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*Randomized Clinical Trial*

# Prevalence of functional gastrointestinal disorders in children with celiac disease on different types of gluten-free die

Fiori Nastro F *et al*. FGIDs and CD

**Abstract**

BACKGROUND

Functional gastrointestinal disorders (FGIDs) are common in pediatric age. FGIDs are not related to biochemical or structural abnormalities, however, since they have a high prevalence, several studies have evaluated an overlap between FGIDs and organic diseases. Individuals with celiac disease (CD) have been shown to be at increased risk for functional abdominal pain, even if they adhere well to the gluten-free diet (GFD). Not many information are available in pediatric age. The aims of our study are to evaluate the prevalence of FGIDS in CD children one year after diagnosis and to compare the prevalence of FGIDs in CD children on GFD with processed foods compared with those on GFD with natural products.

AIM

To assess the prevalence of FGIDs in children with CD after a year of follow-up, and to compare the prevalence of FGIDs in children with CD on a GFD with processed foods and in children on a gluten free diet with natural products.

METHODS

We have recruited pediatric patients aged 1-18 years with a new CD diagnosis. Participants were randomized to two groups: Group A on GFD with processed foods (diet 1); group B on GFD with natural products (diet 2). Clinical monitoring, diet assessment and the questionnaire on pediatric gastrointestinal symptoms-Rome IV version were performed at diagnosis (T0) and after 12 mo of follow up (T1). Dietary intake was assessed using a 3-d food diary record. Data from the diaries were evaluated using Winfood nutrient analysis software. We assessed the prevalence of FGIDs at T1 and the correlation with the type of GFD.

RESULTS

We registered 104 CD children, 55 patients in group A (53%) and 49 patients in group B (47%). Initially, 30 of the 55 (54, 5%) CD children were symptomatic in group A while 25 of 49 (51%) were symptomatic in group B. At T1, in spite of a low or negative serology for CD, FGIDs prevalence was 10/55 (18%) in group A and 8/49 (16, 3%) in group B, with no statistically significant difference between the two groups ($P$ = 0.780). At T1 the macro and micronutrients intake was similar across the two groups with no significant differences in nutrients analysis. However, in both groups at T1 we found that a lower prevalence of FGIDs ($P$ = 0.055) was associated with an inferior caloric [odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.99-1.00] and fat (OR = 0.33, 95%CI: 0.65-0.95) intake.

CONCLUSION

Our results show that CD children on GFD have gastrointestinal symptoms with an elevated prevalence of FGIDS. Our study suggests that developing FGIDs may be linked to caloric intake and percentage of food fat, but it does not change between a GFD with processed foods or GFD with natural products. However, long-term monitoring is required to evaluate a correlation between FGIDs and various types of GFDs.

**Key Words:** Functional gastrointestinal disorders; Celiac disease; Gluten free diet

Fiori Nastro F, Serra MR, Cenni S, Pacella D, Martinelli M, Miele E, Staiano A, Tolone C, Auricchio R, Strisciuglio C. Prevalence of functional gastrointestinal disorders in children with celiac disease on different types of gluten-free die. *World J Gastroenterol* 2022; In press

**Core Tip:** In spite of a strict adhesion to a classic gluten-free diet (GFD), subject with celiac disease are more likely to suffer from functional abdominal pain disorders. Our findings suggest that the prevalence of functional gastrointestinal disorders may be

linked to the caloric intake and fat content in the diet, however it does not differ between a processed GFD with commercial products or a gluten free diet with natural products.

## INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated enteropathy, characterized by mucosal inflammation, villous atrophy[1], triggered by the ingestion of gluten in genetically predisposed individuals. CD is now recognized as a global disease with a prevalence of about 1% of the world's population[2]. The clinical presentation ranges from features of malabsorption such as abdominal pain, diarrhea, steatorrhea, and weight loss or growth failure, to atypical forms of CD with more subtle gastrointestinal manifestations similar to functional gastrointestinal disorders (FGIDs) or asymptomatic individuals diagnosed by screening high-risk groups[3].

The only available treatment for CD is lifetime adherence to gluten free diet (GFD)[4]. Just over a decade ago, Turco *et al*[5] showed that subject with CD have a higher risk of developing FGIDs, fulfilling the Rome III diagnostic criteria, despite strict adherence to a classic GFD but not always concordant data have been produced in this area in recent years[6,7]. When it is present an organic abnormality FGIDs cannot be diagnosed. However, these disorders have a high prevalence so numerous studies have assessed the potential for overlap between FGIDs and organic diseases[8]. A great innovation introduced now in Rome IV criteria compared to Rome III it is the specification that the diagnosis can only be made if 'after appropriate medical evaluation, the symptoms cannot be attributed to another medical condition'. This wording replaces the previous statement that there should be 'absence of inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms'. This change makes it possible for a patient suffering from another organic disease, like CD or inflammatory bowel disease, also have a functional disorder as well (common event) and should also reduce the amount of tests necessary to diagnose a FGIDs[9].

However, little and contrasting data are still available in children about the prevalence of symptoms of functional intestinal disorder in children with CD or the effects of a GFD on those symptoms. The objectives of this study were to evaluate the prevalence of FGIDs among children with CD at the moment of diagnosis and after a year of follow-up comparing a conventional GFD with commercially available products and a GFD based mainly on natural products.

## MATERIALS AND METHODS

### *Patient selection*

We prospectively followed up for 1 year two group of CD children, who received two different GFD, to evaluate if specific dietary factors were involved in the development of FGIDs at 1 year of follow up. This group consisted of 104 consecutive children (34 male children - 69 female children; mean age 7.2 (4.1) years; range: 4-17 years) who received a diagnosis of CD from December 2017 to January 2019 at the Department of Pediatrics, University 'Federico II' in Naples and the Department of Pediatrics, University of Campania, "Luigi Vanvitelli" in Naples, Italy. All these children received a GFD and were followed up for 1 year. CD diagnosis, according to ESPGHAN criteria[10], was based on serum concentrations of anti-transglutaminase-immunoglobulin A (TTG-IgA) determined by an indirect solid-phase enzyme immunoassay test, and serum concentration of endomysial antibodies (EMA) determined by indirect immunofluorescence using monkey's oesophagus sections as substrate. To exclude the presence of selective IgA deficiency, serum IgA levels were assayed by nephelometry. According to ESPGHAN guidelines[11], in children an adolescents with signs or symptoms suggestive of CD, high anti-TTG titers (> 10 times), positivity of EMA and human leukocyte antigen (HLA) DQ2/8, biopsies were omitted. In all other cases, patients underwent upper endoscopy with multiple duodenal biopsies. Class II antigens HLA typing was also performed by polymerase chain reaction sequence-specific oligonucleotide using DQ-CD Typing Plus[12]. We excluded from the study patients with systemic or gastrointestinal infection; patients with other

known gastrointestinal, renal, cardiac, pulmonary, hematological, neurological and cerebral pathologies and patients with inability or unwillingness to give informed consent.

***Study design***

The patients were randomly divided in 2 groups: Group A ($n$ = 55) received a controlled GFD with processed foods (diet 1); group B ($n$ = 49) received a controlled GFD with a percentage of natural products > 60% (diet 2). All registered patients and/or their parents underwent validated questionnaires for gastrointestinal (GI) symptoms according to the Rome IV Criteria. The Pediatric gastrointestinal symptoms Questionnaire-Rome IV version was used to diagnose FGIDs. Subjects were classified as having a FGIDs through their questionnaire responses and were able to meet criteria for multiple disorders.

A clinical follow-up and symptom questionnaire based on the Rome IV criteria were carried out for each child at two different times: at diagnosis (T0) and at 12 mo (T2) follow-up. At 12 mo of follow-up, children were considered in clinical remission from CD, if they reverted positive serological test to negative following treatment with a strict GFD, despite having gastrointestinal symptoms defined as functional, according to the Rome IV criteria. The potential consumption of gluten-containing products was assessed using a combination of CD serology, self-reported adherence questions and interview with an experienced dietician. Dietary intake was assessed on the basis of compiling a 3-d food diary and a dietary interview by an expert nutritionist. The nutrients analysis conduced using the Win Food software.

***Statistical analysis***

Data are presented as frequency (percent) for categorical variables, and as mean (SD) for continuous variables. Differences in nutrients intake between patients in group A and group B were computed with student's $t$ test or Mann-Whitney $U$ as appropriate. Associations between nutrients intake and FGIDs prevalence for each of the two groups

were computed with logistic regression. Comparison between the prevalence of FGIDs at T0 or T1 in patients were computed with McNemar test. For all analyses, a *P*-value of 0.05 was considered significant. All statistical analyses were performed using the R statistical environment, version 4.0.3.

## RESULTS

The symptomatic children at enrollment were 30 of 55 (54.5%) in Group A and 25 of 49 (51%) in group B. Among symptoms, constipation (28.8%) was the most prevalent, followed by abdominal pain (24%), vomiting (4.8%). As expected after 1 year of GFD the frequency of GI symptoms significantly decreased in both groups (Table 1). At 1 year from CD diagnosis children were investigated for repeated serology for CD (endomysial and anti-tissue TTG antibodies), of which 99/104 (95.2%) resulted negative, 2 (1.9%) positive and 3 (2.9%) border line.

Although, despite negative serology for CD, the prevalence of FGIDs, classified according to the Rome IV criteria, was 10/55 (18%) in group A and 8/49 (16,3%) in group B, and there weren't statistically significant difference between the two groups at T1 ($P = 0.780$) in Figure 1. Among CD children with FGIDs, functional constipation (FC) (12.48%) was the most prevalent disorder (7.69% in group A and 6.73% in group B) followed by Postprandial Distress Syndrome (2.88%, 1.92% in group A and 0.96% in group B) a T1.

We observed that children who presented with symptoms at diagnosis, more frequently developed a FGIDs at one year, than patients who were asymptomatic at time of diagnosis. The individual analysis of the intake of macro and micronutrients at T1 showed that there were no important differences in nutrients analysis from group A to group B and that the intake was similar into the two groups (Table 2). However, in both groups, we found a relationship, between a reduced caloric and fat intake [respectively odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.99-1.00 and OR= 0.33, 95% CI: 0.65-0.95] and an inferior prevalence of FGIDs after one year of GFD (*P* =

0.05). No statistically significant difference was found in the sub-categories of fat analyzed (saturated, polyunsaturated and monounsaturated fatty acids) in Figure 2.

## DISCUSSION

To the best of our knowledge this is the first pediatric study that investigates the prevalence of FGIDs in children with CD on a GFD comparing a classic diet with processed products *vs* GFD with natural products. We found that there was no difference in the prevalence of FGIDs according to the type of diet (18.4% *vs* 16.3%), and the most frequent FGIDs was FC in both studied group. Interestingly, in both groups we found an association between lower caloric and fat intake with lower prevalence of FGIDs after 1 year of GFD.

In a previous work we found an higher prevalence 28% of CD patients who continued having GI symptoms and fulfilled Rome III criteria for FGIDs despite the GFD, compared to 8.9% of control, and FC was the most frequent disorder. Most probably the reason for the difference in the current study is related to the application of the Rome IV criteria, which resulted in a lower prevalence of FGIDs as previously described[13,14]. Indeed, our findings are in accordance with the results of a recent large study conducted in Italy from Cristofori *et al*[6] that found a prevalence of functional abdominal pain disorders of 11.5% according to Rome IV criteria among patients with coeliac disease, compared to 6.7% of control. FC and irritable bowel syndrome (IBS) were the most frequent disorders found in CD patients. We also found that FC was the most common disorder, however we noted an increase of functional dyspepsia whilst a decrease of IBS compared to Cristofori *et al*'s study[6]. However two large American reports and our recent European study conducted on healthy subjects has also seen an increased level of functional dyspepsia (3%-7.6%), with postprandial distress syndrome being the most common subtype (2.7%-7.2%), as in our population[13-15]. It is interesting to note that in these studies, the prevalence of functional dyspepsia exceeded that of IBS, which was previously the most prevalent functional abdominal pain disorder[16].

Patients with CD and FGIDs could somehow fall under the "atypical forms" of CD although, usually, the term "atypical" CD is used for patients who present with extraintestinal symptoms like IgA-nephropathy, hemosiderosis of the lungs and a variety of neurological diseases while for FGIDs the symptoms are mainly gastrointestinal. Moreover, another difference is that the atypical forms generally respond to the GFD with the disappearance of symptoms[17].

Although numerous studies have been carried out to study the pathogenesis of both FGIDs and CD, there are still a lot of unanswered questions. Some possible explanation behind the persistence of gastrointestinal symptoms could be the presence of another unrecognized gastrointestinal disease, altered bowel motility due to the persistence of a low-grade of inflammation despite the GFD, microbiota alteration or rarely a continuous intentional or inadvertent gluten intake[6]. Only a few studies have been reported on the overlap between CD and functional abdominal pain disorders in children but it seems likely that intestinal inflammation (infectious and non-infectious) predisposes children to develop visceral hypersensitivity, that can manifest as functional abdominal pain disorders[18].

O'Leary *et al*[19] in their study hypothesize that despite the GFD, in particularly in treated, occasionally noncompliant celiac patients, it persists a low-grade of inflammation that induces sensory or motor dysfunction and IBS-type symptoms and precipitates a motility disturbance in many patients or as in our study persistent intestinal inflammation could be due to too short follow-up on GFD. Moreover, gut microbiota of CD patients is characterized by increased *Bacteroides spp*, *Escherichia coli*, *Proteobacteria*, and *Staphylococcus* and decreased *Bifidobacterium spp* and *Lactobacillus*[20] and multiple studies reported similar changes in the microbiota of IBS patients[21,22]. According to the most recent data, intestinal dysbiosis might be responsable for the persistence of symptoms, even in patients on GFD. In fact, GFD though capable of improving the nutritional status of CD patients without causing nutritional problems, is only partially effective in restoring microbiota and can itself influence its com an may

be partly responsible for intestinal dysbiosis due to the reduction in the intake of polysaccharide (fructans) which has a prebiotic action on bifidobacteria.

Moreover, the reduced amount of fiber of GFD may be considered as one of the reasons why CD patients often suffer from FC[5]. The new appearance of constipation after the introduction of a GFD likely reflects a decrease in fibre intake, and many of these patients may react to the addition of dietary fibre. In other, constipation can reflect a return to a predisposition for constipation after resolution of malabsorption. Another possible explanation could be that functional abdominal pain can be triggered not only by gluten, but also by other components of wheat including α-amylase/trypsin inhibitors, wheat, lectin, agglutinin, and fructans as described in the study by Llanos-Chea and Fasano[23]. They showed that the consumption of wheat, but also other cereal grains, can contribute to the manifestation of chronic inflammation and autoimmune diseases by increasing intestinal permeability and initiating a pro-inflammatory immune response.

Chronically increased intestinal permeability allows for the increased translocation of both microbial and dietary antigens to the periphery which can then interact with cells of the immune system and stimulate pathways of innate immunity. According to Barone *et al*[24] CD patients, compared to healthy individuals, eat significantly higher amounts of fat and sugar, and small amounts of fiber on the GFD[20-23]. Numerous studies have demonstrated that the total fat content of gluten-free foods is at least double that of gluten-containing foods, help improve the taste of these products.

In our study we found that, regarding the prevalence of FGIDs, there was no significant difference between children on an industrial manufactured GFD and among children who follow a GFD using natural products but, noteworthy in both groups we found an association between the lower caloric intake and the lower fat intake with a lower prevalence of FGIDs after 1 year of GFD.

Dietary fat has been associated with onset of symptoms after a meal challenge or reported as inducing symptoms of dyspepsia in some studies[25-27], and specifically with dyspeptic symptoms of nausea[25,26], bloating[25,26], post-prandial

fullness/discomfort[25,27] and epigastric pain[26,27]. It is not entirely clear how food factors cause dyspeptic symptoms. Studies have shown that sensitivity to stomach distention and chemical stimuli like nutrients (fat), acid and gastrointestinal hormones (CCK), and interaction between them have a central role inducing symptomatic response[28]. Zito *et al*[29] in their study have shown that some alimentary regimens or even some meals are able to trigger gastrointestinal symptoms in predisposed individuals. Fats, in particular seems to influence gastric activity, by delaying gastric emptying and promoting relaxation of the fundus, and these mechanisms are closely related to the onset of GI symptoms. Functional dyspeptic patients, for example, usually report that meal size, eating patterns, caloric intake as well as nutrient composition-lipid content in particular-strongly influence the onset of dyspeptic symptoms.

Our study has several strengths: A large sample size representative for the various age groups, well defined CD and FGIDs diagnoses. The main limitations of our study are the shortness of the follow-up associated with the absence of a follow-up endoscopy which could underestimate the persistence of a slight degree of inflammation, and the self-compilation of food diaries associated with an autonomous choice of foods to be consumed during the duration of the study which could have led to both some bias in the comparison of the micro and macronutrients of the two groups possibly responsible for the different persistence of symptoms. The presence of an experienced dietician who performed a diet check with the patient at each visit coupled with a negative serological test trust us to strict adherence to the GFD so accidental and occasional consumption of gluten becomes unlikely to explain gastrointestinal symptoms. However, this approach limits our ability to evaluate whether the lack of compliance could be responsible for the appearance of symptoms.

## CONCLUSION

In conclusion, this is the first study to show that the presence of functional GI symptoms in children with CD on a GFD are possibly related to higher caloric and fat intake. It remains to be determined whether the risk is due to the persistence of a

chronic inflammatory process or to nutritional factors. Longer-term monitoring studies will assist in determining the natural history of these functional symptoms.

## ARTICLE HIGHLIGHTS

### *Research background*

When it is present an organic abnormality functional gastrointestinal disorders (FGIDs) cannot be diagnosed. However, these disorders have a high prevalence so a number of studies have assessed the possibility of overlapping between FGIDs with organic disorders.

### *Research motivation*

Few data are available about the risk that the children experience functional abdominal pain disorders despite strictly adhering to a conventional gluten free diet (GFD).

### *Research objectives*

The objectives of this study were to estimate the prevalence of FGIDs in patients affected by celiac disease (CD) at the moment of the diagnosis (T0) and after a year of follow-up (T1) comparing two different types of GFD.

### *Research methods*

This study involved 104 celiac pediatric patients between (from 1 to 18 years) randomized to: Group A on a GFD with processed foods; and group B on a GFD with natural products. Clinical follow-up, a 3-d dietary diary evaluation and a questionnaire based on the Rome IV criteria. were completed for each child at T0 and T1. We examined the FGIDs after 12 mo and the relationship to the GFD eaten.

### *Research results*

At the time of enrollment, the 54.5% of the CD children had symptoms in group A and the 51% in group B. At T1 in spite of low the or negative CD serology, the prevalence of

FGIDs was 18% in group A and 16.3% in group B, not having a statistically significant difference between A and B group ($P$ = 0.780). In both groups after 12 mo of GFD an intraindividual analysis showed significantly lower prevalence of FGIDs ($P$ = 0.055) was associated with a lower calorie intake and fat consumption.

***Research conclusions***

Many children still have gastrointestinal symptoms and FGIDs despite a strict GFD and it could be linked to the caloric intake and the amount of fat in the diet, but it does not differ between a GFD with commercial or natural products.

***Research perspectives***

To evaluate the correlation between FGIDs and different types of GFDs, long term monitoring is necessary.

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