# Celiac Disease in Children with Functional Constipation: A School-Based Multicity Study

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**Objective** To determine whether children in the community with functional constipation have increased prevalence of celiac disease.

**Study design** Between April 4, 2015, and April 25, 2017, we enrolled 1809 children from 5 schools in Colombia and screened them for functional gastrointestinal disorders (FGIDs), including functional constipation, using questionnaires recommended in the Rome III/IV criteria. We matched children with functional constipation with healthy controls without a FGID and tested them for celiac disease with tissue transglutaminase (tTG)-Immunoglobulin A (IgA) and total IgA screening. In those who tested positive for tTG-IgA, we performed HLA genotyping and endoscopy to obtain 4 duodenal biopsy specimens for classification of celiac disease using the Marsh criteria. Analysis of statistical significance between groups of children with and without functional constipation was done using a 2-tailed Fisher exact test.

**Results** Patients diagnosed with functional constipation (n = 203) were matched with 419 healthy controls without FGIDs. The overall prevalence of celiac disease in the entire cohort was 0.6%. Of those with functional constipation, 1 (0.5%) was diagnosed with celiac disease, and 3 (0.7%) of the control patients without FGIDs had celiac disease ($P$ = .743).

**Conclusions** The prevalence of celiac disease in our cohort was similar to worldwide estimates. The prevalence of celiac disease in schoolchildren with functional constipation in Colombia is similar to those without FGIDs. Thus, routine testing of schoolchildren with functional constipation for celiac disease is not indicated. *(J Pediatr 2020;227:77-80)*.

The worldwide prevalence of celiac disease is approximately 1%,[1] and constipation is found in up to 32% of children.[2] Like constipation, celiac disease usually presents in childhood.[1,3] Cognizant of both comorbidities and in an effort to prevent misdiagnoses, the 2006 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines for the management of constipation in children recommended testing for celiac disease in children with intractable constipation.[4] It was later found that testing all children with long-lasting constipation was too costly, and that celiac disease is rare among children with isolated constipation.[5] The current guidelines no longer recommend celiac testing in children with constipation. Nonetheless, the controversy persists, and recent studies again showed that celiac disease is common in children with constipation.[6]

Previous studies on the comorbidity of constipation and celiac disease were limited because they were conducted at the medical office level. This type of design is prone to selection bias owing to differences in access to care and because consulting children are more likely to complain of more severe symptoms. Studies at the community level can overcome this limitation and thus help elucidate whether the association between celiac disease and constipation is a true association or merely the result of the design of previous studies. In the present study, we aimed to assess the prevalence of celiac disease in schoolchildren with functional constipation and compare that with the prevalence in children without FGIDs to ascertain whether functional constipation in the general population puts a child at increased risk of celiac disease.

## Methods

We conducted a cross-sectional study on a cohort of 4- to 18-year-old children from 5 public schools in 3 geographically dispersed areas in Colombia (Andean, Pacific, and Atlantic regions) between April 4, 2015, and April 27, 2017. Letters were sent inviting all children to participate in the study. Children diagnosed with inflammatory bowel disease, diabetes mellitus, celiac disease, or other autoimmune disease (eg, hypothyroidism) and those with associated chromosomal abnormalities were excluded from the study.

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|---|---|
| EGD | Esophagogastroduodenoscopy |
| FGID | Functional gastrointestinal disorder |
| tTG | Tissue transglutaminase |
| NASPGHAN | North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition |
| ESPGHAN | European Society for Pediatric Gastroenterology, Hepatology, and Nutrition |

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We obtained written informed consent from participants' parents and assent from children aged >7 years. This study was approved by the Institutional Review Board of Cali (Act 008-2015 of the Universidad del Valle in Cali, Colombia).

### Measures and Procedures

Diagnosis of FGID was based on questionnaires recommended according to the Rome III criteria until April 2016 and the Rome IV criteria from May 2016 onward (**Table I**). Parents completed the questionnaire for children aged <10 years, and children aged ≥11 years self-reported. Participants were classified as having or not having an FGID. Children diagnosed with functional constipation were matched for age and sex with controls without FGIDs. Cases and controls underwent formal testing from a fingertip blood sample to screen for celiac disease through tissue transglutaminase (tTG)-IgA and total IgA screening using the Biocard Celiac Test (Ani Biotech, Vantaa, Finland), a rapid immune chromatographic test for the qualitative detection of anti–tTG-IgA antibodies with documented 97.4% sensitivity and 96.9% specificity.[7] In children testing positive for tTG-IgA, we performed HLA genotyping and esophagogastroduodenal endoscopy (EGD) to obtain 4 duodenal biopsy specimens for histological classification of celiac disease by an experienced pathologist using the Marsh criteria. Children who underwent EGD and had a Marsh classification I-IV on EGD were diagnosed with celiac disease ("confirmed"). Those who did not undergo EGD but were positive for both tTG-IgA and HLA were classified as "suspected celiac disease."(**Figure**). The total cost of testing for celiac disease (free for participants) was calculated based on the costs of the laboratory tests and EGD performed.

**Table I. Rome III and Rome IV criteria to diagnosis of functional constipation in pediatric patients**

Rome III criteria for functional constipation in children and adolescents
- Must be at least 4 years old developmentally and must have 2 or more of the following with insufficient criteria for irritable bowel syndrome:
  1. Two or fewer defecations in the toilet per week
  2. At least 1 episode of fecal incontinence per week
  3. History of retentive posturing or excessive volitional stool retention
  4. History of painful or hard bowel movements
  5. Presence of large fecal mass in the rectum
  6. History of large-diameter stools that may obstruct the toilet.

Rome IV criteria for functional constipation in children and adolescents
- Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:
  1. Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
  2. At least 1 episode of fecal incontinence per week
  3. History of retentive posturing or excessive volitional stool retention
  4. History of painful or hard bowel movements
  5. Presence of a large fecal mass in the rectum
  6. History of large-diameter stools that can obstruct the toilet.
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

### Statistical Analyses

We calculated the proportion of children with and without FGIDs and the descriptive measurements with their corresponding SDs and ranges. Analysis of statistical significance between groups of children with and without functional constipation was evaluated with the 2-tailed Fisher exact test. Significance was set at $P = .05$.

## Results

A total of 2035 children were invited to participate, of whom 1809 (84.8%) were deemed eligible. None of the ineligible patients had a preexisting diagnosis of celiac disease. Among the 1809 participants, 407 (22.5%) had an FGID according to the Rome criteria, and 203 (11.2%) had a diagnosis of functional constipation. The 203 subjects with functional constipation were matched for age and gender with 419 controls without an FGID (**Table II**). The geographical breakdown of the 622 participants (203 with functional constipation plus 419 controls) was as follows: Andean region, n = 382 (La Unión, n = 324; Floridablanca, n = 58); Pacific region, n = 152 (Cali, n = 89; Tulua, n = 63); and Atlantic region (Sotavento), n = 88. The results of the celiac workup using the Biocard celiac serologic test revealed that no child was IgA-deficient. Four children in the entire sample had celiac disease confirmed through pathology (0.6%). Only 1 of the 203 children with functional constipation was diagnosed with celiac disease (0.5%), compared with 3 of the 419 control subjects (0.7%) ($P = .743$).

Despite receiving a thorough explanation by a pediatric gastroenterologist about the workup and implications of diagnosing celiac disease, the parents of some children refused HLA typing and EGD. Parents of 2 children refused HLA typing and 5 of 11 children who tested positive for elevated tTG-IgA and had DQ2 or DQ8 HLA refused the EGD and were thus classified as "suspected celiac disease" (1 child with functional constipation and 4 controls). When we tested for significance assuming that all children with "suspected celiac disease" had celiac disease, the difference between the groups remained nonsignificant (functional constipation group, 1% [2 of 203]; control group, 1.7% [7 of 419]; $P = .754$). Each Biocard celiac serologic test cost $15 (USD), HLA testing cost $100, and EGD with biopsy cost $200. The cost to identify the single child with celiac disease in the cohort of all children with functional constipation evaluated was $4045.

## Discussion

Of the children in our cohort with functional constipation, only 0.5% were diagnosed with celiac disease. The matched controls without FGIDs showed a similar prevalence of celiac disease. Thus, our study demonstrates that the prevalence of celiac disease in Colombian children with functional constipation is not increased, as the prevalence of celiac disease in children with functional constipation was similar not only to

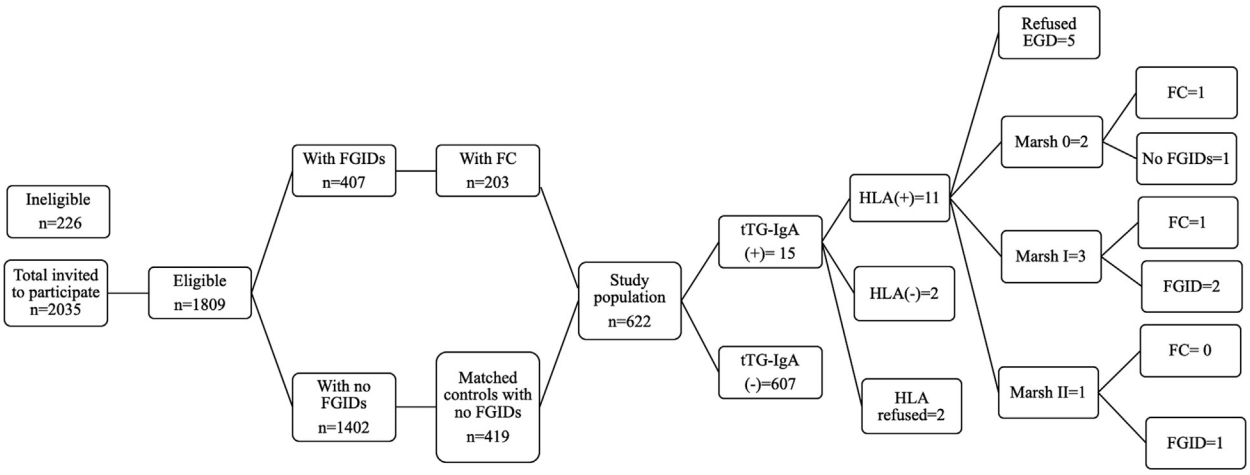


**Figure.** Flowchart of the study design.

that in children without FGIDs, but also to the worldwide estimates of celiac disease in the general population (~1%).[8] Based on our study, the likelihood of diagnosing a child with celiac disease by screening children with functional constipation is no greater than the likelihood of finding a case of celiac disease by random screening of the population.

The indications and cost-effectiveness of testing for celiac disease in children with functional constipation remain controversial. The results of our school-based investigation are in line with previous studies conducted in American and Iranian patients and with the latest guidelines on the management of constipation in children issued by ESPGHAN and NASPGHAN that recommend against systematic testing for celiac disease.[9] Our group previously found that children with intractable constipation were not at increased risk for celiac disease.[5] In a retrospective chart review of all patients presenting with constipation to a pediatric gastroenterology clinic, Chogle et al found that only 1.9% had biopsy-proven celiac disease.[5] Dheghani et al also evaluated pediatric patients presenting to the pediatric gastroenterology clinic with functional constipation and diagnosed celiac disease in only 0.99%.[10] However, a retrospective study by Pelleboer et al concluded that celiac disease is significantly overrepresented in Dutch children with constipation who were referred to general pediatrician because of failure of laxative treatment.[11] Similarly, a study in Turkey found that approximately 4% of children with constipation seen in a clinic were diagnosed with celiac disease.[12]

Whether testing for celiac disease should be indicated in all children with constipation and in every country is not an

**Table II. Characteristics of patients with functional constipation and matched controls with no FGIDs**

| Characteristics | Total (N = 622) | No FGIDs (N = 419) | Functional constipation (N = 203) |
|---|---|---|---|
| Age, y | | | |
| Median ± SD | 14.1 ± 3.3 | 13.8 ± 3.4 | 14.6 ± 3.0 |
| Range | 4-18 | 6-18 | 4-18 |
| Age group, n (%) | | | |
| Preschool | 2 (0.3) | 0 (0) | 2 (.9) |
| School-age | 184 (29.5) | 145 (34.6) | 39 (19.2) |
| Adolescence | 436 (70.2) | 274 (65.4) | 162 (79.8) |
| Sex, n (%) | | | |
| Female | 387 (62.2) | 236 (56.3) | 151 (74.3) |
| Male | 235 (37.8) | 183 (43.7) | 52 (25.7) |
| Origin, n (%) | | | |
| Andian Region (Santander, Nariño) | 382 (61.4) | 305 (72.8) | 77 (37.9) |
| Pacific Region (Cali, Tulua) | 152 (24.4) | 62 (14.8) | 90 (44.3) |
| Atlantica Region (Sotavento) | 88 (14.2) | 52 (12.4) | 36 (17.7) |
| Race, n (%) | (N = 559) | (N = 378) | (N = 191) |
| "Mestizo" | 327 (58.5) | 217 (58.9) | 110 (57.5) |
| White | 152 (27.2) | 106 (28.8) | 46 (24.0) |
| African | 32 (5.7) | 15 (4.1) | 17 (8.9) |
| Native | 48 (8.6) | 30 (8.2) | 18 (9.4) |

inconsequential question. There is significant burden associated with routine screening of all children with functional constipation for celiac disease. Drawing blood from young children can be traumatizing, and serologic testing for tTG-IgA and total IgA and HLA testing carry considerable cost. In our study, the cost of diagnosing a single patient was calculated as ~$4045. However, this does not include additional costs for medical consultations, transportation, and missed wages for parents or childcare for siblings from parents needing to bring their child for undergo blood tests and EGD. Costs of extraction, transportation, and delivery of results in this study were also obviated by being part of a research project. In addition, we obtained a reduced price for testing because it was done as part of a research project. Even with the limited costs of testing associated with this investigation, the cost implications are considerable. Based on the prevalence of functional constipation found in our study (11%), initial screening for celiac disease in all children with functional constipation in Colombia would conservatively cost ~$34 million. The high burden to the healthcare budget is not restricted to countries with limited means. In the American study conducted by Chogle et al almost 10 years ago, the costs associated with diagnosing celiac disease on a single child with constipation exceeded $67 000.[4] With the increasing costs of care, current costs are likely to be even higher. Although it could be argued that because of the negative consequences of missing a diagnosis of celiac disease, the cost of testing should not be considered important, based on the present study and previous studies, testing all children with functional constipation would not have a higher yield than testing all schoolchildren indiscriminately, an approach that currently is not recommended.

Limitations of our study include the fact that it was conducted in Colombia and so our results might not be reproducible in other settings; however, the study included white, black, and Hispanic patients, which is representative of many communities in the US. The omission of antideamidated gliadin peptide IgG from our initial celiac screen might have overlooked IgA-sufficient children who were tTG-IgA–negative yet had biopsy-proven celiac disease, which can occur in up to 12% of children.[13] In addition, though our study population was large and most patients completed all necessary steps of the study, some patients did not complete EGD testing, and so we had to separate our study into confirmed celiac disease and suspected celiac disease, which changed the prevalence in our cohort. Furthermore, the single confirmed case of celiac disease and functional constipation limited our ability to evaluate for statistically significant predictors of celiac disease in patients with functional constipation, such as growth failure. Although we cannot rule out the possibility that the contradictory conclusions of the studies conducted in different countries are the result of the differences in prevalence of celiac disease and constipation in dissimilar regions, 2 of the studies with opposite conclusions came from Turkey.[6,12] Some of the strengths of our study include the large sample size; the recruitment of children from multiple cities, regions, and ethnicities; the low attrition rate; and the community-based approach, which reduces the possibility of selection bias due to access to care or severity of symptoms.

Large international studies that include children from various regions, races, and ethnic backgrounds are recommended to confirm our findings and to evaluate for predictors of celiac disease in children with functional constipation. An evidence-based approach to defining the population of children with functional constipation who are more likely to be diagnosed with celiac disease would be of value, especially considering the large number of consultations for functional constipation in children. ■

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