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# Efficacy of a gluten-free diet in reducing the widespread pain index and symptom severity scale in patients affected by fibromyalgia

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**SUMMARY**

*Objective.* Dietary interventions to improve fibromyalgia (FM) symptoms reported conflicting results. This study aimed to treat FM patients with a gluten-free diet (GFD), alternated with a non-restricted gluten-containing diet, followed by a rechallenge of the GFD.

*Methods.* Twenty postmenopausal women with FM and no history of celiac disease participated. A GFD was assigned for 6 months. This was followed by 3 months of a non-restricted gluten-containing diet and then a new GFD for another 6 months. At each visit, the widespread pain index (WPI) and the symptom severity scale (SS) scores were evaluated.

*Results.* The mean age of the patients enrolled was 53.9±10 years. None of the patients had a diagnosis of irritable bowel disease, although they reported vague gastrointestinal symptoms. After 6 months of a GFD, a statistically significant reduction was observed for the WPI (10.3±1.8 *vs* 7.7±1.4; p<0.0001) and the SS scale (6.4±1.8 *vs* 4.15±1.6; p=0.0002). The Δ percentage reduction of the WPI after 6 months of GFD was -24%±9%, while for the SS scale, it was -36%±21%. The following reintroduction of a gluten-containing diet brought about a statistically significant rise in the absolute SS scale and WPI, as well as a Δ modification of the WPI (21%±13%) and of the SS scale (74%±90%). The rechallenge of the GFD showed a significant improvement in absolute and Δ WPI (-24%±7%) and SS (-36%±11%). No modifications to the body mass index were found.

*Conclusions.* A GFD improved FM symptoms evaluated with WPI and SS. This was confirmed for the first time, also with a rechallenge of the GFD that followed a non-restricted gluten-containing diet.

***Key words**: Fibromyalgia, celiac disease, gluten-free diet, widespread pain index, symptom severity score.*

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## INTRODUCTION

Fibromyalgia (FM) syndrome is a disabling clinical condition of unknown cause characterized by diffuse skeletal muscle pain and other non-specific symptoms such as fatigue, cognitive disorders, depression, and anxiety (1, 2). In a non-negligible percentage of patients, FM is associated with abdominal symptoms characterized by pain and diarrhea, attributable to irritable bowel syndrome (IBS). Some studies show that in IBS patients, there is an overlap with celiac disease (CD) or non-celiac hypersensitivity to gluten (NCGS), and a gluten-free diet (GFD) can improve the symptoms of IBS (3). NCGS is increasingly recognized as a frequent clinical condition with symptoms similar to CD in the absence of the diagnostic features of CD (4, 5). However, patients with celiac disease often have arthritis symptoms or muscle pain (6). It has also been speculated that there is a correlation between CD, NCGS, and FM (7). Numerous studies have also shown that there is an alteration of the intestinal microbiome in IBS and FM patients (8). We know that the microbiome of the gut is strongly influenced by nutrition and that some foods, by modifying the intestinal bacterial flora in a pro-inflammatory sense, can worsen the clinical symptoms of some diseases, such as rheumatoid arthritis (9-11).

The recent European Alliance of Associa-

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tions for Rheumatology therapeutic recommendations have underlined that there is weak evidence regarding the efficacy of drug therapy in FM, while strong evidence for pain control has been highlighted only for exercise (12). This can justify the use of complementary and alternative therapies for this disease, and a GFD can be part of this strategy.

A recent systematic review on dietary intervention in FM showed positive pain and functional repercussions in FM patients after following a hypocaloric diet, a raw vegetarian diet, and a low FODMaps diet (13). There are discordant experiences in this regard and in the face of favorable opinions for a GFD in FM, with therapeutic successes (14-17). Other authors recommend its use only in patients with IBS, FM and lymphocytic enteritis (Marsh stage 1), thus specifying that an intestinal biopsy must be done before GFD, as it does not appear appropriate to normal intestinal mucosa (Marsh stage 0) (18). Even in the case of the presence of lymphocytic enteritis, other authors still recommend further randomized double-blind trials to confirm the effectiveness of the diet (19).

So far, there have been no studies addressing the modifications observed in the widespread pain index (WPI) and symptom severity scale (SS) scores in FM patients in which a GFD was introduced, followed by a non-restrictive gluten-containing diet period, and then a new rechallenge with a GFD.

The study aimed to treat FM patients, refractory to conventional pharmacological therapy, with a GFD followed by a rechallenge diet after a non-restrictive gluten-containing diet period, even without a diagnosis of celiac disease or IBS. For conventional pharmacological therapy, we considered a treatment with at least one of the following: duloxetine, or pregabalin, and/or non-steroidal anti-inflammatory drugs.

## MATERIALS AND METHODS

Patients were enrolled in 2016 at the Department of Internal Medicine and Rheumatology, PO S. Spirito-Nuovo Regina Margherita Hospital (Rome, Italy). In particular, we enrolled consecutive patients diagnosed with FM attending the outpatient clinic from January 2016 to December 2016.

The inclusion criterion was: being a postmenopausal woman affected by FM, according to the latest diagnostic criteria of the American College of Rheumatology (20).

Exclusion criteria were: a previous diagnosis of inflammatory bowel disease, a recent cancer diagnosis, renal insufficiency, liver insufficiency, and obesity. CD was ruled out by negative anti-transglutaminase assay results and IgA Endomysial antibody (EMA). The EMA test has a specificity of almost 100%, thereby making it the most specific test for celiac disease.

All patients signed a written informed consent. The study was approved by the local ethics committee. The presence of chronic diseases was assessed in a face-to-face medical interview. To obtain information on the medication used, the respondent had to show all the medications she was using at the time of the interview.

At baseline, an evaluation using the WPI and SS scale was performed (visit 1). The WPI is an inventory of the occurrence of pain in 19 defined body locations in which the patient has had pain over the last week. The score is between 0 and 19.

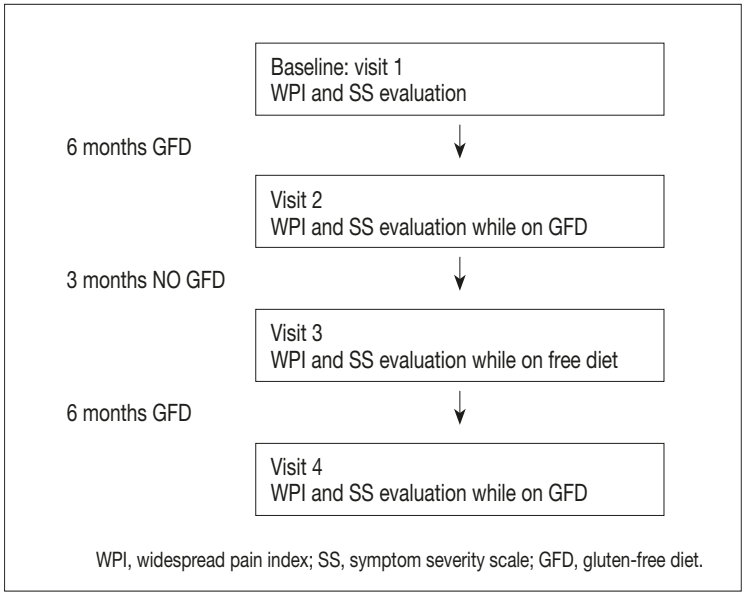


**Figure 1** - Study design including timing of the visit and the diet.

**Table I** - Clinical characteristics of patients affected by fibromyalgia at baseline.

| Patients | N=20 |
|---|---|
| Age (years) | 53.9±10.0 |
| Time since FM diagnosis (years) | 2.1±1.5 |
| *Comorbidities (number of patients)* | |
| Thyroiditis (Hashimoto) | 2 |
| Connective tissue disease | 1 |
| Chronic urticaria | 1 |
| Sjögren syndrome | 1 |
| Previous diagnosis of breast cancer | 2 |
| Previous diagnosis of thyroid cancer | 2 |
| *Drugs for FM (number of patients)* | |
| NSAIDs | 8 |
| Paracetamol | 2 |
| Gabapentin | 1 |
| Vitamin B12 | 5 |
| Duloxetine | 10 |

FM, fibromyalgia; NSAIDs, non-steroidal anti-inflammatory drugs.

The SS scale contains 4 items: fatigue, non-restorative sleep, cognitive symptoms, and an item comprising a multiplicity of other concomitant symptoms. The final score is between 0 and 12.

Patients consented to participate in an open GFD trial. A GFD was followed for 6 months, and WPI and SS were re-evaluated (visit 2). Then a period on a free diet was allowed for another 3 months (visit 3). None of the patients added new drugs or changed their lifestyle during the observational months of the study. Finally, a new 6-month GFD was restarted (visit 4). At each visit, WPI and SS scores were evaluated (Figure 1). The GFD was prescribed by an expert rheumatologist with the collaboration of a dietician, maintaining the patients' eating habits with a balanced caloric intake but with gluten-free foods.

### *Statistical analysis*

The data are expressed as mean ± standard deviation. Comparisons of continuous variables were made using the unpaired t-test. Outcomes were considered statistically significant when two-tailed values for p were lower than 0.5. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, USA). The Pearson association test was used to test associations between WPI and SS with age and time since diagnosis, as well as between Δ changes in WPI and SS with age and time since diagnosis.

## RESULTS

The mean age of the 20 postmenopausal women patients enrolled was 53.9±10 years. The diagnosis of FM was made approximately 2.1±1.5 years before the study was initiated. During that period, patients necessitated the use of drugs to control the pain (Table I). Patients reported vague gastrointestinal symptoms, without fulfilling all the criteria of IBS. Although none of the patients had a diagnosis of celiac disease, they accepted to observe a GFD. The GFD effect was assessed using the WPI and SS scale. There were no statistically significant associations between age or time since diagnosis of FM, and WPI and SS scale.

At baseline, the WPI was 10.3±1.8, and after 6 months of a GFD, a statistically significant reduction was observed (7.7±1.4; p<0.0001) (Figure 2). It is important to note that a worsening of the WPI was reported when a non-restrictive gluten-containing diet was re-introduced for 3 months (7.7±1.4 *vs* 9.2±1.2, p=0.0008). The GFD rechallenge was proposed for 6 months, which brought about a new reduction of the WPI (9.2±1.2 *vs* 6.9±1.1; p<0.0001). The same trend was observed for the SS scale. After 6 months of a GFD, its reduction was statistically significant (6.4±1.8 *vs* 4.15±1.6; p=0.0002), and the reintroduction for 3 months of food that contained gluten brought a worsening of the SS scale (4.1±1.6 *vs* 6.1±1.5; p<0.05). The new GFD, for a subsequent 6 months, resulted in a new significant reduction (6.1±1.5 *vs* 3.9±0.9; p<0.05).

Considering the values of the WPI and SS score at the beginning of the study compared to the values found at the end (after 6 months of a GFD plus 3 months of a non-restrictive gluten-containing diet, followed by a 6-month GFD), we still see the persistent effect of a GFD with a significant reduction in these indexes of the disease (WPI

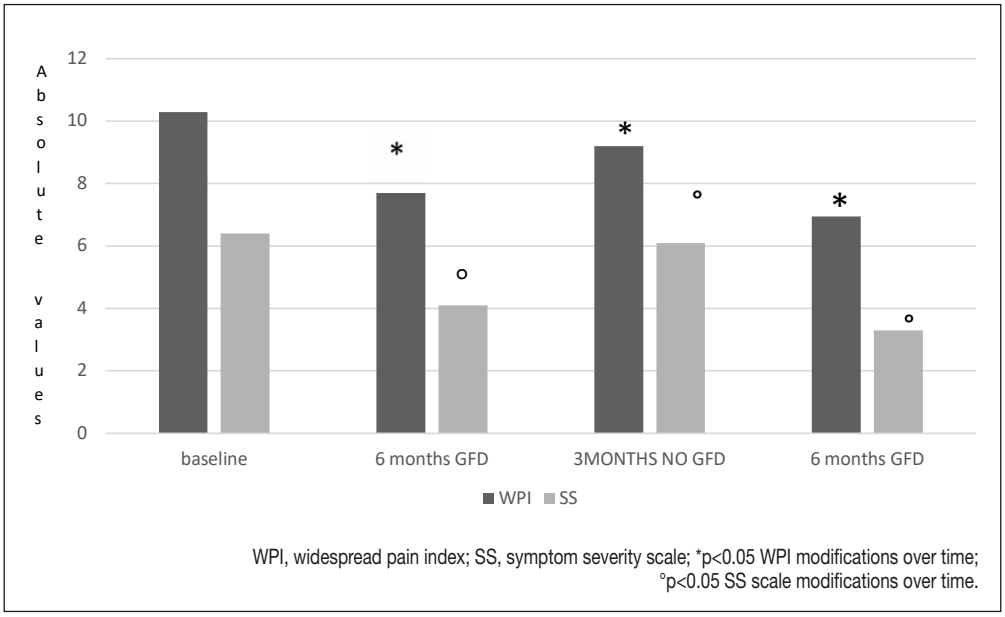


**Figure 2** - Absolute values of widespread pain index and symptom severity scale in each visit during the study period.

**Table II** - Δ modification of widespread pain index and symptom severity scale.

| | GFD diet-baseline | GFD diet-FD | FD diet-reintroduction of GFD | Baseline-end |
|---|---|---|---|---|
| D WPI | -0.24±0.09 | 0.21±0.13* | -0.24±0.07* | -0.31±0.09* |
| D SS | -0.36±0.21 | 0.74±0.90° | -0.36±0.11° | -0.36±0.16° |

GFD, gluten-free diet; FD, free diet (non-restrictive gluten-containing diet); WPI, widespread pain index; SS, symptom severity scale; *WPI p<0.05; °SS p<0.05.

10.3±1.8 *vs* 6.9±1.1,p<0.0001; SS 6.4±1.8 *vs* 3.9±0.9; p<0.0001).

The Δ percentage is also of interest as it showed improvement for both indexes after a GFD, as shown in Table II. The Δ reduction of the WPI, after 6 months of a GFD, was -24%±9%, while for the SS score, it was -36%±21%. The following reintroduction of a free diet brought about a statistically significant rise in the absolute SS and WPI, as well as the Δ modification of WPI (21%±13%) and the SS scale (74%±90%). This new worsening of the disease was a statistically significant difference from the improvement shown after 6 months of GFD, as shown in Table II. The rechallenge of GFD showed a statistically significant improvement of absolute and Δ WPI (-24%±7%) and SS (-36%±11%). Body mass index remained stable over the study period. We found no association between age and time since diagnosis and Δ modifications of the WPI and SS scale.

## DISCUSSION AND CONCLUSIONS

The main finding of this study is that in a population of fibromyalgic postmenopausal women without a clear diagnosis of gluten sensitivity, a GDF showed improvement in the WPI and the SS score.

This observation was further substantiated by a rechallenge of the GFD carried out after 3 months of a non-restrictive gluten-containing diet.

A possible explanation for our findings is that some foods have an anti-inflammatory action and others have a pro-inflammatory action. Gluten could be an inflammatory "trigger",

even in subjects without NCGS, and in those subjects that are genetically predisposed and in which there is damage to the intestinal barrier. Anti-inflammatory medicines or stress may also cause that damage, as is frequently the case in FM patients. Intestinal barrier damage, with consequent greater permeability to both bacteria and food products, has also been found in patients with CD. A high value of zonulin, a biomarker of intestinal permeability, was found in these patients. High zonulin values are accompanied by greater inflammatory damage and an increase in inflammatory cytokines (21). It has also been observed that gliadin induces an increase in intestinal permeability in healthy subjects through an increase in zonulin values (22).

The pro-inflammatory action of gluten is also expressed through other pathogenic mechanisms. Gluten can activate some inflammatory cytokines. In particular, through the action of the toll-like receptor 4, it induces stimulation of the production of the cytokines interleukin-1, interleukin -6, and, above all, interleukin-17. Gluten can alter the epigenetic program with a lack of methylation of the modulating proteins of the genes and therefore cause less protection against diseases. Gluten modulates dendritic cells and can activate the innate immune system. Moreover, it can create dysbiosis with an increase in proinflammatory bacteria (23). It remains to be seen whether we have selected patients with unrecognized NCGS or whether there is a subset of FM patients who still benefit from a GFD. The pathogenic relationship between NCGS and FM and the real pathogenetic role of gluten (24) is still unclear.

A previous randomized control trial in FM patients with IBS showed no improvement after 6 months of GFD (utilizing different methods to assess improvement), but the rechallenge of GFD was not performed contrary to our study (16). Another study in celiac fibromyalgic patients after 1 year of GFD showed outcome measures significantly improved, with a decrease of 51-60% in the tender points test, the fibromyalgia impact questionnaire, the health assessment questionnaire, and the visual analog scales (25). In contrast, another study, which included FM patients and demonstrated a minimum of 5 of the 14 gluten sensitivity symptoms with negative transglutaminase antibodies according to serological testing, did not show the superiority of a GFD compared to a hypocaloric diet in improving pain symptoms (14).

Our study has a few limits. We did not measure biochemical parameters of inflammation, and we did not randomize patients to a GFD or have controls. However, the rechallenge with a GFD strengthened the results obtained because each patient was a control for itself. Another limit may be the small sample studied and the absence of a calculation of the sample size before starting the study. Furthermore, the lack of standardized parameters for assessing patient adherence to GFD is another limitation of the study.

In conclusion, dietary intervention might be a useful new intervention strategy for patients affected by FM (26). Additional double-blind controlled trials on large samples are needed to include GFD as a possible standard therapy for FM and to clarify the exact mechanism that links gluten to FM.

**Contributions**

All authors contributed equally.

**Conflict of interest**

The authors declare no potential conflict of interest.

**Ethics approval and consent to participate**

The study was approved by the Hospital's local ethic committee.

**Informed consent**

All patients signed a written informed consent.

**Availability of data and materials**

Data and materials are available from the corresponding author upon request.

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