaminase antibody test.
Q_1–Q_3=quartiles.

autoantibodies were significantly less often positive at diagnosis. The prevalence of anaemia at diagnosis was 12% among the patients with DH and 17% among the patients with coeliac disease; however, the difference was not statistically significant ($p=0.257$). Median Hb values at diagnosis were similar between male and female patients with DH and those with coeliac disease. At diagnosis, 7% (7/100) of the patients with DH with available data had vitamin B_{12} deficiency and 73% (55/75) had folate deficiency.

When patients with DH with anaemia and those without anaemia at the time of the diagnosis were compared, patients with normal Hb more frequently had gastrointestinal symptoms at diagnosis (52% vs 18%, $p=0.003$), and they also reported a statistically significantly longer duration of gastrointestinal symptoms after diagnosis compared with patients with DH with anaemia ($p=0.004$) (**Table II**). Age, sex, severity and duration of skin symptoms before or after diagnosis, small bowel histology, and coeliac seropositivity at diagnosis did not differ between patients with DH with and without anaemia. In addition, the prevalence of vitamin B_{12} and folate deficiencies were similar between patients with and without anaemia.

Among the patients with DH, anaemia was slightly more common in males compared with females, but the difference was not statistically significant (15% vs 9%, $p=0.136$). Male patients with DH more frequently had severe skin symptoms at diagnosis compared with females (38% vs 25%, $p=0.022$), and males also needed dapsone treatment more often than females did (84% vs 68%, $p=0.004$). The presence of villous atrophy did not differ between male and female patients with DH (74% vs 73%, $p=0.924$).

Table II. Demographic, clinical, histological, and serological data of 31 patients with dermatitis herpetiformis (DH) with anaemia[a] and 219 patients with DH with normal blood haemoglobin (Hb) values at the time of diagnosis

	Patients with DH with anaemia $n=31$ (12%)		Patients with DH with normal Hb $n=219$ (88%)		
	n/median	%/Q_1–Q_3	*n*/median	%/Q_1–Q_3	*p*-value
At diagnosis					
Females	11	35	109	50	0.136
Age, years	46	32–64	43	32–58	0.528
Duration of skin symptoms, months	17	6–60	11	5–36	0.185
Severity of skin symptoms[b]					0.680
Mild	4 /27	15	38/206	18	
Moderate	16/27	59	101/206	49	
Severe	7/27	26	67/206	33	
Dapsone initiated	23/30	77	158/209	76	0.898
Small bowel histology					0.945
Normal	8/31	26	56/215	26	
Partial villous atrophy	12/31	39	77/215	36	
Subtotal or total villous atrophy	11/31	35	82/215	38	
Gastrointestinal symptoms	4/22	18	93/179	52	0.003
Positive coeliac serology[c]	17/27	63	125/195	64	0.908
Vitamin B_{12} deficiency[d]	2/13	15	5/87	6	0.073
Folate deficiency[e]	5/10	50	50/65	77	0.084
After diagnosis					
Dapsone treatment at 1-year follow-up	16/20	80	53/100	53	0.026
Duration of skin symptoms					0.368
<1 years	3/16	19	52/143	36	
1–2 years	6/16	38	44/143	31	
>2 years	7/16	44	47/143	33	
Duration of gastrointestinal symptoms					0.004
No symptoms	12/12	100	37/86	43	
< 3 months	0		18/86	21	
3–12 months	0		17/86	20	
>12 months	0		14/86	16	
Positive coeliac serology[e] at 1-year follow-up	8/18	44	19/75	25	0.109

[a]Blood Hb value <117 g/l for females and <134 g/l for males at diagnosis. [b]Graded according to the presence of a few, several, or many blisters, macular eruptions, and erosions. [c]IgA-class anti-reticulin, endomysium, or tissue transglutaminase antibody test. [d]Serum vitamin B_{12} value <145 pmol/l or transcobalamin II-bound vitamin B_{12} value <35 pmol/l. [e]Erythrocyte folate value <1,187 nmol/l or serum folate value <8.8 nmol/l.
Q_1–Q_3 = quartiles.

At time of follow-up

Of all patients with DH, 78% had adopted a GFD and 58% were on dapsone treatment at the 1-year follow-up. The prevalence of anaemia was 19% among 160 patients with DH, and in the patients with DH adhering to GFD and with available data ($n=76$), the prevalence was higher among those using dapsone compared with those not using dapsone (28% vs 0%, $p=0.001$). Also, anaemia prevalence was higher in males with DH compared with females with DH (25% vs 14%), although the difference did not reach statistical significance ($p=0.085$). The median Hb value in males with DH had decreased significantly, from 146 to 141 g/l (Q_1–Q_3 = 135–149, $p<0.001$) and in females non-significantly, from 131 to 128 g/l (Q_1–Q_3 = 121–137, $p=0.490$).

Patients with DH who had anaemia at the 1-year follow-up more frequently had ongoing dapsone treatment compared with those with normal levels of Hb (80% vs 53%, $p=0.026$), and dapsone was more often used among males than females (66% vs 47%, $p=0.015$). In addition, patients with DH who had anaemia at follow-up had a significantly ($p=0.006$) longer duration of skin symptoms after diagnosis than those without anaemia (>2 years, 65% vs 28%), but the duration of skin symptoms did not differ between the sexes. Otherwise, statistically significant differences were not detected between patients with DH with normal Hb and with anaemia at the follow-up in terms of age, adherence to GFD, duration or severity of skin symptoms at diagnosis, presence or duration of gastrointestinal symptoms before or after diagnosis, small bowel histology at diagnosis, and positivity of coeliac serology, either at diagnosis or at 1-year follow-up.

When patients with DH were further divided into 3 groups depending on whether the Hb had decreased, remained constant, or increased at the 1-year follow-up compared with the Hb level at diagnosis, 16% of the patients had decreased, 76% constant, and 8% increased Hb levels. Those with decreased Hb levels at follow-up had the highest median Hb levels at diagnosis (135 g/l in females and 155 g/l in males; $p<0.001$) and those who had increased Hb at follow-up the lowest (median values at diagnosis 117 g/l in females and 125 g/l in males; $p=0.001$ in both sexes). Patients with DH whose Hb had decreased during follow-up, had a longer duration of skin symptoms after diagnosis ($p=0.005$) and also used dapsone more frequently at the 1-year follow-up compared with those with constant or increased Hb ($p=0.015$) at follow-up, but no other significant differences were detected between the groups in demographic or clinical data, positivity of coeliac serology at diagnosis or follow-up, or bowel histology at diagnosis.

DISCUSSION

This study established that anaemia is a rather infrequent finding in untreated DH; only 12% of patients had anaemia at diagnosis. The presence of anaemia was not associated with the severity of skin symptoms or degree of small bowel villous atrophy. Although the prevalence of anaemia was slightly higher, at 17%, in untreated coeliac disease, in which small bowel damage is known to be more severe than in DH, the difference did not reach statistical significance in the current study. A relevant finding was that clinical recovery was equal in patients with DH with and without anaemia when diagnosed, as the duration of skin symptoms was similar and gastrointestinal symptoms alleviated even more rapidly among those with anaemia at diagnosis. At the 1-year follow up, the prevalence of anaemia had increased to 19%, but this appeared to be associated mainly with prolonged skin symptoms and ongoing medication with dapsone.

The prevalence of anaemia at diagnosis in the current study was lower than that in the only previously performed study, which investigated 65 patients with untreated DH in India and reported a 23% prevalence of anaemia (26). In patients with coeliac disease, in which anaemia has been far more extensively studied than in DH, the prevalence of anaemia in untreated coeliac disease has been reported to be slightly higher (23–40%) in European studies (16, 19, 22, 30) compared with the current study. However, the prevalence of anaemia in patients with coeliac disease has been reported to be as high as 93% in India (20), and thus the prevalence of anaemia appears to be highly dependent on geographical location. Different geographical locations could therefore offer a possible explanation for the lower prevalence of anaemia in the current study compared with the previous Indian study of DH (26).

The current study also analysed the factors associated with anaemia at diagnosis of DH, and found that anaemia was not associated with the severity of skin symptoms and, rather surprisingly, that the patients without anaemia had gastrointestinal symptoms more frequently than those with anaemia. The results of previous studies of coeliac disease are conflicting regarding the association of anaemia and gastrointestinal symptoms (19, 31, 32), and current evidence thus suggests that clinical symptoms are not reliable markers of anaemia in coeliac disease or DH. In addition, in the current study, small bowel mucosal damage, or the presence of serum coeliac autoantibodies was also not associated with anaemia. In coeliac disease, some studies have shown an association between anaemia and more severe villous atrophy and higher levels of serum TG2-antibody (18, 21, 22), whereas the opposite results also exist (33) in line with the current study of DH. This supports the suggestion that the aetiology of anaemia in coeliac disease and DH is multifactorial; even though malabsorption of nutrients due to small bowel damage exists, other aetiologies also contribute (17, 34). The multifactorial aetiology of anaemia is also suggested in the current study, as the majority of the patients with available results were

shown to have vitamin B_{12} or folate deficiencies. This is a rather surprising finding, as vitamin B_{12} and folate deficiencies are known to be quite rare in coeliac disease; instead, iron deficiency is a much more common finding. The high prevalence of vitamin B_{12} or folate deficiencies in the current study may be due to selection bias, since vitamin B_{12} and folate values were not routinely tested in DH, but only in cases with a high pre-test likelihood of low values. Also, in the current study, we were unable to investigate iron parameters.

In the current study, the prevalence of anaemia at the 1-year follow-up, when most patients adhered to a GFD, was slightly higher than that in untreated DH. One obvious reason for this is dapsone medication, since 58% of the patients with DH used this drug at the 1-year follow-up, and a well-known side-effect of dapsone is dose-dependent haemolysis and anaemia (25). This is further supported by the facts that decreasing Hb values were significantly associated with the longer duration of skin symptoms after diagnosis and ongoing dapsone treatment, and anaemia prevalence was significantly higher among GFD-treated patients with DH using dapsone compared with those not using dapsone. In addition, males had lower Hb values and males also used dapsone more frequently than did females at 1-year follow-up. There are scant previous studies of the occurrence of anaemia in patients with treated DH. In a study by Fry et al. (23) 5 out of 12 patients with DH undergoing dapsone treatment had anaemia. In another study from the UK (24), 86 patients with DH were investigated, of which 73% were on a GFD and 45% were on dapsone or sulphapyridine treatments. In that study, the total prevalence of anaemia was not reported, but 8 patients (8%) had macrocytic anaemia and, in 6 of these, the cause was probably dapsone treatment. One explanation for the rather low prevalence (19%) of anaemia among patients with treated DH in the current study may be the good adherence to a GFD in Finland. Even though the adherence to a GFD in the current study was relatively low (78%) at the 1-year follow-up, we have previously shown that, in Finland, in the long-term, 98% of our patients with DH adhere to a GFD (35). An additional explanation could be the recommendations for moderate dosage of dapsone in Finland. Dapsone is initiated in the majority of patients with DH (35) as a 25–50 mg daily dose, and it is increased up to 100 mg only if necessary.

Study strengths and limitations

The main strengths of the current study were the large, prospectively gathered, and carefully followed-up, series of patients with DH with a skin immunofluorescence biopsy-proven diagnosis and histologically confirmed coeliac disease control group. An additional strength was the availability of clinical, serological, and small bowel histological data for most patients with DH. Moreover, the study was performed in an area with a high prevalence of DH (36) and excellent GFD adherence rates (35). A limitation was that the study did not include healthy controls, and, in the follow-up, some information was based on questionnaires gathered retrospectively, which may have caused selection or recall bias. In addition, where was insufficient information on the weight, height, or iron status of the patients, and thus the current study was unable to thoroughly investigate the malabsorption status of the study patients. Furthermore, the dapsone doses were not counted.

Conclusion

This study found that the prevalence of anaemia in untreated DH was rather low, at only 12%. The presence of anaemia was not associated with the severity of skin symptoms or villous atrophy at diagnosis, and it did not significantly differ between patients with DH and those with classical coeliac disease. Furthermore, the prevalence of anaemia in the dapsone and/or GFD-treated patients with DH increased to 19% at the 1-year follow-up. Decreased levels of Hb seemed to be confined mostly to those patients with DH who had ongoing skin symptoms and dapsone treatment.

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PUBLICATION III

Long-term safety and quality of life effects of oats in dermatitis herpetiformis

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The Long-Term Safety and Quality of Life Effects of Oats in Dermatitis Herpetiformis

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Abstract: The treatment of choice for dermatitis herpetiformis (DH), a cutaneous manifestation of coeliac disease, is a life-long gluten-free diet (GFD). In a GFD, wheat, rye and barley should be strictly avoided, but the role of oats is more controversial. This study aimed to investigate the safety and long-term quality of life and health effects of oat consumption in 312 long-term treated DH patients. Baseline data were gathered from patient records and follow-up data from questionnaires or interviews, and validated questionnaires were used to assess quality of life. We found that altogether 256 patients (82%) were consuming oats as part of their GFD at the follow-up. Long-term follow-up data showed that there were no differences in the presence of long-term illnesses, coeliac disease complications or the usage of medication between those consuming and not consuming oats. However, oat consumers had a better quality of life and reported ongoing gastrointestinal symptoms less frequently (4% vs 19%, $p = 0.004$) at the follow-up than those not consuming oats. The study established that oats are safe for DH patients and in the long-term seem to improve the quality of life of DH patients.

Keywords: dermatitis herpetiformis; coeliac disease; gluten-free diet; oats; quality of life; complications; follow-up

1. Introduction

Dermatitis herpetiformis (DH), a blistering and itching autoimmune skin disease, is considered a cutaneous manifestation of coeliac disease [1]. In DH and coeliac disease, the disorder is induced by gluten in genetically susceptible individuals. Although patients with DH infrequently suffer from prominent gastrointestinal symptoms, the majority of them have classical coeliac-type villous atrophy in the small intestine at diagnosis [2,3]. Moreover, targeted antibody response in the serum to tissue transglutaminase (TG2) is characteristic of both coeliac disease and DH [4,5]. Pathognomonic for DH, however, is the presence of granular IgA deposits in the dermis targeted against epidermal transglutaminase (TG3), not TG2 [6].

The treatment of choice for DH and coeliac disease is a lifelong gluten-free diet (GFD). Strict adherence to a GFD eventually leads to the disappearance of clinical symptoms and improvement of the small-intestinal villous architecture [7–10], as well as the normalisation of serum TG2 antibodies [11,12]. Additional advantages of a GFD include a decreased risk for lymphoproliferative malignancies [13,14] and bone fractures [15], and increased quality of life [16,17].

There are, however, some disadvantages to a GFD, as it is restrictive and expensive to maintain [18], and it may lead to suboptimal nutrition, such as high sugar and low fibre and mineral intake [19]. There is also some confusion about the contents of the GFD recommended to coeliac disease and DH patients. Generally, there is worldwide consensus on the toxicity of wheat, rye and barley in coeliac disease and DH. However, the role of oats—which have a different storage protein composition from wheat, rye and barley—in a GFD remains controversial [20]. In coeliac disease, the majority of performed studies with short- and long-term follow-ups have demonstrated that the consumption of oats is safe [21–24]. However, gastrointestinal symptoms, intestinal inflammation and even small-intestinal villous atrophy have also been associated with an oat-containing GFD in coeliac disease [25–27]. Moreover, only scarce knowledge exists concerning the safety of oat consumption in DH. According to previously performed DH oat challenge studies with a follow-up of up to six months, oats seem to be safe for DH patients [28,29]. However, the long-term safety of oat consumption in DH remains uncertain, and further evidence is called for especially since oats are an essential source of vitamins, minerals, soluble fibre and polyunsaturated fatty acids. Moreover, oats are known to have multiple health advantages, such as positive effects on blood glucose and cholesterol levels and the maintenance of normal body weight and blood pressure [30,31]. Importantly, in coeliac disease and DH, the consumption of oats diversifies the diet of the patients [32].

In Finland, uncontaminated oats have been accepted as a constituent of a GFD for more than two decades [32], and nowadays products containing uncontaminated oats are widely available in grocery stores. Furthermore, DH prevalence and DH patients' adherence to a GFD are known to be exceptionally high in Finland [33,34]. This offered us an excellent opportunity to evaluate for the first time the long-term safety and quality of life effects of oat consumption in DH.

2. Materials and Methods

2.1. Patients and Study Design

The study comprised 312 DH patients, who were gathered from two different cohorts: 224 patients were collected in 2016 from DH patients diagnosed at the Department of Dermatology, Tampere University Hospital between 1970 and 2014 (cohort 1); and the remaining 88 DH patients were recruited between 2006 and 2010 by a nationwide search via a newspaper advertisement and with the help of national and local coeliac disease societies (cohort 2).

For each patient, the DH diagnosis was based on the typical clinical picture and the demonstration of granular IgA deposits in the papillary dermis with direct immunofluorescence examination. After the diagnosis, all DH patients were routinely recommended to undergo gastroscopy with small bowel biopsies. After the gastroscopy, patients were advised to adhere to a strict, life-long GFD by a dermatologist, and dietary advice was given by a dietician. In those patients with severe skin symptoms, dapsone medication was also initiated.

DH patients diagnosed at any age were included in the study and serological response to GFD was evident in all 79 DH patients with available follow-up data. Five DH patients not adherent to a GFD, one patient without follow-up data on oat consumption, and seven patients without biopsy proven DH diagnosis were excluded from the final analysis. In addition, 11 patients were excluded from cohort 2 as they were already included in cohort 1.

Follow-up data from cohort 1 study patients were gathered using a special study questionnaire designed for DH patients [35] and from cohort 2 study patients via interviews conducted by an experienced physician or study nurse.

The Regional Ethics Committee of Tampere University approved the study protocol and usage of register-based data. All subjects gave their written informed consent.

2.2. Clinical and Dietary Information

Data on demographic characteristics, the presence and severity of DH- and coeliac disease-related clinical symptoms, small bowel mucosal findings and the results of serum coeliac autoantibodies at diagnosis were gathered from the patient records. The small bowel mucosal histological analysis, interpreted by an experienced pathologist, was available from 243 patients, and the result was graded as subtotal or total villous atrophy, partial villous atrophy or normal mucosa, as previously described [2]. The serum coeliac disease autoantibody tests used were reticulin antibody (ARA), endomysium antibody (EmA) or TG2 antibody tests, depending on the time of the testing. In the ARA and EmA tests, titers 1:≥5 were considered positive, and in the TG2 antibody tests, the reference value was 20 or 5, depending on whether an INOVA (INOVA Diagnostics, San Diego, CA, USA) or Celikey (Celikey Pharmacia, Uppsala, Sweden) test was used. The ARA, EmA and TG2 antibody tests are all directed against TG2 [36], and they are collectively referred to as serum coeliac autoantibodies in this article. Data on the duration and severity of skin symptoms at diagnosis and initiation of dapsone were only gathered from cohort 1 patients. The skin symptoms were graded as mild, moderate or severe by one dermatologist, and the grading was based on the presence of a few, several or many blisters, macular eruptions and erosions.

At the follow-up, data on oat consumption and the duration, adherence and possible lapses of the GFD were gathered. GFD adherence was interpreted as no dietary lapses, dietary lapses less than once a month or dietary lapses once a month or more often. Data on chronic illnesses, coeliac disease complications, and the family history of coeliac disease or DH were recorded at the follow-up. Further, previous bone fractures and malignancies were recorded, but excessive trauma fractures and non-melanoma skin cancers were excluded from further analysis. Specific questions about the frequency of oat consumption (classified as twice a week or more often, less than two times a week or no use), the presence of ongoing skin and gastrointestinal symptoms, the current usage of dapsone and other physician-prescribed and over-the-counter (OTC) medications, physical exercise, smoking, number of children born and current weight and height were asked in the study questionnaire gathered from cohort 1 patients diagnosed, but not recorded during the study interviews of cohort 2 patients.

2.3. Questionnaires

The study questionnaire and interviews used in the current study were structured and included multiple choice and open questions designed by physicians with expertise in coeliac disease and DH. In addition, all participants filled the validated gastrointestinal symptom and quality of life questionnaires (see below in more detail).

Validated Questionnaires

The presence of gastrointestinal symptoms and quality of life at the time of the follow-up were gathered with the Gastrointestinal Symptom Rating Scale (GSRS) [37], Psychological General Well-Being (PGWB) [38] and Dermatologic Life Quality Index (DLQI) [39] questionnaires. GSRS and PGWB are validated questionnaires that have been broadly used in previous coeliac disease studies [21,25,40]. DLQI is a validated questionnaire commonly used to assess quality of life associated with any type of dermatological disease [41].

GSRS is a 15-item questionnaire that evaluates the severity and occurrence of gastrointestinal symptoms in five sub-categories: diarrhoea, indigestion, constipation, abdominal pain and reflux. It uses a seven-point Likert scale for each question. Sub-scores for each of the five categories are calculated as the average of three relevant items and the total score is calculated as the average of all 15 items. The total score ranges from 1 to 7, and a higher score means more severe symptoms.

PGWB is a 22-item questionnaire that estimates self-perceived health-related well-being and distress. It includes six dimensions: anxiety, depressed mood, positive well-being, self-control, vitality and general health. The total score ranges from 22 to 132. Higher scores indicate better quality of life.

The DLQI is a 10-item quality of life implement. The questionnaire includes six different divisions: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The scores of all ten questions are calculated together, and the total score varies from a minimum of 0 to a maximum of 30. A higher score indicates poorer quality of life. dermatology-specific.

2.4. Statistics

The participants were divided into two groups depending on the consumption of oats and then compared. Categorical variables are presented as percentages and continuous variables as medians with ranges or quartiles (Q_1–Q_3). Cross-tabulation with a two-sided chi-squared test was used to compare the categorial variables, and the Mann–Whitney *U* test was used to measure the difference between continuous variables. All statistical analyses were made using SPSS version 25.0. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline data of DH Patients on a Gluten-Free Diet with and without Oats

The median age of the 312 DH patients was 37 years and 49% were females. There were no differences in the gender, age, year of the DH diagnosis, or duration of skin symptoms or gastrointestinal symptoms before being diagnosed between DH patients using and not using oats. There was a trend towards patients not using oats having more severe skin symptoms at diagnosis, but the difference did not reach statistical significance ($p = 0.076$). The severity of villous atrophy and the percentage of serum coeliac antibody-positive patients at diagnosis did not differ between the study groups (Table 1). After being diagnosed, dapsone treatment was initiated in 129 (73%) out of the 176 DH patients using oats and in 30 (86%) out of the 35 DH patients not using oats ($p = 0.119$).

Table 1. Demographic data and clinical, serological and histological findings at diagnosis in 312 dermatitis herpetiformis (DH) patients currently on a gluten-free diet with or without oats.

	Oats, *n* = 256 (82%)	**No Oats, *n* = 56 (18%)**	***p*-Value**
Females, *n* (%)	125 (49)	26 (46)	0.745
Age at diagnosis, median (Q1–Q3), years	37 (27–50)	39 (24–48)	0.481
Year of diagnosis (dg), median (Q1–Q3)	1993 (1982–2002)	1988 (1982–2000)	0.184
Dg < 1985, *n* (%)	74 (29)	18 (32)	
Dg 1985–1999, *n* (%)	96 (38)	24 (43)	
Dg 2000–2014, *n* (%)	86 (34)	14 (25)	
Duration of skin symptoms before diagnosis, median (Q1–Q3), months [1]	11 (6–36)	10 (5–60)	0.671
Severity of skin symptoms [2] at diagnosis, *n* (%)[3]			0.076
Mild	26/167 (16)	6/31 (19)	
Moderate	90/167 (54)	10/31 (32)	
Severe	51/167 (31)	15/31 (48)	
Gastrointestinal symptoms at diagnosis, *n* (%)	108/227 (48)	25/50 (50)	0.756
Small bowel histology at diagnosis, *n* (%)			0.530
Normal	43/207 (21)	5/36 (14)	
Partial villous atrophy	78/207 (37)	13/36 (36)	
Subtotal/total villous atrophy	86/207 (42)	18/36 (50)	
Positive coeliac serology [3] at diagnosis, *n* (%)	121/164 (74)	19/31 (61)	0.156

Q1–Q3: Interquartile ranges. [1] Data available in 224 study patients (188 using oats, 36 not using oats). [2] Graded according to the presence of a few, several or many blisters, macular eruptions and erosions; [3] IgA-class anti-reticulin, endomysium or tissue transglutaminase antibody test.

3.2. Follow-Up Data of DH Patients on a Gluten-Free Diet with or without Oats

In all, 256 patients (82%) were currently using oats, and oat consumption did not differ significantly between cohort 1 and cohort 2 (84% vs 79%, $p = 0.168$). Out of all oat consumers, 72% were consuming oat-based products two times a week or more and 28% were consuming oat-based products less than two times a week. There were no differences in the median duration of the GFD, adherence to the GFD or the prevalence of current skin symptoms between the two study groups (Table 2). However, DH patients not consuming oats reported suffering from gastrointestinal symptoms significantly more often (19% vs 4%, $p = 0.004$), and they needed dapsone treatment more frequently (14% vs 4%, $p = 0.040$) at the follow-up compared to the oat consumers (Table 2). The number of long-term illnesses, previous bone fractures and malignancies, and regularly used prescription or OTC medications were similar in the two study groups (Table 2). Likewise, there were no differences between the study groups in the amount of physical exercise taken or BMI, but patients not using oats were more frequently current smokers ($p = 0.032$) (Table 2).

Table 2. Long-term follow-up data of 312 dermatitis herpetiformis (DH) patients on a gluten-free diet (GFD) with or without of oats.

	Oats, *n* = 256 (82%)	**No Oats, *n* = 56 (18%)**	***p*-Value**
Age, median (range), years	62 (18–96)	62 (32–85)	0.963
Duration of GFD, median (range), years	21 (1–47)	24 (2–41)	0.161
GFD adherence			0.229
Strict, no dietary lapses, *n* (%)	200/254 (79)	49/56 (88)	
Dietary lapses less than once a month, n (%)	36/254 (14)	6/56 (11)	
Dietary lapses once a month or more often, n (%)	18/254 (7)	1/56 (2)	
Skin symptoms, *n* (%)[1]	30/188 (16)	10/36 (28)	0.090
Dapsone treatment, *n* (%)[1]	8/188 (4)	5/36 (14)	0.040
Gastrointestinal symptoms, *n* (%)[1]	8/188 (4)	7/36 (19)	0.004
The total number of long-term illnesses, median (range)[1]	1 (0–12)	1 (0–9)	0.850
Coronary heart disease, *n* (%)	20 (8)	2 (4)	0.261
Cerebrovascular disease, *n* (%)	7 (3)	1 (2)	1.000
Osteoporosis or osteopenia, *n* (%)	15 (6)	3 (6)	1.000
Bone fractures, *n* (%)	49 (19)	12 (21)	0.696
Malignancy, *n* (%)	22 (9)	2 (4)	0.273
Number of prescription medications used, median (range) [1]	2 (0–4)	2 (0–9)	0.510
Number of over-the-counter medications used, median (range) [1]	1 (0–5)	1 (0–5)	0.769
Current smoking, *n* (%)[1]	18 (7)	9 (16)	0.032
Body mass index, kg/m^2, median (range)[1]	25 (17–40)	26 (20–33)	0.242

[1] Data available in 224 study patients (188 using oats, 36 not using oats).

In the GSRS questionnaire, the total scores did not differ significantly between the two study groups. In the sub-score analysis the diarrhoea sub-score was significantly higher among those not consuming oats ($p = 0.045$, Table 3). In the PGWB questionnaire, general health as well as vitality were significantly higher in the oat-consuming group ($p = 0.020$ and $p = 0.025$, respectively), but the total score and other sub-scores did not differ between the study groups (Table 3). Likewise, in the DLQI questionnaire, dermatological quality of life scores were higher among oat consumers compared to those not consuming oats ($p = 0.028$) (Table 3).

Table 3. Median values and quartiles (Q_1–Q_3) for the Gastrointestinal Symptom Rating Scale (GSRS), Psychological General Well-Being (PGWB) and Dermatology Life Quality Index (DLQI) questionnaires' total scores and sub-scores for the 312 dermatitis herpetiformis patients on a gluten-free diet with or without oats.

	Oats, *n* = 256 (82%)	**No Oats, *n* = 56 (18%)**	***p*-Value**
	median (Q_1–Q_3)	**median (Q_1–Q_3)**	
GSRS scores [1]			
Total score	1.7 (1.3–2.2)	1.7 (1.4–2.2)	0.322
Abdominal pain	1.7 (1.0–2.0)	1.7 (1.0–2.0)	0.722
Reflux	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.483
Diarrhoea	1.3 (1.0–2.0)	1.3 (1.0–2.7)	0.045
Indigestion	2.0 (1.5–2.8)	2.0 (1.5–2.5)	0.931
Constipation	1.3 (1.0–2.3)	1.7 (1.0–2.3)	0.570
PGWB scores [2]			
Total score	110 (99–117)	103 (94–118)	0.083
Anxiety	26 (23–27)	25 (22–27)	0.364
Depressed mood	17 (16–18)	17 (15–18)	0.181
Positive well-being	18 (16–20)	17 (15–20)	0.266
Self-control	16 (15–17)	15 (14–17)	0.145
General health	14 (12–16)	13 (11–15)	0.020
Vitality	19 (17–21)	18 (15–20)	0.025
DLQI score [3,4]	0 (0–0)	0 (0–1)	0.028

A higher score indicates [1] more severe symptoms, [2] better health-related well-being or [3] more impaired quality of life. [4] Data available in 224 study patients (188 using oats, 36 not using oats).

4. Discussion

The current study showed that as many as 82% of Finnish DH patients on a GFD consume oats regularly. Comparisons with DH patients not using oats established that the long-term consumption of oats does not cause additional skin symptoms or morbidity, as the incidence of DH-related complications and other long-term illnesses was shown to be comparable between DH patients consuming and not consuming oats as part of their GFD. Importantly, the usage of oats by DH patients on a GFD was associated with fewer gastrointestinal symptoms and better quality of life.

To our knowledge, there are only three previous studies concerning oat consumption in DH, two of which are oat challenges. Hardman et al. [29] performed a three-month oat challenge study involving 10 GFD-treated DH patients, and they observed no rash, serum coeliac autoantibodies, or damage to the small bowel mucosa. In a previous Finnish study [28], 11 GFD-treated DH patients were challenged daily with 50g of oats for six months, while a control group of 11 DH patients continued their conventional GFD without oats. The oat challenge did not cause any changes in the villous architecture or coeliac serology, but two challenged patients experienced a transient rash and one patient withdrew because of a more persistent, albeit mild, rash. Although the numbers of patients in the challenge studies were small and the follow-up times short, the results are in line with the current study demonstrating the safety of long-term oat consumption by DH patients. Moreover, a previous questionnaire study from Finland [32] investigated oat consumption in GFD-treated coeliac disease and DH patients. It demonstrated that several DH patients (19%) had stopped using oats mainly because of cutaneous symptoms. However, it remained unknown whether the skin symptoms were oat-related, nor was it known how long the patients had been using oats before cessation. As previously suggested [28], it is possible that some DH patients may experience mild and transient skin symptoms after the introduction of oats to the GFD. However, this seems to be of minor importance in the long run, since as many as 82% of the DH patients in the present long-term study continued to consume oats in their GFD.

Compared to DH, there are considerably more studies addressing oat consumption in coeliac disease. According to a recent meta-analysis [42], the vast majority of the performed studies have demonstrated that oat consumption does not cause short- or long-term harm to coeliac disease patients. In most of the studies, which feature oat consumption lasting up to ten years, no changes in duodenal villous architecture, coeliac disease serology or gastrointestinal symptoms were detected among those using oats [21,22,24]. However, since there are also a few reports demonstrating increased gastrointestinal complaints, intraepithelial lymphocytosis and even damage of the small bowel mucosal villi in coeliac disease patients consuming oats [25,26], this issue is not totally undisputable. Hence, in a recent review of GFD treatment in coeliac disease [20], it is stated that the long-term risks of consuming oats in coeliac disease remain unknown and further studies are warranted.

The present study also investigated the factors predicting oat consumption in DH. Other than the detected – albeit not statistically significant – difference in the severity of skin symptoms, the baseline characteristics among those using and not using oats did not differ. Intriguingly, at the follow-up, DH patients not using oats reported suffering from gastrointestinal symptoms more often than those consuming oats. Moreover, they had slightly more frequent skin symptoms and more often used dapsone treatment than the oat consumers. It is possible that the DH patients with more severe and/or persistent skin symptoms are not willing to include oats in their GFD due to the fear of worsening their symptoms. At the follow-up, the DH study patients did not differ in terms of BMI and the presence of long-term illnesses or coeliac disease complications, and the number of prescription medications was similar. These results show that oat consumption does not have negative effects on the long-term prognosis of DH.

In fact, an important finding in the present study was that the quality of life measured with the DLQI questionnaire was significantly better in patients consuming oats than in patients not consuming oats. Correspondingly, oat consumers reported significantly better general health and vitality when measured with the PGWB questionnaire. Our findings are in line with previous reports on the quality of life effects of oat use in Finnish coeliac disease patients, with the quality of life of oat consumers being even better than that of those not consuming oats [21,25]. It has been reported that coeliac disease patients find that oats diversify their GFD in many ways; patients especially appreciate the taste, ease of use, and low cost of oats [32], all of which most likely have positive effects on their quality of life.

The main strengths of the present study are the large, well-defined study group with a skin immunofluorescence biopsy-proven DH diagnosis and the long duration of follow-up (a median of over 20 years). Further strengths include the use of validated questionnaires to investigate quality of life and gastrointestinal symptoms, and the possibility to gather comprehensive follow-up data in terms of the prognosis of DH.

A limitation was that the follow-up information was based on questionnaires and interviews, which may have yielded selection and recall bias. Further, we did not ask the reasons for not consuming oats and the duration of oat consumption is not known in those using oats. Finally, duodenal biopsies and coeliac serology were not available at the follow-up. On the other hand, it has previously been shown that duodenal recovery in GFD-treated DH patients is excellent in Finland [43]

5. Conclusions

To conclude, we demonstrated that oats are widely used as a constituent of a GFD among Finnish DH patients. Long-term consumption of uncontaminated oats is safe and even seems to improve the quality of life of DH patients. Based on the current long-term study and earlier challenge studies, the inclusion of uncontaminated oats in the diet of DH patients is justified.

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PUBLICATION IV

Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients

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Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients

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Conflicts of interest
None declared.

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Summary

Background Dermatitis herpetiformis (DH) is an extra-intestinal manifestation of coeliac disease and most patients adhere to a life-long gluten free diet (GFD). Increased mortality rates have been reported in coeliac disease but knowledge in DH is scanty.

Objectives To survey the mortality rate and causes of death in a large cohort of patients with DH.

Material and methods Patients with DH (n = 476 consecutive patients) diagnosed from 1970 onwards at the Tampere University Hospital were analysed for causes of death during 1971–2010. A questionnaire survey on key aspects of health behaviour was performed in patients with DH and comparisons were made with the Finnish population.

Results The total number of deaths during 9079 person years followed up was 77 whereas 110 were expected. The standardized mortality rate (SMR) for all causes of death was significantly reduced, being 0·70 (95% CI 0·55–0·87), and similar in both sexes. The SMR was equal in the patients with DH with (0·73) and without (0·77) small bowel villous atrophy. The SMR was significantly reduced (0·38) for deaths due to cerebrovascular diseases. The SMR due to lymphoproliferative malignancies was significantly increased (6·86) in the first 5 years of follow-up but not thereafter. The questionnaire survey documented that 97·7% of the patients with DH adhered to a GFD. The patients reported significantly less hypercholesterolaemia and there were fewer current and past smokers compared with the age- and sex-matched control population.

Conclusions The present long-term follow-up study of DH documented significantly reduced all-cause and cerebrovascular disease mortality. Strict adherence to a GFD, less smoking and hypercholesterolaemia may play a role in the observed health benefit.

Dermatitis herpetiformis (DH) is a gluten-sensitive skin disease characterized by an itchy blistering rash with predilection sites on elbows, knees and buttocks.[1] The diagnosis is based on the typical clinical picture and demonstration of granular immunoglobulin (Ig) A deposits in the papillary dermis. Patients with DH rarely have gastrointestinal symptoms, although about 75% have small bowel villous atrophy, and the remainder minor bowel mucosal changes compatible with coeliac disease.[2,3] Also the rash responds to a gluten-free diet (GFD), which is the treatment of choice for the patients with DH.[4–6] Nowadays DH is considered as an extra-intestinal manifestation of coeliac disease occurring in 12% of patients with coeliac disease.[7]

Several studies in patients with coeliac disease have reported increased, up to 3·8-fold, mortality rates compared with general population.[8–13] The increased number of deaths has

mainly been from non-Hodgkin lymphoma and gastrointestinal malignancies. DH shares the same increased risk for developing non-Hodgkin lymphoma.[14–19] However, in contrast to coeliac disease the mortality rates have not increased in DH.[20–22] Surprisingly, we could even show a significantly reduced mortality rate in our DH series from Tampere.[21] We therefore extended our DH patient series collected prospectively from 1970 and evaluated whether the observed decreased mortality rate still holds true in a larger series with a long follow-up. We were also interested to see whether special disorders would explain the possible decreased mortality rate, and therefore analysed the causes of death in our large DH cohort. To look for possible confounding factors we sent a health behaviour postal questionnaire survey to the patients with DH who were alive and compared the results with the age- and sex-matched Finnish control population.

Material and methods

Patients

The study group comprised all 476 consecutive patients with DH diagnosed at the Department of Dermatology, Tampere University Hospital in the period 1970–2009. The mean age of patients at diagnosis was 42·8 (range 3–84) years and the male to female ratio 1·1.

This department is the only place in a defined area where the patients with dermatological problems are sent for more thorough examination and specialist care.[7] All patients with DH are diagnosed in this unit, because the frozen skin biopsies required for the diagnosis are not taken elsewhere. The diagnosis of DH was based on the clinical picture and the demonstration of granular IgA deposits in the papillary dermis by direct immunofluorescence examination. All patients with an intensive rash were started on dapsone. Gastroscopy with small intestinal biopsy was performed on more than half of the patients with DH and small bowel villous atrophy was graded morphologically as subtotal or partial villous atrophy or normal mucosa.[23] All patients were placed on a GFD. They were given written dietary instructions and also encouraged to join the local Coeliac Society. The patients also received a monthly reimbursement of 21 euros from the National Social Insurance Institution to compensate for the extra costs of their GFD treatment.

All patients with DH were followed up at the special outpatient clinic run by two experienced dermatologists for at least 1–2 years or longer until dapsone could be stopped. A dietician was consulted when the patients failed to respond to GFD treatment as expected. After surveillance at the outpatient clinic, the patients were followed up several times with special inquiries regarding their GFD treatment, associated diseases and occurrence of DH or coeliac disease in their first-degree relatives. They also got regular up-to-date information from the circulars of the National Coeliac Society regarding GFD treatment, and the availability of new commercial gluten-free products. In 1998 it was stated that oat products are safe for the patients with DH.[24]

Methods

The date and cause of death of the patients with DH were identified by linking the personal identification codes with the death certificate files held by Statistics Finland, which covers virtually all causes of death in our country. The causes of death were coded according to ICD-10 (International Classification of Diseases). For mortality analysis, the number of person-years followed up was calculated starting on 1 January in the year following the diagnosis of DH. The end-point was the date of death or 31 December 2010. Data were available on each of the 476 patients with DH. The expected number of deaths was calculated on the basis of sex-, age- and calendar-period-specific mortality rates in the Finnish population. The standardized mortality ratio (SMR) was calculated as the ratio of observed and expected number of deaths, for all-cause mortality and 53 specific cause-of-death categories included in the selection of categories of the longitudinal time series of Statistics Finland. The corresponding 95% confidence intervals (CIs) were defined assuming Poisson distribution of the observed number of deaths.

The all-cause SMRs were calculated for the whole DH cohort ($n = 476$) and separately for men ($n = 249$) and women ($n = 227$). SMRs for the different causes of death were calculated for the whole period, and separately for the first 5 years of follow-up and then for follow-up after 5 years. Finally, all-cause SMRs were calculated for those patients with DH who at diagnosis had small bowel villous atrophy ($n = 281$) and for those who had normal villous mucosa ($n = 88$).

Two questionnaires were sent in 2011 to all 391 patients with DH who were living in Finland; a total of 311 (79·5%) patients responded. The first included questions about the use of dapsone, strictness of GFD and chronic illnesses. The second questionnaire surveyed key aspects of health behaviour: food habits, smoking, alcohol consumption and physical activity. This questionnaire, with over 100 special questions, has been employed annually from 1978 to survey health behaviour of the Finnish working-age population.[25] As we had no control data for older patients with DH, the analysis of health behaviour was limited to 179 (57·6%) of the patients with DH who were aged between 15 and 64 years and were used as cases in the analysis of health behaviour. The cases of DH included 102 men and 77 women and their mean age was 52·0 and 50·8 years, respectively. Five age- and sex-matched controls from the latest Finnish health behaviour survey consisting of 2943 respondents were chosen for every case of DH.[26] The differences between the cases and controls were analysed with the chi-square test.

The Ethical Committee of the Pirkanmaa Hospital District approved the study protocol.

Results

In the whole DH cohort, a total of 9079 person-years were followed up, 4670 in men and 4409 in women (Table 1).

Table 1 The all-cause standardized mortality rate (SMR) in the series of 476 patients with dermatitis herpetiformis collected prospectively in the Tampere University Hospital from 1970 and followed up to the end of 2010

	Person years of follow-up	Number of deaths		SMR (95% CI)
		Observed	Expected	
Whole period				
All (n = 476)	9079·1	77[a]	110·4	0·70 (0·55–0·87)***
Men (n = 249)	4669·6	43	63·2	0·68 (0·49–0·91)**
Women (n = 227)	4409·5	34	47·2	0·72 (0·50–1·00)
Follow-up to 5 years				
All	2254·2	10	19·9	0·50 (0·24–0·92)*
Men	1179·3	5	12·6	0·40 (0·13–0·92)*
Women	1074·9	5	7·3	0·69 (0·22–1·60)
Follow-up > 5 years				
All	6824·9	67	90·6	0·74 (0·57–0·93)*
Men	3490·3	38	50·7	0·75 (0·53 – 1·02)
Women	3334·6	29	39·9	0·73 (0·49–1·04)

[a]Including deaths from all diseases and deaths from accidents and violence. *P < 0·05; **P < 0·01; ***P < 0·001.

The observed number of deaths during follow-up was 77, whereas 110 deaths were expected. The all-cause SMR was significantly reduced at 0·70 (95% CI 0·55–0·87). In 249 men SMR was significantly reduced (0·68; 95% CI 0·49–0·91) whereas in 227 women it was in borderline of significance (0·72; 95% CI 0·50–1·00).

In the first 5 years of follow-up SMR was 0·50 (95% CI 0·24–0·92) and after that 0·74 (95% CI 0·57–0·93) (Table 1). SMR in men for the whole period was 0·68 (95% CI 0·49–0·91) and in women 0·72 (95% CI 0·50–1·00).

Table 2 shows that in the whole cohort there was a significant decrease in the mortality rates of cerebrovascular (SMR 0·38; 95% CI 0·10–0·97) and alcohol-related diseases (SMR 0; 95% CI 0·00–0·88). The SMR for deaths from malignant neoplasms was 0·93 (95% CI 0·60–1·39). However, the SMR for lymphoproliferative malignancy was significantly increased in the first 5 years of follow-up (6·86; 95% CI 1·41–20·05), but not in the whole cohort (2·49; 95% CI 0·91–5·40) (Table 2).

Table 3 shows that in the 369 patients with DH who underwent small bowel biopsy before GFD treatment there were 56 deaths, whereas 75·2 were expected (SMR 0·75; 95% CI 0·56–0·96). The all-cause SMR was similarly decreased and SMR for lymphoproliferative malignancy similarly increased, although not significantly, in patients with villous atrophy and in those with normal mucosa (Table 3).

The questionnaires received from the 311 patients with DH showed that 97·7% of the patients adhered to a GFD; 71·5% adhered strictly to the diet whereas the remaining patients reported some failures at least once a month (6·5%) or less often (19·9%); 203 (65·3%) patients had used dapsone when starting GFD treatment but at present only 25 (8·0%) patients needed the drug to control the rash.

The major findings from the health behaviour questionnaire are presented in Table 4. No significant differences were found between the DH cases and controls in occurrence of high blood pressure, ischaemic heart disease or use of antihypertensive drugs. However, the patients with DH reported significantly less hypercholesterolaemia than the controls (15·1% vs. 24·2%; P = 0·008). Present (7·3% vs. 15·9%; P = 0·003) or past smoking (48·0% vs. 64·2%; P < 0·001) was also significantly less common in the DH cases than in the controls. Alcohol consumption was similar in the DH cases and controls (86·0% vs. 85·9%). No difference between the groups

Table 2 Causes of death in 476 patients with dermatitis herpetiformis

Cause of death	Number of deaths		SMR (95% CI)
	Observed	Expected	
All diseases	73	101·4	0·72 (0·56–0·90)**
Men	41	56·6	0·72 (0·52–0·98)*
Women	32	44·8	0·72 (0·49–1·00)
Diseases of circulatory system	35	47·9	0·73 (0·51–1·01)
Ischaemic heart diseases	25	29·1	0·86 (0·56–1·26)
Other heart diseases	3	4·1	0·73 (0·15–2·13)
Cerebrovascular diseases	4	10·5	0·38 (0·10–0·97)*
Malignant neoplasms	24	25·7	0·93 (0·60–1·39)
Lymphoproliferative neoplasms	6	2·4	2·49 (0·91–5·40)[a]
Gastric cancer	2	1·6	1·25 (0·15–4·40)
Oesophagus cancer	1	0·5	1·97 (0·05–11·00)
Respiratory system diseases	3	7·1	0·42 (0·09–1·23)
Alcohol-related diseases	0	4·2	0·00 (0·00–0·88)*
Accidents and violence	4	8·9	0·45 (0·12–1·14)

CI, confidence intervals; SMR, standardized mortality rate. *P < 0·05; **P < 0·01. [a]Significantly increased in the first 5 years of follow-up (SMR 6·86; CI 1·41–20·05).

Table 3 All-cause mortality, lymphoproliferative malignancies and small bowel histopathology in 369 patients with dermatitis herpetiformis

	Number of deaths		
	Observed	Expected	SMR (95% CI)
All-cause mortality			
All patients (n = 369)	56	75·2	0·75 (0·56–0·96)*
With villous atrophy (n = 281)	34	46·7	0·73 (0·50–1·01)
With normal mucosa (n = 88)	22	28·5	0·77 (0·48–1·16)
Lymphoproliferative malignancies			
All patients (n = 369)	5	1·7	3·04 (0·99–7·08)
With villous atrophy (n = 281)	3	1·1	2·83 (0·58–8·27)
With normal mucosa (n = 88)	2	0·6	3·41 (0·41–12·33)

SMR, standardized mortality rate. *P < 0·05.

Table 4 Major findings in the health behaviour survey of DH cases and age- and sex-matched controls from the random sampling of the Finnish working-age population

	DH cases, n = 179	Controls, n = 895	P-value
Hypertonia[a]	36 (20·1%)	234 (26·2%)	0·089
Use of antihypertensive drugs	33 (18·4%)	210 (23·5%)	0·14
Ischaemic heart disease[a]	2 (1·1%)	16 (1·8%)	0·52
Hypercholesterolaemia[a]	27 (15·1%)	217 (24·2%)	0·008
Smoking, present	13 (7·3%)	142 (15·9%)	0·003
Smoking, past	86 (48·0%)	575 (64·2%)	< 0·001
Alcohol consumption[a]	154 (86·0%)	769 (85·9%)	0·97
No beer	90 (50·3%)	218 (24·4%)	< 0·001
No heavy drinks	35 (19·6%)	202 (22·6%)	0·37
No milk	70 (39·1%)	219 (24·5%)	< 0·001
Butter on bread	12 (6·7%)	27 (3·0%)	0·016
Animal fats in cooking	58 (32·4%)	153 (17·1%)	< 0·001
Physical activity low	53 (29·6%)	285 (31·8%)	0·56

[a]During the last 12 months.

was found in daily physical activity. The height of the 311 patients with DH was 173·3 ± 8·8 cm (mean ± SD) and weight 79·5 ± 14·7 kg. The body mass index [weight/height^2 (kg m^{-2})] was equal in patients with DH and controls, 26·4 ± 3·9 and 26·5 ± 4·5, respectively, (P = 0·71).

Discussion

In the present study we analysed the mortality rate and causes of death in our extended cohort of 476 patients with DH collected in Tampere from 1970 onwards. The patients were followed up for a total of 9079 person years and we were able to show a significantly reduced all-cause mortality rate (SMR 0·70) compared with the general population. SMR was significantly reduced in 249 men (0·68); the SMR was equally decreased in 227 women (0·72), although it was of borderline significance. These findings are in line with our previous DH report from Tampere,[21] although it consisted of a smaller number of patients and a shorter follow-up (Table 5). For comparison, Swerdlow *et al.*[20] analysed a hospital-based series of 152 patients with DH from London and found a similarly reduced mortality rate (SMR 0·87), which, however, was not significant (Table 5). Lewis *et al.*[22] in Nottingham studied 846 patients with DH collected from the General Practice Research Database and found a slightly but nonsignificantly reduced mortality rate (hazard ratio 0·93; Table 5).

DH is considered an autoimmune manifestation of coeliac disease[27] and thus it is of interest to compare the mortality rates of these two conditions, both of which are treated with a GFD. In our previous study[21] the mortality rate in our DH cohort was significantly reduced (SMR 0·52), whereas the opposite (SMR 1·26) was true for the patients with coeliac disease. Peters *et al.*[11] in Sweden analysed the mortality rate in 10 032 hospitalized patients with coeliac disease including a subgroup of 221 patients with DH. In this study the mortality rate in the patients with DH was increased (SMR 1·4) but lower than that in the whole coeliac disease cohort (SMR 2·0). Overall, several extensive studies in coeliac disease have shown increased mortality rates, SMR from 1·9 to 3·8, compared with the general population.[8–12] A recent meta-analysis study of coeliac disease confirmed an increased risk for all-cause and non-Hodgkin lymphoma mortality.[28] DH shares with coeliac disease an increased risk for developing non-Hodgkin lymphoma,[14–19] especially in those patients with DH not adhering to a GFD.[18] It has also been shown that GFD treatment for over 5 years seems to be protective against non-Hodgkin lymphoma.[29] In agreement with this, we found a

Table 5 Mortality studies in dermatitis herpetiformis

First authors, year, country, reference	Number of patients (M/F)	Years when diagnosed (end of follow-up)	Patient source	Person years	Mortality rate (95% CI)
Present series, Finland	476 (249/227)	1970–2009 (2010)	Hospital-based case series	9079	SMR 0·70 (0·55–0·87)
Lewis, 2008, U.K.[22]	846 (404/442)	1987–2002 (2002)	General practice database	3496	HR 0·93 (0·70–1·23)
Viljamaa, 2006, Finland[21]	366 (190/176)	1960–2000 (2002)	Hospital-based case series	6288	SMR 0·52 (0·36–0·72)
Swerdlow, 1993, U.K.[20]	152 (106/46)	1950–1985 (1989)	Hospital-based case series	2288	SMR 0·87 (0·61–1·19)

CI, confidence interval; HR, hazard ratio; SMR, standardized mortality ratio.

significantly increased mortality rate due to lymphoproliferative malignancy during the first 5 years of follow-up but not thereafter.

Patients with coeliac disease have subtotal or partial villous atrophy in the small bowel, whereas one-quarter of the patients with DH present at diagnosis with normal mucosal morphology, which, however, shows typical coeliac-type inflammatory changes.[3] In the present DH series, patients with and without small bowel villous atrophy showed similarly reduced mortality rates (Table 3). Therefore, it seems evident that the reduced mortality rate observed in DH is not dependent on small bowel mucosal damage. In agreement with this, Ludvigsson *et al.*[30] showed that the increased mortality rate in coeliac disease was not associated with the severity of small bowel villous damage.

The reason for the significantly reduced mortality rate in our DH cohort is not easy to explain especially when the mortality rate in coeliac disease seems to be significantly increased.[8–12,28] Grainge *et al.*[31] recently showed that the increased mortality rate in coeliac disease has remained unchanged over the last 25 years. Similarly, we did not find any major changes in the reduced mortality rate during the present DH study although age at diagnosis has significantly increased over the last 40 years.[7] Biagi and Corazza[13] presented a hypothesis that mortality rate in patients with coeliac disease would be associated with the extent of mucosal lesion along the small bowel and the quantity of gluten consumed before and after the diagnosis. A recent review showed that in coeliac disease the rates for strict adherence to a GFD ranged from 42% to 91%.[32] In our previous survival rate study 81% of the patients with coeliac disease adhered to a GFD in contrast to 93% of the patients with DH.[16] Of our patients with DH in the present mortality study, 97·7% adhered to a GFD and only 8% needed dapsone to control the rash according to the questionnaire survey. Dietary faults and controlled gluten challenge cause flare-ups of harmful itchy rash in most patients with DH.[33,34] In contrast, patients with coeliac disease often experience mild or no gastro-intestinal symptoms,[35] which may explain their less strict adherence to a GFD. Whether compliance levels had any effect on the increased mortality rate in coeliac disease, however, could not be verified in a recent meta-analysis.[27] We consider that the monthly compensation of 21 euros for the extra dietary costs is so low that it will not have any impact on health behaviour in patients with DH.

Extensive cohort studies from Sweden[36,37] have shown that patients with coeliac disease have increased risks for stroke and ischaemic heart disease, although the risks were small and persisted for stroke only for a short period after the diagnosis and dietary treatment. It is therefore intriguing that we observed in the present cohort of patients with DH (SMR 0·38) and in our previous study in coeliac disease patients (SMR 0·15)[21] significantly reduced mortality rates to cerebrovascular diseases. There is one earlier study suggesting that patients with DH would have a lower mortality rate for ischaemic heart disease.[20] In the present study the finding was similar although not significant. It is noteworthy that our DH cases reported in questionnaire survey similar frequencies of hypertension and antihypertensive drug usage to the control population. Moreover, the body mass index of DH cases did not differ from that in the controls. It seems possible that the reduced mortality rates in patients with DH due to diseases of the circulatory system and especially to cerebrovascular diseases might be related to the GFD treatment. Studies in patients with DH and coeliac disease have shown low levels of serum cholesterol which have not increased during GFD treatment.[38–41] In agreement with this, our DH cases reported significantly less hypercholesterolaemia than the controls even though their consumption of butter and animal fat in cooking was higher than in the controls. Less smoking, although not uniformly,[22] has been reported in the patients with DH and coeliac disease.[38,42] This was verified in our present survey: in our DH cases past and current smoking was significantly less common than in the controls, again a factor which could affect the reduced mortality rate to diseases of the circulatory system in general and to cerebrovascular diseases in particular. A possible limitation of the present health behaviour questionnaire survey is that it did not include DH cases or controls older than 64 years. Therefore, the findings of less hypercholesterolaemia and smoking, although highly significant, are not necessarily applicable for older patients.

In the DH mortality study by Swerdlow *et al.*,[20] one-third of the patients did not have a diagnosis based on histological or immunofluorescence examination. Moreover, 18% of the diagnosed patients had to be excluded due to inappropriate follow-up data. The study by Lewis *et al.*[22] was based on the patients with DH collected from the General Practice Research Database. Similarly, the data did not include diagnostic findings for each patient and one-third of them had no record of having received either dapsone or GFD product prescription. In contrast to these two DH cohorts from the U.K., our series of 476 patients showing a significantly reduced mortality rate was collected and followed up prospectively since 1970. The diagnostic criteria for DH were firm and included the presence of dermal IgA deposits in all patients. A small bowel biopsy had been taken at diagnosis from 60% of the patients. Moreover, over 95% of the patients adhered to a GFD and they had been followed up for at least 1–2 years in a specialist outpatient clinic. This surveillance at the onset of GFD treatment and several postal surveys performed later are factors which seem to improve their attitude and adherence to the GFD. Moreover, the response rate to the present postal questionnaire survey was good and as many as 97·7% of the patients with DH reported adherence to a GFD. While the regular follow-up after the diagnosis and the strict adherence to the GFD could be one reason for the significantly reduced mortality rate in our DH cohort, more firm evidence is required.

In conclusion, we documented a significantly reduced mortality rate in our large, single-centre DH cohort prospectively collected from 1970. This finding is in sharp contrast to coeliac disease, which has shown increased mortality rates. Strict adherence to a GFD, less smoking and hypercholesterolaemia in the DH patients could explain the favourable prognosis.

What's already known about this topic?

- Dermatitis herpetiformis is an extra-intestinal manifestation of coeliac disease.
- The mortality rate is increased in coeliac disease whereas a few studies suggest a reduced rate in dermatitis herpetiformis.

What does this study add?

- This large cohort of patients with dermatitis herpetiformis showed significantly reduced all-cause and cerebrovascular disease mortality.
- Strict adherence to a gluten-free diet, less smoking and hypercholesterolaemia in DH than in the population in general could contribute to this finding.

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