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Original Article

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Fecal Calprotectin Levels Significantly Correlate with Polyp Size in Children and Adolescents with Juvenile Colorectal Polyps

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ABSTRACT

Purpose: We aimed to investigate factors that correlate with fecal calprotectin (FC) levels in children and adolescents with colorectal polyps.
Methods: Pediatric patients aged <19 years who underwent colonoscopic polypectomy for a juvenile polyps (JPs) and FC tests were simultaneously conducted in a multicenter, retrospective study. Baseline demographics, colonoscopic and histological findings, and laboratory tests, including FC levels, were investigated. Correlations between the factors were investigated, and linear regression analysis revealed factors that correlated with FC levels. FC levels measured after polypectomies were investigated and the FC levels pre- and post-polypectomies were compared.
Results: A total of 33 patients were included in the study. According to Pearson correlation analysis, the polyp size was the only factor that showed a statistically significant correlation with FC levels (r=0.75, p<0.001). Furthermore, according to the multivariate linear regression analysis, polyp size was the only factor that showed a statistically significant correlation with FC levels (adjusted $R2$=0.5718, β=73.62, p<0.001). The median FC level was 400 mg/kg (interquartile range [IQR], 141.6–1,000 mg/kg), and the median polyp size was 14 mm (IQR, 9–20 mm). Nineteen patients underwent post-polypectomy FC tests. FC levels showed a significant decrease after polypectomy from a median of 445.2 mg/kg (IQR, 225–1,000) to 26.5 mg/kg (11.5–51) (p<0.001).

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Conflict of Interest
The authors have no financial conflicts of interest.

Conclusion: FC levels significantly correlated with polyp size in children and adolescents with JPs.

Keywords: Calprotectin; Juvenile polyp; Polyp size

INTRODUCTION

Colorectal juvenile polyps (JPs) are the most common cause of isolated lower gastrointestinal bleeding in children [1]. The prevalence of JPs ranges from 0.08–3.7% in children and adolescents, and JPs are most commonly diagnosed between 3 and 10 years of age [2,3]. JPs comprise 70–80% of pediatric colorectal polyps and are mainly observed as solitary polyps [4,5].

Tissue neutrophilia is a characteristic of JPs, and degradation and exfoliation of neutrophils into stool may lead to elevated fecal calprotectin (FC) levels [6]. Recent reports and studies have shown that FC levels are elevated in JPs and are normal post-polypectomy [3,6,7]. Although JPs are associated with increased FC, normal FC levels do not exclude JPs' presence [2]. Therefore, a recent paper from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommended the use of FC as a screening tool in children suspected of having colorectal polyps. Despite this recommendation from ESPGHAN experts, there have been ongoing attempts to utilize FC in predicting the presence of colorectal polyps by combining it with other screening modalities, such as abdominal ultrasonography [8].

Recent data show that JPs can recur after removal of solitary JPs in 17% of pediatric patients [4]. Although there is no consensus on FC utilization during polyp recurrence surveillance, some centers utilize it as a surrogate marker for recurrence [3]. Meanwhile, a recent case series postulated that polyp size may correlate with an increase in calprotectin levels [6]. However, no study has yet confirmed this association.

Therefore, we aimed to investigate whether factors such as polyp size correlate with FC levels in children and adolescents with JPs. In addition, we aimed to investigate whether FC levels normalized after the removal of the JPs. Based on these results, we aimed to examine the possibility of utilizing FC as a tool to survey JP recurrence after removal.

MATERIALS AND METHODS

Patients and study design

This study was a multicenter, retrospective chart review conducted at 14 medical centers in South Korea: Kyungpook National University Children's Hospital affiliated with Kyungpook National University Chilgok Hospital, Ajou University Medical Center, Eulji University Hospital, Soonchunhyang University Bucheon Hospital, Kosin University Gospel Hospital, Jeonbuk National University Medical School, Keimyung University Dongsan Hospital, Korea University Anam Hospital, Kyungpook National University Hospital, Chung-Ang University Hospital, Wonju Severance Christian Hospital, and Hallym University Sacred Heart Hospital. From January 2016 to June 2021, pediatric patients aged ≤19 years who had undergone colonoscopic polypectomy and FC examination within one week before polypectomy were included. Medical charts were reviewed, and those with polyps other than JPs, such as

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adenomatous polyps, juvenile polyposis syndrome, Peutz-Jeghers syndrome, and familial adenomatous polyposis were excluded. Patients whose colonoscopy failed to intubate up to the cecum were also excluded.

Baseline demographics, colonoscopic and histological findings, and laboratory tests, including FC levels, were investigated. To measure the FC levels, an enzyme-linked immunosorbent assay was conducted in two centers, while a fluorescence immunoassay was conducted in 12 centers. Data on the polyp sizes were derived from histological reports, and the maximum length of the polyp, excluding the length of the stalk, was designated as the polyp size. Patients were divided into two groups according to the median FC level, and factors were compared between the two groups. Correlations between continuous factors were investigated, and linear regression analysis revealed factors that were correlated with FC levels. FC levels conducted after polypectomies were also investigated, and FC levels pre-and post-polypectomies were compared.

Statistical analysis

A chi-square test or Fisher's exact test was used for statistical comparison of the categorical variables between the two groups, and Student's *t*-test or Wilcoxon's rank-sum test was used for continuous variables. Comparative data for continuous variables were reported as median (interquartile range [IQR]) or mean (standard deviation). Pearson's correlation analysis was used to evaluate the correlation between FC and continuous variables. Univariate and multivariate linear regression analyses were conducted to evaluate the correlations between the continuous variables. Factors showing a significance of $p<0.1$ were included in the multivariate linear regression analysis. The results were expressed as adjusted βs with 95% confidence intervals (CIs). The data were considered statistically significant at $p<0.05$. Statistical analyses were performed using R version 3.2.3 (http://www.r-project.org).

Ethics statement

This study was conducted with the approval of 16 participating institutions, including the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No. 2021-08-066). The requirement for informed consent was waived due to the retrospective nature of the study.

RESULTS

Baseline characteristics

A total of 39 patients had undergone colonoscopic polypectomy and simultaneous FC examination during the study period. Among these patients, six patients with polyps other than JPs were excluded, leaving 33 patients for inclusion (**Fig. 1**). Males comprised 54.5% of the patients (18/33), and the median age at diagnosis was 6.9 years (IQR, 4.5–13.5 years). All but one patient had a solitary polyp (97.0%), and 69.7% of the patients had pedunculated polyps (23/33). The median FC level of the patients was 400 mg/kg (IQR, 142–1,000 mg/kg), and the median quantitative fecal immunochemistry test was 594 ng/mL (IQR, 100–921 ng/mL). The other baseline characteristics are shown in **Table 1**.

Comparison between patients divided according to median FC

Patients were divided into two groups, based on a median FC level of 400 mg/kg. A comparison between these two groups revealed significant differences in polyp size and pedunculated

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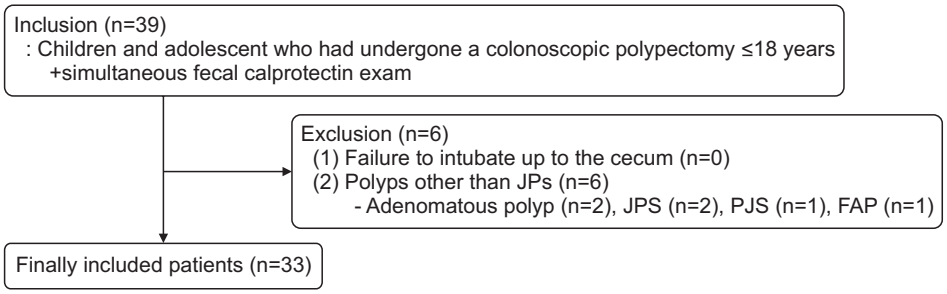

Fig. 1. Flow diagram of patient inclusion and exclusion.
JPs: juvenile polyps, JPS: juvenile polyposis syndrome, PJS: Peutz-Jeghers syndrome, FAP: familial adenomatous polyp.

Table 1. Baseline characteristics of the patients

Variable	Value (n=33)
Male	18 (54.5)
Age at diagnosis (yr)	6.9 (4.5–13.5)
Height	127.0±29.4
Weight	22.6 (19.3–45.8)
BMI (kg/m^2)	17.4 (16.0–18.8)
Number of polyps	
1	32 (97.0)
2	1 (3.0)
Polyp located only in the left colon	29 (87.9)
Polyp size (mm)	14 (9–20)
Polyp morphology	
All pedunculated	23 (69.7)
Any sessile	10 (30.3)
Fecal calprotectin (mg/kg)	400 (142–1,000)
Quantitative FIT (ng/mL) (n=19)	594 (100–921)
Positive qualitative FIT (n=30)	15 (45.5)
WBC count (/μL)	7,690 (6,100–9,895)
Eosinophil count (/μL)	155 (64–261)
Hematocrit (%)	36.9 (33.5–40.2)
Platelet count (×10^3/μL)	354 (310–398)
Albumin (g/dL)	4.5±0.3
CRP (mg/dL)	0.06 (0.02–0.12)
ESR (mm/hr)	7 (2–14)
Anemia	9 (27.3)
Hypoalbuminemia	1 (3.0)

Values are presented as number (%), median (Interquartile range), or mean±standard deviation.
BMI: body mass index, FIT: fecal immunochemistry test, WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

morphology. Polyp size was significantly larger in patients with FC levels ≥400 mg/kg (median 12 vs. 20 mm, p=0.016). The proportion of patients with pedunculated polyps was also significantly higher in those with FC levels ≥400 mg/kg (88.2% vs. 50.0%, p=0.026) (**Table 2**).

Correlation analysis between FC and continuous variables

According to Pearson correlation analysis, polyp size was the only factor that showed a statistically significant correlation with FC levels (r=0.75, p<0.001). Furthermore, univariate linear regression analysis showed that the age, polyp size, white blood cell count, serum albumin, and height were significantly correlated with FC levels. However, according to the multivariate linear regression, polyp size was the only factor that showed a statistically significant correlation with FC levels (adjusted R^2=0.5729, β=0.72, 95% CI 0.45–0.99, p<0.001) (**Table 3**, **Fig. 2**).

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Table 2. Comparison between patients divided according to median fecal calprotectin

Variable	FC<400 (n=16)	FC≥400 (n=17)	*p*-value
Male	11 (68.8)	7 (58.8)	0.215
Age at diagnosis (yr)	7.3±4.3	10.0±6.3	0.167
Height (cm)	122.6±26.3	131.1±32.3	0.414
Weight (kg)	27.5±15.4	34.5±19.0	0.255
BMI (kg/m^2)	17.1±1.9	18.2±2.9	0.217
Solitary polyp	16 (100.0)	16 (94.1)	1.000
Located in left colon	14 (87.5)	15 (88.2)	1.000
Polyp size (mm)	12 (7–16)	20 (11–25)	0.016
Pedunculated morphology	8 (50.0)	15 (88.2)	0.026
Quantitative FIT (ng/mL) (n=19)	718 (50–921)	594 (133–925)	0.967
Positive qualitative FIT (n=30)	6 (40.0)	9 (60.0)	0.465

Values are presented as number (%), mean±standard deviation, or median (Interquartile range).
BMI: body mass index, FIT: fecal immunochemistry test.

Table 3. Linear regression analyses of factors correlated with fecal calprotectin

Variable	Univariate analysis			Multivariate analysis		
	β	95% CI	*p*-value	β	95% CI	*p*-value
Age at diagnosis (yr)	−0.42	−0.92–0.08	0.095	0.36	−0.58–1.30	0.438
Polyp size (mm)	0.64	0.21–1.06	0.006	0.72	0.45–0.99	<0.001
Polyp in left colon	0.75	0.50–0.99	0.506			
Quantitative FIT (ng/mL)	0.26	−0.27–0.80	0.305			
WBC count (/μL)	−0.49	−0.97–−0.01	0.044	−0.27	−0.57–0.03	0.076
Albumin (g/dL)	−0.53	−1.00–−0.07	0.028	0.36	−0.07–0.78	0.096
Height (cm)	−0.49	−0.97–−0.01	0.047	−0.71	−1.71–0.29	0.158

CI: confidence interval, FIT: fecal immunochemistry test, WBC: white blood cell.

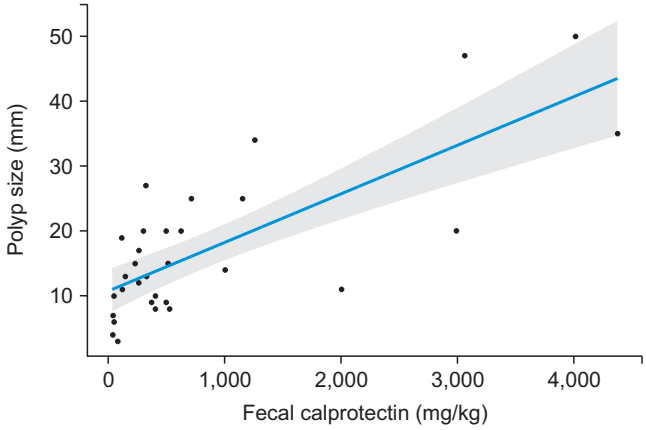

Fig. 2. Linear regression analysis investigating the correlation between fecal calprotectin and polyp size.

Correlation analysis between polyp size and continuous variables

According to the univariate linear regression analysis, age at diagnosis, FC level, serum albumin level, height, and weight were significantly correlated with polyp size. However, according to multivariate linear regression analysis, FC level was the only factor that showed a statistically significant correlation with polyp size (adjusted R^2=0.5293, β=0.77, 95% CI 0.48–1.06, p<0.001) (**Table 4**).

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Table 4. Linear regression analyses of factors correlated with polyp size

Variable	Univariate analysis			Multivariate analysis		
	β	95% CI	*p*-value	β	95% CI	*p*-value
Age at diagnosis (yr)	−0.57	−1.02–−0.11	0.018	−0.04	−1.17–1.10	0.946
Polyp in left colon	−0.55	−1.64–0.54	0.311			
Fecal calprotectin (mg/kg)	0.64	0.21–1.06	0.006	0.77	0.48–1.06	<0.001
Quantitative FIT (ng/mL)	0.31	−0.21–0.83	0.226			
WBC count (/μL)	−0.44	−0.94–0.05	0.075	0.11	−0.24–0.45	0.527
Albumin (g/dL)	−0.74	−1.11–−0.37	<0.001	−0.40	−0.85–0.05	0.078
Height (cm)	−0.63	−1.06–−0.20	0.007	0.52	−0.69–1.73	0.382
Weight (kg)	−0.54	−1.00–−0.08	0.026	−0.19	−1.23–0.85	0.713

CI: confidence interval, FIT: fecal immunochemistry test, WBC: white blood cell.

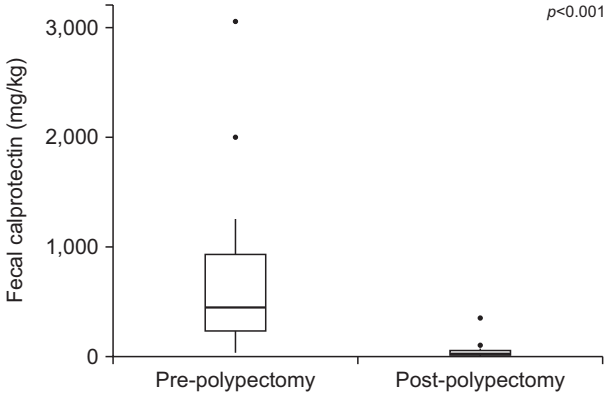

Fig. 3. Comparison of the fecal calprotectin levels pre- and post-polypectomy.

Comparison of FC levels between pre- and post-polypectomies

Nineteen patients underwent FC tests at a median of 18 days (IQR, 14–105 days) after polypectomy. FC levels showed a significant decrease after polypectomy from the median of 445.2 mg/kg (IQR, 225–1,000) down to 26.5 mg/kg (11.5–51) (p<0.001) (**Fig. 3**).

DISCUSSION

This study is the first to investigate the association between factors that correlate with FC levels in children and adolescents with colorectal polyps. We found that FC levels were increased in individuals with JPs at the time of diagnosis, and that FC decreased to normal levels after polypectomy. Moreover, there was a positive correlation between the size of JPs and FC levels. To our knowledge, these results are the first to demonstrate a quantitative relationship between JP size and FC levels.

FC is an antimicrobial protein that is abundant in neutrophils, macrophages, and monocytes. Based on its biochemical stability at room temperature and the consistency of test results, it is widely used as a screening and monitoring tool for disease activity in various clinical fields, including inflammatory bowel disease [2,9,10]. Several previous reports have suggested an increasing tendency to utilize FC in JPs [3,6-8]. However, the underlying mechanism is yet to be elucidated and there is no clear consensus on its usefulness [2].

The results of this study may improve the current limited use of FC as a screening tool for children and adolescents with colorectal polyps and has the potential to improve clinical practice guidelines for JPs. First, the current guidelines have posed a substantial burden on clinicians to repeatedly perform invasive procedures in young children by recommending full colonoscopy after diagnostic sigmoidoscopy [11]. However, according to our results, FC levels may be used to guide the decision in conducting an additional complete colonoscopy based on the FC level findings after sigmoidoscopy. If FC levels are normalized after an initial sigmoidoscopy with polypectomy, an additional complete colonoscopy can be postponed until FC levels are elevated. Meanwhile, an additional complete colonoscopy is warranted if FC levels are continuously elevated after sigmoidoscopy. Using this approach, the burden of repeated examinations on clinicians and patients can be reduced. Second, although the recurrence rate of JPs is reported to be up to 17%, there is no clinical consensus on when to follow up a colonoscopy [4,12], and the real-world recurrence rate may be higher than acknowledged. However, a median follow-up of 18 days in this study did not confirm a sufficiently long duration to conclude that FC can be used as a tool to detect polyp recurrence. This suggests that there is a potential for utilizing FC measurements for future polyp recurrence. The development of future treatment protocols utilizing FC may lead to successful outcomes with an uncovered epidemiology.

However, our suggestions should be complemented by further research. To date, there has been no laboratory evidence of the cause of FC elevation in JPs. Intestinal polyps are classified as hamartomatous or adenomatous according to their histological characteristics [4]. JPs are hamartomatous polyps, enlarged stromal compartments with distortion and dilation of the glands, and the crypts are commonly observed on histological examination. Increased vascularization with heterogeneous overgrowth is thought to result in tissue auto-infarction and inflammatory responses. As a result, neutrophils and eosinophils are increased in crypt mucus and intraepithelial neutrophils are frequently observed [13]. In addition, the classic JP has been reported to have a more erosive surface, and it is thought that FC is more easily released into the intestinal tract through the exfoliated mucosal layer [14]. This hypothesis may partially explain the relationship between pedunculated polyps and FC levels in our cohort, given that the areas exposed to the eroded surfaces and blood supply are readily restricted. Although FC elevation has been reported to be related to other types of polyps [15], it is thought that independent factors with quantitative relevance differ depending on the histological characteristics. Accordingly, the conclusions of our study should be limited to the JPs.

Furthermore, this study had some critical limitations. Therefore, caution is required when interpreting the results. First, statistical significance was limited because of the small number of included subjects. Second, as a retrospective analysis was conducted through a multicenter study without control for the indications for colonoscopy, the results cannot be free from selection bias of the target patients. Third, polyp size was determined using the maximum length of the specimen instead of the surface or volume. Since juvenile polyp is a complex three-dimensional piece of tissue, it would have been better to assess the volume of the polyp. However, we were unable to do so because of the retrospective nature of this study, which was based on a chart review. Fourth, the differences in the FC test results among centers may have affected the results. However, it has been reported that the accuracy of FC measurement is comparable to the enzyme-linked immunosorbent assays and fluorescence immunoassay [16].

In conclusion, most FC levels were elevated in JPs and were positively correlated with the polyp size. FC may help predict polyp recurrence after polypectomy and play a role in

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deciding when to conduct follow-up colonoscopy. However, well-designed prospective studies are required to elucidate the role of FC in the diagnosis and management of JPs.

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