

REVIEW ARTICLE

Fatigue in celiac disease: A review of the literature

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Introduction

Fatigue can be defined as “an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion”¹ and can interfere with physical and mental work, affecting the quality of life of many patients.^{2,3} Fatigue has increasingly been recognized as a substantial complaint in patients with chronic inflammatory and autoimmune diseases, including inflammatory bowel disease, as well as cancer and neurodegenerative diseases.^{4–6}

The pathogenesis of fatigue is only partially understood. A conceptual model for understanding fatigue is the “sickness behavior response,” an evolutionarily preserved survival-enhancing strategy in humans and animals that occurs during states of infection or damage.^{7,8} The sickness behavior response is characterized by several phenomena, such as decreased activity, tiredness, fatigue, depression, social withdrawal, and loss of thirst and hunger. The response is triggered by pro-inflammatory cytokines, especially interleukin-1 β . In inflammatory states, this cytokine is rapidly produced and released by innate immune cells and transported into the brain, where it binds to specific receptors on cerebral neurons and induces sickness behavior.² Several other factors are known to influence fatigue, including depression, pain, and sleep disturbances.⁹

Celiac disease is a chronic, immune-mediated, small intestinal enteropathy that affects approximately 1% of the North

Abstract

Fatigue is increasingly recognized as a significant problem in patients with chronic inflammatory and autoimmune diseases. In celiac disease, a chronic immune-mediated disease triggered by dietary gluten, conflicting opinions exist regarding both the size of the problem and the effect of a gluten-free diet (GFD) on fatigue. We reviewed the existing literature regarding fatigue in celiac disease. We conducted a systematic search in the Embase, Ovid Medline, and Cochrane databases using subject terms from controlled vocabularies. Articles were reviewed based on language, type of article, title, and abstract or full text. Eighteen articles were finally selected for review. Fatigue was significantly greater in patients with celiac disease compared to healthy control subjects. Fatigue prevalence ranged from 8 to 100%. Fatigue severity was assessed in six studies. The fatigue visual analogue scale was the most frequently used fatigue instrument with scores from 57 to 79 prior to starting a GFD and from 39 to 59 in patients on a GFD. Seven studies investigated the effect of a GFD on fatigue, including five studies that reported less fatigue while on the diet and two studies that showed no significant difference. This review concludes that fatigue is a substantial complaint in patients with celiac disease. A GFD seems to reduce fatigue, but existing data are limited.

European population.¹⁰ The disease is caused by exposure to dietary gluten in genetically predisposed individuals and is characterized by chronic intestinal inflammation that varies from a barely increased number of intraepithelial lymphocytes to mucosal atrophy.¹¹ The clinical presentation of celiac disease varies from the classical malabsorption symptoms with diarrhea, weight loss, and abdominal pain to constipation, reflux, and various neurological symptoms.^{11,12} Diagnosis is based on histopathological findings in duodenal biopsies, in addition to positive serology, elevated serum levels of tissue transglutaminase IgA antibodies, specific endomysial antibodies, and/or deamidated gliadin peptide antibodies, either IgA or IgG isotype.¹⁰ The only well-established treatment for celiac disease is to avoid gluten in the diet, which in the majority of patients leads to normalization of the small intestinal mucosa and reduced blood levels or loss of specific plasma antibodies.

The quality of life in patients suffering from celiac disease is reduced and is at least partly linked to the dietary restrictions with regard to a gluten-free diet (GFD).^{13,14} Although existing data are scarce, the chronic inflammatory nature of the disease implies that fatigue constitutes a significant problem in celiac disease. Clinical experience and findings from previous studies indicate that, in some patients, fatigue may be the presenting and single symptom of celiac disease,^{15,16} and in our clinical

experience, fatigue is not infrequently perceived as disabling in untreated patients. It is generally assumed that most celiac disease-related symptoms disappear when a GFD has been implemented, but whether this also applies to fatigue is unclear.

The aim of this review was to evaluate the existing literature regarding fatigue in patients with celiac disease to elucidate fatigue prevalence, severity, and response to GFD.

Methods

We conducted a systematic literature search on 27 June 2017 using the Embase, Ovid Medline, and Cochrane Library databases. We used subject terms from controlled vocabularies Emtree and MeSH: “*celiac disease, celiac sprue, gluten enteropathy, gluten sensitive enteropathy, non tropical sprue, gluten hypersensitivity, gluten sensitivity, duodenal atrophy, fatigue, tiredness*” and combinations thereof.

A total of 265 articles were considered for inclusion in this review. Non-English language publications were excluded. Abstracts, case reports, and review articles not including original data analysis were also omitted. A total of 229 papers were excluded based on the title, language, or type of article, whereas 17 were excluded based on their abstracts or full text. One article¹⁷ was excluded to avoid confounding because it presented the same data material as another¹⁸. Thus, 18 articles were finally included in this review.

Results

Articles included in the review are shown in Table 1.

Study designs. Of the 18 included studies, only one was multicenter, randomized, double-blind, and placebo-controlled.¹⁹ Eleven of the studies were prospective. Three studies were non-randomized controlled,^{20–22} and seven were uncontrolled observational studies.^{23–29} Seven trials were retrospective in design.^{14,18,30–34} Six of the studies were longitudinal, with a follow-up period from 3 months to 15 years.^{19,23–26,28}

Fatigue instruments. In six studies, a specific instrument to measure fatigue was used,^{14,19–21,23,24} and the remaining studies dichotomized fatigue into questions of yes or no. Three studies used the fatigue visual analogue scale (fVAS),^{20,21,24} whereas the daily fatigue impact scale (D-FIS),²³ fatigue severity scale (FSS),²⁰ Gießener symptom check list (GBB-24),¹⁴ fibromyalgia impact questionnaire (FIQ),²⁴ chronic fatigue syndrome-questionnaire (CFS-Q),²⁰ and celiac disease patient reported outcome (CeD PRO)¹⁹ were all applied in one study each.

Validated generic fatigue instruments. The fVAS is a single-item scale consisting of a horizontal line with vertical anchors, usually 100 mm. The wording on the left end of the line (0 mm) is “no fatigue,” and on the right end, it is (100 mm) “fatigue as bad as it can be.” The patient puts a mark on the horizontal line to describe the degree of fatigue in the prior week. The score ranges from 0 to 100 mm (0–10 cm).³⁵ The scale is sensitive to change in fatigue.³⁶ Clinically relevant fatigue has been defined as fVAS scores ≥ 50 mm,^{5,37} although one study used fVAS scores ≥ 20 mm as a cut-off for significant fatigue.³⁸

The D-FIS is an eight-item scale designed to capture the daily impact of fatigue on health-related quality of life.³⁹ Cognitive, psychosocial, and physical symptoms are addressed. Each item is rated on a 5-point scale ranging from 0 (no problem) to 4 (extreme problem). The added scores represent the D-FIS score, ranging from 0 to 32, with 12 as the cut-off for significant fatigue.⁴⁰

The FSS aims to evaluate and quantify fatigue associated with chronic disease.⁴¹ The questionnaire includes nine questions rated from 1 to 7. The FSS score is usually reported as the mean score of the nine questions, ranging from 1 to 7, or as the sum of all the rated items, ranging from 9 to 63. Significant fatigue has been defined as a mean FSS score > 4 .⁴²

Disease-specific fatigue instruments. The FIQ is an instrument developed to assess the current health status of women with fibromyalgia syndrome, including fatigue. Fatigue is scored in a similar way as on the fVAS; patients are asked to put a mark on a 10-cm horizontal line to show how tired they felt in the prior week. The total FIQ score ranges from 0 to 100 and summarizes the scores from all 10 items: fatigue, stiffness, anxiety, depression, pain, physical impairment, feel good, work missed, do work, and rested.⁴³

The CFS-Q has not been validated but was developed for a study that compared chronic “postviral” fatigue with neuromuscular and affective disorders. The questionnaire consists of eight items addressing physical fatigue and five items addressing mental fatigue. Each item is scored from 0 to 2, giving a total score from 0 to 26.⁴⁴

Other fatigue instruments. The CeD PRO Non-GI domain evaluates tiredness combined with headache but does not evaluate fatigue separately. The score ranges from 0 to 10 points, with a higher score indicating greater symptom severity.¹⁹ The GBB-24 is a check list that assesses bodily symptoms in four subscales, including fatigue.⁴⁵

In two studies, a combination of fatigue instruments was used: fVAS, CFS-Q, and FSS in one study,²⁰ whereas another study used the fVAS and FIQ.²⁴

Fatigue prevalence. Fourteen studies reported the prevalence of fatigue in celiac disease, ranging from 8 to 100% at the time of diagnosis, with a mean of 52% and median of 52.5%.^{18,19,22,24–34}

Fatigue severity. Six studies investigated the severity of fatigue in patients with celiac disease.^{14,19–21,23,24} The fVAS was the most frequently used instrument to measure fatigue and was used in three studies.^{20,21,24} The fVAS scores reported among celiac patients before GFD in these studies ranged from 57 to 79 (mean 66). In celiac patients who were on a GFD, the reported fVAS scores ranged from 39 to 59 (mean 51).^{20,21,24} Two of the studies reported fVAS scores in patients who had been on the diet for at least a year (patients on annual control for their celiac disease).^{20,21} The last study presented fVAS scores at diagnosis and after 1 year on a GFD.²⁴ In the controlled studies, mean fVAS scores were significantly higher in celiac disease patients (57–61; mean 59)^{20,21} than in healthy control subjects (HCS) (34–44; mean 39).^{20,21} The FSS scores were also

Table 1 Articles included in the review, sorted according to study design and year of publication

Author, year	Primary end-point	Study design	No. of patients (HCS)	Fatigue instrument	Fatigue-related findings
Multicenter randomized controlled study					
Leffler <i>et al.</i> , 2015 ¹⁹	Efficacy and safety of larazotide acetate in celiac disease patients on GFD	Multicenter, randomized, double-blind, placebo-controlled study	342	CeD PRO Non-GI domain (headache and tiredness)	Approximately 70% of patients reported tiredness during placebo run-in phase, mean score 2.75 After larazotide 0.5 mg, mean change from baseline -0.25, headache and tiredness evaluated together
Prospective controlled studies					
Zingone <i>et al.</i> , 2010 ²¹	Quality of sleep in celiac patients	Prospective, cross-sectional, controlled trial; treated versus untreated celiac, no follow-up	60 (30)	fVAS	More fatigue in celiac disease patients than in HCS. Lower fVAS scores (not significantly) when on GFD
Siniscalchi <i>et al.</i> , 2005 ²⁰	Fatigue and depression	Prospective, cross-sectional, controlled trial; treated versus untreated celiac, no follow-up	130 (80)	fVAS, CFS-Q, FSS	Significantly more fatigue in patients with celiac disease (treated and untreated) than HCS. Lower FSS and higher fVAS scores when on GFD, but not significant. Fatigue related to depression
Ludvigsson <i>et al.</i> , 2004 ²²	Symptoms and signs of celiac disease	Prospective, controlled cohort study, no follow-up	79 (108)	Yes/no	28% of children with celiac disease versus 2.4% of healthy children were "tired"
Prospective uncontrolled studies					
Silvester <i>et al.</i> , 2016 ²⁶	Reactions to gluten in celiac disease patients on a GFD	Prospective observational study, uncontrolled, 6-month follow-up	105	Yes/no	59% fatigue at time of diagnosis, 33% reported fatigue when exposed to gluten
Rodrigo <i>et al.</i> , 2013 ²⁴	Effect of GFD on HR-QoL in patients with fibromyalgia and associated celiac disease	Prospective trial, irritable bowel syndrome and fibromyalgia patients with screening-detected celiac disease, 1 year follow-up, uncontrolled	7	fVAS, FIQ, Yes/no	Significant reduction in fatigue after starting GFD, 100% had fatigue at presentation
White <i>et al.</i> , 2012 ²⁷	Incidence of childhood celiac disease in Scotland	Prospective observational study, uncontrolled	91	Yes/no	31.9% fatigue at time of diagnosis
Saleem <i>et al.</i> , 2011 ²⁵	Presenting symptoms of celiac disease, associated conditions, and complications	Prospective case series study, uncontrolled, median follow-up 15 years	106	Yes/no	8% fatigue as presenting symptom
Jordá <i>et al.</i> , 2010 ²³	Fatigue and HR-QoL	Prospective, cross-sectional, treated versus untreated celiac, uncontrolled	51	D-FIS	Significantly worse fatigue D-FIS scores in untreated celiac patients. Fatigue and quality of life inversely

Table 1 (Continued)

Author, year	Primary end-point	Study design	No. of patients (HCS)	Fatigue instrument	Fatigue-related findings
					correlated. Less fatigue after 1 year on GFD
Cook <i>et al.</i> , 2000 ²⁸	Prevalence of celiac disease in Christchurch and clinical significance of screening-detected celiac disease	Prospective uncontrolled, follow-up 3–6 months	12	Yes/no	46% of celiac disease patients had tiredness/lethargy, 50% of celiac disease patients with tiredness improved after introduction of GFD
Bodé <i>et al.</i> , 1996 ²⁹	Degree of atypical symptoms, change in clinical pattern, delay in diagnosis	Prospective, observational study, uncontrolled, consecutive patients diagnosed over 22 years. Follow-up not quantified	50	Yes/no	78% tiredness as presenting symptom
Retrospective cohort/cross-sectional studies					
Spijkerman <i>et al.</i> , 2016 ³⁰	Presenting symptoms and concomitant disorders	Retrospective cohort study, uncontrolled	412	Yes/no	35% fatigue as presenting symptom
Masjedizadeh <i>et al.</i> , 2006 ³¹	Clinical, laboratory, and histological features of celiac disease	Retrospective, cross-sectional study, uncontrolled	52	Yes/no	73.1% fatigue as presenting symptom (study included adults and children)
Retrospective cross-sectional, mail studies					
Pulido <i>et al.</i> , 2013 ³³	Clinical features of adult celiac disease	Retrospective, cross-sectional survey among celiac patients in patient support groups; uncontrolled, mail study	5912	Yes/no	74.2% reported extreme weakness/tiredness at time of diagnosis, improvement on GFD (65.7% fully recovered)
Häuser <i>et al.</i> , 2006 ¹⁴	HR-QoL in celiac disease patients	Retrospective cross-sectional survey among celiac patients in patient support group; comparative, mail study	446	GBB-24	Greater fatigue in celiac patients, mean 9.8 versus 4.0 in representative German population
Zipser <i>et al.</i> , 2003 ³²	Presentations of celiac disease	Retrospective cross-sectional survey among celiac patients in patient support group; uncontrolled, mail study	1032, 134 detailed symptom descriptions	Yes/no	82% of adult celiac disease patients presented with fatigue
Retrospective chart reviews					
Khatib <i>et al.</i> , 2016 ³⁴	Presenting symptoms in pediatric celiac disease	Retrospective chart review, uncontrolled	165	Yes/no	9% fatigue as presenting symptom
Jericho <i>et al.</i> , 2016 ¹⁸	Effectiveness of GFD on extraintestinal symptoms	Retrospective chart review, uncontrolled, follow-up 2.3 (adults) and 2.6 (children) years	328, 157 < 18 years old	Yes/no	28% fatigue in children, 37% fatigue in adults. 81% of children improve on GFD, 51% of adults improve on GFD

CeD PRO, celiac disease patient reported outcome; CFS-Q, chronic fatigue syndrome-questionnaire; D-FIS, daily fatigue impact scale; FIQ, fibromyalgia impact questionnaire; FSS, fatigue severity scale; fVAS, fatigue visual analog scale; GBB-24, Gießener symptom check list; GFD, gluten-free diet; GI, gastrointestinal; HCS, healthy control subjects; HR-QoL, health-related quality of life.

significantly higher in celiac disease patients (mean 36.3 vs 16.7, median 35 vs 15) than in HCS.²⁰

Effect of a GFD on fatigue. Seven studies explored the effect of GFD on fatigue.^{18,20,21,23,24,28,33} Five studies reported less fatigue after the patients were on a GFD,^{18,23,24,28,33} but only two of these studies used specific fatigue instruments, namely, the D-FIS, fVAS, and FIQ.^{23,24} The median D-FIS score in untreated patients was 16.0 versus 3.0 on the diet.²³ After 1 year on the GFD, the median D-FIS decreased from 13.0 to 7.0.²³ The mean fVAS was reduced from 79 to 39 after introducing a GFD, and the mean FIQ score was reduced from 74.3 to 36.6.²⁴ In two other studies, there was no significant difference in fatigue scores between patients on a GFD and patients on a regular diet.

Discussion

Fatigue in celiac disease has not been investigated much previously. However, clinical experiences, as well as previous case reports, indicate that it may represent a significant problem for these patients.^{46,47} In the current review, 18 studies addressing fatigue in celiac disease were finally included, but only 4 studies presented fatigue as a specific end-point.^{20,21,23,24} In the remaining 14 studies, fatigue was registered as one of many possible phenomena that patients with celiac disease may experience. Thus, fatigue has not been the main focus of interest in the currently available literature.

The fatigue prevalence reported in previous studies is variable, ranging from 8 to 100%. The only study presenting prevalence rates and using a fatigue-specific instrument (fVAS) reported a fatigue prevalence of 100% before the GFD.²⁴ In this group of patients with both irritable bowel syndrome and fibromyalgia, along with associated celiac disease, the prevalence of fatigue was probably overestimated. The other studies reporting prevalence have registered and presented fatigue or tiredness dichotomously with a yes/no response, and the definition of fatigue is unclear. The prevalence at the time of diagnosis in these studies ranged from 8 to 82%.^{25,32} As no validated fatigue instrument or cut-off was used, and fatigue was not clearly defined in most studies, these results should be interpreted with caution. No fatigue prevalence data are available regarding patients who are on a GFD.

In most previous studies, fatigue severity has been investigated using a more specific approach, with selected fatigue instruments to aid in the diagnosis. This is reflected in less variety in the reported data regarding fatigue severity than in fatigue prevalence. However, only three studies applied the same fatigue instrument and are directly comparable. Moreover, none of the studies addressing fatigue severity defined a cut-off score for significant fatigue. Fatigue severity was consistently higher in celiac patients than in healthy controls.

A GFD is the only established treatment for celiac disease; it leads to mucosal normalization or improvement in 65 to 100% of patients and improves or eradicates symptoms.¹⁰ However, data regarding the effect of GFD on fatigue are sparse. Previous studies have reported that fatigue persists after GFD in some patients.^{48,49} In the current review, the seven studies that registered fatigue before and after GFD demonstrated less fatigue after commencing the GFD. One study reported higher fVAS scores

but lower FSS scores on the GFD, although these differences were not significant.²⁰ Two of the studies reporting fatigue before and after GFD were not longitudinal,^{20,21} meaning that the patients reporting fatigue after GFD are not the same as the patients reporting fatigue at the time of diagnosis, and it is unknown how the patients already on a GFD scored before they commenced the diet. Three studies addressing change in fatigue with GFD did not use validated fatigue scores; they just stated that fatigue was reduced.^{18,28,33} Two studies evaluating the effect of GFD on fatigue had very small sample sizes of 3 and 7 patients.^{23,24} Taken together, the limited amount of data suggests that fatigue may improve with a GFD.

The fatigue experienced by patients is influenced by several factors, including disturbed sleep, pain, and psychological conditions, such as depression.² Most of the studies included in our review report fatigue as a dichotomous variable with a yes/no response and did not evaluate fatigue in association with other symptoms. One of the included studies looked at the quality of sleep in patients with celiac disease, finding that reduced sleep quality and sleep disorders are directly related to fatigue.²¹ One study found that fatigue was correlated with depression in untreated patients, but in patients on a GFD, depression persisted or worsened as fatigue was reduced.²⁰

A recent review that evaluated psychological morbidity in celiac disease suggested that celiac disease has a considerable psychological impact, related both to the disease itself and to the patient's subjective perception of the disorder and the GFD treatment.⁵⁰ Moreover, fatigue is often rated by patients with chronic inflammatory diseases as one of the most important features leading to decreased quality of life.³ Celiac patients consistently reported reduced quality of life compared to healthy controls in previous studies. Furthermore, fatigue has been linked to undetected celiac disease,¹⁶ and it is likely that fatigue contributes to the reduced quality of life. One of the included studies looked at the influence of fatigue on patients' health-related quality of life and found that fatigue is inversely proportional to health-related quality of life.²³

Measuring fatigue represents a challenge due to its non-specific and subjective nature. The definition of fatigue among celiac patients has varied in previous studies. Moreover, whether different dimensions of fatigue exist, such as peripheral, physical, mental, or central (general), or if fatigue only represents a unidimensional trait is unclear. This makes it difficult to compare fatigue prevalence and severity across different studies. Several validated instruments are available to evaluate fatigue, but no "gold standard" of fatigue measurement exists. Several scores have been validated in chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, but have not yet been used or validated in celiac disease.^{36,41} Only four studies in our review applied validated fatigue scores in celiac disease. Two studies presented a clear definition of fatigue. Thus, the terminology for fatigue has been variable, using different terms such as tiredness, fatigue, weakness, and lethargy in the included articles. Consequently, it is difficult to ascertain if all studies have addressed the same subjects and if the different terms have been equally understood by the participants.

The variable study design of several previous studies hampers their results. Data originate mostly from cross-sectional or

retrospective studies instead of randomized controlled trials or cohort studies. In many cases in which follow-up data were included, the sample size has been small. Fatigue has not been the primary end-point in most studies. Six of the prevalence studies are retrospective, including retrospective chart reviews and mail studies. Retrospective mail or chart studies are less credible than prospective controlled trials as they are less accurate and subject to recall bias, and the diversity in results regarding prevalence may be due to differences in study design and limited methodological quality.

In conclusion, previous studies indicate that fatigue is a substantial complaint among patients with celiac disease. GFD may improve fatigue, but data are limited. Previous studies are difficult to interpret due to different study designs, inadequate definitions of fatigue, and imperfect use of validated instruments to measure fatigue. Thus, longitudinal studies using appropriate fatigue instruments are warranted.

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