Published in final edited form as:

Clin Gastroenterol Hepatol. 2020 February ; 18(2): 375–384.e1. doi:10.1016/j.cgh.2019.05.011.

Increased Gut Permeability in First-degree Relatives of Children with Irritable Bowel Syndrome or Functional Abdominal Pain

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Abstract

Background & Aims: Increased gut permeability might contribute to the pathogenesis of irritable bowel syndrome or functional abdominal pain (IBS or FAP). We investigated whether siblings and parents of children with IBS or FAP have increased gut permeability.

Methods: We performed permeability tests (using sucrose, lactulose, mannitol, and sucralose) on 29 siblings and 43 parents of children with IBS or FAP, and 43 children (controls) and 42 parents of controls, from primary and secondary care. Permeability studies were repeated in 7 siblings and 37 parents of children with IBS or FAP and 23 controls and 36 parents of controls following ingestion of 400 mg of ibuprofen. Percent recovery of sucrose was calculated based on analyses of urine, collected overnight; the lactulose/mannitol ratio and percent recovery of sucralose were based on analyses of urine samples collected over a 24-hour period.

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Disclosures:

The authors have nothing to disclose

Results: When we controlled for age, sex, and family membership, siblings of children with IBS or FAP had increased small bowel permeability (urinary lactulose/mannitol ratio) vs controls ($P=.004$). There was no difference in gastroduodenal (percent sucrose recovery) or colonic (percent sucralose recovery) permeability between groups. Similarly, parents of children with IBS or FAP also had increased small bowel permeability, compared with parents of controls ($P=.015$), with no differences in gastric or colonic permeability. After administration of ibuprofen, gastroduodenal and small bowel permeability tended to be greater in IBS or FAP siblings ($P=.08$) and gastroduodenal permeability tended to be greater in IBS or FAP parents ($P=0.086$).

Conclusions: Siblings and parents of children with IBS or FAP have increased baseline small intestinal permeability compared with control children and their parents. These results indicate that there are familial influences on gastrointestinal permeability in patients with IBS or FAP.

Keywords

NSAID; intestinal barrier; genetics; environmental factor

INTRODUCTION

Childhood recurrent abdominal pain is a common complaint affecting up to 15–20% of school age children and adults world-wide.^{1, 2} The majority are considered to have a functional gastrointestinal disorder: irritable bowel syndrome (**IBS**), functional abdominal pain (**FAP**).³ FAP and IBS exhibit similar pain and psychological characteristics and children may move back and forth between the two.⁴ Studies of families and twins have highlighted the clustering of IBS and FAP, suggesting a heritable contribution to their expression.⁵

While the etiologies of IBS and FAP are not known, several factors are thought to contribute (e.g., visceral hypersensitivity, dietary factors, psychosocial distress).^{6, 7} Recently, data have focused on the potential role of increased gastrointestinal (**GI**) permeability in the pathogenesis and generation of symptoms in IBS and FAP.⁸

Adult and pediatric patients with inflammatory bowel disease (**IBD**) also demonstrate increased GI permeability.^{9–11} Increased GI permeability may be a fundamental contributor to the development of IBD.^{11, 12} A significant proportion of first degree relatives of patients with IBD have increased baseline small intestinal permeability or in response to administration of nonsteroidal antiinflammatory drugs (**NSAIDs**) comparable to the index IBD patient and greater than in controls.^{9, 13}

Given the known clustering of IBS and IBD within families and the increased GI permeability in IBS and in IBD and, in the case of IBD, their first degree relatives, we hypothesized that permeability in first degree relatives of children with IBS or FAP might also be increased compared with that in healthy children and their parents. We also hypothesized that ibuprofen would increase permeability to a greater degree in siblings and parents of children with IBS or FAP versus control children and their parents.

MATERIALS AND METHODS

Subjects

Both sibling and parent groups (IBS and FAP, control) were recruited by contacting families that had participated in our previous observational studies that recruited both IBS and FAP children and age- and sex-matched controls.^{14–17} One of these studies examined gut permeability in children with IBS and FAP in comparison to healthy children.¹⁴ We estimated a sample size of 15–21 children and 26–33 adults would be needed to detect a statistically significant difference between groups using a power = 0.8 and $P < 0.05$.^{9, 14, 18}

Upon phone contact, the family was queried as to whether any family members had general health issues (e.g., heart disease, renal disease, diabetes) or GI diseases (e.g., IBD, *H. pylori* infection, celiac disease). If they answered affirmatively, they were excluded from participating.

Eligible families were scheduled for a home visit, at which time they were queried further as to whether they had taken NSAIDs within two weeks, alcohol within 48 hours, or antibiotics within 4 weeks of the study. If so, the permeability study for the entire family was delayed to avoid potential interferences. At the home visit children completed the Rome III Diagnostic Questionnaire for Pediatric Functional GI Disorders and adult participants completed the Rome III Diagnostic Questionnaire for Adult Functional GI Disorders (including Alarm Questions) and Scoring Algorithm. They then received detailed instructions on how to carry out the permeability study, including avoiding any foods (including artificial sweeteners), drugs, or drinks that could affect the results.

The study was approved by the Baylor College of Medicine Institutional Review Board. Consent was obtained from the adults for themselves as well as assent from the children.

GI permeability Testing and Sugar Analyses

The permeability sugar solution contained sucrose (10g), lactulose (5g), mannitol (1g), and sucralose (1g) and was ingested following a 4-hour fast after the evening meal.¹⁹ See Supplementary materials for complete details.

Testing was repeated one week later after ingestion of 400 mg of ibuprofen every 8 hours for 3 doses prior to administration of the sugar solution. The last dose was given 4 hours prior to sugar ingestion. Ibuprofen was chosen as NSAIDs increase gastric and small bowel permeability although it is not clear if they increase colonic permeability.^{20–22} The dose administered was based on previous studies demonstrating increased gut permeability after NSAID administration.²¹

Data Analysis

Data presented in Tables are expressed as mean $\pm$ SD except where noted. Differences in demographics were tested using Student's t-test. Differences in proportions between the frequencies of Rome diagnoses were tested using Chi-square.

Since the sugar measurements were not normally distributed, with some outliers present, a rank transform was applied as more complex analyses can be done, such as controlling for covariates and accounting for clustering.²³ P-values for the permeability data are based on analyses of the rank transformed data. Differences in urinary recovery and permeability of the sugars between groups were tested using general estimating equation techniques, which accounts for the clustering of individuals within families. Analyses controlled for age and sex as these have been shown to affect the results of gut permeability testing.¹⁹ We also controlled for the presence of a Rome diagnosis in the siblings and the parents based on their responses to the Rome questionnaire.

RESULTS

Subjects

A total of 43 families with a child who had IBS or FAP and 42 families with control children completed the baseline study (Table 1). There were no differences in age or sex between the IBS or FAP and control children or between IBS or FAP and control adults (Table 1). BMI was similar between groups with the exception it was greater in male IBS and FAP siblings than in male control siblings (Table 1).

Seven siblings and 37 parents of children with IBS or FAP were willing to repeat the permeability testing following ibuprofen administration (Table 1). Twenty-three control children and 36 control parents underwent permeability testing following ibuprofen administration.

Based on the Rome questionnaires, a small number of siblings and parents had a Rome diagnosis (Table 2). However, there was no difference between IBS or FAP and control families with regard to the proportion with a Rome diagnosis (siblings, $P=.8$; parents, $P=.3$) or in the proportion with IBS specifically (siblings, $P=.8$; parents, $P=.6$; Table 2).

Sibling Results

Urinary recoveries (expressed in mg) of sucrose, lactulose, mannitol, and sucralose were similar in the siblings of children with IBS or FAP compared with control children (Table 3).

The baseline lactulose/mannitol ratio was significantly greater in siblings of children with IBS or FAP than in control children ($P=.004$, Table 4). This difference remained significant when controlling for a Rome diagnosis ($P=.012$). There were no differences between the groups in the percent sucrose or sucralose recovery (Table 4).

There was a correlation (0.524, $P=.031$) between the lactulose/mannitol ratio of the children with IBS/FAP from our original study¹⁴ and that of their siblings in the present study (Supplementary Figure). There was no correlation between % sucrose or sucralose recovery in children with IBS/FAP from our original study and that of their siblings (data not shown).

Ibuprofen numerically increased the percent sucrose recovery and the lactulose/mannitol ratio in the siblings of children with IBS or FAP but the results did not reach significance (Table 5). Percent sucralose recovery did not differ between groups (Table 5).

Parent Results

Urinary recoveries of sucrose, lactulose, mannitol, and sucralose were similar in the parents of children with IBS or FAP compared with control parents (Table 2).

Similar to the child results, the baseline lactulose/mannitol ratio was significantly greater in parents of children with IBS or FAP than in control parents ($P=.015$, Table 4). As was the case for the siblings, this difference remained significant when controlling for a Rome diagnosis ($P=.007$). There were no differences between the groups in the percent sucrose or sucralose recovery (Table 4).

Following administration of ibuprofen, percent sucrose recovery was numerically greater in the parents of IBS/FAP children but did not reach significance (Table 5). The lactulose/mannitol ratio and sucralose recovery did not differ between groups (Table 5).

DISCUSSION

To our knowledge, our study is the first evaluating GI permeability in first-degree relatives of children with IBS or FAP. Our results show that siblings and parents of children with IBS or FAP have increased baseline lactulose/mannitol ratio compared with siblings of control children and their parents (Table 3). Baseline sucrose and sucralose permeability did not differ between groups.

It might be assumed that the increased permeability in the IBS or FAP families might be associated with GI symptoms. However, like IBD, IBS and FAP are believed to be disorders precipitated by a predisposition and a confluence of events. It is unlikely that increased gut permeability alone is responsible for either IBD or IBS and FAP.^{8, 24} A small proportion of siblings and parents in both groups had a Rome diagnosis based on questionnaire. However, the proportion did not differ between groups (Table 2). Further, the difference between the groups in the lactulose/mannitol ratio remained significant in the presence/absence of a Rome diagnosis.

Given that previous studies have not examined GI permeability in first-degree relatives, we discuss our results in the context of studies done in children and adults with IBS or FAP. A number of reviews have summarized adult studies demonstrating increased gut permeability (primarily lactulose/mannitol ratio) in IBS.^{8, 25, 26}

Baseline Permeability

The lactulose/mannitol ratio was increased in the siblings and parents of children with IBS or FAP compared with siblings and parents of controls (Table 4). Our current results differ somewhat from what we reported previously in children with IBS or FAP versus controls. In our previous study using a 3-hour collection time, the lactulose/mannitol ratio was similar in children with IBS or FAP versus controls.¹⁴ The current study controlled for age and sex which may explain, in part, the different findings.¹⁴ Other pediatric studies have reported an increased ratio in IBS.^{27,28} There was a strong correlation (see Supplementary Figure) between the lactulose/mannitol ratio in our previous study in children with IBS/FAP and

their siblings in our current study, underscoring the potential pathophysiologic importance of our finding.

In our prior study, percent sucrose recovery did not differ between children with IBS or FAP and controls similar to a report for adults with IBS vs controls.^{14, 29} These results fit with our current findings in siblings and parents (Table 4).

Similarly, there were no differences in the percent recovery of sucralose in siblings and parents of children with IBS or FAP vs controls (Table 4); similar to our previous report in children with IBS or FAP vs controls, albeit, collection time was much shorter in the previous study.¹⁴ To our knowledge, only one study has examined sucralose recovery in adults with IBS.²⁹ Using a 5-hour collection time, sucralose recovery in adult IBS patients was less than controls; a finding that would seem counterintuitive and might be due to an artifact related to the short collection time.²⁹

Impact of Sex and Age on Gut Permeability

We previously have shown that age and sex can affect gut permeability results in children and adults.¹⁹ Sucrose recovery declines with age regardless of sex.¹⁹ In contrast, the lactulose/mannitol ratio and sucralose recovery decline with age in females but not in males.¹⁹ These findings fit with more recent studies.^{30, 31} Thus, it was important that the analyses controlled for these variables.

Studies investigating the role of sex steroids on paracellular permeability are scarce.^{31, 32} Although contradictions exist, evidence suggests that female sex steroids decrease gut permeability.³¹ For example, in vitro studies using a HT-29 colorectal adenoma cell line suggested that exposure to estrogen increases mucin content and viscosity and barrier function.³⁸ Sex-steroid depleted mice have increased gut permeability with related decreases in gap junction protein transcripts.³³ Whether differences in sex hormones and related differences in gut permeability (and related low grade gut inflammation) contribute to the female predominance in adult IBS is unclear.³¹ It is striking to note, however, that the differences in permeability between the IBS or FAP and control families was primarily driven by increased permeability in girls and women rather than males (Table 4). Whether sex differences in the gut permeability response to NSAIDs exists is, to our knowledge, unknown.

Post-ibuprofen Permeability

Ibuprofen, like other NSAIDs, increases gastric and small bowel permeability although it is not clear if they always increase colonic permeability.^{20–22} To our knowledge, no studies have evaluated gut permeability following ibuprofen administration in children or adults with IBS or FAP. Kerckhoffs et al. measured permeability in adults with IBS and controls using various size polyethylene glycols to measure whole gut permeability before and after two doses (750 mg each) of naproxen.³⁴ The drug increased the area under the urinary recovery curve in the IBS group compared with controls.³⁴

After ibuprofen administration the percent sucrose recovery was numerically greater in siblings and parents of children with IBS or FAP and the lactulose/mannitol ratio was

numerically greater in the IBS and FAP siblings but the results did not reach significance (Table 5). Whether this was due to the small number of subjects and/or an inadequate dose of ibuprofen is unclear. Thus, these results should be seen as exploratory.

Site of Increased Gut Permeability

The use of sucrose, lactulose, mannitol, and sucralose has been proposed to assess site-specific permeability of the GI tract.³⁵ There is strong support for sucrose as a measure of gastroduodenal permeability both in adults and children.^{36, 37} The lactulose/mannitol ratio long has been considered a marker of small intestinal permeability although this continues to be debated.³⁵ Recently, it has been argued that lactulose and mannitol are absorbed substantially in the colon and thus, also measure colonic permeability.³⁸ However, fermentation of lactulose occurs in under two minutes after arrival into the human colon and lactulose and mannitol are fermented to the same extent; findings that parallel in vitro studies.^{35, 39, 40, 41} The fact that lactulose and mannitol can be recovered in urine hours after they have entered the colon also has been used as evidence they are absorbed in the colon.³⁸ However, even after intravenous administration of these and similar probes, the sugars are excreted over 24 hours.^{42–45}

Lactulose/mannitol urine collection time recommendations have ranged from 2–24 hours. Studies combining scintigraphy with permeability studies in adults suggests that by 3 hours a substantial proportion of the isotope (and presumably, sugars) is in the colon.^{38, 44} We recently showed in children that there is a tight correlation ($r=0.98$) between the lactulose/mannitol ratios at 4 and 24 hr.⁴⁶ In addition, we found a strong correlation (0.524) between the ratio in the IBS/FAP children from our original study and their siblings in the current study. That said, the implication that the ratio in the current study represents small bowel permeability should be viewed cautiously.

Sucralose has been used as a marker of whole bowel permeability as it does not undergo fermentation by colonic bacteria.^{35, 47} Because residence time is greatest in the colon, it has been considered a measure of colonic permeability.³⁵ Indirect support comes from studies using different NSAIDs which alter the lactulose/mannitol ratio but do not affect sucralose recovery.^{20, 48}

There are some limitations to our study. Although we provide evidence above regarding the interpretation of the site specificity of the sugars, as noted, it is a point of debate. Consequently, although we observed a difference in gut permeability between the groups, we cannot say with absolutely certainty the location of this difference (i.e., small bowel, colon, or both). We were not able to differentiate the influence of genetics from environment on the results (e.g., changes in the gut microbiome which might influence mucosal permeability); this will require additional studies. A similar need exists for IBD given that relatives of patients with IBD also have increased gut permeability.^{9, 13} Another limitation is the relatively small number of individuals who underwent repeat permeability testing following ibuprofen. Finally, we were not able to differentiate IBS from FAP or define subgroups in our original study.¹⁴ However, it should be noted that children with IBS and FAP share similar clinical and psychological characteristics and that small changes in how

the pediatric Rome criteria are interpreted can dramatically affect whether a child is denoted as having IBS or FAP.^{4, 49, 50}

Strengths of our study include the relatively large number of subjects undergoing baseline permeability testing. Sex and age influence gut permeability yet rarely have been controlled for in prior studies.¹⁹ Thus, these variables were addressed in our analyses. We also controlled for the presence/absence of a Rome diagnosis; it did not affect our primary finding of increased permeability. Additionally, the increased permeability in children with IBS or FAP parallels that in their siblings (Supplemental Figure).

In summary, to our knowledge we have shown for the first time that first-degree siblings and parents of children with IBS and FAP have increased GI permeability compared with siblings and parents of control children. Elucidating whether permeability differences are genetically and/or environmentally engendered may allow for more targeted research and/or treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support:

This study was supported in part by R01 NR05337 from the National Institutes of Health, the Daffy's Foundation, the USDA/ARS under Cooperative Agreement No. 6250-51000-043, and P30 DK56338 which funds the Texas Medical Center Digestive Disease Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work is a publication of the USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital. The contents do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Abbreviations:

IBS	irritable bowel syndrome
FAP	functional abdominal pain
GI	gastrointestinal
IBD	inflammatory bowel disease
NSAID	nonsteroidal antiinflammatory drug

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What You Need to Know

Background:

Patients with inflammatory bowel diseases have increased gut permeability as do their family members compared to persons in families without inflammatory bowel diseases. Some patients with irritable bowel syndrome and functional abdominal pain also have increased gut permeability.

Findings:

Siblings and parents of children with irritable bowel syndrome and functional abdominal pain have increased baseline small intestinal permeability compared with control children and their parents.

Implications for Patient Care:

There could be familial influences on gastrointestinal permeability in patients with irritable bowel syndrome and functional abdominal pain.

Table 1

Demographics of Subjects

	Siblings				Parents			
	IBS and FAP	Control	43	P Value	IBS and FAP	Control	42	P Value
Baseline								
Number	29	43						
Sex								
Female	16 (53%)	22 (47%)		.58	29 (64%)	25 (57%)		.46
Male	14 (47%)	20 (53%)			16 (36%)	19 (43%)		
Age (yrs.)								
Female	9.9 ± 3.0 *	9.3 ± 3.0		.45	43.9 ± 6.1	41.3 ± 6.0		.50
Male	10.6 ± 3.3	9.0 ± 3.2		.17	41.0 ± 5.8	40.0 ± 5.5		.21
Body Mass Index								
Female	17.5 ± 3.9	18.8 ± 5.3		.44	27.8 ± 25.1	25.1 ± 7.2		.26
Male	23.1 ± 5.0	16.1 ± 2.2		.003	31.2 ± 8.6	28.2 ± 4.6		.35
Post-Ibuprofen								
Number	7	23			37	36		
Sex								
Female	2 (29%)	11 (48%)			22 (59%)	21 (58%)		
Male	5 (71%)	12 (52%)			15 (41%)	15 (42%)		
Age (yrs.)								
Female	9.0 ± 1.4	9.1 ± 2.1		.95	42.6 ± 4.1	39.9 ± 5.2		.06
Male	10.0 ± 2.5	7.0 ± 1.6		.05	44.1 ± 6.3	41.3 ± 6.2		.24

* Years, mean ± SD

Table 2

Results of Subjects' Rome Questionnaires

	Siblings		Parents	
	IBS and FAP	Control	IBS and FAP	Control
Number	29	43	43	42
Functional dyspepsia	1	0	4	0
IBS	1	1	7	5
Functional constipation	2	2	4	1
Functional abdominal pain	1	1	0	0

No differences between IBS and FAP and control families with regard to the proportion with a Rome diagnosis (siblings, $P=.8$; parents, $P=.3$). No difference between groups in the proportion with IBS (siblings, $P=.8$; parents, $P=.6$).

Table 3

Sugar Recovery (mg) in Siblings and Parents

Baseline	Siblings		Parents	
	IBS and FAP n=29	Control n=43	IBS and FAP n=43	Control n=42
		P Value		P Value
Sucrose ^a	13.7 ± 9.9 ^c	.32	16.2 ± 10.5	15.1 ± 7.5
	10.4 ^d	13.0	13.8	13.2
	8.7 / 12.8 / 18.5 ^e		8.8 / 13.8 / 19.2	
Lactulose ^b	33.7 ± 22.0	.09	35.9 ± 44.7	21.2 ± 13.4
	25.1	21.1	24.3	17.0
	16.1 / 21.9 / 33.3		10.7 / 18.0 / 31.0	
Mannitol ^b	295 ± 153	.68	428 ± 209	398 ± 155
	296	298	401	373
	199 / 294 / 360		275 / 346 / 496	
Sucralose ^b	22.3 ± 12.5	.72	24.5 ± 12.7	24.5 ± 8.5
	15.8	21.5	22.9	22.6
	14.7 / 20.5 / 27.2		17.6 / 22.7 / 28.8	
Post Ibuprofen	n=7	n=23	n=37	n=36
		P Value		P Value
Sucrose ^a	23.0 ± 22.0	.38	27.0 ± 54.0	20.8 ± 27.4
	12.9	7.1	10.7	12.3
	5.0 / 7.4 / 14.9		6.7 / 10.8 / 24.4	
Lactulose ^a	22.2 ± 6.6	.41	27.8 ± 16.6	40.4 ± 73.6
	19.7	18.0	24.3	24.0
	14.5 / 18.9 / 23.0		14.0 / 24.3 / 40.3	
Mannitol ^a	312 ± 131	.70	400 ± 174	389 ± 180
				.80

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	Siblings			Parents		
	IBS and FAP n=29	Control n=43		IBS and FAP n=43	Control n=42	
	251	250		364	386	
	181 / 251 / 363			263 / 378 / 492		
Sucralose ^a	30.7 ± 20.5	16.5 ± 14.0	.13	39.1 ± 56.8	30.3 ± 28.8	.41
	21.2	14.4		24.5	21.1	
	9.2 / 15.1 / 21.4			14.2 / 21.6 / 36.1		

^a = overnight recovery

^b = 24-hour recovery

^c = Mean ± SD

^d = Median

^e = 25th / 50th / 75th percentiles

Table 4

Baseline Permeability Sugar Results

	Girls		Boys		Children P Value ^f		Women		Men		Adult P Value ^f	
	IBS and FAP n=17	Control n=20	IBS and FAP n=12	Control n=23	IBS and FAP vs Control	IBS and FAP n=27	Control n=24	IBS and FAP n=16	Control n=18	IBS and FAP vs Control		
Sucrose % Recovery ^a	0.349 ^c ± 0.881	0.310 ± 0.668	0.103 ± 0.081	0.084 ± 0.082	.48	0.280 ± 0.851	0.101 ± 0.092	0.105 ± 0.104	0.064 ± 0.061	.30		
	0.091 ^d	0.093	0.076	0.072		0.080	0.080	0.077	0.056			
		0.040 / 0.079 / 0.159 ^e					0.027 / 0.079 / 0.109					
Lactulose/Mannitol Ratio ^b	0.116 ± 0.072	0.065 ± 0.041	0.094 ± 0.050	0.083 ± 0.055	.004	0.128 ± 0.290	0.050 ± 0.030	0.055 ± 0.033	0.041 ± 0.025	.015		
	0.098	0.054	0.093	0.060		0.057	0.042	0.045	0.036			
		0.049 / 0.078 / 0.115					0.030 / 0.044 / 0.068					
Sucralose % Recovery ^b	3.57 ± 4.32	2.03 ± 0.95	2.28 ± 1.28	2.33 ± 1.27	.91	2.44 ± 1.43	2.27 ± 0.87	1.92 ± 0.77	2.24 ± 0.59	.42		
	1.94	1.95	1.93	2.04		2.04	2.17	1.95	2.36			
		1.25 / 1.94 / 2.73					1.46 / 2.13 / 2.76					

^a = overnight recovery^b = 24-hour recovery^c = Mean ± SD^d = Median^e = 25th / 50th / 75th percentiles

Table 5

Post-Ibuprofen Permeability Sugar Results

	Girls		Boys		Children P Value*		Women		Men		Adult P Value*	
	IBS and FAP n=2	Control n=11	IBS and FAP n=5	Control n=12	IBS and FAP vs Control	IBS and FAP n=22	Control n=21	IBS and FAP n=15	Control n=15	IBS and FAP vs Control		
Sucrose % Recovery ^a	0.019 ± 0.019 ^c	0.113 ± 0.105	0.252 ± 0.209	0.109 ± 0.063	.08	0.156 ± 0.160	0.142 ± 0.154	0.157 ± 0.174	0.090 ± 0.098	.086		
	0.019 ^d	0.083	0.180	0.097		0.108	0.098	0.010	0.053			
		0.057 / 0.089 / 0.160 ^e					0.045 / 0.098 / 0.169					
Lactulose/Mannitol Ratio ^b	0.052 ± 0.020	0.054 ± 0.024	0.073 ± 0.033	0.063 ± 0.034	.08	0.059 ± 0.026	0.212 ± 0.679	0.071 ± 0.054	0.059 ± 0.040	.57		
	0.052	0.059	0.064	0.061		0.055	0.059	0.055	0.041			
		0.041 / 0.061 / 0.075					0.035 / 0.056 / 0.082					
Sucralose % Recovery ^b	1.38 ± 0.48	1.81 ± 1.85	3.56 ± 1.91	1.53 ± 0.74	.29	2.82 ± 2.39	2.89 ± 2.37	4.67 ± 7.96	2.55 ± 2.35	.74		
	1.38	1.14	4.51	1.50		2.13	2.12	1.73	1.86			
		1.02 / 1.50 / 2.10					1.42 / 2.00 / 2.99					

^a = overnight recovery^b = 24-hour recovery^c = Mean ± SD^d = Median^e = 25th / 50th / 75th percentiles