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Fecal calprotectin in the prediction of postoperative recurrence of Crohn's disease in children and adolescents☆

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ABSTRACT

Background: Fecal calprotectin (FC) correlates with endoscopic recurrence of Crohn's disease (CD) in adults but has not been studied among children postoperatively. We aimed to analyze whether FC relates with postoperative CD recurrence in children.
Methods: Altogether 51 postoperative endoscopies and FC measurements from 22 patients having undergone surgery for CD at age ≤18 years were included.
Results: Ileocecal resection (n = 15), small bowel resection (n = 6), or left hemicolectomy (n = 1) was performed at median age of 15.1 (interquartile range 14.4–17.6) years. Following surgery, FC decreased significantly (659 vs. 103 μg/g, p = 0.001). During median follow-up of 5.7 (4.2–7.7) years, either endoscopic or histological recurrence occurred in 17 patients (77%). FC >139 μg/g at time of endoscopy or FC increase of 79 μg/g compared to first postoperative value was suggestive of endoscopic recurrence (Rutgeerts score i2-i4), while FC >101 μg/g or increase of 21 μg/g indicated histological recurrence. Best accuracy for prediction of recurrence was obtained by combining FC at endoscopy and the postoperative increase of FC. The corresponding AUROC values were 0.74 (95% 0.58–0.89) for endoscopic recurrence whereas 0.81 (95% CI 0.67–0.95) for histological recurrence.
Conclusion: FC is a useful surrogate marker of postoperative recurrence also in pediatric CD patients.

Crohn's disease (CD) is a chronic relapsing inflammatory disorder of the alimentary tract with a continuously increasing incidence in the pediatric population [1–5]. Compared to adults, childhood-onset CD typically shows a more active disease pattern and greater need for immunosuppressant therapy [4]. Ileum is affected in 70% of children and is prone to stricture and fistula formation, which occur in about 25% of pediatric CD patients [3,4,6]. Resection of the affected bowel segment either because of such complications or for unresponsive luminal disease is performed in 30–50% of pediatric CD patients by young adulthood [4,7] and as many as 70% of operated patients require further surgery during their lifetime [8,9].

Recurrent mucosal inflammation is observed in endoscopy in 70–90% of adult CD patients within a year of surgery although only one third present with symptomatic relapse of the disease [1,8–10]. Histological activity may develop at the site of the anastomosis as soon as after a week of bowel resection [11]. Even though longer postoperative remission periods are reported for children, most studies have monitored clinical recurrence rates instead of endoscopic follow-up [2,12–15]. As clinical symptoms are frequently absent and serum biochemical markers normal until significant inflammatory changes have developed, ileocolonoscopy with histological verification should be considered as the gold standard for assessing disease activity and postoperative recurrence [6,8–10,16].

Calprotectin is a neutrophil-derived protein excreted in stool in abundance in the presence of mucosal inflammation [17–20]. Fecal calprotectin (FC) outperforms serum markers in the detection of bowel wall inflammation and reflects the endoscopic activity of CD reliably in both children and adults [17,18,20–23]. Its concentration has been shown to increase in the presence of histological pouch inflammation following proctocolectomy for ulcerative colitis [24]. In addition, FC levels correlate with endoscopic disease recurrence rates after bowel resection in adult CD patients [8,25], although not all studies have confirmed this association [26,27]. In pediatric Crohn patients, FC has not been evaluated postoperatively and neither has its correlation with histological recurrence been assessed after surgery. We aimed to evaluate

Abbreviations: CD, Crohn's disease; FC, fecal calprotectin; MRE, magnetic resonance enterography; IQR, interquartile range; AUROC, area under receiving operating characteristic; PPV, positive predictive value; NPV, negative predictive value; AZA, azathioprine; TNF, tumor necrosis factor; MTX, methotrexate.

☆ Conflicts of interest: None to declare.

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the postoperative course of FC and its accuracy in the detection of endoscopic and histological recurrence in children and adolescents having undergone bowel resection for CD.

1. Methods

This was a retrospective study including all patients with childhood-onset CD having undergone bowel resection at age ≤18 years as well as postoperative endoscopies and FC measurements in a tertiary care children's hospital during 1994–2015 (n = 22). Patients without follow-up endoscopy and FC data were excluded (n = 7). The diagnosis of CD was based on upper and lower gastrointestinal endoscopies and evaluation of histopathological biopsies in all cases. The medical records including operative, endoscopy, and pathology reports were reviewed. The type of surgery, number of bowel resections, possible postoperative complications as well as medications before and after surgery were recorded.

1.1. Endoscopy data

Altogether 46 ileocolonoscopies, 3 capsule endoscopies, and 2 magnetic resonance enterographies (MRE) (total n = 51) from 22 patients were included. Endoscopies were performed when clinically considered necessary. Endoscopy findings were classified according to Rutgeerts score where remission was defined as i0 (no lesions) or i1 (less than five aphthous lesions) and recurrence as i2 (>5 aphthous lesions or larger lesions confined to anastomosis), i3 (diffuse ileitis), or i4 (diffuse inflammation with large ulcers and/or narrowing) [28,29]. Indications for MRE were follow-up of ileal disease or terminal ileum not reached in ileocolonoscopy. Both examinations showed a clearly strictured bowel segment and were graded as i4.

1.2. Biopsy specimens

Biopsies were taken in ileocolonoscopies from the anastomosis, the ileum, cecum, ascending colon, colon transversum, descending colon, sigmoid colon, and rectum. The specimens were evaluated by pediatric pathologists and the histological findings were graded as quiescent CD (0) if no inflammation or chronic inflammation without active component was present, and active CD (1) if signs of acute inflammation, such as inflammatory infiltration, crypt injury, crypt abscesses, or ulcerations were detected. In total 43 histology reports from 46 ileocolonoscopies were reviewed.

1.3. Fecal calprotectin

FC was measured with quantitative enzyme immunoassay as previously described and expressed as μg/g [30]. Preoperative (n = 17) and postoperative FC measurements (n = 19) were recorded. Follow-up FC samples (n = 51) were included in the study if measured within 6 months of the endoscopy or MRE.

1.4. Statistical analyses

The descriptive results are presented as medians with interquartile ranges (IQR). Spearman rank correlation was used to examine associations between variables. Kruskal–Wallis test and Mann–Whitney U test were used to compare continuous variables, Wilcoxon signed-rank test to compare repeated measurements within groups, and Fisher exact test was applied when comparing frequencies between groups. Receiving operating characteristic (ROC) curves and areas under ROC curves (AUROC) were used to evaluate the ability of FC to detect the presence endoscopic or histological recurrence of CD. The optimal cutoff values were calculated using the maximum sum of specificity and sensitivity. To evaluate the combination of two different parameters for the prediction of CD recurrence, the predicted probabilities from a binary logistic regression model were used to plot the respective ROC curve. The analyses were carried out with SPSS version 22 (SPSS Inc., Chicago, IL) and the level of significance was set at $p < 0.05$.

1.5. Ethics

The study was approved by the ethical committee of Helsinki University Hospital.

2. Results

2.1. Patient characteristics

Altogether 22 eligible patients were identified. Half had extraintestinal manifestations of CD, of which mild arthralgia was the most common. Symptomatic upper gastrointestinal disease was present in one, however, aphthous ulcers were seen in endoscopy in the esophagus of two additional patients. Full medication data were available for 21 patients, of whom 67% (n = 14) had used immunosuppressive medications preoperatively while 33% (n = 7) had not (Table 1).

2.2. Operative details

First bowel resection was performed median 2.2 (1.0–4.2) years after the diagnosis of CD. The strictured or severely affected bowel segment, most commonly the ileocecal area, was removed in laparoscopy (n = 9, 41%) or in open surgery (n = 13, 59%) (Table 2). Urgent or emergency surgery for perforation, bleeding, infection, or occlusion was scheduled in six patients (27%) while others underwent elective operations. Postoperative complications were uncommon (Table 2). Corticosteroids, used prior to surgery in 90% (n = 18), were gradually tapered and discontinued. Postoperative medications were designed individually according to disease behavior and estimated risk of recurrence (Table 2). Postoperative FC, measured median 1.8 (0.75–2.7) months after surgery, was significantly lower when compared to preoperative FC, measured 4.5 (1.5–5.5) months prior surgery (103 vs. 659 μg/g, p = 0.001, Table 2).

2.3. Follow-up endoscopies

Endoscopy or MRE (n = 51) was performed 38 (15–58) months following the latest surgery at the age of 19.2 (17.5–22.9) years. Endoscopic disease recurrence was observed in half of cases while histological recurrence was present in two thirds (Table 3). Patients with endoscopic recurrence were more likely to be on immunosuppressive medication at time of endoscopy compared to those without recurrence (88% vs. 60%, p = 0.025, Table 3). FC at time of endoscopy and the increase of

Table 1
Baseline patient characteristics (total n = 22) and medications used preoperatively.

Sex, n (%)	
Male	7 (32%)
Female	15 (68%)
Median age at diagnosis (years)	13.6 (11.9–14.2)
Extraintestinal manifestations, n (%)	
Arthralgia	9 (41%)
Primary sclerosing cholangitis	2 (9%)
Erythema nodosum	1 (4.5%)
Gallstones	1 (4.5%)
None	12 (55%)
Perianal CD, n (%)	3 (14%)
Medications used preoperatively,[a] n (%)	
AZA	11 (52%)
Anti-TNF-α agents	6 (29%)
MTX	3 (14%)

CD = Crohn's disease, AZA = azathioprine, TNF-α = tumor necrosis factor α, MTX = methotrexate.
[a] Reported for 21 patients.

Table 2
Operative details, including type of surgery, age at surgery, indications, possible postoperative complications, as well as fecal calprotectin levels before and after surgery.

Type of first bowel resection for CD, n (%)	
Small bowel resection	6 (27%)
Ileocecal resection	15 (68%)
Left hemicolectomy	1 (4.5%)
Median age at surgery (years)	15.1 (14.4–17.6)
Indication for surgery, n (%)	
Stricture	10 (45%)
Luminal disease	7 (32%)
Gastrointestinal bleeding	2 (9%)
Perforation	1 (4.5%)
Fistula	1 (4.5%)
Not reported	1 (4.5%)
Postoperative complications	
Leakage, n (%)	0 (0%)
Infection, n (%)	2 (9%)
Medications at discharge[a]	
AZA (±5-ASA or metronidazole)	8 (40%)
Metronidazole	4 (20%)
5-ASA	3 (15%)
Anti-TNF-α agents (±other medications)	1 (5%)
None	4 (20%)
Median fecal calprotectin (μg/g)	
Before surgery	659 (135–1225)*
After surgery	103 (53–284)*

CD = Crohn's disease, AZA = azathioprine, TNF-α = tumor necrosis α, 5-ASA = 5-aminosalicylic acid.
[a] Reported for 20 patients.
* Significant difference between subgroups ($p < 0.05$).

FC compared to postoperative level correlated with the presence of endoscopic ($r = 0.354$, $p = 0.011$ and $r = 0.416$, $p = 0.006$) and histological recurrence ($r = 0.469$, $p = 0.002$ and $r = 0.331$, $p = 0.042$), as well as with Rutgeerts score ($r = 0.295$, $p = 0.036$ and $r = 0.359$, $p = 0.018$).

2.4. Diagnostic accuracy of follow-up fecal calprotectin

Follow-up FC was measured within 1.5 (0.20–3.6) months of the follow-up endoscopy and was significantly higher in the presence of endoscopic recurrence compared to i0-i1 (Fig. 1A, Table 3) as well as in the presence of histological recurrence vs. quiescent CD (Fig. 2A, Table 3). Fig. 1B displays the ROC curve for FC for the prediction of endoscopic recurrence. The optimal cutoff point was 139 μg/g, with sensitivity of 0.73, specificity of 0.64, positive predictive value (PPV) of 0.68, and negative predictive value (NPV) of 0.70. For the detection of histological recurrence, the optimal cutoff point was 101 μg/g, with sensitivity of 0.85, specificity of 0.63, PPV of 0.79, and NPV of 0.71, respectively (Fig. 2B).

2.5. Diagnostic accuracy of the increase of fecal calprotectin

When compared to first postoperative FC, the concentration of FC increased significantly more in patients with either endoscopic or histological recurrence vs. no recurrence (Table 3, $p = 0.007$ for endoscopic recurrence and $p = 0.044$ for histological recurrence). The respective AUROC value for detection of endoscopic recurrence was 0.74 (95% CI 0.59–0.89) and the optimal cutoff value 79 μg/g, with sensitivity of 0.73, specificity of 0.71, PPV of 0.73, and NPV of 0.71. For detection of histological recurrence, the AUROC value was 0.70 (95% CI 0.53–0.87) with an optimal cutoff value of 21 μg/g, sensitivity of 0.74, specificity of 0.67, PPV of 0.77, and NPV of 0.63, respectively.

Combining two predictors in the same model – the increase of FC and FC at time of endoscopy – improved the diagnostic accuracy for the detection of histological recurrence. The AUROC value of the combination model was 0.81 (95% CI 0.67–0.95), with sensitivity and specificity of 0.78 and 0.80 ($p = 0.001$). For detection of endoscopic recurrence, the combination model resulted in an AUROC value of 0.74 (95% CI 0.58–0.89), with sensitivity and specificity of 0.64 and 0.89 ($p = 0.008$), respectively.

2.6. Follow-up characteristics

All patients were alive at last follow-up 5.7 (4.2–7.7) years postoperatively. Either endoscopic or histological recurrence had occurred in 77% ($n = 17$) of patients during follow-up. Fig. 3 illustrates the behavior of FC before and after surgery as well as during follow-up. One third of patients ($n = 8$) required further operations during follow-up, including small bowel resections ($n = 5$ patients), ileocecal resections ($n = 4$), colectomy ($n = 2$), proctectomy or proctocolectomy with an endostomy ($n = 2$), and colon resection ($n = 1$). Postoperatively, azathioprine (AZA) had been used by 52% ($n = 11$), anti-tumor necrosis factor (TNF)-α agents by 62% ($n = 13$), and methotrexate (MTX) by 29% ($n = 6$). Four patients (19%) had not required other medications than metronidazole. No risk factors related to recurrence or need for second surgery were identified; sex, age at diagnosis, age at operation, disease duration prior to surgery, stricturizing or penetrating disease behavior, preoperative FC, first postoperative FC, use of thiopurines, anti-TNF-α agents, or MTX did not differ between patients with or without recurrence or further surgery during follow-up (data not shown).

3. Discussion

This is the first study evaluating the diagnostic accuracy of FC in the prediction of postoperative recurrence of CD in children. As previously

Table 3
Fecal calprotectin (FC) levels and postoperative increase of FC according to follow-up endoscopy findings.

	n (%)	n (%) on immunosuppressive medication	Fecal calprotectin at endoscopy (μg/g)	Increase of fecal calprotectin (μg/g)
Endoscopic recurrence				
No (i0-i1)	25 (49%)	15 (60%)*	111 (31–230)*	−1 (−151 to 170)*
Yes (i2-i4)	26 (51%)	23 (88%)*	451 (112–1066)*	320 (42–996)*
Endoscopic scoring				
i0	8 (16%)	5 (63%)*	224 (98–523)	−5 (−151 to 212)
i1	17 (33%)	10 (59%)*	103 (29–222)*	3 (−38 to 170)
i2	5 (10%)	4 (80%)	28 (24–35)	3.5 (−39 to 1057)
i3	5 (10%)	4 (80%)	189 (148–449)	138 (107–267)
i4[a]	16 (31%)	15 (100%)*	700 (207–1279)*	479 (129–996)
Histological recurrence[b]				
No (quiescent CD)	16 (37%)	8 (50%)	74 (16–185)*	−1 (−29 to 128)*
Yes (active inflammation)	27 (63%)	22 (81%)	230 (112–857)*	318 (17–820)*

CD = Crohn's disease.
[a] Medication data at endoscopy missing in one patient.
[b] Histological reports available for 43 endoscopies.
* Significant difference between subgroups ($p < 0.05$).

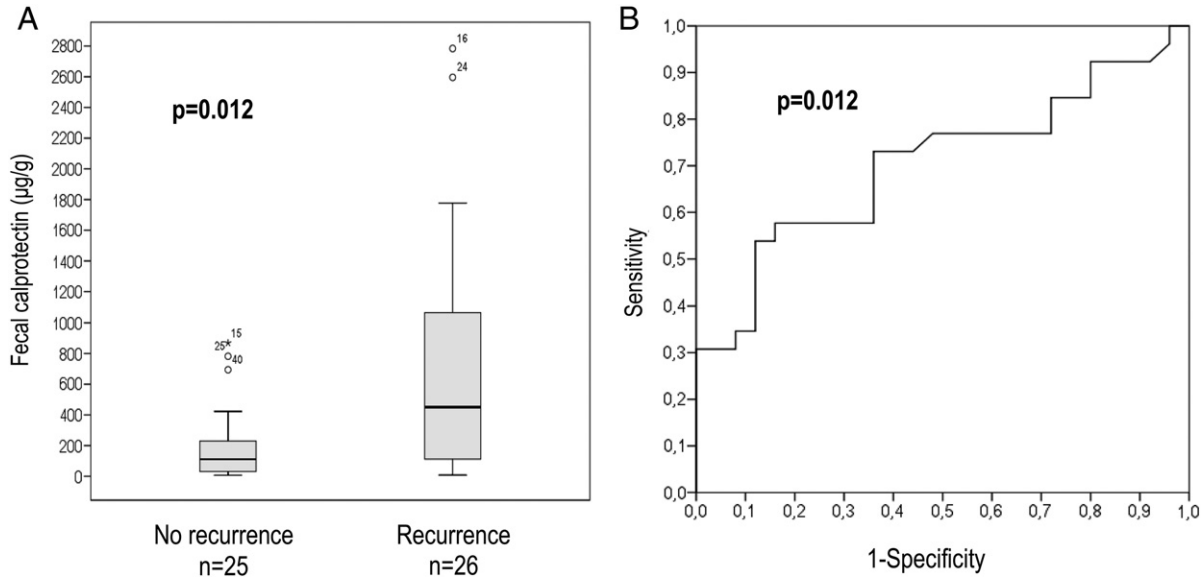

Fig. 1. Box plots of postoperative fecal calprotectin (FC) (µg/g) levels (A) at time of follow-up endoscopy in pediatric Crohn patients with (n = 26) or without (n = 25) endoscopic recurrence as well as ROC curve for FC for detection of endoscopic recurrence (B). The length of the box represents the IQR within which 50% of the values are located. The line through the middle of each box represents the median. Error bars show minimum and maximum values. The round dots represent values larger than the upper quartile plus 1.5 times the IQR. The area under the ROC curve was 0.71 (95% CI 0.56-0.85).

reported among adults, FC concentration decreased significantly during first weeks after surgery and increased during follow-up in patients with recurrent disease. FC was a relatively accurate predictor of both endoscopic and histological disease recurrence with AUROC values of 0.71 and 0.78. Even though this is a retrospective study based on a small sample, our results strongly suggest postoperative FC behaves in children and adolescents similarly as previously demonstrated among adult CD patients [8,25].

Fasting, bowel preparation, and requirement of anesthesia make endoscopies particularly demanding for children. As endoscopies are also invasive, expensive, and time-consuming with a risk of complications, there is a need for noninvasive screening methods for detecting relapse and postoperative recurrence of CD. Clinical activity indices and serum inflammatory markers correlate poorly with endoscopic disease activity [9,17,18,21]. Fecal calprotectin, which is excreted by migrating neutrophils to the lumen of the inflamed bowel, has been demonstrated a useful surrogate marker for disease activity in both children and adults [18,21,22,31,32]. However, FC is not specific to inflammatory bowel disease and may increase in the presence of other gastrointestinal disorders, such as infectious colitis and polyposis [33,34]. In addition, bowel leaks and abscesses may raise the level of FC for several weeks and complicate its interpretation in the postoperative setting [27].

Despite resolution of active mucosal inflammation during medical therapy for CD, FC levels may remain elevated reflecting persistent

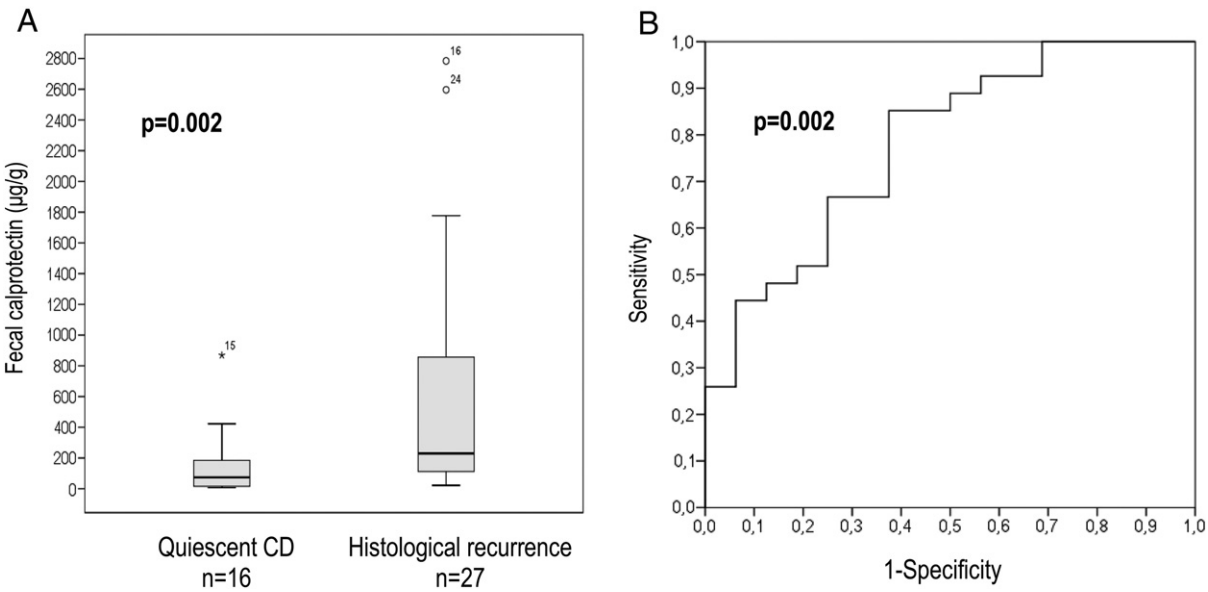

Fig. 2. Box plots of postoperative fecal calprotectin (FC) (µg/g) levels (A) at time of follow-up endoscopy in pediatric Crohn patients with (n = 27) or without (n = 16) histological recurrence as well as ROC curve for FC for detection of histological recurrence (B). The length of the box represents the IQR within which 50% of the values are located. The line through the middle of each box represents the median. Error bars show minimum and maximum values. The round dots represent values larger than the upper quartile plus 1.5 times the IQR. The area under the ROC curve was 0.78 (95% CI 0.64–0.92). CD = Crohn's disease.

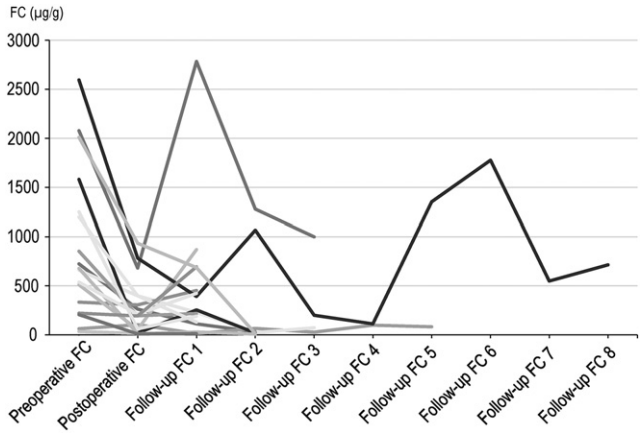

Fig. 3. Preoperative, postoperative, and follow-up fecal calprotectin (FC) measurements presented for all cases with preoperative FC measurement available (n = 17).

microscopic inflammation of the bowel wall [17,18,21,22,31,32]. Suggested cutoff values for detection of relapse vary between 150 and 275 μg/g, usually with moderate sensitivity but good specificity [17,18,21,32]. Instead, after successful surgery, FC levels should normalize, and consequently the cutoff values for detection of postoperative recurrence are lower [8,25,27,35]. Recent studies among adults report sensitivity and specificity values of 0.82–0.89 and 0.58–0.61 for FC for the prediction of endoscopic recurrence after surgery and suggest FC levels above 100 μg/g as an indication for endoscopy [8,25,36]. Accordingly, we found FC levels in children to fall close to 100 μg/g after surgery, and cutoffs of 139 μg/g and 101 μg/g predicted the presence of endoscopic and histological recurrence with good sensitivity. On the other hand, an increase of 20–80 μg/g compared to postoperative FC level was suggestive of disease recurrence. Compared to nonoperated patients, both children and adults, FC appears to be a more delicate marker of mucosal inflammation in the postoperative setting when it detects the early inflammatory changes developing in a previously unaffected intestine.

The few studies that have evaluated FC in relation to histology of CD report a high correlation with biopsy-proven disease activity [17,32,37]. One strength of our study is that both endoscopic and histological disease activities were evaluated. Consistent with previous findings, we found FC a sensitive marker of histological inflammation. Although the best cutoff of 101 μg/g for detection of histological inflammation was no different from median postoperative FC and therefore inconvenient for clinical use, taking into account also the postoperative increase of FC improved its diagnostic accuracy, resulting in an AUROC value of 0.81. In clinical practice, following the postoperative trend of FC instead of single measurements would probably be useful.

Lower levels of FC were observed in the presence of histological recurrence compared to endoscopic recurrence. Histological derangement with an early-stage inflammation precedes the development of ulcers [11,38], and likely increases FC concentration before any disease activity can be observed in endoscopy. The rapid development of inflammation at the site of anastomosis has been suggested to result from the backwash of intestinal contents in the case of ileocecal resection [11]. Indeed, despite endoscopic grading of i0-i1, biopsies suggested active inflammation in seven of our patients with previous ileocecal resection and the inflammatory changes were located in the neoterminal ileum or at the anastomosis in five of them. However, biopsies may also give false negative results as they are not necessarily taken from areas of inflammation. Poor visibility and bowel preparation as well as the presence of strictures or transmural inflammation under a healthy-looking mucosa may in turn result in false endoscopic grading [39]. As both scaling systems are subject to intraobserver and interobserver variability, biopsy specimens should be routinely taken in endoscopies performed for CD patients to improve the accuracy of the examination and to facilitate later decision-making [17,39].

A recent multicenter randomized trial among adult CD patients recommended postoperative endoscopic monitoring at 6-month intervals [9]. FC measurement could reduce the need for postoperative ileocolonoscopies by recognizing patients with probable disease recurrence who require medication intensification. By using the best cutoff of 139 μg/g for endoscopic recurrence, 19 out of 26 patients with disease recurrence were correctly recognized, whereas a lower cutoff of 112 μg/g would give sensitivity and specificity values of 0.77 and 0.52. Postoperative FC values clearly over 100 μg/g should raise a suspicion of disease recurrence [8,25,36]. In case of indeterminate results, FC is easy to control at short time intervals. Further, as FC is supposed to decrease near 100 μg/g after successful surgery, the postoperative increase of FC may serve as another useful method when deciding whether stepping up medication would be necessary.

The present study is limited by its small sample size, retrospective nature, and the lack of routine postoperative FC and endoscopic monitoring, which resulted in relatively long time gaps between surgery and follow-up endoscopies. However, FC measurements were obtained within median 1.5 months of follow-up endoscopy and therefore likely reflected the endoscopic disease activity reliably. Despite some limitations, this is the first report on postoperative FC measurement among pediatric patients and our results suggest postoperative FC can be interpreted in children similarly than earlier demonstrated among adult patients. Monitoring FC is currently part of our routine follow-up in children having undergone surgery for CD. By using recurrent FC measurements, postoperative endoscopies could be spared to children who have signs of complicated CD or who fail to respond to therapy.

In conclusion, postoperative FC levels predicted both endoscopic and histological recurrence of CD relatively accurately in a small sample of patients having undergone bowel resection during childhood. FC levels decreased near normal after surgery and increased significantly in patients with recurrent disease in a similar manner as previously reported in adults. FC is a promising surrogate marker of postoperative CD recurrence also in children and adolescents, and its use may reduce the need for endoscopic monitoring after surgery.

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References

[1] Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohn's Colitis 2014;8:1179–207.

[2] Boualit M, Salleron J, Turck D, et al. Long-term outcome after first intestinal resection in pediatric-onset Crohn's disease: a population-based study. Inflamm Bowel Dis 2013;19:7–14.
[3] de Bie CI, Paerregaard A, Kolacek S, et al. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS Registry. Inflamm Bowel Dis 2013;19:378–85.
[4] Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis 2010;16:953–61.
[5] Lehtinen P, Ashorn M, Iltanen S, et al. Incidence trends of pediatric inflammatory bowel disease in Finland, 1987–2003, a nationwide study. Inflamm Bowel Dis 2011;17:1778–83.
[6] Pfefferkorn MD, Marshalleck FE, Saeed SA, et al. NASPGHAN clinical report: evaluation and treatment of pediatric patients with internal penetrating Crohn's disease: intra-abdominal abscess with and without fistula. J Pediatr Gastroenterol Nutr 2013;57:394–400.
[7] Turunen P, Ashorn M, Auvinen A, et al. Long-term health outcomes in pediatric inflammatory bowel disease: a population-based study. Inflamm Bowel Dis 2009;15:56–62.
[8] Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology 2015. http://dx.doi.org/10.1053/j.gastro.2015.01.026 (Published online Jan 22.).
[9] De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet 2015;385:1406–17.
[10] Buisson A, Chevaux JB, Allen PB, et al. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther 2012;35:625–33.
[11] D'Haens GR, Geboes K, Peeters M, et al. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology 1998;114:262–7.
[12] Blackburn SC, Wiskin AE, Barnes C, et al. Surgery for children with Crohn's disease: indications, complications and outcome. Arch Dis Child 2014;99:420–6.
[13] Hojsak I, Kolacek S, Hansen LF, et al. Long-term outcomes after elective ileocecal resection in children with active localized Crohn's disease—a multicenter European study. J Pediatr Surg 2015;10:1630–5.
[14] Piekkala M, Pakarinen M, Ashorn M, et al. Long-term outcomes after surgery on pediatric patients with Crohn disease. J Pediatr Gastroenterol Nutr 2013;56:271–6.
[15] Pacilli M, Eaton S, Fell JM, et al. Surgery in children with Crohn disease refractory to medical therapy. J Pediatr Gastroenterol Nutr 2011;52:286–90.
[16] Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–63.
[17] Canani RB, Terrin G, Rapacciuolo L, et al. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. Dig Liver Dis 2008;40:547–53.
[18] D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2218–24.
[19] Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009;15:1190–8.
[20] Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and metaanalysis. Am J Gastroenterol 2014;109:637–45.
[21] Sipponen T, Savilahti E, Kolho KL, et al. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. Inflamm Bowel Dis 2008;14:40–6.
[22] Vieira A, Fang CB, Rolim EG, et al. Inflammatory bowel disease activity assessed by fecal calprotectin and lactoferrin: correlation with laboratory parameters, clinical, endoscopic and histological indexes. BMC Res Notes 2009;2:221. http://dx.doi.org/10.1186/1756-0500-2-221.
[23] Hoog CM, Bark LA, Broström O, et al. Capsule endoscopic findings correlate with fecal calprotectin and C-reactive protein in patients with suspected small-bowel Crohn's disease. Scand J Gastroenterol 2014;49:1084–90.
[24] Pakarinen MP, Koivusalo A, Natunen J, et al. Fecal calprotectin mirrors inflammation of the distal ileum and bowel function after restorative proctocolectomy for pediatric-onset ulcerative colitis. Inflamm Bowel Dis 2010;16:482–6.
[25] Qiu Y, Mao R, Chen BL, et al. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-analysis of prospective studies. Inflamm Bowel Dis 2015;21:315–22.
[26] Lasson A, Strid H, Ohman L, et al. Fecal calprotectin one year after ileocaecal resection for Crohn's disease—a comparison with findings at ileocolonoscopy. J Crohn's Colitis 2014;8:789–95.
[27] Lamb CA, Mohiuddin MK, Gicquel J, et al. Faecal calprotectin or lactoferrin can identify postoperative recurrence in Crohn's disease. Br J Surg 2009;96:663–74.
[28] Rutgeerts P, Geboes K, Vantrappen G, et al. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut 1984;25:665–72.
[29] Khanna R, Bouguen G, Feagan BG, et al. A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design. Inflamm Bowel Dis 2014;20:1850–61.
[30] Kolho KL, Raivio T, Lindahl H, et al. Fecal calprotectin remains high during glucocorticoid therapy in children with inflammatory bowel disease. Scand J Gastroenterol 2006;41:720–5.
[31] Sipponen T, Kolho KL. Faecal calprotectin in children with clinically quiescent inflammatory bowel disease. Scand J Gastroenterol 2010;45:872–7.
[32] Diamanti A, Colistro F, Basso MS, et al. Clinical role of calprotectin assay in determining histological relapses in children affected by inflammatory bowel diseases. Inflamm Bowel Dis 2008;14:1229–35.
[33] Chen CC, Huang JL, Chang CJ, et al. Fecal calprotectin as a correlative marker in clinical severity of infectious diarrhea and usefulness in evaluating bacterial or viral pathogens. J Pediatr Gastroenterol Nutr 2012;55:541–7. http://dx.doi.org/10.1097/MPG.0b013e318262a718.
[34] Zijlstra M, Pluimakers V, Nikkels P, et al. Elevated faecal calprotectin does not differentiate between inflammatory bowel disease and a juvenile polyp. J Pediatr Gastroenterol Nutr 2016. http://dx.doi.org/10.1097/MPG.0000000000000921.
[35] Lobaton T, Lopez-Garcia A, Rodriguez-Moranta F, et al. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. J Crohns Colitis 2013. http://dx.doi.org/10.1016/j.crohns.2013.05.005 (Published online Jul 1).
[36] Boschetti G, Laidet M, Moussata D, et al. Levels of fecal calprotectin are associated with the severity of postoperative recurrence in asymptomatic patients with Crohn's Disease. Am J Gastroenterol 2015;110:865–72.
[37] Hradsky O, Ohem J, Mitrova K, et al. Fecal calprotectin levels in children is more tightly associated with histological than with macroscopic endoscopy findings. Clin Lab 2014;60:1993–2000.
[38] Bressenot A, Peyrin-Biroulet L. Histologic features predicting postoperative Crohn's disease recurrence. Inflamm Bowel Dis 2015;21:468–75.
[39] Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol 2005;3:11–24.