ORIGINAL ARTICLE

Sex-differences in Gluten-free Dietary Adherence and Clinical Symptoms in Patients with Long-term Treated Dermatitis Herpetiformis

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Dermatitis herpetiformis is a blistering autoimmune skin disease, and a cutaneous manifestation of coeliac disease. The burden of coeliac disease is increased especially in females, but studies concerning sex differences in patients with long-term treated dermatitis herpetiformis are scarce. This questionnaire study compared adherence to a gluten-free diet, clinical symptoms and well-being between females and males in a cohort of 237 long-term treated (median 24 years) patients with dermatitis herpetiformis. Females had better adherence to a gluten-free diet ($p = 0.022$) and they used dapsone significantly less often at the time of the study than did males (4% vs 13%, $p = 0.017$). The occurrence of skin symptoms was equal in both sexes, but dermatological quality of life was lower in females ($p = 0.024$), and gastrointestinal symptoms were more severe among females with dermatitis herpetiformis than among males ($p = 0.027$). In conclusion, long-term treated female patients with dermatitis herpetiformis have better adherence to a gluten-free diet, but they also experience more severe clinical symptoms compared with males.

Key words: dermatitis herpetiformis; gluten-free diet; gastrointestinal symptoms; quality of life; sex differences.

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SIGNIFICANCE

Dermatitis herpetiformis is a blistering, itchy skin disease and a cutaneous manifestation of coeliac disease. Treatment for dermatitis herpetiformis is a life-long gluten-free diet. This study, which includes long-term treated patients with dermatitis herpetiformis, found that male patients with dermatitis herpetiformis had lower adherence to a gluten-free diet and used dapsone medication more often compared with female patients. In addition, gastrointestinal symptoms were more severe and the skin symptoms-related quality of life was lower in females with dermatitis herpetiformis than in males with dermatitis herpetiformis. These observations indicate that additional dietary support should be considered, especially among males with dermatitis herpetiformis, as dietary transgressions might lead to an unfavourable disease prognosis. Furthermore, the more severe clinical symptoms experienced by females should be acknowledged by physicians who are following up these patients.

Dermatitis herpetiformis (DH) is an autoimmune skin disease, and an extraintestinal manifestation of coeliac disease (1). In DH, dietary gluten induces an intensively pruritic polymorphic vesicular rash, mainly on the elbows, knees and buttocks. In addition, patients with DH evince coeliac enteropathy, and some patients also experience gastrointestinal symptoms at the time of diagnosis (1–3). Currently, the male-to-female ratio in DH is close to equal (4, 5), whereas coeliac disease is significantly more prevalent in females (6).

Like coeliac disease, DH is treated by eliminating gluten from the diet. A gluten-free diet (GFD) leads to recovery of the enteropathy, resolution of the skin and possible gastrointestinal symptoms, and reduction in the risk of DH complications, such as the development of lymphoma (1, 7). Because skin symptoms alleviate slowly with GFD treatment, dapsone medication is initiated for the majority of patients after diagnosis of DH (1, 8). Dapsone is highly effective towards skin symptoms, but does not affect the enteropathy or prevent DH-related complications, and thus strict adherence to a GFD is vital (1). However, maintaining a life-long GFD may be challenging and might complicate social life and travelling, in particular (9).

A significant burden of disease is associated with long-term GFD-treated coeliac disease. Based on current data, female patients with coeliac disease experience a lower quality of life, and they have more pronounced gastrointestinal symptoms on a GFD compared with male patients (10–15). However, no association between sex and adherence to a GFD in coeliac disease has been detected (16–19). In contrast to coeliac disease, little is known about the differences in clinical symptoms and GFD adherence between treated females and males with DH. Our previous study including 78 long-term treated patients with DH showed that female patients experience more severe gastrointestinal symptoms and have decreased vitality compared with males (20). Conversely, our recent study did not detect a sex association in the

presence of persistent skin symptoms (8), and studies concerning sex differences in the GFD adherence of patients with DH are lacking. Therefore, the aim of this study was to investigate the associations between sex, clinical symptoms, treatment compliance and burden of disease in long-term treated patients with DH.

MATERIALS AND METHODS

Study patients

In 2016 a questionnaire study was conducted among patients diagnosed with DH at the Department of Dermatology at Tampere University Hospital between 1970 and 2014. The study protocol is described in detail elsewhere (21). The response rate was 56%, and the study cohort included 237 patients with DH responding to the questionnaires. The DH diagnosis of each patient was based on a clinical picture compatible with DH, and on the detection of granular IgA deposits from the papillary dermis using direct immunofluorescence (22). All patients were diagnosed at the outpatient clinic for patients with DH at the Department of Dermatology and, according to the national guidelines at the time, patients were recommended to undergo gastroscopy with small bowel biopsies. A strict life-long GFD was recommended to all patients with DH, and a visit to a dietitian was advised to support dietary adherence. Dapsone medication was initiated for patients with troublesome skin symptoms. The dose of dapsone was reduced gradually, and the medication was discontinued once the skin symptoms were controlled by a GFD alone. The patients with DH were followed up by a dermatologist until the skin symptoms resolved, and for those taking dapsone, until the medication was discontinued. Thereafter, according to national current care guidelines, clinical and serological follow-up in primary healthcare was recommended every 2–3 years (23). For the purpose of this study, the patient's age and the degree of small-bowel mucosal damage at the time of DH diagnosis were documented from the medical records. The study was conducted according to the principles of the Declaration of Helsinki, and the study protocol was approved by the Regional Ethics Committee of Tampere University Hospital (R15143).

Questionnaires

In total, 4 questionnaires were sent to the study patients: a DH-specific questionnaire designed by the authors for research purposes; the Dermatology Life Quality Index (DLQI); the Psychological General Well-Being (PGWB); and the Gastrointestinal Symptoms Rating Scale (GSRS) questionnaires.

The DH-specific questionnaire asked about DH-related skin symptoms at the time of the study. The frequency of skin symptoms was categorized as: at least once a month; 1–4 times a year; and less than once a year. Patients were asked to assess the duration of gastrointestinal symptoms after initiation of a GFD, and, if the symptoms had not yet subsided, patients were considered to have ongoing gastrointestinal symptoms at the time of the study. Patients also reported their adherence to a GFD at the time of the study, and the strictness of the diet was categorized as: a strict diet with no dietary lapses, dietary lapses, or normal diet. In addition, the survey comprised questions on whether the participant had, at some point after the DH diagnosis and GFD initiation, been on a normal gluten-containing diet for at least 1 month, and thus had a clear intentional break from maintaining a GFD. Patients were asked to report their current height and weight, and their body mass index (BMI) was calculated. Also, the diagnosed long-term illnesses, the use of long-term medication, and current use of dapsone were surveyed. In addition, the presence of first-degree relatives with DH or coeliac disease, membership of the Finnish Coeliac Society, and current smoking were recorded.

The DLQI is a validated questionnaire assessing the quality of life associated with dermatological diseases during the previous week in areas of symptoms and feelings, daily activities, leisure, work or school, personal relationships and treatment (24). The DLQI contains 10 items, and the total score ranges from 0 to 30 points; scores less than 2 indicate no effect, 2–5 a small effect, 6–10 a moderate effect, 11–20 a very large effect, and 21–30 an extremely large effect on the patient's life (25). The GSRS and PGWB questionnaires are validated questionnaires and, although they are not coeliac disease-specific, they have been widely used in coeliac disease and DH studies (11, 12, 14, 20). The GSRS comprises 15 items that cover gastrointestinal symptoms in 5 categories: diarrhoea, indigestion, constipation, abdominal pain, and reflux. Each item uses a 7-point Likert scale, and the total score is calculated as a mean of all items, and subscores as a mean of each sub-dimension. A higher score indicates more severe symptoms (26). The PGWB is a 22-item questionnaire that maps the quality of life in 6 different emotional states: anxiety, depressed mood, self-control, positive well-being, general health and vitality. The questionnaire uses a 6-point Likert scale for each question. The subscores and the total score are calculated as a sum of the items. Thus, the total score ranges between 22 and 132 points, a higher score representing better quality of life (27).

Statistical analysis

In this study, female patients with DH were compared with male patients with DH. As the data were not normally distributed, median values, interquartile ranges (IQR), and minimum and maximum values were used as descriptives. All testing was 2-sided, and $p < 0.05$ was considered statistically significant. The χ^2 test and Fisher's exact test were used in cross-tabulations, and the Mann–Whitney U test was used for continuous variables. All the statistical analyses were performed with SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. USA).

RESULTS

Of the 237 patients with DH, 126 (53%) were male, and the median age at the time of the DH diagnosis was 37 years (range 5–78 years). The duodenal biopsy at the time of the diagnosis disclosed normal architecture in 22%, partial villous atrophy in 37%, and subtotal or total villous atrophy in 41% of the patients with available data ($n = 177$). The median age at the time of the study was 65 years (range 18–96), and the age distribution between the sexes was equal (**Table I**). The patients had been on a GFD for a median of 24 years. The duration of the GFD did not differ between the sexes (Table I), but females reported better adherence to a GFD ($p = 0.022$); 81% of females and 64% of males were on a strict diet, and among males 2% reported eating normal gluten-containing food, whereas all females followed a GFD with or without dietary lapses. Intentional breaks from a GFD, at some point after being diagnosed with DH, were reported by 14% of the females and 8% of the males with DH, but this difference was not statistically significant.

There was no significant difference in the frequency of experienced DH-related skin symptoms between the

Table I. Demographic data, adherence to gluten-free diet (GFD), clinical symptoms and life-style factors in 237 long-term treated female and male patients with dermatitis herpetiformis (DH)

	Female, $n=111$	Male, $n=126$	p-value
Age at the time of the study, years, median, IQR	63, 54–72	65, 55–75	0.210
Duration of GFD, years, median, IQR	23, 15–35	25, 14–35	0.450
Adherence to GFD, n (%)			0.022
Strict[a]	89 (81)	84 (67)	
Dietary lapses	21 (19)	38 (30)	
Normal diet	0 (0)	3 (2)	
Intentional breaks from GFD after DH diagnosis[b], n (%)	15 (14)	10 (8)	0.173
Frequency of DH-related skin symptoms, n (%)			0.221
Less than once a year	77 (69)	98 (74)	
1–4 times a year	22 (20)	15 (12)	
At least once a month	12 (11)	12 (10)	
Uses dapsone, n (%)	4 (4)	16 (13)	0.017
DLQI total score[c], n (%)			0.024
No effect on life quality (0–1 points)	94 (86)	116 (94)	
Small effect on life quality (2–5 points)	11 (10)	8 (7)	
At least a moderate effect on life quality (≥ 6 points)	5 (5)	0 (0)	
Psychological General Well-Being total, median, IQR	109, 98–117	111, 99–118	0.470
Ongoing gastrointestinal symptoms, n (%)	11 (10)	5 (4)	0.076
First-degree relatives with coeliac disease or DH, n (%)	37 (35)	43 (34)	0.977
Member of Finnish Coeliac Society, n (%)	82 (75)	70 (58)	0.008
Body-mass index, kg/m^2, median, IQR	25.4, 22.3–28.6	25.7, 23.7–28.7	0.213
Current smoker, n (%)	9 (8)	14 (12)	0.429

[a]No dietary lapses. [b]Adherence to normal gluten-containing diet for at least a period of 1 month at some point after the DH diagnosis. [c]Higher points indicate worse quality of life.
IQR: interquartile range; DLQI: Dermatology Life Quality Index.

sexes (Table I), but 13% of the male patients used dapsone regularly at the time of the study, compared with 4% of the females ($p=0.017$). Concerning the dermatological life quality, 15% of the female patients and 7% of the males scored at least 2 points on the DLQI, indicating that the skin symptoms affected their quality of life at least to some degree ($p=0.042$). In addition, 5% of the female patients (5 out of 110) scored 6 points or more on the DLQI, signifying at least a moderate effect on life quality, while no male scored higher than 5 points ($p=0.022$).

In the DH-specific questionnaire, 10% of the female and 4% of the male patients reported ongoing gastrointestinal symptoms at the time of the study, but this difference did not reach statistical significance ($p=0.076$) (Table I). However, when measured with the GSRS questionnaire, the females had a higher GSRS total score than the males, indicating more severe gastrointestinal symptoms at the time of the study ($p=0.027$) (**Fig. 1**). The generic quality of life measured with the PGWB questionnaire showed no sex differences (Table I), but the female patients with DH had a non-significant trend towards a worse PGWB vitality subscore when compared with the male patients with DH (median, IQR: 19, 16–20 vs 20, 17–21, $p=0.061$).

The female patients with DH were more often members of the Finnish Coeliac Society than the male patients (75% vs 58%, $p=0.008$) (Table I). Neither the presence of first-degree relatives with DH or coeliac disease, nor the BMI or current smoking status differed between the sexes. Female patients with DH had been more often diagnosed with thyroid disease than male patients, but the occurrence of other self-reported long-term illnesses did not differ (**Table II**). Likewise, the pain medications or medications used for treating gastrointestinal symptoms (mainly proton-pump inhibitors and medications affecting bowel function) did not differ between the sexes, and the reported current use of topical glucocorticoids was in general minor. Female patients reported using vitamins or other dietary supplements significantly more often than did male patients.

When the male patients with DH following a strict GFD were compared with those with dietary lapses or consuming a normal diet, dapsone was used significantly less often (5% vs 29%, $p<0.001$) and skin symptoms were less frequent at the time of the study (annual skin symptoms 14% vs 38%, $p=0.005$), but the skin symptoms-related life quality was lower among those males adhering to a strict GFD ($p=0.051$). Moreover, among males with DH, the strict diet was associated positively with being a member of the Finnish Coeliac Society

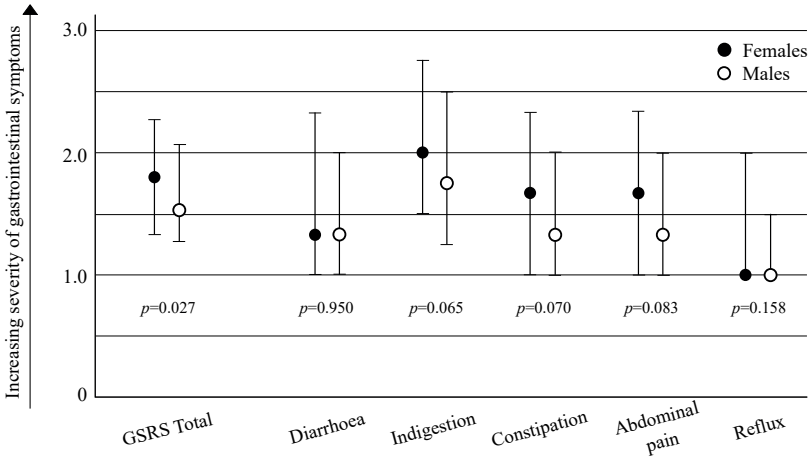

Fig. 1. Differences in the severity of gastrointestinal symptoms measured with the Gastrointestinal Symptoms Rating Scale (GSRS) between long-term treated male and female patients with dermatitis herpetiformis. Markers show the median values, and the whiskers present the interquartile ranges.

Table II. Comorbidities and use of selected medications in treated male and female patients with dermatitis herpetiformis

	Female, $n=111$ n (%)	Male, $n=126$ n (%)	p-value
Thyroid disease	22 (20)	8 (8)	0.008
Diabetes mellitus			0.901
Type 1	3 (3)	3 (2)	
Type 2	11 (10)	15 (12)	
Rheumatoid disease	3 (3)	4 (3)	0.830
Hypercholesterolaemia	21 (20)	26 (22)	0.738
Hypertension	31 (28)	41 (33)	0.441
Cerebrovascular disease	5 (5)	3 (2)	0.479
Coronary artery disease	8 (7)	11 (9)	0.654
Malignancy	10 (9)	11 (9)	0.955
Lymphoma	1 (1)	1 (1)	0.928
Other skin disease[a]	7 (6)	8 (6)	0.989
Other gastrointestinal disease[b]	11 (10)	14 (11)	0.764
Use of vitamins or dietary supplements	79 (71)	54 (43)	<0.001
Use of medication for gastrointestinal symptoms[c]	14 (13)	18 (14)	0.707
Use of pain killers	15 (14)	11 (9)	0.240
Use of topical glucocorticoids	2 (1)	1 (1)	0.488

[a]Other than dermatitis herpetiformis. [b]Other than coeliac disease. [c]Mainly proton-pump inhibitors and medication affecting bowel function

(65% vs 43%, $p=0.019$) and negatively with being a smoker at the time of the study (6% vs 23%, $p=0.014$). No statistically significant differences were observed when females with DH with a strict adherence to a GFD were compared with females with dietary lapses. The strictness of the diet was not associated with the GSRS and PGWB scores, or with age at the time of the study or with the duration of the disease in either sex.

DISCUSSION

This is the first study evaluating the differences in GFD adherence between the sexes in long-term treated DH. It revealed, in a large DH cohort, that the female patients have significantly better adherence to a GFD compared with male patients. Moreover, the frequency of skin symptoms did not differ between the sexes, but male patients with DH regularly used dapsone more often. Intriguingly however, females reported that skin symptoms affected their quality of life significantly more than the males, and females also experienced more severe gastrointestinal symptoms.

There have been only a few studies addressing the differences between males and females affected by DH, and the main focus has been on newly diagnosed patients. Previous studies have linked male sex with younger age at the onset of DH symptoms, more severe skin symptoms at diagnosis and more frequent initiation of dapsone after diagnosis (28–30). Furthermore, 2 studies have shown an increased risk for delayed diagnosis in females (21, 29), but, in contrast, 1 study associated increased diagnostic delay with male sex (30). In addition, male patients with DH seem to have a better quality of life at diagnosis compared with females (31).

Even less is known about sex differences in long-term GFD-treated patients with DH. In the current long-term study, male patients used dapsone significantly more often than did females, and among males the use of dapsone and frequency of current skin symptoms were both negatively associated with adherence to a strict GFD. In addition, although the reported frequency of skin symptoms and the general quality of life was equal for both sexes, females reported that the skin symptoms affected their quality of life significantly more than did the males, despite the better adherence to the strict GFD observed among females. Furthermore, also among males the poor dermatology-related quality of life was associated with strict adherence to the GFD. These observations suggest that the experienced burden of skin symptoms, rather than the frequency of symptoms, might increase the motivation of adhering strictly to the GFD. As the dermatological life quality is worse and the use of dapsone less common in females, and as we have also previously detected a longer diagnostic delay in DH among females compared with males in Finland (21), it is possible that the skin symptoms are more easily overlooked in females than in males with DH. However, refractory DH, defined as persistent DH skin symptoms despite at least a 3-year-long treatment with a strict GFD, has been demonstrated to be more common among males with DH than among females (32), which could, at least partially, explain the more common dapsone usage among males in this study.

The current study also established that the long-term GFD-treated female patients with DH had more severe gastrointestinal symptoms according to the GSRS questionnaire. This result is parallel with our previous study with an entirely different and smaller ($n=78$) DH cohort, which, likewise, found that GFD-treated females with DH have more severe gastrointestinal symptoms, especially constipation, compared with males (20). Similar increased gastrointestinal symptom severity in females has been shown for coeliac disease (13–15). In this study no association was found between the severity of gastrointestinal symptoms and the strictness of the GFD in either sex, although dietary lapses are one of the most common reasons for persistent gastrointestinal symptoms in patients with coeliac disease (33). However, persistent gastrointestinal symptoms can also be related to factors beyond DH and GFD as, for example, the prevalence of irritable bowel syndrome-type symptoms been shown to be frequent among patients with coeliac disease (34).

In this study, female patients with DH reported following a strict GFD significantly more often than did male patients. Females were also more often members of the Finnish Coeliac Society, and they used vitamins or other dietary supplements more often than did males. In addition, among male patients, being a member of the Finnish Coeliac Society and being a non-smoker were associated with strict adherence to a GFD. There are no previous studies focusing on the factors related to GFD

adherence in patients with DH, but in coeliac disease no consistent association between sex and dietary adherence has been observed (16–19). However, in coeliac disease, a better adherence to a GFD has been associated with being a member of a patient organization and being a non-smoker, in parallel with our current results (16, 17, 35, 36). These findings emphasize the need for support, especially among males in sustaining a strict life-long adherence to GFD, and they show that patients with DH also benefit from being a member of the Finnish Coeliac Society. However, despite the differences in the GFD adherence between sexes, there were no differences in the number of complications, such as the presence of lymphomas or other malignancies. Furthermore, the presence of long-term illnesses, except for thyroid disease, was equal between the sexes.

As an obvious strength, this study included a large cohort of biopsy-proven patients with DH diagnosed and treated similarly by dermatologists specialized in DH. Moreover, the patients were long-term treated, as they had been on a GFD for a median of 24 years, and there were no differences between the sexes in terms of age or duration of treatment. In addition, structured and validated questionnaires were used in evaluating the quality of life and severity of gastrointestinal symptoms. The limitations of this study are the questionnaire-based design and the lack of clinical evaluation of patients at the time of the study. In addition, there is a possibility of a selection bias, as the study could include only those patients who agreed to answer the questionnaires. Thus, the possible differences, for instance, in experienced clinical symptoms and in GFD adherence between those responding and not-responding to the questionnaires remain unknown.

In conclusion, this study showed that long-term treated female patients with DH have better treatment compliance compared with male patients, as they have significantly better adherence to a strict GFD and were also more often members of the Finnish Coeliac Society. Although the occurrence of DH-related skin symptoms was equal between the sexes, female patients had a lower skin symptoms-related quality of life. Regardless of this fact, female patients were found to use dapsone less often than did males, and thus it is possible that the skin symptoms are overlooked in females more easily than in males. Overall, the observed lower adherence to a strict GFD in the male sex should be counteracted by giving additional dietary support and encouraging more men to join a group such as the Finnish Coeliac Society.

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