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INCREASED GASTROINTESTINAL PERMEABILITY AND GUT INFLAMMATION IN CHILDREN WITH FUNCTIONAL ABDOMINAL PAIN AND IRRITABLE BOWEL SYNDROME

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Abstract

Objectives—To determine GI permeability and fecal calprotectin concentration in children 7–10 years of age with functional abdominal pain and irritable bowel syndrome (FAP/IBS) vs Controls and ascertain potential relationships with pain symptoms and stooling.

Study design—GI permeability and fecal calprotectin concentration were measured. Children kept a two-week diary of pain episodes and stooling pattern.

Results—Proximal GI permeability was greater in the FAP/IBS group (n = 93) compared with controls (n = 52) (0.59 ± 0.50 vs. 0.36 ± 0.26, respectively; mean ± SD; $P < 0.001$) as was colonic permeability (1.01 ± 0.67 vs. 0.81 ± 0.43, respectively; $P < 0.05$). Gastric and small intestinal permeability were similar. Fecal calprotectin concentration was greater in children with FAP/IBS compared with control children (65.5 ± 75.4 μg/g stool vs. 43.2 ± 39.4, respectively; $P < 0.01$). Fecal calprotectin concentration correlated with pain interference with activities ($P = 0.01$, $r^2 = 0.36$). There was no correlation between GI permeability and pain related symptoms. Neither permeability nor fecal calprotectin correlated with stool form.

Conclusions—Children with FAP/IBS have evidence of increased GI permeability and low grade GI inflammation with the latter relating to the degree to which pain interferes with activities.

Surveys suggest that 10% –17% of children between the ages of 4 and 16 years meet the criteria for recurrent abdominal pain (1–3). It has been suggested that the term recurrent abdominal pain be replaced by the terms functional abdominal pain (FAP) and irritable bowel syndrome (IBS) (4;5). FAP/IBS in children bear many similarities to IBS in adults and may be precursors for IBS (6–8).

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GI permeability is increased in adults with IBS (9;10); however, the limited data in children are unclear. Similarly, a few studies report GI inflammation (i.e., increased fecal calprotectin concentration) in adults with IBS (9). Little data are available regarding calprotectin in children (11;12). To our knowledge no pediatric studies have sought to determine if changes in GI permeability and/or fecal calprotectin concentration relate to FAP/IBS symptoms (e.g., pain severity or frequency, stooling pattern).

The objectives of this study were to measure permeability throughout the GI tract (using sugar permeability tests) and gut inflammation (using fecal calprotectin) in a large group of well characterized children with FAP/IBS and to compare the results to healthy children without GI complaints. We used a site-specific version of the GI permeability test in order to identify potential sites of abnormal mucosa. Calprotectin is a measure of inflammation wherever it occurs in GI tract. Additionally, we sought to determine if GI permeability and/or gut inflammation related to FAP/IBS symptoms.

METHODS

Participants

Participants were 7 – 10 years of age and recruited from a large pediatric health care network which includes primary (pediatric) and tertiary (i.e., pediatric gastroenterologist) care serving the Houston metropolitan area. Participants also were recruited from two private pediatric gastroenterology practices so that the vast majority of gastroenterology referrals in Houston and surrounding areas were identifiable. The study was conducted from October 2002 to June 2007.

Children with FAP or IBS were identified using the Pediatric Rome II criteria for functional abdominal pain and irritable bowel syndrome (13). To clarify better the severity of pain prior to enrollment we included the definition of von Baeyer and Walker (pain episodes severe enough to either cause the child to stay at home, or terminate or avoid play, or take medication for pain, or rate the pain as moderate or severe ($\geq$ 3/10 on a scale of pain intensity) (14).

Children in either group were excluded if they had organic GI illness or other significant chronic health condition with potential GI manifestations (e.g. cystic fibrosis). Other exclusion criteria as prescribed by the Rome II criteria included the presence of “alarm signs” (e.g., an abnormal physical examination, GI blood loss) (13). Other exclusions were the use of antiinflammatory (e.g., ibuprofen) medications within two weeks of testing, or glucocorticoids. Use of GI medications (e.g., proton pump inhibitors, antacids, H_2 receptor blockers, laxatives, or motility agents) were not an exclusion criteria unless once the medication was started it relieved some or all of their symptoms. This latter criterion was used to exclude children who may have had a disorder other than FAP or IBS (e.g., acid reflux, constipation).

Eight children in the FAP/IBS group underwent either upper and/or lower GI endoscopy. The endoscopies were grossly normal and the histology was unremarkable as would be required to meet the definition of FAP/IBS. Similarly, fourteen children underwent radiological evaluations and these were normal. Disaccharidases were not measured. Five FAP/IBS had lactose breath tests and 8 had H. pylori breath tests (all normal). At least seven children had celiac serology done which was negative (records on serology testing were not available for all children). This limited evaluation is in keeping with the Rome and AAP recommendations that in the absence of “red flags” the evaluation be limited.

Procedure

All recruitment and study procedures were approved by the Baylor College of Medicine Institutional Review Board and informed consent of the parents and assent of the child were

obtained. Medical charts then were screened for inclusion and exclusion criteria. Charts and available laboratory records were reviewed. Control subjects were recruited from the same primary care pediatrician offices by reviewing billing codes for well child visits. Parents were screened further by phone regarding their child's symptoms. If the child met eligibility, a home visit was scheduled where the parent and child provided written consent and assent and completed questionnaires. The questionnaire used in telephone screening was the Rome II Investigator questionnaire and the one used on the home visit was the Rome II Clinical Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders (15;16).

The research coordinators provided the child and parent with standardized training as well as written instructions on how to collect urine (GI permeability test) and stool specimens (calprotectin test) and how to record pain and stooling episodes in the diary. The research coordinators maintained weekly contact with the subject and parents to help insure that the tests and diaries were completed.

Measures

Gastrointestinal Permeability—Children fasted overnight. Following the first morning-voided urine children drank 127.5 mL of a solution containing sucrose (10 g/dL), lactulose (5 g/dL), mannitol (1 g/dL), and sucralose (1 g/dL) followed by 240 mL of water. A plastic "hat" was placed over the toilet seat to capture the urine. For the next 3 hours during which time they fasted, urine was collected then placed into a container containing 35 μL of 10% thimerosal to inhibit bacterial growth. Urine was kept on ice and after arrival at our laboratory was frozen at −70°C until analyzed. Urine was analyzed as we have described previously with slight modification for the analysis of sucralose (17). The sucralose is eluted with 5 mL HPLC grade acetonitrile. The eluent is evaporated to dryness and then reconstituted in 0.5 mL of Nanopure water. A 20 μL aliquot is injected onto the analytical column protected with a "Carbo-C Cartridge". The assay is sensitive to 1 μg/mL for sucrose, lactulose, and mannitol and to 10 μg/mL for sucralose. Sugar ratios are expressed per m^2 body surface area.

Gut Inflammation—A plastic "hat" was placed over the toilet seat to capture the passed stool. Stool was analyzed as previously reported using a commercially available ELISA technique (Genova Diagnostics, Asheville, NC). Fecal calprotectin results are expressed as μg/g of stool.

FAP/IBS Symptoms—Ratings of pain intensity and the degree to which pain interfered with activity were made 3 times a day (awakening, after lunch, and evening) over a two week period as we have described previously (18). The child rated their pain using a visual analogue scale (VAS) (20–22). The child rated interference with activity on a 4-point scale from no interference (1), a little interference (2), much interference (3), to unable to participate in activity (4) as we and others have described previously (18;23;24).

Stooling Pattern—Parents were asked to assist the child with the stooling diary to ensure that the record was kept and assist with comparison to the pictures on the stooling diary. Stooling pattern was tracked daily over the two week period. The child identified whether the stool was watery, mushy, formed, hard balls, or if there was no stool passed based on pictures provided in the diary, which was analogous to the Bristol Stool Chart, albeit with fewer categories (25).

Data Analysis

Statistical analyses were conducted using SAS version 9.0 (SAS Institute, Cary, North Carolina). Categorical variables were compared using Chi Square analyses and continuous variables were compared with Student's t-test. The folded-f test was used to determine if the

two samples had equal variances. If the variances were unequal the Satterthwaite test correction was used to accommodate for the differences in variance. Multiple regressions were used to determine if GI permeability and gut inflammation predicted symptoms of pain and stooling patterns.

RESULTS

A total of 109 children with FAP/IBS and 66 controls were recruited for the study. Six FAP/IBS children and 3 Control children did not complete the urine collection properly. Ten FAP/IBS and 11 Control children appeared to be outliers (i.e., had permeability ratios greater than three standard deviations from the mean) and so were excluded. Therefore, a total of 93 FAP/IBS and 52 Control children comprised the sample for the permeability analyses. Of that sample, 9 FAP/IBS and 3 Control children did not provide stool samples so the calprotectin analyses were comprised of 84 FAP/IBS and 49 Control children. Similarly, 8 FAP/IBS and 3 Control children did not complete the two week pain diary so the regression analyses with GI permeability and fecal calprotectin using the pain diary was comprised of 76 FAP/IBS and 46 Control children.

There were no differences between groups in age, race, or sex (Table I). Children were re-contacted a mean of 12.3 months after the initial study (range 6 to 48). Only one of the FAP/IBS children had been diagnosed with an organic cause for their abdominal pain (ulcerative colitis) and subsequently was removed from all analyses.

GI Permeability

The percent recovery of the permeability sugars was similar between the groups (Table II). Proximal GI and colonic permeability (sucrose/lactulose and sucralose/lactulose urinary ratios, respectively) were greater in children with FAP/IBS compared with Controls (Table III). Gastric permeability as measured by the percent recovery of sucrose did not differ between the groups (Table III). There were no differences in total small intestinal permeability between the groups (lactulose/mannitol urinary ratio) (Table III).

Gut Inflammation

Calprotectin was greater in children with FAP/IBS than in Controls (Table III). There was no correlation between GI permeability and fecal calprotectin concentration.

Pain, Interference, and Stooling

As shown in Table IV, and as is recognized clinically, Control children may report episodes of abdominal pain (18). However, there were significantly more pain episodes in the FAP/IBS group compared with Controls. The FAP/IBS group reported significantly higher mean and maximum levels of pain severity overall. Pain interfered with activities significantly more often and at a higher level of intensity in the FAP/IBS group compared with Control group.

There were no differences between groups in the number of stools passed per child over the two week period (Table IV). Similarly, there were no differences between groups on the type of stools such as mushy, hard balls, watery, or the number of days without a bowel movement. Using the criteria of having a pain episode with a change in stool character that day or the day after, 70 children had IBS and 12 had FAP (18).

Relationship between GI Permeability and Calprotectin and Pain/Stooling

There was no significant correlation between the GI permeability tests and any pain symptoms. This was true even in the subset of children with the most severe pain ratings. In contrast, fecal calprotectin concentration correlated with the pain interfering with activity rating ($r^2 = 0.36$,

P < 0.01). Fecal calprotectin was not correlated with the other measures of pain. There were no correlations between stool characteristics (e.g., hard, mushy) and GI permeability or calprotectin results.

DISCUSSION

Our data suggest that children with FAP/IBS have increased permeability in the proximal GI tract and colon. These data are in contrast to adults with IBS where increased small intestinal permeability (i.e., increased lactulose/mannitol ratio) has been found although site specific testing has not been done throughout the GI tract (26) (10) (27).

Only a few studies have measured intestinal permeability in children with recurrent abdominal pain and these studies were for the most part prior to the recommendation that recurrent abdominal pain be differentiated into FAP/IBS. Amery and Forget used ^{51}Cr-EDTA which measures permeability throughout the GI tract (i.e., not site specific) (28–30). These investigators found increased permeability but only in children with documented duodenitis (i.e., they did not meet criteria for FAP/IBS) (28–30). Barau and Dupont carried out permeability testing in a small number of children (n = 17; 2–14 years of age) with IBS as defined by recurrent abdominal pain or chronic diarrhea > 3 months; a definition that does not meet criteria for IBS (31). Their findings suggested that the increased lactulose/mannitol in some children may be related to food allergy (31). However, the one child in the FAP/IBS group and the one child in the Control group who reported food allergies were already on an exclusion diet.

One study in adults with IBS measured colonic permeability by timing the collection of the ^{51}CR-EDTA (10). Using this technique no increase in permeability was noted (10). Whether the increased colonic permeability noted in the children with FAP/IBS reflects the low grade inflammation found in some adults with IBS requires further study (32).

Our results suggest that children with FAP/IBS also have increased fecal calprotectin. GI inflammation can increase fecal calprotectin concentration, a calcium binding protein found in neutrophils, monocytes, and macrophages that resists degradation in the GI tract and is excreted in feces (33). Up to one third of adult patients with IBS also have increased fecal calprotectin concentration (9).

In contrast, the few previous data in children with recurrent abdominal pain suggested that fecal calprotectin concentration was not increased compared with controls (11;12). However, a study by Olafsdottir et al demonstrated a significant decline in fecal calprotectin concentration in children with age and the mean age of the Control children (5.3 years of age; n = 23) was much less than the children with recurrent abdominal pain (11.9 years of age; n = 19) (11). These two factors (decline of fecal calprotectin concentration with age and older age of the recurrent abdominal pain children) and the smaller sample size compared with our study may have obscured potential differences between groups (11). Berni Canani et al measured fecal calprotectin concentration in children with functional disorders (n = 44) and Controls (n = 76) (12). There were no differences between the groups in fecal calprotectin concentrations. However, the functional disorders were not defined further (e.g., FAP/IBS, dyspepsia, colic) and the age ranges were wide (Controls: 1 – 18 years, Functional disorders: 1 – 13 years) (12). Thus, it is difficult to compare their results with ours.

We anticipated there would be a relationship between mucosal abnormalities as defined by increased GI permeability and fecal calprotectin concentration and pain symptoms and stool characteristics. To our surprise, only fecal calprotectin concentration was related to pain symptoms, and in that case, only to how much the pain interfered with activity. These data suggest that the relationship between GI permeability, mucosal inflammation, and pain

symptoms is more complex than initially thought. Indeed, our data fit with the observation in adults with constipation-predominant or postinfectious IBS that there is no correlation between GI permeability and GI symptoms (10). Data from neonatal stress models suggest that a stress engendered shortly after birth can manifest as increased GI permeability in the neonatal period and into adulthood (34). These animal data fit with clinical observations that humans stressed as infants are more likely to develop functional bowel symptoms (35–37). Thus, we speculate that increased permeability in our children may be present from a young age perhaps explaining, in part, the disconnect between increased permeability and pain and stooling symptoms in our children 7–10 years of age.

Fecal calprotectin concentration did correlate with the degree to which pain interfered with the children's activities. Similar to our findings in children, in adults there also appeared to be no correlation between GI permeability and fecal calprotectin concentration (10). It may be that different mechanisms are operative in engendering an increase in GI permeability vs. fecal calprotectin concentration in children with FAP/IBS or adults with IBS.

There are some limitations to our study. Although all children with FAP/IBS were thoroughly screened and had some diagnostic testing, it is possible that some children may have had other conditions. However, given that the children had to have had at least three months of pain prior to admission into the study and had been evaluated by their pediatrician and in some cases by a pediatric gastroenterologist prior to recruitment, the actual time from onset of symptoms to follow up was much greater than our mean of 12.3 months. Thus, it is unlikely that a significant organic disorder would have been missed. Also, despite the relatively large sample size, it is possible that a larger study may have uncovered further correlations among the variables studied.

In summary, we have shown that children with FAP/IBS have evidence of increased proximal GI and colonic permeability and have GI inflammation as reflected by fecal calprotectin concentration. We also have demonstrated that fecal calprotectin concentration bears some relationship with the degree to which pain limits activities.

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Reference List

1. Liebman WM. Recurrent abdominal pain in children: a retrospective survey of 119 patients. Clin Pediatr 1978;17:149–153.
2. Hyams JS, Treem WR, Justinich CJ, Davis P, Shoup M, Burke G. Characterization of symptoms in children with recurrent abdominal pain: resemblance to irritable bowel syndrome. J Pediatr Gastroenterol Nutr 1995;20:209–214. [PubMed: 7714688]
3. Hyams JS, Burke G, Davis PM, Rzepski B, Andrulonis PA. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. J Pediatr 1996;129:220–226. [PubMed: 8765619]
4. Rasquin A, Di LC, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527–1537. [PubMed: 16678566]

5. DiLorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT, Hyams JS, et al. Chronic Abdominal Pain In Children: a Technical Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005;40:249–261. [PubMed: 15735476]
6. Jarrett M, Heitkemper M, Czyzewski DI, Shulman RJ. Recurrent abdominal pain in children: forerunner to adult irritable bowel syndrome? J Soc Pediatr Nurs 2003;8:81–89.
7. Burke P, Elliott M, Fleissner R. Irritable bowel syndrome and recurrent abdominal pain. A comparative review. Psychosomatics 1999;40:277–285. [PubMed: 10402871]
8. DiLorenzo C, Youssef NN, Sigurdsson L, Scharff L, Griffiths J, Wald A. Visceral hyperalgesia in children with functional abdominal pain. J Pediatr 2001;139:838–843. [PubMed: 11743510]
9. Tibble JA, Sigthorsson G, Foster R, Forgacs I, Bjarnason I. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. Gastroenterology 2002;123:450–460. [PubMed: 12145798]
10. Dunlop SP, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. Am J Gastroenterol 2006;101:1288–1294. [PubMed: 16771951]
11. Olafsdottir E, Aksnes L, Fluge G, Berstad A. Faecal calprotectin levels in infants with infantile colic, healthy infants, children with inflammatory bowel disease, children with recurrent abdominal pain and healthy children. Acta Paediatr 2002;91:45–50. [PubMed: 11883817]
12. Berni Canani R, Rapacciuolo L, Romano MT, Tanturri de HL, Terrin G, Manguso F, et al. Diagnostic value of faecal calprotectin in paediatric gastroenterology clinical practice. Dig Liver Dis 2004;36:467–470. [PubMed: 15285526]
13. Rasquin-Weber A, Hyman PE, Cucchiara S, Fleisher DR, Hyams JS, Milla PJ, et al. Childhood functional gastrointestinal disorders. Gut 1999;45:SII60–SII68.
14. Von Baeyer CL, Walker LS. Children with recurrent abdominal pain: issues in the selection and description of research participants. Develop Behav Pediatr 1999;20:307–313.
15. Drossman, D.; Corazziari, E.; Thompson, WG.; Talley, NJ.; Whitehead, WE., editors. Rome II The Functional Gastrointestinal Disorders. Second ed. McLean: Degnon Associates; 2000. Research Diagnostic Questions for Functional Gastrointestinal Disorders" Rome II Modular Questionnaire; p. 670-688.
16. Drossman, D.; Corazziari, E.; Thompson, WG.; Talley, NJ.; Whitehead, WE., editors. Rome II The Functional Gastrointestinal Disorders. Second ed. McLean: Degnon Associates; 2000. Clinical Diagnostic Questionnaire for Pediatric Functional Gastrointestinal Disorders; p. 715-722.
17. Shulman RJ, Schanler RJ, Lau C, Heitkemper M, Ou C-N, Smith EO. Early feeding, antenatal glucocorticoids, and human milk decrease intestinal permeability in preterm infants. Pediatr Res 1998;44:519–523. [PubMed: 9773840]
18. Shulman RJ, Eakin MN, Jarrett M, Czyzewski DI, Zeltzer LK. Characteristics of pain and stooling in children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2007;44:203–208. [PubMed: 17255832]
19. Czyzewski DI, Eakin MN, Lane MM, Jarrett M, Shulman RJ. Recurrent Abdominal Pain in Primary and Tertiary Care: Differences and Similarities. Child Health Care 2007;36:137–153.
20. McGrath PJ, Beyer J, Cleeland C, Eland J, McGrath PA, Portenoy R. American Academy of Pediatrics Report of the Subcommittee on Assessment and Methodologic Issues in the Management of Pain in Childhood Cancer. Pediatrics 1990;86(5 pt 2):814–817. [PubMed: 2216643]
21. Varni JW, Walco GA, Katz ER. A cognitive-behavioral approach to pain associated with pediatric chronic diseases. J Pain Symptom Manage 1989;4:238–241. [PubMed: 2607181]
22. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol 1994;62:306–314. [PubMed: 8201068]
23. Wong DI, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14:9–17. [PubMed: 3344163]
24. Gaylord N, Carson S. Assessing recurrent abdominal pain in children. Nurse Pract 1983;8:19–24. [PubMed: 6633981]

25. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–924. [PubMed: 9299672]
26. Marshall JK, Thabane M, Garg AX, Clark W, Meddings J, Collins SM. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario. Aliment Pharmacol Ther 2004;20:1317–1322. [PubMed: 15606393]
27. Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804–811. [PubMed: 11076879]
28. Amery WK, Forget PP. The role of the gut in migraine: The oral 51-Cr EDTA test in recurrent abdominal pain. Cephalalgia 1989;9:227–229. [PubMed: 2507165]
29. van der Meer SB, Forget PP, Heidendal GAK. Abnormal small bowel permeability and duodenitis in recurrent abdominal pain. Arch Dis Child 1990;65:1311–1314. [PubMed: 2125404]
30. van der Meer SB, Forget PP, Arends JW. Small bowel permeability to 51Cr-EDTA in children with recurrent abdominal pain. Acta Paediatr Scand 1990;79:422–426. [PubMed: 2112296]
31. Barau E, Dupont C. Modifications of intestinal permeability during food provocation procedures in pediatric irritable bowel syndrome. J Pediatr Gastroenterol Nutr 1990;11:72–77. [PubMed: 2117653]
32. Bercik P, Verdu EF, Collins SM. Is irritable bowel syndrome a low-grade inflammatory bowel disease? Gastroenterol Clin North Am 2005;34:235–237. [PubMed: 15862932]
33. Roseth AG, Fagerhol MK, Aadland E, Schjonsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol 1992;27:793–798. [PubMed: 1411288]
34. Barreau F, Ferrier L, Fioramonti J, Bueno L. New insights in the etiology and pathophysiology of irritable bowel syndrome: contribution of neonatal stress models 3. Pediatr Res 2007;62:240–245. [PubMed: 17622962]
35. Anand KJ, Runeson B, Jacobson B. Gastric suction at birth associated with long-term risk for functional intestinal disorders in later life. J Pediatr 2004;144:449–454. [PubMed: 15069391]
36. Andrews KA, Desai D, Dhillon HK, Wilcox DT, Fitzgerald M. Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. Pain 2002;100:35–46. [PubMed: 12435457]
37. Bengtson MB, Ronning T, Vatn MH, Harris JR. Irritable bowel syndrome in twins: genes and environment. Gut 2006;55:1754–1759. [PubMed: 17008364]

Table 1

Description of Study Sample

	FAP/IBS	Control
Female, n (%)	65 (71%)	39 (73%)
Age (yr.)	8.2 ± 1.4*	8.5 ± 1.3
Race/Ethnicity, (%)		
White, non-Hispanic	66%	77%
Black, non-Hispanic	15%	19%
Hispanic	14%	4%
Asian	2%	1%

* Mean ± SD

Table 2

Sugar Percent Dose Recovered

	FAP/IBS	Control
Sugars		
Sucrose	0.02 ± 0.03*	0.02 ± 0.03
Lactulose	0.10 ± 0.08	0.09 ± 0.06
Mannitol	7.6 ± 5.5	7.6 ± 4.7
Sucralose	0.44 ± 0.42	0.42 ± 0.32

* Mean ± SD

Table 3

Permeability Sugar Ratios and Fecal Calprotectin Concentrations

	FAP/IBS	Control	P Value
Sugar Ratios			
Sucrose/lactulose	0.59 ± 0.50*	0.36 ± 0.26	0.001
Lactulose/mannitol	0.06 ± 0.03	0.07 ± 0.03	
Sucralose/lactulose	1.01 ± 0.67	0.81 ± 0.43	0.05
Fecal Calprotectin (μg/g stool)	65.5 ± 75.4	43.2 ± 39.4	0.01

* Mean ± SD

Table 4

Pain Frequency and Severity and Interference with Activity over Two Weeks

	FAP/IBS	Control	P Value [a]
Pain and Interference Episodes			
Pain episodes over 2 weeks	7.4 ± 9.1 [*]	1.5 ± 3.6	0.001
Severity of all pain episodes	13.2 ± 13.7	4.9 ± 9.3	0.001
Severity of maximum reported pain	57.1 ± 30.6	24.3 ± 27.3	0.001
Number of episodes of interference [b]	0.35 ± 0.93	0.05 ± 0.23	0.01
Percent of interference ratings: #	2340	1798	
No interference	86.5%	94.4%	0.01
A little interference	9.1%	4.3%	0.01
Much interference	2.9%	1.1%	
Unable to participate in activity	1.4%	0.1%	0.05
Stool Characteristics			
Total Number of Stools in 14 days	1083	626	
Watery	3.1%	2.1%	
Mushy	13.5%	11.5%	
Normal	69.6%	70.7%	
Hard	13.8%	15.7%	

[*] Mean ± SD

[a] Note: P-values were based on t-test for continuous variables and Chi Square for categorical variables.

[b] Number of episodes of Interference = Number of episodes of “much interference” or “unable to participate in activity”.