Clinical Nutrition 38 (2019) 357–363

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Long term effects of gluten-free diet in non-celiac wheat sensitivity

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ARTICLE INFO

Article history:
Received 22 August 2017
Accepted 17 December 2017

Keywords:
Gluten
Celiac disease
Non-celiac gluten sensitivity
Quality of life
Gluten free diet
Outcome

SUMMARY

Background & aims: Information about the clinical outcome of patients with non-celiac wheat sensitivity (NCWS) treated with gluten-free diet (GFD) derive from studies assessing the symptom response in the first few weeks of treatment. We aimed to evaluate the clinical response to the GFD and the quality of life (QoL) of NCWS patients in the long term.

Methods: Forty-four NCWS (diagnosed according to the Salerno criteria) participated in the study. Participants rated their symptoms according to a 0–10 scale patients and filled in a QoL questionnaire (CDQ) before the beginning of the GFD and during a follow-up evaluation performed after at least one year. To assess the reliability of the questionnaire we also included a control group of 43 matched patients with celiac disease (CD).

Results: Upon diagnosis, NCWS patients had a high prevalence of intestinal and extraintestinal symptoms. Also, most symptoms were described as severe and the QoL questionnaire showed high scores. On follow-up, both prevalence and severity of the most common symptoms were significantly reduced. However, persistent intestinal and extraintestinal symptoms of mild severity were found in 65.9 and 72.7% of NCWS patients. In comparison, in the CD group, the prevalence was lower (32.6 and 23.2% respectively) and consistent with previous studies.

The analyses of the determinant of QoL showed that, upon diagnosis, NCWS patients had higher scores in the CDQ "gastrointestinal symptoms" ($p < 0.001$), "emotional aspects" ($p < 0.001$) and "social problems" ($p < 0.001$) subclasses compared to CD patients. After the GFD, NCWS and CD patients shared similar scores in all of the subclasses.

Conclusions: A significant proportion of NCWS patients still complains of intestinal and extraintestinal symptoms, even if significantly attenuated by the GFD, even years after the diagnosis. A comprehensive nutritional evaluation of these patients is required to further improve their symptoms and their QoL.

1. Introduction

Non-celiac wheat sensitivity (NCWS) is the youngest member of the family of gluten related disorders (GRD). It is characterized by intestinal and extra-intestinal symptoms occurring after the ingestion of gluten containing food in subjects in whom celiac disease (CD) and wheat allergy have been ruled out [1].

NCWS is an increasingly hot topic in the field of GRD, however many aspects of this condition remain elusive, especially in pathogenic and diagnostic terms [2].

The improvement of clinical manifestations after a gluten free diet (GFD) and their recurrence after reintroduction of gluten are required elements for the diagnosis of NCWS [1].

Recently, a group of experts proposed new diagnostic criteria for NCWS, underlining the importance of symptomatic scores to assess the response and the relapse of gluten-related symptoms [3].

The effect of the GFD on the symptomatic score of NCWS patients in the setting of the diagnostic double blinded placebo controlled challenge (DBPCC) was first reported by Carroccio et al. in a retrospective study [4] and was subsequently evaluated in two prospective studies [5,6].

These trials provided very interesting information about NCWS clinical presentation and early response to the GFD. However, the

Abbreviations: NCWS, non-celiac wheat sensitivity; GRD, gluten related disorders; CD, celiac disease; GFD, gluten free diet; DBPCC, double blinded placebo controlled challenge; QoL, quality of life.

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https://doi.org/10.1016/j.clnu.2017.12.017
0261-5614/

symptomatic response was evaluated only in a timeframe not more than two weeks [5,6]. Data regarding the long-term effects of the GFD on NCWS patients are still lacking.

In particular two aspects still remain unknown: how many NCWS patients still complain of intestinal or extraintestinal symptoms (even if attenuated) in the long term and whether and to which extent the GFD represents a social burden for NCWS patients.

Trying to answer these questions, we evaluated gastrointestinal symptoms and social aspects of NCWS patients upon diagnosis and after a long term follow-up.

2. Methods

2.1. Study group

We evaluated patients with a diagnosis of NCWS, which required all of the following criteria to be confirmed: 1) intestinal and extra-intestinal symptoms consistent with a gluten-related medical condition; 2) absence of diagnostic criteria for CD or wheat allergy; 3) resolution or amelioration of symptoms when gluten was withdrawn for a period of at least 6 months GFD; and 4) new appearance or worsening of symptoms after reintroduction of gluten for a period ranging from 20 to 30 days.

Specifically, gluten was reintroduced in a blind manner, according to the criteria recently proposed by an expert group [3].

After the diagnostic confirmation and the prescription of a GFD, patients performed regular follow-up evaluations about once every 18 months. On the occasion of each visit, clinical and laboratory data were collected. As part of an internal protocol, patients were administered symptoms-focused questionnaires (see the '*Recorded data*' paragraph) to assess the burden of disease both at the beginning of the GFD and after at least 1 year.

The use of questionnaires is highly validated and still represents the only tool to assess the response to the GFD in NCWS [3,7].

We retrospectively analyzed the prospectively collected data of patients enrolled in our outpatients clinic (a tertiary referral centre for CD) from 2012 to 2016.

Patients reporting either a low adherence to the GFD or accidental food contaminations were excluded from the study, as well as patients without a follow-up examination.

2.2. Controls

One of the most common problems associated with the use of questionnaire is a possible over/underestimate of symptoms. To rule out this possibility, the questionnaires were administered also to a matched group of CD subjects.

The sole purpose of designing a control group was to verify whether the models deriving for the selected questionnaires were able to catch the correct rate of CD patients still symptomatic after the GFD, which has been extensively reported in literature [8]. Thus, the CD group acted as a sort of "internal quality control" of the questionnaires fitness, mainly to rule out a possible under- or over-estimation of NCWS symptoms.

The diagnosis of CD was performed according to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition [9]. All of the patients also satisfied the diagnostic criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [10].

The matching parameters included age, duration of GFD and associated medical conditions.

A matching for sex and number of symptoms was not performed since we did not aim to compare the efficacy of the GFD between the two groups, but rather to create a control group representative of the typical CD population of a tertiary centre. In fact, the sharp female predominance found in NCWS [2] as well as the higher symptomatic burden of NCWS (partly deriving from the diagnostic criteria) are well known. Thus, a matching for these factors would have generated a selection bias and hindered our effort of enrolling a typical CD population.

Patient disposition is reported in Fig. 1.

2.3. Recorded data

Documentation for each patient included registration of symptoms, associated medical conditions, biochemistry, autoantibody profile, duodenal histology and, when appropriate, genetic data.

In particular the following manifestations were thoroughly evaluated: diarrhoea, bloating, abdominal pain, constipation, weight loss, fatigue, headache, "foggy mind" (i.e. symptoms of confusion, forgetfulness, and lack of focus and mental clarity), myalgia, skin rash, aphthous oral lesions, menstrual cycle alterations, depression, anxiety, osteopenia/osteoporosis, iron deficiency anaemia and elevated aminotransferase levels.

These conditions with potentially similar symptoms were analyzed by appropriate means: lactose intolerance, irritable bowel syndrome, small intestinal bowel overgrowth [9,10].

We also asked our patients to fill in 2 different questionnaires to evaluate their clinical response to the GFD (both at the diagnosis and on the occasion of the follow-up evaluation after at least one year of GFD):

1) Single-symptom response. Patients were asked how much their symptoms impacted their daily life before and after the beginning of the GFD. Each subject was asked to quantify this impairment using a 0-to-10 numeric rating scale (0 = no impact at all; 10 = extreme difficulties limiting common daily activities).
2) Celiac disease questionnaire (CDQ). The CDQ is a disease-specific health-related quality of life (QoL) questionnaire developed and validated for CD patients already on a GFD [11] CDQ has already been translated and validated into Italian language in a previous study [12].

Briefly, this instrument consists of a 28-item questionnaire whose responses are scored in a seven-point Likert scale in which "7" corresponds to the best function and "1" to the worst. The CDQ scores are computed overall and over four areas according to the scoring manual: emotion (seven items), gastrointestinal symptoms (seven items), gastrointestinal worries (seven items), and social problems (seven items).

The original version of CDQ included an item named "fear of getting cancer" (gastrointestinal worries area) which is not applicable for NCWS patients, for whom such a risk has not been demonstrated [2]. As such, this item was removed for both CD and NCWS patients in our study.

2.4. Ethics

The study was approved by our Institutional review board and performed according to the Declaration of Helsinki guidelines. All patients signed an informed consent before entering the study.

2.5. Statistical analysis

Categorical variables were compared according to Fisher's exact test. The distribution of continuous variables was verified with a Kolmogorov–Smirnoff test. According to their distribution, continuous variables were compared with a t-test or a

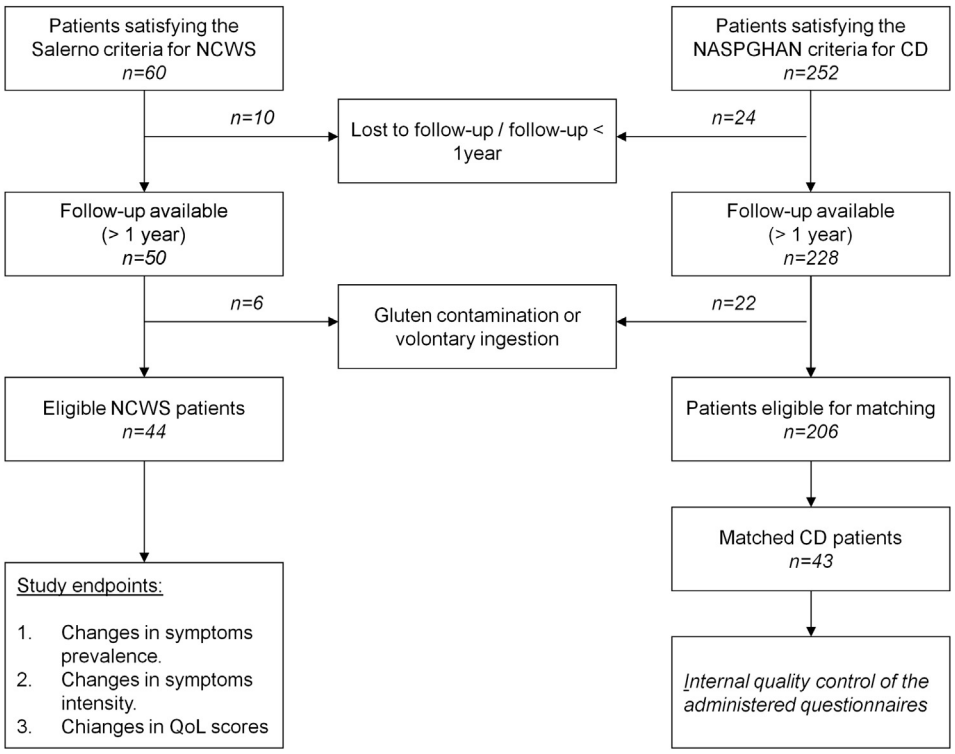

Fig. 1. Patients disposition. NCWS: non-celiac wheat sensitivity; NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; CD: celiac disease.

Mann–Whitney–Wilcoxon test, as appropriate. Variations in the prevalence of symptoms were evaluated with the McNemar test. Pre- and post-GFD questionnaire scores were compared with a Wilcoxon signed ranks test. For each test, we considered as statistically significant p values <0.05. Data analyses were performed with SPSS version 20.0 (SPSS Inc. Chicago, IL, USA).

3. Results

3.1. General features of study and control group

The demographic data of the study and control group are reported in Table 1.

As mentioned in the Methods, the control group was matched for age, duration of the GFD and concurrent conditions. As expected, the NCWS group had a significantly higher female prevalence (90.9 vs 65.1%, p = 0.008) compared to the CD group.

Table 1
Demographic and clinical characteristics of non-celiac wheat sensitivity (NCWS) and celiac disease (CD) patients.

	NCWS (n = 44)	CD (n = 43)	p
Baseline demographic			
Sex (M/F)	4/40 (9.1/90.9%)	14/29 (34.9/65.1%)	0.008
Age – median (range)	40 (18–65)	41 (18–74)	0.421
Concurrent conditions			
IBS	9 (20.5%)	8 (18.6%)	1.000
Lactose intolerance	3 (6.8%)	1 (2.3%)	0.616
SIBO	0	0	N/A
Follow-up: GFD duration			
12–24 months	6	5	0.984
25–36 months	8	6	
37–48 months	22	26	
49–60 months	8	6	

IBS: irritable bowel syndrome; GERD: gastroesophageal reflux disease; SIBO: small intestinal bacterial overgrowth.

The clinical presentation of the study and control group are shown in Table 2.

Even if the total prevalence of symptomatic patients was not different between the two groups (p = 0.241), NCWS has more

Table 2
Symptoms and manifestations characterizing non-celiac wheat sensitivity (NCWS) and celiac disease (CD) patients at the diagnosis.

	NCWS (n = 44)	CD (n = 43)	p
Any manifestation	44 (100%)	41 (95.3%)	0.241
Intestinal manifestations	44 (100%)	32 (74.4%)	<0.001
Diarrhoea	34 (77.3%)	16 (37.2%)	<0.001
Bloating	36 (81.8%)	17 (39.5%)	<0.001
Abdominal pain	37 (84.1%)	11 (25.6%)	<0.001
Constipation	12 (27.3%)	11 (25.6%)	1.000
Weight loss	7 (15.9%)	10 (23.3%)	0.429
Up to two intestinal manifestations	18 (40.9%)	36 (83.7%)	0.001
At least three intestinal manifestations	26 (59.1%)	7 (16.3%)	
Extraintestinal manifestations	44 (100%)	32 (74.4%)	<0.001
Fatigue	34 (77.3%)	9 (20.1%)	<0.001
Iron deficiency anaemia	7 (15.9%)	16 (37.2%)	0.030
Osteopenia/osteoporosis	7 (15.9%)	19 (44.1%)	0.005
Foggy mind	29 (65.6%)	4 (9.3%)	<0.001
Headache	28 (63.6%)	5 (11.6%)	<0.001
Arthromyalgia	11 (25%)	3 (7.0%)	0.039
Alopecia	3 (6.8%)	2 (4.5%)	1.000
Menstrual cycle alterations	9 (20.4%)	8 (18.6%)	1.000
Skin rash	15 (34.9%)	5 (11.6%)	0.021
Elevated liver enzymes	1 (2.2%)	5 (11.6%)	0.101
Aphthous oral lesions	7 (14%)	6 (13.9%)	1.000
Depression/anxiety	6 (13.6%)	3 (6.9%)	0.484
Up to two extraintestinal manifestations	17 (38.6%)	30 (69.8%)	0.005
At least three extraintestinal manifestations	27 (61.4%)	13 (30.2%)	

often three or more intestinal and extraintestinal symptoms and thus a greater prevalence of most of the analyzed manifestations.

Unsurprisingly, malabsorption related manifestations, such as anaemia (37.2 vs 15.9%, p = 0.03) and osteopenia/osteoporosis (44.1 vs 15.9%, p = 0.005), were more frequent in CD than in NCWS patients.

3.2. Study group – non celiac wheat sensitivity

3.2.1. Prevalence of symptoms

As required by the inclusion criteria, all of the NCWS patients had at least one intestinal and one gastrointestinal symptoms. Further, as mentioned earlier, the prevalence of each of the intestinal symptoms was very high, especially diarrhoea (77.3%), bloating (82.8%) and abdominal pain (84.1%). The most prevalent extraintestinal manifestations were fatigue (77.3%), headache (65.6%) and foggy mind (63.6%). Arthromyalgia (25%) and aphthous oral lesions (14%) were also well represented manifestations.

At the follow-up evaluation, the prevalence of intestinal symptoms had decreased significantly except constipation (Table 3).

The picture was similar when extra-intestinal manifestations were analyzed. Specifically, significantly less NCWS patients complained of fatigue, headache, menstrual cycle alterations and skin rash after the GFD.

Overall, 29 (65.9%) and 32 (72.7%) patients still referred intestinal and extraintestinal symptoms of any severity, respectively.

Compared to the baseline, the benefit was statistically significant (p = 0.002).

3.2.2. Severity of symptoms

The single symptom questionnaire showed that the most symptoms of NCWS patients were severe (i.e. score >7) before the GFD. The highest median severity scores were reached by fatigue and arthromyalgia (score 9.0), constipation (score 8.5), diarrhoea, bloating, abdominal pain, foggy mind, headache and skin rash (score 8.0). Aphthous oral lesions (score 6.0), depression/anxiety (score 6.0) and menstrual cycle alterations were described as moderately disturbing.

Following the GFD, these patients experienced a sharp reduction in the intensity of all of the gluten-related symptoms, particularly evident for intestinal symptoms (Fig. 2).

The final median intensity of symptoms was moderate for arthromyalgia (score 4.0) and mild for all of the other manifestations ranging from 3.0 for diarrhoea and fatigue to 0.50 for constipation. All of the patients with skin rash showed a complete regression of this symptom.

Table 3
Prevalence of symptoms in non-celiac wheat sensitivity (NCWS) and celiac disease (CD) patients before the gluten free diet and at the follow-up.

Symptom	NCWS (n = 44)		
	Before	After	p
Diarrhoea	34 (77.3%)	18 (40.9%)	<0.001
Bloating	36 (81.8%)	27 (61.3%)	0.007
Abdominal pain	37 (84.1%)	25 (56.8%)	0.002
Constipation	12 (27.3%)	7 (15.9%)	0.074
Fatigue	34 (77.3%)	25 (56.8%)	0.008
Foggy mind	29 (65.6%)	18 (40.9%)	0.003
Headache	28 (63.6%)	18 (40.9%)	0.004
Arthromyalgia	11 (25%)	8 (18.1%)	0.248
Menstrual cycle alterations	9 (20.4%)	0	0.008
Skin rash	15 (34.9%)	5 (11.4%)	0.004
Aphthous oral lesions	7 (14%)	5 (11.5%)	0.480
Depression/anxiety	6 (13.6%)	3 (6.8%)	0.248

3.2.3. Determinants of quality of life

Consistently with the aforementioned results, the median scores in the CDQ subclasses were particularly high at the baseline ["gastrointestinal symptoms" 32.50 (IQR 28.00–35.00); "emotional aspects" 34.50 (IQR 24.00–43.00); "social problems" 15.50 (11.00–25.50); "gastrointestinal worries" 14.50 (9.00–20.75)].

The GFD led to a significant improvement of the "gastrointestinal symptoms" and "emotional aspects" scores (p < 0.001 in both cases, Wilcoxon signed ranks test).

Instead, neither "social problems" (including items related to the difficulties in eating outside home) or "health worries" scores (including items related to long-term health issues) were significantly modified (Fig. 3).

3.3. Control group – celiac disease

3.3.1. Prevalence of symptoms

Forty-one out of 43 patients (95.3%) were symptomatic at the diagnosis, with the remaining 2 patients being diagnosed in the setting of a family screening. Intestinal manifestations were found in 32 (74.4%) patients with diarrhoea and bloating as the most frequent symptoms (Table 2). Extraintestinal manifestations were found in 32 (74.4%) patients as well. Osteopenia (44.1%), iron deficiency anaemia (37.2%) and fatigue (20.1%) were the most frequently found manifestations.

As expected, the GFD led to a significant reduced prevalence of diarrhoea (23.0%, p = 0.041), bloating (25.6%, p = 0.041) and abdominal pain (11.6%, p = 0.041). As for extraintestinal manifestations, all of the 8 patients (18.6%) reporting menstrual cycle alterations reported a complete resolution of this symptom (p = 0.013).

On the whole, 14 (32.6%) and 10 (23.2%) patients still referred intestinal and extraintestinal symptoms of any severity, respectively.

Compared to the baseline, the benefit was statistically significant (p < 0.001).

3.3.2. Severity of symptoms

CD perceived as severely invalidating symptoms such as diarrhoea (median score 9.0), fatigue (median score 8.0), headache (median score 8.0) and skin rash (median score 7.0). Bloating, abdominal pain and aphthous oral lesions were perceived as symptoms of moderate intensity (median score 6.0), as well as constipation (median score 4.0), menstrual cycle alterations (median score 4.0) and depression/anxiety (median score 5.0).

Following the GFD, CD patients experienced a significantly reduced severity of diarrhoea (median 3.0, p = 0.001), bloating (median 3.0, p = 0.017), abdominal pain (median 1.0, p = 0.003), fatigue (median 3.0, p = 0.007), headache (median 2.0, p = 0.041) and aphthous oral lesions (median 2.0, p = 0.027).

The post-GFD intensity of any gluten related symptom was not significantly different between the two groups.

3.3.3. Aspects of quality of life

The CDQ scores were significantly lower in CD compared to NCWS patients at the diagnosis with the exception of the "health worries" subclass, as seen in Fig. 3.

Since the CD and the NCWS groups were not matched for sex, multivariable linear regressions was performed. Using the four subscores as independent variables in four different models, NCWS was the only factor independently associated with higher scores at the baseline (gastrointestinal symptoms: beta 0.581, p < 0.001; emotional aspects: beta 0.591, p < 0.001; social issues: beta 0.384, p = 0.001). On the contrary, age (p = 0.410), gender (p = 0.241) and

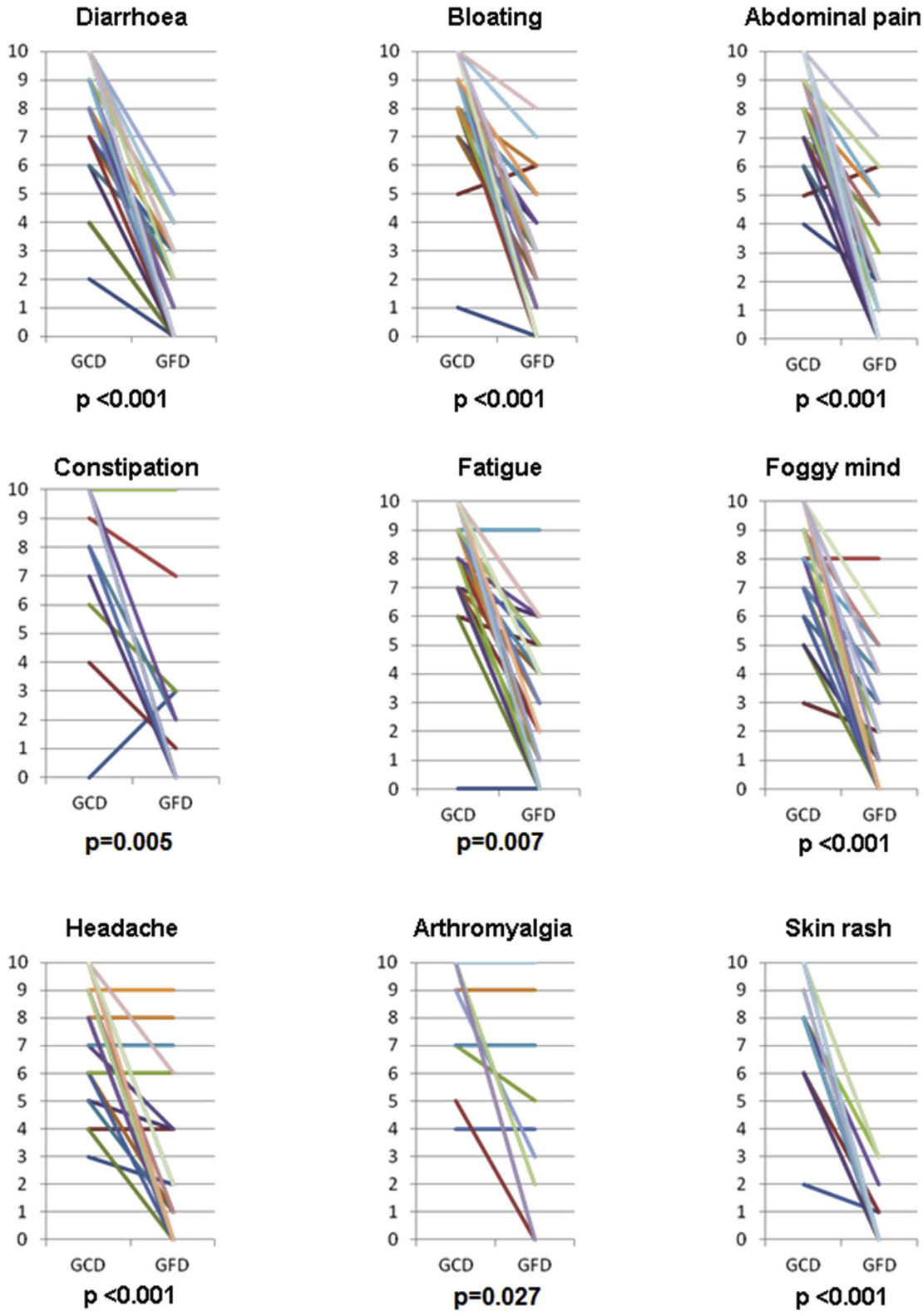

Fig. 2. Variation in symptoms intensity, evaluated according single-symptom questionnaire, in patients with non-celiac wheat sensitivity treated with a gluten-free diet.

duration of the GFD ($p = 0.097$) did not significantly correlate with QoL scores.

In the CD group, the "gastrointestinal symptoms" scores significantly improved from 18.00 (IQR 13.00–25.00) to 11.50 (IQR 9.00–18.75) ($p = 0.005$) after the GFD.

The "emotional aspects" scores were not significantly modified [from 18.00 (9.00–23.00) to 16.00 (10.00–22.00), $p = 0.969$].

Both "social problems" (including items related to the difficulties in eating outside home) and "health worries" scores (including items related to long-term health issues) worsened in

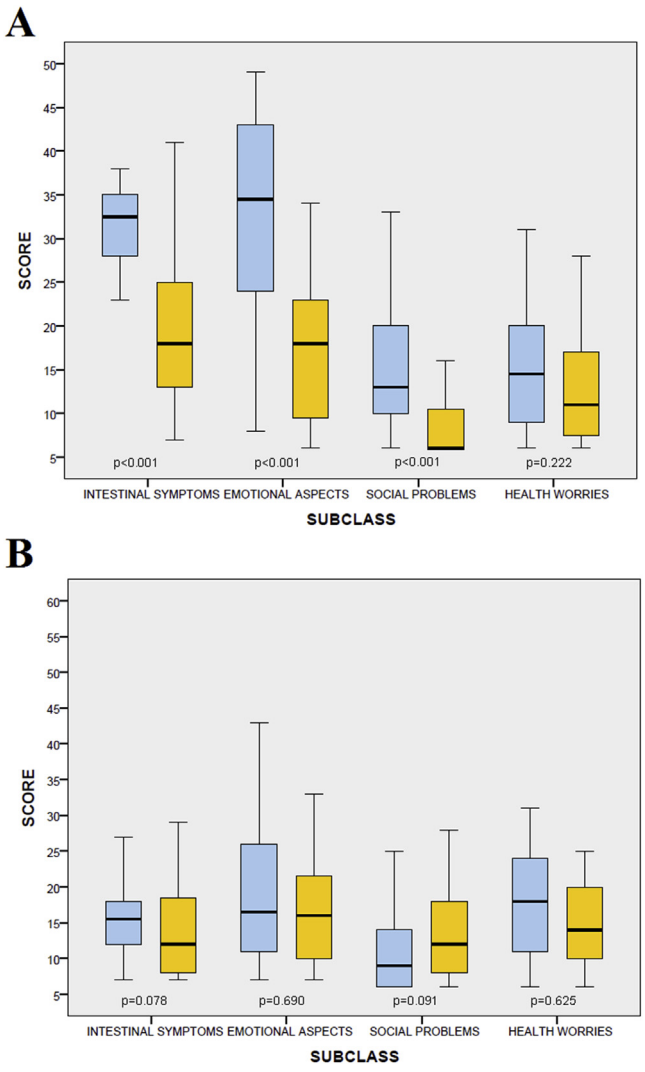

Fig. 3. Comparison of celiac disease questionnaire (CDQ) scores in non-celiac wheat sensitivity (NCWS – blue boxes) and celiac disease (CD – yellow boxes) patients, as calculated at the diagnosis (A) and at the follow-up (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the CD group ["social problems" from 6.00 (IQR 6.00–9.50) to 11.50 (9.75–19.00, p = 0.001; "health worries" from 11 (IQR 7.00–17.00) to 15.00 (IQR 11.00–21.00), p = 0.014)].

As a result of these modifications, NCWS and CD shared very similar post-GFD scores in all of the four areas included in the CDQ (Fig. 3).

4. Discussion

NCWS is a condition that received major scientific attention only in the last decade [13]. The creation of widely accepted diagnostic criteria occurred very recently [3]. So far, clinical trials account for one of the largest source of information about NCWS but only assess the clinical response to the GFD in the short-term [5,6].

Our study tried to address the scarcity of information about the long-term therapeutic response of NCWS and the main challenges faced by NCWS patients in everyday life.

As expected, the GFD led to a sharp and significant improvement in the severity of both intestinal and extra-intestinal symptoms of NCWS subjects.

However, a significant proportion of NCWS patients still complained of intestinal (65.9%) or extra-intestinal symptoms (72.7%) even years since the beginning of the GFD. This prevalence was significantly higher when compared to that of CD patients following the same diet (32.6 and 23.3% respectively). In turn, our prevalence of CD patients who were symptomatic despite the GFD is similar to that reported in literature [8].

To the best of our knowledge, this finding is novel. Different reasons may be advocated to justify the high prevalence of persisting intestinal symptoms in NCWS patients.

First, a proportion of our NCWS patients (20%) met the Rome III criteria [14] for irritable bowel syndrome (IBS). This substantial overlap between the two conditions is consistent with extent in the literature [4,13] and provides a first explanation for the incomplete remission of symptoms in a subgroup of NCWS patients. This explanation, however, is not fully satisfactory as patients with IBS accounted only for a minority of the NCWS patients who complained persistent symptoms. Further, IBS prevalence was similar in NCWS and CD group, not justifying the different prevalence of persisting intestinal symptoms in the two groups.

Second, it has been demonstrated that factors different from gluten are also involved in the pathogenesis of NCWS. In particular, fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) are known to play a pivotal role in the genesis of symptoms, causing a distension of the intestinal lumen with intraluminal recall of liquid and increased fermentability [15,16].

It must be noted that FODMAPs can be found in many other foods including milk, honey, legumes, rice, and cherries as well as vegetables such as chicory, leeks, and beets [2]. Therefore a sensitivity to the FODMAPs found in non-gluten containing foods may be a convincing explanation.

The persistence of extra-intestinal symptoms, instead, is more surprising and daunting to justify. The most resilient extra-intestinal manifestation after GFD were arthromyalgia (prevalence 18.7%, median score 4), fatigue (prevalence 56.8%, median score 3) and foggy mind (prevalence 40.9%, median score 2). The presence of arthromyalgia unresponsive to the GFD is well known in celiac patients (often hiding a concomitant fibromyalgia) [17], but the possibility of a similar association even in NCWS patients has been suggested in a recent case series [18]. Fibromyalgia is a chronic condition with possible breakthrough pain, as such a partial persistence of symptoms even after the GFD is possible. Similarly, we propose that fatigue may be affected by a tensive component generated at first by the state of protracted malaise and, later, by the high social impact of the GFD. This hypothesis will obviously need further confirmation by future studies.

As already specified, no studies evaluated the long term response to the GFD in NCWS patients and therefore comparisons with other studies are not easy. Comparison can be made only with previous descriptions of short-term response to the GFD, such as the perspective studies by Elli et al and Di Sabatino et al [5,6]. Indeed, these papers reported persistence of attenuated symptoms even during the periods of gluten withdrawal. In the study by Di Sabatino et al, in particular, intestinal symptoms were less respondent than extraintestinal manifestations. Instead, in a retrospective description by Carroccio et al. [4], all of the NCWS patients were almost completely asymptomatic after the GFD.

In comparison with these studies, our findings suggest that the neuropsychological symptoms (including foggy mind, headache and fatigue) play a more relevant role in the long rather than in the short term.

As a final element of our study, we evaluated the effects of the GFD on the four different areas of CDQ, a validated questionnaire to assess QoL in CD patients. To the best of our knowledge, this is the

first time that the long-terms effects of GFD on the determinants of QoL have been investigated in NCWS patients.

Again, a preliminary analyses of the results of the QoL questionnaire in the CD control group was necessary to verify the reliability of the results in NCWS patients. Our CD patients showed the typical improvement of the symptoms-related scores paired with negative responses to specific QoL questions including dining out, travel, family, and career which has been previously described [19,20].

As a final result of our study, the scores in all of the 4 areas of CDQ were similar in NCWS and in CD patients, suggesting that both groups face similar challenges in everyday life.

We are aware that CDQ has been validated for CD but not for NCWS. As no specific questionnaire has been validated for NCWS in the literature, the alternative would have been to use a generic, unspecific questionnaire (e.g. Euro-QOL) for both groups rather than for one, overall worsening the quality of our study. We welcome future research dedicated to the validation of a QoL questionnaire for NCWS.

In conclusion, the majority of NCWS patients still complain of intestinal and extraintestinal symptoms of lesser entity even after years on a GFD. Further, their QoL indices suggest that they face difficulties and challenges in everyday life which are comparable with those of celiac patients. Our results underline the importance of a comprehensive and dedicated nutritional evaluation of NCWS patients, helping in the identification of possible food contaminants and other potentially noxious compounds, including FODMAPs.

Statement of authorship

Tovoli F, Granito A, Faggiano C, Bolondi L designed the research; Tovoli F, Negrini G, Bolondi L analyzed the data; Tovoli F, and Granito A wrote the paper. All authors have read and approved the final version of this article.

Conflict of interest

The authors have no conflict of interest to declare.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

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