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Association between body mass index and fecal calprotectin levels in children and adolescents with irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common pediatric functional gastrointestinal disorder. It is characterized by recurrent abdominal pain and changes in bowel habits and is more prevalent in obese patients. We investigated the association between obesity and IBS in pediatric patients through fecal calprotectin testing.

Patients under 18 years of age with IBS who underwent fecal calprotectin testing from January 2015 through April 2020 were retrospectively investigated. The patients were divided into groups based on body mass index (BMI): group I (BMI < 85th percentile) and group II (BMI ≥ 85th percentile). Group II was divided into group IIa, overweight (85th percentile ≤ BMI < 95th percentile), and group IIb, obese (BMI ≥ 95th percentile).

Among 277 included patients, 202 (72.9%) were in group I, and 75 (27.1%) were in group II (mean calprotectin levels, 75.60 ± 103.48 vs 45.89 ± 66.57 μg/g, respectively; P = .006). There were significant differences in mean calprotectin levels between groups I and IIa (75.60 ± 103.48 vs 45.45 ± 63.38 μg/g, respectively; P = .028) and groups I and IIb (75.60 ± 103.48 vs 46.22 ± 69.59 μg/g, respectively; P = .025). There was a significant difference in mean calprotectin levels between groups I and II (85.69 ± 142.13 vs 32.04 ± 28.17 μg/g, respectively; P = .029) among patients between 6 and 12 years of age but not among adolescents aged between 12 and 18 years (P = .139). Fecal calprotectin was lower when moderate-to-severe fatty livers were observed by ultrasound compared with normal livers (68.52 ± 97.22 vs 18.53 ± 18.56 μg/g, respectively; P = .017).

Fecal calprotectin levels were higher in normal-weight pediatric IBS patients than in their obese counterparts, and this difference was more prominent in younger patients. In young children, IBS symptoms are thought to be influenced more by factors other than intestinal inflammation.

Abbreviations: BMI = body mass index, FGID = functional gastrointestinal disorder, IBS = irritable bowel syndrome.

Keywords: calprotectin, irritable bowel syndrome, obesity, pediatrics

1. Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) that features abdominal pain and changes in bowel habits, such as stool frequency and structure, in the absence of organic causes.[1,2] IBS is the most common FGID and is more prevalent in Asia.[3] In Asian children, prevalence estimates range from 2.8% to 25.7% (pooled prevalence: 12.4%), with variation between regions. In particular, IBS is highly prevalent among Korean girls.[4,5] The pathophysiology of IBS has not yet been fully elucidated, but there are many associated factors, such as lifestyle, mental illness, and chronic inflammation. Recently, it has also been thought that IBS is caused by various mechanisms, such as changes in brain–gut axis-related gastrointestinal motility, intestinal microbiota, epithelial barrier function, mucosal immune responses, and changes in intestinal inflammation.[6–10]

The prevalence of IBS is higher in obese individuals; this association can be explained by numerous obesity-related factors,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study was conducted with approval from the institutional review board (IRB) of Chung-Ang University Hospital (IRB no.: 2005-019-19318), and informed consent was waived due to the retrospective nature of the study.

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including lifestyle, dietary patterns, anorexigenic hormones, physiological disorders, psychological disorders, changes in gut microbiota, and chronic inflammation.[11–14] The incidence of obesity is increasing worldwide, and the World Health Organization considers obesity to be among the most serious global public health challenges of the 21st century.[15] In particular, the prevalence of obesity is increasing among pediatric patients in South Korea, and the rates of various associated complications, including obesity-related FGIDs and IBS, are also increasing.[16,17] Against this backdrop, studies on the causes, pathophysiology, and factors associated with obesity-related IBS and bowel inflammation have been conducted, but few studies have investigated pediatric patients of various age groups. Therefore, this study aimed to investigate the association between gastrointestinal inflammation and obesity among pediatric IBS patients of various age groups by measuring and comparing levels of fecal calprotectin, which is an objective marker of intestinal inflammation.

2. Methods

2.1. Patients and data extraction

We included data from inpatient and outpatient pediatric patients (under age 18) between January 2015 and April 2020 at 4 hospitals (Chung-Ang University Hospital, Soonchunhyang University Bucheon Hospital, Inje University Ilsan Paik Hospital, and Eulji University Hospital) after their IBS diagnoses. The medical records of patients who underwent fecal calprotectin testing during the study period were analyzed retrospectively, and symptoms of IBS, such as changes in stool frequency and appearance, were identified, along with abdominal pain lasting >3 months, based on the Rome IV criteria.[2] Additionally, hematological test results and fecal calprotectin results were checked, and the results of stool polymerase chain reaction testing and stool cultures were also reviewed to check for the presence of gastrointestinal infections. If radiologic tests, such as computed tomography or ultrasonography, were performed, the presence of fatty livers was investigated. We excluded patients diagnosed with organic diseases, such as inflammatory bowel disease (IBD), *Helicobacter pylori* infections, or Henoch–Schönlein purpura. We also excluded patients who had positive stool polymerase chain reaction or culture results accompanied by acute gastroenteritis, as well as those who were treated for constipation (Fig 1).

Subjects were divided into 3 groups according to age classifications developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development: early childhood (4–6 years), middle childhood (6–12 years), and adolescence (12–18 years).[18] The patients were divided into the following groups according to body mass index (BMI): group I (BMI < 85th percentile) and group II (BMI ≥ 85th percentile). Group II was divided into group IIa, overweight (85th percentile ≤ BMI < 95th percentile), and group IIb, obese (BMI ≥ 95th percentile).[16]

2.2. Statistical analysis

Statistical analysis was performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL). Analysis of variance, Student *t* test, and Pearson χ^2 test were used to analyze between-group differences. A *P* value of <.05 was considered statistically significant.

2.3. Ethics statement

This study was conducted with approval from the institutional review board of Chung-Ang University Hospital (institutional review board no.: 2005-019-19318), and informed consent was waived due to the retrospective nature of the study.

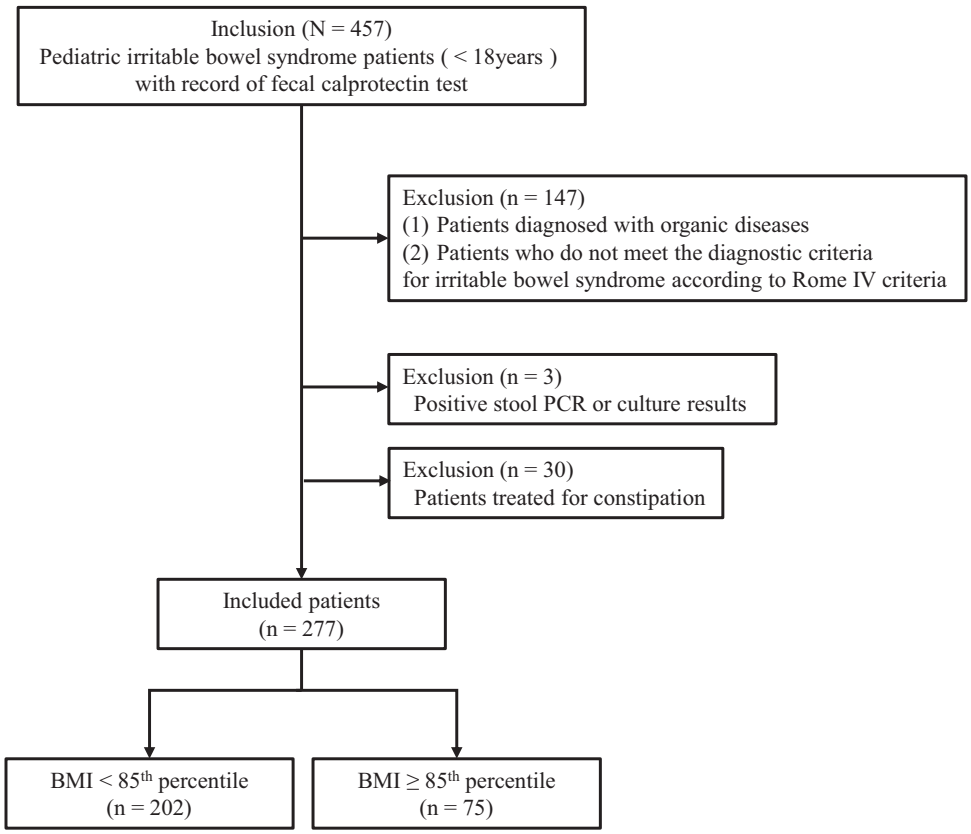

Figure 1. Flowchart of subject selection. BMI = body mass index.

Table 1

Clinical manifestations according to body mass index among pediatric patients with irritable bowel syndrome.

Variable	Total (n = 277)	Group I (n = 202)	Group II (n = 75)	*P* value
Age (yr)	13.39 ± 2.98	13.41 ± 3.02	13.35 ± 2.89	.909
Age group				
Early childhood(4 ≤ age < 6) (n = 6)	6	6 (3.0%)	0 (0%)	.690
Middle childhood(6 ≤ age < 12) (n = 56)	56	39 (19.3%)	17 (22.7%)	
Adolescence(12 ≤ age < 18) (n = 215)	215	157 (77.7%)	58 (77.3%)	
Male gender (n = 152)	152	110 (54.5%)	42 (56.0%)	.892
Height (cm)	157.48 ± 23.69	155.62 ± 15.58	162.48 ± 37.39	.032*
Body weight (kg)	52.33 ± 16.10	47.14 ± 12.71	66.32 ± 16.00	.000*
BMI (kg/m^2)	20.80 ± 4.27	19.00 ± 2.63	25.67 ± 4.03	.000*

Group I: BMI < 85th percentile, group II: BMI ≥ 85th percentile.

BMI = body mass index.

*Significant findings at $P < .05$.

3. Results

3.1. Clinical and laboratory manifestations according to BMI in pediatric IBS patients

From January 2015 through April 2020, a total of 457 pediatric patients under age 18 with gastrointestinal tract diseases were tested for fecal calprotectin at the 4 study hospitals. Of these, 277 pediatric IBS patients who fulfilled the Rome IV criteria were included in the study (Table 1). There were 202 patients (72.9%) in group I (BMI < 85th percentile) and 75 patients (27.1%) in group II (BMI ≥ 85th percentile). There were no between-group differences in age, age group, or gender, but there were significant differences in height, weight, BMI, and recent weight change between the 2 groups. Mean platelet and white blood cell counts, absolute neutrophil counts, aspartate aminotransferase/alanine aminotransferase levels, uric acid levels, and serum cholesterol levels were all significantly higher in group II ($P = .004$, $P < .001$, $P < .001$, $P = .016$, $P < .001$, $P < .001$, and $P = .016$, respectively; Table 2). Mean C-reactive protein (CRP) levels were higher in group II than in group I, but the difference was not significant (0.73 ± 2.03 vs 1.38 ± 5.55, respectively; $P = .172$).

3.2. Fecal calprotectin levels according to BMI

The mean calprotectin level in group I was significantly higher than that in group II (75.60 ± 103.48 vs 45.89 ± 66.57 μg/g, respectively; $P = .006$; Table 2). When group II was divided into overweight (group IIa, 85th percentile ≤ BMI < 95th percentile) and obese subgroups (group IIb, BMI ≥ 95th percentile), groups I, IIa, and IIb did not vary significantly from one another (75.60 ± 103.48 μg/g, 45.45 ± 63.38 μg/g, and 46.22 ± 69.59 μg/g, respectively; $P = .071$). However, when we compared group I to groups IIa and IIb individually, there were statistically significant differences in mean calprotectin levels ($P = .028$ and $P = .025$, respectively). There was no significant difference between group IIa and IIb calprotectin levels ($P = .867$).

We investigated the association between BMI and fecal calprotectin levels according to age group (Table 3). In middle childhood, there was a significant difference in fecal calprotectin between groups I and II (85.69 ± 142.13 vs 32.04 ± 28.17 μg/g, respectively; $P = .029$), but there was no significant difference between the 2 groups in adolescence (69.07 ± 87.13 vs 49.95 ± 73.87 μg/g, respectively; $P = .139$).

3.3. Fecal calprotectin according to radiologic findings of fatty livers

A total of 109 patients underwent liver ultrasonography or computed tomography. Of these, 19 patients were confirmed to have fatty livers: 3 (15.8%) in group I and 16 (84.2%) in group II ($P < .001$; Table 4). There was no statistically significant difference in mean fecal calprotectin levels according to the presence of fatty livers (68.52 ± 97.22 vs 40.63 ± 41.78 μg/g, $P = .104$). However, when the degree of liver fattiness was divided into mild and moderate-to-severe, mean fecal calprotectin levels were significantly lower in patients with moderate-to-severe liver fattiness compared with patients without fatty livers (68.52 ± 97.22 vs 18.53 ± 18.56 μg/g, $P = .017$).

Table 2

Comparison of laboratory findings according to BMI among pediatric patients with irritable bowel syndrome.

Variable	Group I (n = 202)	Group II (n = 75)	*P* value
Hemoglobin (g/dL) (n = 258)	13.69 ± 1.22 (n = 190)	14.01 ± 1.15 (n = 68)	.063
Platelet count (×10^9/L) (n = 258)	281.9 ± 65.9 (n = 190)	309.2 ± 64.8 (n = 68)	.004*
White blood cell count (×10^9/L) (n = 258)	6550.0 ± 1890.0 (n = 190)	7621.0 ± 1964.1 (n = 68)	.000*
Absolute neutrophil count (μL) (n = 258)	3554.0 ± 1458.8 (n = 190)	4150.9 ± 1513.8 (n = 68)	.000*
Aspartate aminotransferase (IU/L) (n = 255)	20.5 ± 7.2 (n = 188)	26.9 ± 20.9 (n = 67)	.016*
Alanine aminotransferase (IU/L) (n = 255)	12.6 ± 6.7 (n = 188)	32.5 ± 37.6 (n = 67)	000*
Uric acid (mg/dL) (n = 253)	5.02 ± 1.22 (n = 186)	5.83 ± 1.40 (n = 67)	.000*
Serum glucose (mg/dL) (n = 255)	98.3 ± 46.7 (n = 188)	99.1 ± 23.5 (n = 67)	.890
Serum cholesterol (mg/dL) (n = 150)	156.5 ± 31.6 (n = 101)	169.4 ± 27.5 (n = 49)	.016*
C-reactive protein (mg/L) (n = 248)	0.73 ± 2.03 (n = 182)	1.38 ± 5.55 (n = 66)	.172
Fecal calprotectin (μg/g) (n = 277)	75.60 ± 103.48 (n = 202)	45.89 ± 66.57 (n = 75)	.006*

Group I: BMI < 85th percentile, group II: BMI ≥ 85th percentile.

BMI = body mass index.

* $P < .05$.

4. Discussion

Calprotectin is a heterodimer composed of S100A8 (MRP-8) and S100A9 (MRP-14) that binds calcium and zinc; it has a mass of 36.5 kDa.[19–21] This complex can be used to identify intestinal inflammation by indicating the migration of neutrophils to the intestinal mucosa. It is a useful marker of intestinal inflammation because it is resistant to enzyme degradation and can be measured in feces for >1 week.[22–25] Fecal calprotectin is elevated in association with diseases characterized by inflammation, such as IBD; therefore, it is useful

Table 3

Fecal calprotectin results according to age group among pediatric patients with irritable bowel syndrome.

Variable	Fecal calprotectin (μg/g)		*P* value
	Group I (n = 202)	Group II (n = 75)	
Early childhood (4 ≤ age < 6) (n = 6)	180.81 ± 157.07 (n = 6)	(n = 0)	
Middle childhood (6 ≤ age < 12) (n = 56)	85.69 ± 142.13 (n = 39)	32.04 ± 28.17 (n = 17)	.029*
Adolescence (12 ≤ age < 18) (n = 215)	69.07 ± 87.13 (n = 157)	49.95 ± 73.87 (n = 58)	.139

Group I: BMI < 85 percentile, group II: BMI ≥ 85 percentile.
BMI = body mass index.
*$P < .05$.

in the diagnosis and treatment of IBD.[26,27] Additionally, fecal calprotectin is useful for diagnosing other diseases associated with gastrointestinal inflammation, such as Henoch–Schönlein purpura, necrotizing enterocolitis, juvenile polyps, and acute gastroenteritis.[28,29]

Various gastrointestinal symptoms or nonorganic gastrointestinal diseases are more prevalent in obese children, and it is thought that the gut microbiome and chronic inflammation play important roles in this phenomenon.[12–14] There is a dynamic relationship between obesity and gut microbiota because gut microbiome changes can affect nutrient absorption, intestinal barrier characteristics, and intestinal inflammation. A large amount of visceral adipose tissue secretes proinflammatory factors, such as cytokines, tumor necrosis factor-α, and interleukin-6, which exacerbate chronic systemic inflammation.[30,31] This means that intestinal inflammation may also contribute to the pathophysiology of IBS.[11] In a study by Choi et al,[32] fecal calprotectin was used to assess intestinal inflammation in pediatric IBS patients. Fecal calprotectin levels were significantly higher among IBS patients than healthy controls, and the values were distributed in the intermediate range (50–150 μg/g), confirming that IBS was also associated with low-grade bowel inflammation. In our study, fecal calprotectin results among the group I patients were also in the intermediate range above the normal value of 50 μg/g, and the fecal calprotectin results of patients in group II were lower than those of group I. This suggests that pediatric IBS is affected by low-grade bowel inflammation, but other factors influence the higher prevalence among obese patients more. Therefore, aside from treating the inflammation, IBS treatment in obese children should place more emphasis on nutrition, lifestyle, psychological interventions, anorexigenic hormones, and multifaceted approaches.[33] Furthermore, our research found that the level of fecal calprotectin was significantly lower in pediatric IBS patients with moderate-to-severe fatty livers than in patients without fatty livers. Nonalcoholic fatty liver disease is associated with chronic obesity and systemic inflammation.[34] In a study by Fatma et al,[35] children with fatty livers had higher fecal calprotectin due to low-grade inflammation and insulin resistance caused by obesity. However, the level was not significantly higher, and the range was wide. In addition, it was compared with healthy controls without any other diseases. However, in our study, we compared it with IBS patients without fatty livers or mildly fatty livers. This suggests that children and adolescents with chronic systemic inflammation may have less bowel inflammation than those without it. As mentioned previously, the cause of abdominal pain in children who are obese and have IBS is likely to be due to factors other than bowel inflammation.

In a study by Park and Kim,[36] fecal calprotectin levels were higher in obese adults than those of normal weight, but fecal calprotectin levels were lower in obese children than in children of normal weight. In our study, we also observed that fecal calprotectin levels were lower in obese pediatric IBS patients and that the degree of obesity affected intestinal inflammation in adults differently than in children. This suggests that the pathophysiologic mechanisms underlying pediatric IBS may differ from those underlying adult IBS, particularly in terms of the interplay between obesity and intestinal inflammation.

CRP is involved in several stages of inflammatory reactions in the body, serving both proinflammatory and anti-inflammatory roles. Its main function is the triggering of an additional immune response by binding to phosphocholine to recognize external pathogens and damaged autologous cells. Therefore, CRP is used as a representative marker for measuring systemic inflammation and for evaluating the risk of chronic and acute inflammatory diseases.[37] Existing studies in adults have confirmed that systemic inflammation in overweight and obese patients increases CRP levels.[38] Our study found that both groups I and II had mean CRP levels within normal ranges and that the mean CRP in group II was higher than that of group I, although it was not significantly higher.

Most existing studies of obesity and inflammation, and related studies evaluating fecal calprotectin levels, have involved adult subjects. Children develop and grow rapidly each year and because lifestyles vary by age group, detailed investigations involving children of varying age groups are warranted. Our study showed that fecal calprotectin levels were significantly lower in association with obesity in middle childhood but not significantly lower in adolescents. These results indicate that the effect of intestinal inflammation on disease increases with age in children, particularly in obese IBS patients. Further studies analyzing age-based subgroups are warranted.

Our study had some limitations. First, it was retrospective. All patients were retrospectively classified based on clinical symptoms, physical examination findings, hematologic test results, fecal test results, and imaging findings. Then we analyzed all patients based on the Rome IV criteria and excluded them from the analysis if they had organic diseases. Nevertheless, the study sample may have included patients with unidentified organic diseases. Second, in a study by Choi et al,[32] fecal calprotectin levels varied by IBS subtypes, with the diarrhea-predominant IBS subtype associated with the highest levels. Our study did not classify IBS according to subtypes. If there was a difference

Table 4

Fecal calprotectin results according to radiologic fatty liver findings among pediatric patients with irritable bowel syndrome.

Variable	No fatty liver (n = 90)	Fatty liver (n = 19)			
		Mild (n = 13)	*P* value	Moderate-to-severe (n = 6)	*P* value
Group I	71 (78.9%)	2 (15.4%)	.000*	1 (16.7%)	.000*
Group II	19 (21.1%)	11 (84.6%)		5 (83.3%)	
Fecal calprotectin (μg/g)	68.52 ± 97.22	50.82 ± 46.02	.648	18.53 ± 18.56	.017*

Group I: BMI < 85 percentile, Group II: BMI ≥ 85 percentile.
BMI = body mass index.
*$P < .05$.

in the distribution of IBS subtypes between groups I and II, an excess of 1 subtype may have affected the between-group mean fecal calprotectin differences. Therefore, future studies should consider IBS subtypes when analyzing fecal calprotectin values. Furthermore, the number of patients in the early childhood group was insufficient, and a retrospective approach to studying this patient group is more difficult than for other groups. Due to their young ages, their records contain limited medical histories and fecal examinations. These issues make it difficult to exclude the presence of other diseases using medical records alone. In addition to these issues, the small number of groups may have biased the results.

In conclusion, in pediatric patients with IBS, as the level of obesity increases, factors other than bowel inflammation become more important. Moreover, considering that previous research has demonstrated that fecal calprotectin levels are higher among obese adult IBS patients, our study suggests that obesity and intestinal inflammation might influence the development and manifestations of IBS in children differently from in adults. Future larger-scale research studies should focus on age groups and IBS subtypes.

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Soo Ahn Chae (Writing–review and editing)
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