J Neurogastroenterol Motil, Vol. 28 No. 1 January, 2022
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm20231
Journal of Neurogastroenterology and Motility

Original Article

Role of Glucose Breath Test for Small Intestinal Bacterial Overgrowth in Children and Adolescents With Functional Abdominal Pain Disorders in Korea

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Background/Aims
Small intestinal bacterial overgrowth (SIBO) is expected in children and adolescents with functional abdominal pain disorders (FAPDs). This study is conducted to estimate the prevalence of SIBO and to investigate the role of SIBO in children and adolescents with FAPDs.

Methods
This prospective study enrolled children with FAPDs fulfilling the Rome IV criteria. A hydrogen-methane glucose breath test was used to diagnose SIBO. A survey of bowel symptoms using questionnaires, birth history, types of feeding, and the presence of allergy was conducted.

Results
Sixty-eight children and adolescents (range, 6-17 years; median, 12.5 years) were enrolled. SIBO was detected in 14 patients (20.6%). Age (≥ 12 years) ($P < 0.003$) and loose stool ($P = 0.048$) were significantly more common in children with SIBO than in children without SIBO. However, the history of allergies ($P = 0.031$) was less common in children with SIBO than those without SIBO. No significant differences were observed in other demographic findings. In multivariate analysis, age (≥ 12 years) was the independent factor predicting SIBO in children with FAPDs.

Conclusions
SIBO is not uncommon in children and adolescents with FAPDs. Among children aged above 12 years and diagnosed with FAPDs, SIBO is a suspected clinical target for treatment to relieve intestinal symptoms. A further study to investigate the association between intestinal bacteria and history of allergy is needed.
(J Neurogastroenterol Motil 2022;28:78-85)

Key Words
Adolescent; Child; Functional abdominal pain disorders; Glucose breath test; Small intestinal bacterial overgrowth

Received: October 11, 2020 Revised: January 15, 2021 Accepted: January 28, 2021

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Introduction

The symptoms of functional abdominal pain disorders (FAPDs) based on Rome IV criteria, previously referred to as abdominal pain-related functional gastrointestinal disorders, represent some of the most common gastrointestinal complaints, and affect up to 20% of children in Western countries.[1,2] Although the pathophysiological mechanisms of FAPDs are still poorly understood and any definitive treatment has yet to be established, altered gastrointestinal motility, hypersensitivity to bowel distension, impaired brain-gut interaction, intestinal dysbiosis, psychosocial problem, and immune mechanism have been suggested as possible multifactorial mechanisms. Recently, small intestinal bacterial overgrowth (SIBO) has been cited as one of the etiologic factors for FAPDs, demonstrated by a breath test.[3,4]

SIBO is defined as an increase in the number of bacteria in the small intestine. Jejunal aspirate culture is considered a gold standard test for SIBO diagnosis. However, this diagnostic method is invasive, expensive, and uncomfortable. Thus recently, a non-invasive breath test has been preferred, because of its simplicity and lower expense. The increase in hydrogen (H_2) excretion is generally considered a diagnosis of SIBO in clinical practice. However, nearly 30% of the general population carries mostly intestinal methanogens and produces methane (CH_4) as a major by-product of carbohydrate fermentation.[5] Therefore, adding CH_4 to H_2 measurement may avoid false-negative results. Although the relatively high prevalence of SIBO in children with functional gastrointestinal disorder (FGID) was suggested, there is a paucity of evidence involving children with FAPDs based on concurrent H_2 and CH_4 breath tests.

The study estimated the prevalence of SIBO using a glucose H_2-CH_4 breath test and investigated the clinical role of SIBO in children with FAPDs.

Materials and Methods

The protocol was approved by the Institutional Review Boards of Hanil General Hospital of Korea (IRB No. HIRB-2017-003). The study was conducted in compliance with the tenets of the Declaration of Helsinki and International Committee on Harmonization Guidelines for Good Clinical Practice. A written Informed consent was obtained from all children or the authorized legal representatives prior to enrolling the subjects in the study.

Study Population

The study was conducted at a secondary teaching hospital in Seoul, Korea, from July 2017 to April 2020. We enrolled consecutive children who visited the institution, fulfilling the Rome IV criteria for FAPDs between 6 years to 18 years of age. The subjects voluntarily participated in the study and their guardians agreed to participate. Exclusion criteria were a history of diabetes, thyroid disease, connective tissue disease, inflammatory bowel disease, or gastrointestinal or gynecologic surgery. Children who were treated with antisecretory agents such as proton pump inhibitors or histamine H2 receptor blockers, antibiotics, probiotics, prokinetics, narcotics, laxatives, bulking agents, or antidiarrheal agents within the previous 4 weeks; and those with renal insufficiency, major psychiatric problem, hearing disturbance, masticatory dysfunction, and incomplete data, or those who had underwent colonoscopy within the last 3 months, were also excluded.

Study Design

The survey design encompassed the clinical demographics, type of feeding (breast milk or formula) during infancy, type of delivery (vaginal delivery or Cesarean section), and history of allergy of all the enrolled children. Bowel symptoms were surveyed using a questionnaire, and glucose H_2-CH_4 breath test was used for the diagnosis of SIBO. The children were presented to the pediatric clinic after a minimum of 12 hours of fasting before the test. Physical exercises was not allowed during the test, starting 30 minutes before the test. The end expiratory breath samples were collected at baseline after ingestion of oral glucose solution in 2 g/kg (maximum 50 g) (DIASOL-S SOLN; Tae Joon Pharma, Seoul, Korea), and then for 120 minutes at every 10-minute intervals. Breath tests of the samples with breath test kit (The EasySampler Breath Test Kit; Quintron Instrument Company, Milwaukee, WI, USA) were performed each time by gas chromatography equipment (Quintron BreathTracker SC; Quintron Instrument Company).

Definition of Small Intestinal Bacterial Overgrowth and Assessment of Intestinal Symptom

A positive glucose breath test (GBT) indicating SIBO was defined and classified as follows[6,7]: (1) an increase in H_2 concentration of more than 12 ppm above baseline within 90 minutes (glucose H_2 breath test [GHBT+] group) or (2) an increase in CH_4 concentration of more than 10 ppm above baseline within 90 minutes (glucose CH_4 breath test [GMBT+] group). The GBT (mixed)+ group was defined when both conditions (GHBT and GMBT

groups) were met. All participants completed the bowel symptom questionnaire. The Korean version of the Irritable Bowel Syndrome Quality of Life questionnaire was based on the Rome criteria together with additional questions about gastro intestinal symptoms, and has been verified and used in previous studies.[8,9] Besides, 13 questions related to various gastrointestinal symptoms experienced in the last 4 weeks were included. Information on bowel symptoms of discomfort, pain, hard or lumpy stools, loose or watery stools, straining during bowel movements, bowel urgency, mucus passing during bowel movements, abdominal fullness/bloating or swelling, flatus, chest pain or heartburn, the feeling of being full soon after a meal, urinary frequency, and nausea was collected. The severity of symptoms was estimated by the total symptom score, defined by the cumulative scores of event frequency and intrusiveness. The frequency and intrusiveness of each symptom were evaluated by each patient using a 7-point scale from 0 to 6. Since the total symptom score was defined as the sum of the symptom frequency and intrusiveness scores, the range of a score by each symptom was 0-12.

Statistical Methods

Clinical evaluations included age, sex, body mass index (BMI), types of feeding or delivery, allergy history, intestinal symptoms, and presence of irritable bowel syndrome (IBS) according to the presence of SIBO. The profiles of breath H_2 and CH_4 in children with FAPDs were compared with those of historically healthy controls who were previously registered in the determination of normal GBT value at the Catholic University of Medicine.[10] Continuous data were expressed as mean ± SD and were analyzed using independent-sample *t* tests, whereas the categorical variables were expressed as quantities and analyzed using χ^2 tests. Multiple stepwise logistic regression was used to identify independent factors correlated with the existence of the SIBO. A *P*-value less than 0.05 was considered significant for all tests.

Table 1. Baseline Characteristics of Children and Adolescents With Functional Gastrointestinal Disorders (N = 68)

Demographics	
Age (yr)	12.24 ± 2.94 (range 6-17)
Gender	
Male	25 (36.8)
Female	43 (63.2)
Height (cm)	152.35 ± 14.60
Weight (kg)	46.00 ± 15.18
BMI (kg/m^2)	19.27 ± 3.56
Types of feeding	
Breast milk	26 (38.2)
Formula	46 (25.0)
Mixed	25 (36.8)
Types of delivery	
Vaginal delivery	42 (61.8)
Cesarean section	26 (38.2)
Allergy history	20 (29.4)
Positive GBT	14 (20.6)
H_2	6 (8.8)
H_2 + CH_4	8 (11.8)

BMI, body mass index; GBT, glucose breath test; H_2, hydrogen; CH_4, methane.
Data are expressed as mean ± SD or n (%).

Results

Study Populations

Seventy children enrolled in the study. Two subjects were excluded from the analysis due to a sampling error, and incompletion of demographic data or bowel symptom questionnaire. Baseline characteristics including demographics and type of feeding, delivery and allergy are shown in Table 1. Twenty children were allergic, and involved several types of allergy: atopic dermatitis (n = 5), allergic rhinitis (n = 4), pollen allergy (n = 2), food allergy involving mushroom (n = 1) or fruits such as apple, kiwi, and watermelon (n = 2), insect allergy (n = 1), dust allergy (n = 1), cold allergy (n = 1), urticaria (n = 1), asthma with allergic rhinitis (n = 1), allergic rhinitis with atopic dermatitis (n = 1), or cat allergy combined with allergy to nuts (n = 1).

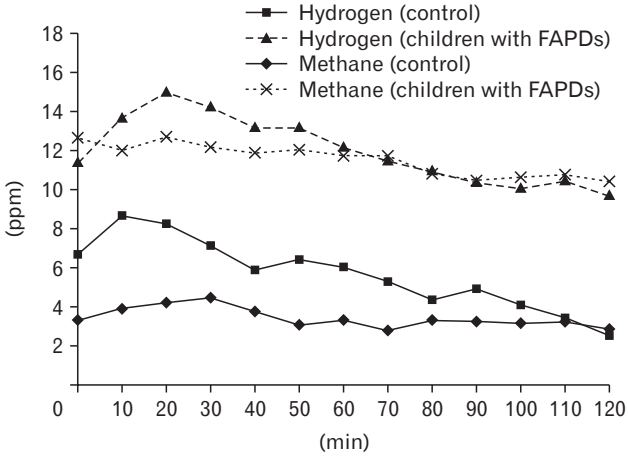

Figure 1. Comparison of breath hydrogen and methane profiles (parts per million [ppm]) between historic controls and children with functional abdominal pain disorders (FAPDs).

Glucose Breath Test in Children With Functional Abdominal Pain Disorders and Healthy Controls

Fourteen of 68 children (20.6%) were positive in the GBT; 6 (8.8%) excreted H_2, and 8 (11.8%) were combined excreters, whereas none was included in the CH_4 excreters (Table 1). There were significant differences in the exhaled H_2 at intervals of 0, 30, 50, 60, 70, 80, 100, 110, and 120 minutes, and in CH_4 from 10 to 120 minutes intervals between the children with FAPDs and controls, respectively (Fig. 1).

Characteristics of Children With Functional Abdominal Pain Disorders According to Glucose Breath Test Positivity

No difference was found between GBT positive (GBT+) and negative (GBT−) children regarding gender, BMI, types of feeding, and types of delivery. In the GBT+ children with FAPDs, the age was significantly higher whereas the presence of allergy histories was significantly lower than those of GBT− children with FAPDs (Table 2). In multivariable logistic regression, age ≥ 12 was the only significant independent factor predicting SIBO in children with FAPDs. A history of allergy inversely correlated with SIBO with statistically significant tendency (Table 3). The breath H_2 profiles at all the time points were significantly higher in children with a history of allergy compared with those without (Fig. 2).

Table 2. The Characteristics of Children With Functional Gastrointestinal Disorders to the Positivity to Glucose Breath Test

Demographics	GBT		*P*-value
	Negative (n = 54)	Positive (n = 14)	
Age (yr)	11.91 ± 3.00	13.50 ± 2.38	0.070
< 12	32 (59.3)	2 (5.9)	0.003
≥ 12	22 (40.7)	12 (85.7)	
Gender			
Male	20 (37.0)	5 (35.7)	0.927
Female	34 (63.0)	9 (64.3)	
BMI (kg/m^2)	18.88 ± 3.27	20.75 ± 4.34	0.080
Types of feeding			
Breast milk	24 (44.4)	2 (14.3)	0.079
Formula	11 (20.4)	6 (42.9)	
Mixed	19 (35.2)	6 (42.9)	
Types of delivery			
Vaginal delivery	32 (59.3)	10 (71.4)	0.404
Cesarean section	22 (40.7)	4 (28.6)	
Allergy history			
No	35 (64.8)	13 (92.9)	0.031
Yes	19 (35.2)	1 (7.1)	
IBS			
No	38 (70.4)	6 (42.9)	0.056
Yes	16 (29.6)	8 (57.1)	

GBT, glucose breath test; BMI, body mass index; IBS, irritable bowel syndrome.
Data are expressed as mean ± SD or n (%).

Bowel Symptoms According to Glucose Breath Test Positivity in Children With Functional Abdominal Pain Disorders

Although GBT+ children with FAPDs had high individual total symptom scores regarding abdominal pain, hard stool, strain, urgency, bloating, flatus, satiety, frequent urination, and nausea (Fig. 3), the total frequency scores (32.50 ± 12.23 vs 28.76 ± 12.43, $P = 0.321$), total bothersome scores (24.86 ± 15.64 vs 21.43 ± 13.34, $P = 0.411$), and total sum scores (57.36 ± 27.16 vs 50.19 ± 24.77, $P = 0.347$) compared to those of GBT− children with

Table 3. Multivariate Analysis for the Independent Factors of Positive Glucose Breath Test

Demographics	OR	95% CI	*P*-value
Age ≥ 12 yr	11.364	1.621-76.923	0.014
BMI (kg/m^2)	1.023	0.819-1.276	0.844
The presence of allergy	0.129	0.011-1.546	0.106
IBS	3.390	0.691-16.667	0.133
Types of feeding			
Breast milk	0.526	0.055-5.053	0.578
Powdered milk	3.540	0.572-21.914	0.174

GBT, glucose breath test; BMI, body mass index; IBS, irritable bowel syndrome.

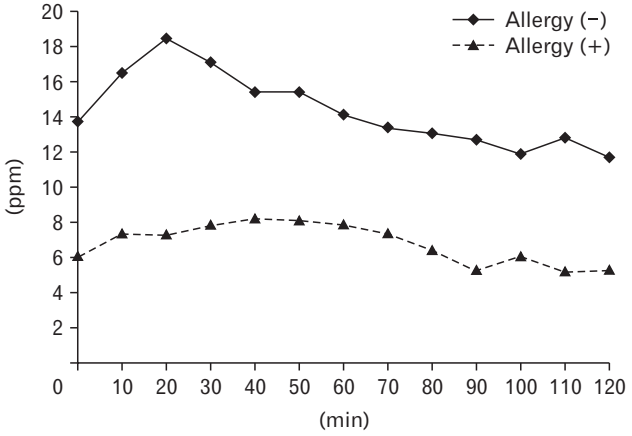

Figure 2. Profiles (parts per million [ppm]) of breath hydrogen in children with functional abdominal pain disorders (FAPDs) based on history of allergic disease.

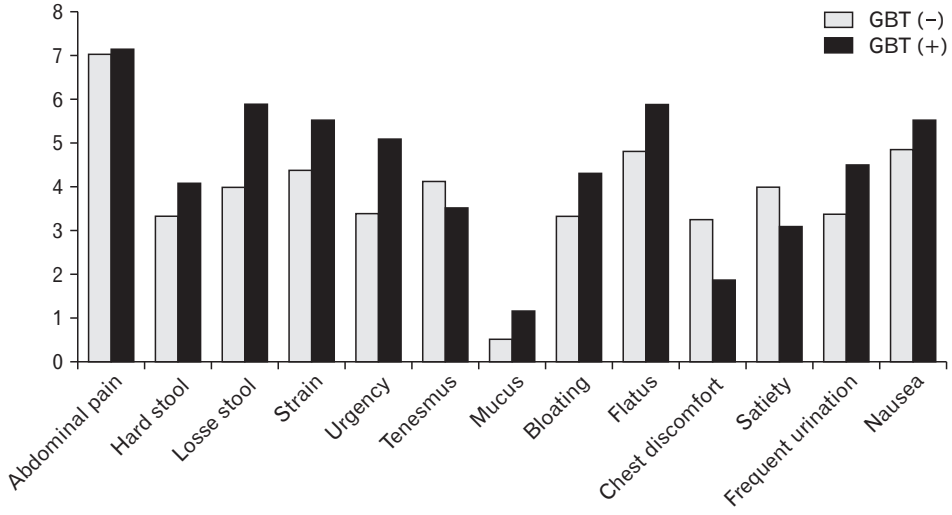

Figure 3. Total symptom scores of individual bowel symptoms based on positive glucose breath test (GBT) results in children with functional abdominal pain disorders.

FAPDs, showed no significant differences between the 2 groups. In the GBT+ group, the total symptom scores of loose stool were significantly higher than those of the GBT− group (5.86 ± 3.03 vs 3.98 ± 3.13, $P = 0.048$) (Fig. 3).

Discussion

The current study showed that SIBO is not uncommon in children and adolescents with FAPDs. It appears to be closely related to worsening intestinal symptoms in children older than 12 years diagnosed with FAPDs, and represents a meaningful therapeutic target for amelioration of functional intestinal symptoms.

The causes of FGID include not only SIBO but also a number of factors including altered bowel motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and activation of the immune system.[11] SIBO could induce functional gastrointestinal symptoms in adults or children, such as chronic abdominal pain, bloating, diarrhea, flatulence, and/or constipation.[3,12-14]

Direct jejunal aspirate culture is the gold standard method for diagnosing SIBO. However, this method has limitations such as difficulty in accessing the distal small bowel, possibility of contamination during sampling, low reproducibility, and potential for false negative results.[15-17] It is also somewhat uncomfortable and invasive. Thus a breath test is a simple alternative and an acceptable diagnostic method for SIBO. Various factors including substrate types, criteria for test results, gas types measured (H_2 or CH_4), and research design could directly affect the results of breath test. Accordingly, a wide variety of prevalence of SIBO has been reported.[18,19] There are still controversy to usefulness for breath tests to reflect SIBO in patients with FGID.[20,21] In addition, most proposed guidelines[22,23] for breath tests are based on research for adults, and thus it is unclear whether this proposal will also apply to children.

However, this non-invasive method may be more appropriate in children who are burdened with invasive tests. The first Rome H_2-Breath Testing Consensus Conference Working Group (2009) recommended the GBT instead of lactulose breath test for diagnostic accuracy.[22] The advantage of breath test using glucose as a substrate over lactulose is low false positivity and superior diagnostic ability of proximal SIBO.[24,25] In children who are expected to have a low BMI compared to that of adults, the intestinal transit time is also relatively short, and therefore, glucose was selected for breath tests. During lactulose breath tests, it is difficult to distinguish SIBO from colonic bacteria if intestinal transit is fast,[26,27] and importantly lactulose itself induces rapid small intestine transit.[28] The study demonstrated that the prevalence of SIBO in children with FAPDs was 20.6% (14/68) using the H_2-CH_4 GBT, which was consistent with other study results with a prevalence of 22.5% in children.[6] Only a single study[3] involving children with abdominal pain-related FGIDs according to the Rome III criteria demonstrated an SIBO prevalence of 14.3% in English literature, which measured only H_2 produced by SIBO, and included baseline breath $H_2 \geq 20$ ppm testing positive to GHBT. Our study evaluates both breath H_2 and CH_4 to detect hydrogenic and methanogenic bacteria, respectively. It is known that about 15-27% of SIBO patients are CH_4 producers.[5] The prevalence of SIBO can be underestimated without measuring breath CH_4. Recently, the North American Consensus did not recommend the baseline breath profile as positivity to breath test due to the need for clarifying whether it was a result of improper test preparation or represented a SIBO variant.[23] We excluded the fasting breath profiles as diagnostic criteria for SIBO, and only in-

cluded positivity to GBT using a cutoff of increased breath profiles compared with participant baselines.[23] However, these recommendations are based on studies of adults and extrapolation to children needs further investigation.

The other strength of this study is that it was conducted in Asia. The clinical use of breath test in Asia has occurred only in the last few years, being lagging in time compared to the West. The prevalence of SIBO is thought to be different between patients with Asian and Western countries due to main dietary habit, physical status, or bowel transit time.[29-31] This study provided evidence that SIBO using breath test play an important role in children with functional intestinal symptoms in Asia as well as in Western children. Future studies are needed to conduct additional comparative studies on the different targeting age groups, effects of dietary habits and lifestyles between those in Asia and Western countries, or research on immigrants in Korea.

The potential limitation relates to the use of fewer historical adult controls compared with the cases. However, the breath H_2 profiles at most time points during the tests involving cases were increased compared with those of adult controls as shown in Figure 1. Because age itself is a known risk factor for SIBO, the profiles of breath tests in adult controls were expected to be higher than in controls with children.[32] Nevertheless, the range of prevalence of SIBO in children is still very wide due to various diagnostic cutoff values and methodologies.[4] Therefore, further research is needed to verify the diagnosis of bacterial overgrowth in children by GBT.

The age of 12 years and older equivalent to that of subjects in middle school and high school is a significant predicting factor for SIBO in children and adolescents with FAPDs. SIBO seems to be more prevalent among older individuals despite studies involving adults,[32] who are more likely to have reduced intestinal motility, small bowel diverticulosis, low gastric secretory function, or a strong history of medication usage. Although non-significant statistical differences in multivariate analysis were shown, a low level of BMI, the presence of IBS, or loose stool were associated with SIBO in this study. Still in debate, the prevalence of SIBO is reported to be high in patients with IBS, or chronic diarrhea.[21] The prevalence of breast feeding and allergic history tended to be low in the presence of SIBO. Representative factors predicting the status of gut microbiota during infancy include the types of delivery and feeding practices. A study suggested that dysbiosis was significantly related to lack of breastfeeding, but showed no evidence of association with mode of delivery,[33] which is consistent with our results. However, the relationship between breastfeeding and gut microbiome is mostly evaluated using fecal samples. More studies are needed to investigate the link between SIBO and breastfeeding using breath tests.

Evidence shows that intestinal microflora is a crucial factor in immune system maturation and tolerance.[34,35] Interestingly, a history of allergy is inversely correlated with the GBT profiles in Figure 2, which is contrary to previous studies. A recent study has shown that SIBO was linked to allergic disease.[36] However, the study design was retrospective and involved a small number of subjects. Very few studies correlating SIBO and allergy have been reported. In 1 study, the prevalence of SIBO in patients with chronic urticaria was higher than in the healthy population, but the eradication of SIBO was not related to clinical improvements in patients with chronic urticaria.[37] A well-designed prospective study with a larger number of patients is needed. The hygiene hypothesis in allergy suggests that exposure to enriched microbial environment improves the immune response in patients with allergic diseases.[38] Although the breath test failed to detect the diversity of gut microbiota, the presence of bacteria demonstrated by breath test may indirectly reflect the beneficial status of allergic diseases. It is also possible that the SIBO negative results were caused by frequent overuse of antibiotics in patients with allergic diseases that manifested as upper respiratory tract infections. The antibiotic prescription rate is very high in Korea, where the study was conducted. According to data presented by the Organisation for Economic Co-operation and Development (OECD) in 2014, the rate of antibiotic consumption in Korea was 31.7 defined daily doses per 1000 inhabitants/day (DID), which is higher than the average rate of 20.5 DID in OECD countries.[39] A future study is needed to validate the diagnosis of bacterial overgrowth based on breath tests and diversity of microbiota.

Loose stool can occur significantly in FAPD children with SIBO. We evaluated each gastrointestinal symptom using a validated questionnaire. Although the symptom scores of abdominal pain, hard stool, strain, urgency, bloating, flatus, satiety, frequent urination, and nausea were higher in GBT+ compared with those of GBT− children, no significant differences were observed between the 2 groups. The foregoing results are based on a small sample size. The symptoms of hard stool and strain related to slow intestinal transit may be associated with CH_4.[5,40] However, no pure CH_4 excretors were detected in our study, and the clinical characteristics of subjects with CH_4 gas related symptoms could not be investigated. The prevalence of CH_4 excretors with age is known to be high, ranging from 3% in the 6-10 years old group to 45% in the 46-50 years old group.[41] Thus, children with SIBO excreting CH_4 constituted a relatively low proportion in our study.

In conclusion, SIBO in children and adolescents with FAPD

was not uncommon. SIBO is a suspected therapeutic target for alleviating bowel symptoms of children older than 12 years manifesting functional gastrointestinal symptom such as loose stool. Further studies are needed to elucidate the role of SIBO in children and adolescents diagnosed with FAPD by demonstrating the potential response to antibiotic treatment.

Acknowledgements: This study was supported by the Korean Society of Pediatric Infectious Diseases. The authors are solely responsible for the content, which does not necessarily represent the official views of the Korean Society of Pediatric Infectious Diseases.

Financial support: None.

Conflicts of interest: None.

Author contributions: Jin Lee and Chang-Nyol Paik contributed to the study design, data interpretation, and writing of the manuscript; Jin Lee, Yeon-Ji Kim, Dae Bum Kim, Ji Min Lee, Sik Kyung Choi, Yeon Jong Cho, and Chang-Nyol Paik collected and interpreted the data; and Jin Lee, Chang-Nyol Paik, and Dae Bum Kim contributed to the study design and critically reviewed the manuscript. All authors approved the final draft.

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