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Endoscopic Factors Influencing Fecal Calprotectin Value in Crohn's Disease

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Abstract

Background and Aims: Fecal calprotectin [fcal] is a biomarker of Crohn's disease [CD] endoscopic activity. Identifying the endoscopic situations in which fcal is less reliable remains unexplored. We aimed to determine the endoscopic factors influencing fcal level in CD.
Methods: Overall, 53 CD patients consecutively and prospectively underwent colonoscopy, with CD Endoscopic Index of Severity [CDEIS] calculation and stool collection. Fcal was measured using a quantitative immunochromatographic test. Correlation analysis was done with Pearson statistics.
Results: Fcal was correlated with CDEIS [0.66, $p < 0.001$]. In univariate analysis, fcal was correlated with the affected surface [0.65, $p < 0.001$] and the ulcerated surface [0.47, $p < 0.001$]. Fcal was significantly associated with ulceration depth, with median fcal of 867.5 µg/g, 1251.0 µg/g, and 1800.0 µg/g, in patients presenting with non-ulcerated lesions, superficial ulcerations [SU], and deep ulcerations [DU], respectively. Lesion locations did not influence fcal. In multivariate analysis, fcal was associated with affected surface [$p = 0.04$] and the presence of CD lesions. Moreover, fcal increased with the ulceration depth [$p = 0.03$]. However, ulcerated surface and CD location did not affect fcal. Using a receiver operating characteristic [ROC] curve, we showed that fcal of 400 µg/g was the best compromise between sensitivity [0.76] and specificity [0.77], whereas fcal ≥ 200 µg/g was highly sensitive [0.86] to detect SU or DU.
Conclusions: Fcal is a very reliable biomarker to detect endoscopic ulcerations in CD. We suggest repeating measurement in case of intermediary results [200–400µg/g] in daily practice. Fcal level is mostly influenced by the presence of CD lesions [even non-ulcerated], in a depth-related manner and by the affected surface.

Key words: Crohn' s disease; fecal calprotectin; Crohn's Disease Endoscopic Index of Severity; endoscopy; biomarker

1. Introduction

Crohn's disease [CD] is a chronic relapsing and remitting disorder which can involve the entire length of the digestive tract.[1] In the era of biologicals, new therapeutic goals, such as achieving mucosal healing or preventing digestive damage, have emerged and require objective tools to evaluate disease activity.[2,3,4,5,6] As ileocolonoscopy remains, to date, the gold standard to assess ileocolonic CD, reaching these therapeutic goals implies repeating endoscopies, to monitor the disease activity. However, the burden experienced by patients and the potential risks [7] have led physicians to seek for alternative non-invasive approaches. Therefore, surrogate markers reflecting the severity of mucosal inflammation have been investigated.

One of the most attractive methods is the measurement of inflammatory proteins secreted by neutrophils in the stool, such as fecal calprotectin. Fecal calprotectin is reliably and reproductively measured in stool samples and this dosage might even be eligible for patient home-based measurement in the near future.[8] Fecal calprotectin level significance has been studied in CD clinical trials for more than 10 years.[8,9,10,11,12,13,14,15,16,17,18,19,20,21] Its ability to differentiate inflammatory bowel disease [IBD] from irritable bowel syndrome patients, to predict clinical relapse, and to avoid useless colonoscopies in CD or ulcerative colitis patients has been extensively demonstrated.[10,13,15,18,19,20,21,22] As a consequence, fecal calprotectin has been increasingly used in the diagnosis and the monitoring of CD in daily practice.[17]

More recently, some reports showed a significant correlation between fecal calprotectin level and both the Crohn's Disease Endoscopic Index of Severity [CDEIS] and the Simple Endoscopic Score of Crohn's Disease [SES-CD].[14,23] However, some studies suggest that fecal calprotectin results are less relevant in patients with pure ileal CD,[14,23] even if the data remain conflicting [9]. Knowing in which conditions fecal calprotectin might be less reliable as a predictor of endoscopic activity is a key point in daily practice.

The correlation between fecal calprotectin level and specific items composing the CDEIS, such as ulceration depth, affected surface, ulcerated surface, and stenosis, has never been investigated so far and could lead to an explanation of the weaknesses of fecal calprotectin in some clinical situations.

In the present study, we aimed to determine endoscopic factors influencing fecal calprotectin level, including each independent item of the CDEIS [24].

2. Methods

2.1. Ethical considerations

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study has been approved by the local Ethics Committee [IRB 00008526 – Ref. 2015 / CE 24].

2.2. Patients

We led an observational study of a single-centre cohort in which standardised evaluation was performed by experienced clinicians, in all patients. Patients from the Clermont-Ferrand IBD Unit with an established diagnosis of CD according to Lennard-Jones criteria,[25] undergoing ileocolonoscopy regardless of the indication were prospectively and consecutively included between December 2013 and December 2014. Clinical parameters including the Crohn's Disease Activity Index [CDAI] were collected [Table 1]. Blood samples were taken before the endoscopy and were used to measure the highly sensitive serum C-reactive protein [CRP] level.

Patients who took non-steroidal anti-inflammatory drugs [NSAIDs] or aspirin within the 4 weeks preceding the measurement of calprotectin were not included.

2.3. Endoscopy

Patients followed a bowel-cleansing protocol via oral ingestion of 2l of polythene glycol [PEG] [Fortrans, Ipsen Pharma, Paris, France] the previous evening, and 2l on the morning of the examination. Endoscopies were performed under anaesthesia with propofol [PROPOFOL DAKOTA PHARM; Sanofi-Aventis, Paris, France], by two experienced endoscopists [AB, GB], using column video colonoscopy [QFC L 140; Olympus, Tokyo, Japan]. The endoscopists were blinded to the results of fecal calprotectin dosage. An affected area was defined as the presence of at least one CD lesion [deep or superficial ulceration, aphthoid erosion, frank erythema, frankly swollen mucosa, stenosis, pseudopolyp] according to Mary *et al.* [24]. An ulcerated area was defined as the presence of deep or superficial ulceration according to the CDEIS definitions.[24] The lower digestive tract was divided into five segments according to CDEIS calculation [terminal ileum, caecum/right colon, transverse colon, left/sigmoid colon, and rectum]. The affected or ulcerated surfaces were evaluated in each segment. The calculation of the overall affected or ulcerated surface was performed according to the following formula: sum of each segmental surface divided by the number of segments [exception: for affected surfaces of 5% in the ileum, 20% in the right colon, 0% in the transverse colon, 0% in the left/sigmoid colon, and 5% in the rectum, we calculated [5 + 20 + 0 + 0 + 5]/5 = 6 %]. In case of no previous surgery, each segment represented 20% of the overall surface; otherwise, the number of segments was adapted to the surgery extension and location.

Table 1. Baseline population characteristics.

	n = 53
Female, *n* [%]	30 [56.6]
Age at inclusion[years], mean ± SD	31 [21–44]
BMI, median [IQR]	22.1 [18.5–26.3]
Disease duration [months], median[IQR]	3.5 [1–9]
Active smokers, *n* [%]	17 [31.1]
Previous intestinal resection, *n* [%]	14 [26.4]
Anoperineal lesion, *n* [%]	14 [32.1]
Montreal classification	
Age at diagnosis, *n* [%]	
A1	13 [24.5]
A2	12 [22.7]
A3	28 [52.8]
Location, *n* [%]	
L1	13 [24.5]
L2	12 [22.6]
L3	28 [52.8]
L4	4 [7.5]
Behaviour, *n* [%]	
B1	28 [52.8]
B2	12 [22.6]
B3	11 [20.8]
Concomitant therapies	
Anti-TNF, *n* [%]	
Infliximab	13 [26.0]
Adalimumab	12 [23.5]
5-ASA, *n* [%]	9 [18.4]
Budesonide, *n* [%]	3 [6]
Corticosteroids, *n* [%]	8 [15.7]
Thiopurines, *n* [%]	13 [31.4]
Methotrexate, *n* [%]	1 [2.0]
CDAI, median [IQR]	198.5 [101–258]
CRP, median [IQR], mg/l	11.20 [4.6–71]

SD, standard deviation; IQR, interquartile range; BMI, body mass index; TNF, tumour necrosis factor; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein.

2.4. Fecal calprotectin measurement

To reduce intra-individual variation, stools were collected in the morningof the day before the endoscopy and were immediately stored at 4°C. The bowel cleansing was started in all patients after stool collection. Patients were instructed to transport the stool

samples in a dedicated container at 4°C. Fecal samples were immediately transferred upon patient arrival to the Clermont-Ferrand hospital Biochemistry Laboratory. Calprotectin was measured using quantitative immunochromatographic test Quantum Blue® High Range [Bühlmann Laboratories AG, Schönenbuch, Switzerland], according to the manufacturer's instructions. Laboratory personnel, who were blinded to the current clinical and endoscopic disease activity of the patients, performed the analyses. The lower and the upper limits of detection were 100 µg/g and 1800 µg/g, respectively. Consequently, all calprotectin levels < 100µg/g and > 1800µg/g were considered as equal to 100 µg/g and 1800 µg/g, respectively.

2.5. Data managing and statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Clermont-Ferrand University Hospital.

REDCap [Research Electronic Data Capture] is a secure, web-based application designed to support data capture for research studies, providing: 1] an intuitive interface for validated data entry; 2] audit trails for tracking data manipulation and export procedures; 3] automated export procedures for seamless data downloads to common statistical packages; and 4] procedures for importing data from external sources[26].

Statistical analysis was performed using Stata software [version 13, StataCorp, College Station, TX, US]. The tests were two-sided, with a type I error set at $\alpha = 0.05$. Baseline characteristics were presented as mean [± standard deviation] or median [interquartile range] according to statistical distribution [assumption of normality assessed using the Shapiro–Wilk test] for continuous data and as the number of patients and associated percentages for categorical parameters. Comparisons of patient's characteristics between the independent groups were performed using the chi-square or Fisher's exact tests for categorical variables, and using ANOVA or the Kruskal-Wallis test for quantitative parameters [homoscedasticity verified using the Bartlett test]. Correlation coefficients [Pearson or Spearman, according to statistical distributions] were calculated to study relations between quantitative parameters [calprotectin vs others, for example]. In multivariate situations, linear regression was performed according to univariate results and clinical relevance. Considering the statistical distribution of calprotectin, a log-transformation was proposed to achieve the normality. Results were expressed as regression coefficients with 95% confidence intervals [CIs]. A ROC curve was used to define the best fecal calprotectin threshold to detect superficial or deep ulceration in CD, taking into account the clinical relevance and using two different approaches, ie a usual test [Liu or Youden's tests] or positive likelihood ratio calculation.

3. Results

Population characteristics

IN all, 53 CD patients were included [57% female], with a median age of 31 (interquartile range [IQR] [21–44]) years and a median CD duration of 3.5 [1.0–9.0] years at the inclusion time. Of these, 13 patients [24.5%] presented with pure ileal disease [L1 according to Montreal classification], 12 [22.7%] with colonic disease [L2], and 28 [52.8%] with ileocolonic CD [L3]. The median CDAI and CRP were 198.5 [101–258] and 11.40 [4.20–33.70] mg/l, respectively. Patients' characteristics are shown in Table 1.

3.2. Endoscopic evaluation

All but five ileocolonoscopies [48/53, 90.5%] reached the terminal ileum. Median CDEIS was 3.6 [2.66–6.4]. Endoscopic ulcerations were reported in 40 patients [75.5%]. The median percentage of affected surface was 9.00% [IQR 0.02–24.50]. The affected surface was significantly greater in colonic CD [L2 according to Montreal classification] than in ileal [L1] or ileocolonic [L3] CD [$p = 0.03$] [Table 2]. The median percentage of ulcerated surface was 0.60% [IQR 0.00–6.50]. Endoscopic data are given in Table 2.

3.3. Fecal calprotectin measurements

Median fecal calprotectin level was 1105 µg/g [191–1800] and was not significantly different according to disease location. We found a median fecal calprotectin level of 841 µg/g [265–1800], 1575 µg/g [1032– 800], and 416.5 µg/g [140–1800] in patients with pure ileal CD, colonic CD, and ileocolonic CD, respectively [$p = 0.27$] [Table 3]. The ulceration locations and the presence of stenosis did not impact on the fecal calprotectin values. Fecal calprotectin levels were significantly higher according to ulceration depth, with median calprotectin levels of 867.5 µg/g [273.0–1575.5], 1251.0 µg/g [396.0–1800.0] and 1800.0 µg/g [1019.0–1800.0] in patients presenting with non-ulcerated lesions [including aphthoid erosions], superficial ulcerations, and deep ulcerations, respectively [Table 3].

3.4. Correlations studies

Fecal calprotectin values were correlated with CDEIS [rho = 0.66, $p < 0.001$] [Figure 1]. We observed the same correlation in the

Table 2. Description of baseline endoscopic characteristics.

	n [%]
Crohn's disease endoscopic lesions	
None	9 [21.5]
Stenosis	13 [24.1]
Aphthoid erosions	4 [9.5]
Superficial ulceration	25[59.5]
Deep ulceration	4 [9.5]
Most distal lesions location, *n* [%]	
None	11 [20.7]
Ileum	10 [18.9]
Caecum/right colon	3 [5.7]
Transverse colon	4 [7.5]
Left/ sigmoid colon	7 [13.2]
Rectum	18 [34.0]
Most distal ulcerations location, *n* [%]	
None	15 [28.3]
Ileum	13 [24.6]
Caecum/right colon	4 [7.5]
Transverse colon	3 [5.7]
Left/ sigmoid colon	7 [13.2]
Rectum	11 [20.7]
Overall affected surface, median [IQR]	9.00% [0.02–24.50]
Overall affected surfaces according to disease location	
Ileal [L1 according to Montreal classification]	*0.60%[0.00–10.00]
Colonic [L2]	*23.50%[6.00–43.00]
Ileocolonic [L3]	*8.00%[0.00–24.00]
Overall ulcerated surface, median [IQR]	0.60% [0.00–6.50]
CDEIS, median [IQR]	3.60 [2.66–6.40]

IQR, interquartile range; CDEIS: Crohn's disease Endoscopic Index of Severity.

*Significantly different [$p = 0.03$].

non-operated patients subgroup [rho = 0.70, $p < 0.001$]. Fecal calprotectin values were also correlated with CRP [rho = 0.64, $p < 0.001$] and CDAI [rho = 0.48, $p < 0.001$], but CRP and CDAI were moderately correlated with CDEIS [rho = 0.59, $p < 0.05$ and rho = 0.47, $p < 0.05$, respectively].

Table 3. Univariate analysis of endoscopic factors [qualitative factors] associated with fecal calprotectin levels.

	Fecal calprotectin [µg/g], median [IQR]	*p*-value
Location		
L1	841.0 [265.0–1800.0]	NS
L2	1575.5 [1032.0–1800.0]	
L3	416.5 [140.5–1800.0]	
Lesions type, *n* [%]		
None	100.0 [100.0–145.0]	0.003
Aphthous ulcer	867.5 [273.0–1575.5]	
Superficial ulceration	1251.0 [396.0–1800.0]	
Deep ulceration	1800.0 [1019.0–1800.0]	
Most distal lesions location, *n* [%]		
None	100.0 [100.0–162.0]	NS
Ileum	1570.0 [265.0–1800.0]	
Caecum/right colon	1351.0 [410.0–1800.0]	
Transverse colon	1075.0 [777.5–1554.5]	
Left/ sigmoid colon	1105.0 [191.0–1800.0]	
Rectum	1655.0 [384.0–1800.0]	
Most distal ulcerations location, *n* [%]		
None	162.0 [100.0–1105.0]	NS
Ileum	1800.0 [437.0–1800.0]	
Caecum/right colon	163.5 [129.0–300.5]	
Transverse colon	841.0 [714.0–1309.0]	
Left/ sigmoid colon	1800.0 [238.0–1800.0]	
Rectum	1800.0 [1251.0–1800.0]	

IQR, interquartile range; NS, non-significant.

In univariate analysis, fecal calprotectin level was correlated with the affected surface [surface involved by CD lesions] [rho = 0.65, $p < 0.001$] [Figure 2] as well as with the ulcerated surface [rho = 0.47, $p < 0.001$].

We did not observe any difference regarding the correlation between CDEIS and fecal calprotectin value in disease location subgroups (pure ileal disease [rho= 0.66, $p < 0.001$] vs colonic or ileocolonic CD [rho = 0.67, $p < 0.001$]).

3.5. Multivariate analysis

In the multivariate analysis, the fecal calprotectin level was related to the presence of at least one CD lesion [even non-ulcerated] [$p = 0.04$] and the affected surface [$p = 0.04$] [Table 4]. Moreover, fecal calprotectin level increased with the ulceration depth [$p = 0.03$] [Table 4]. Ulcerated surface and CD location were not associated with fecal calprotectin value.

3.6. ROC curve analysis

Using a ROC curve (area under the curve [95% CI] = 0.795, [0.624–0.966]), we attempted to determine the best fecal calprotectin threshold to detect the presence of superficial or deep ulcerations in CD [Figure 3]. We showed that a cut-off value of 400 /g was the best compromise between sensitivity [0.76] and specificity [0.77] (area under the curve [95% CI] =0.795, [0.624–0.966]) to detect superficial or deep ulcerations, with positive predictive value and negative predictive value of 0.88 and 0.56, respectively [Figure 3]. A cut-off value of 200 µg/g detected superficial or deep ulcerations with sensitivity, specificity, positive predictive value, and negative predictive value of 0.86, 0.70, 0.86, and 0.70, respectively [Figure 3].

4. Discussion

To our knowledge, this study [including multivariate analysis] is the first to attempt to identify endoscopic factors, including each item composing the CDEIS, that could influence fecal calprotectin level in CD.

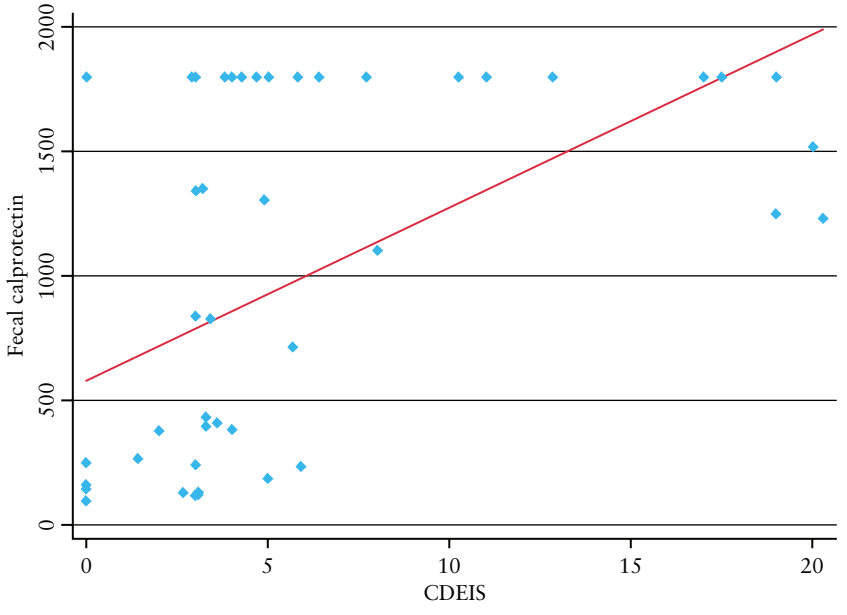


Figure 1. Correlation between fecal calprotectin level and Crohn's disease endoscopic index of severity [CDEIS] in Crohn's disease.

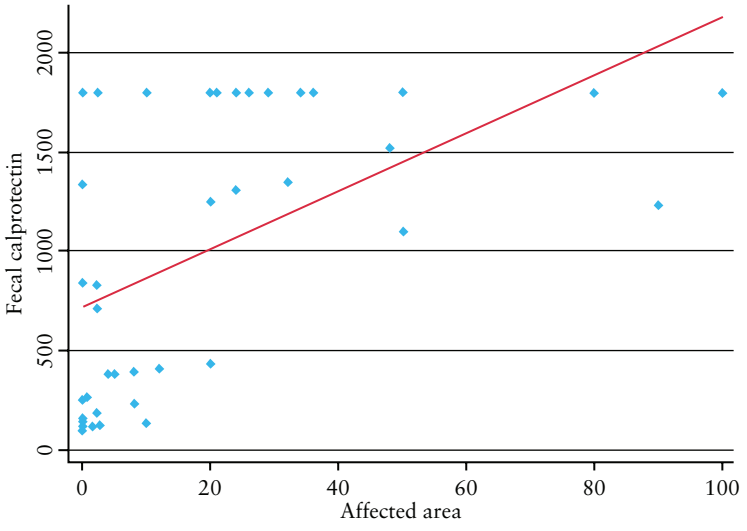


Figure 2. Correlation between fecal calprotectin level and endoscopic affected area in Crohn's disease patients.

Table 4. Multivariate analysis of factors influencing fecal calprotectin in Crohn's disease.

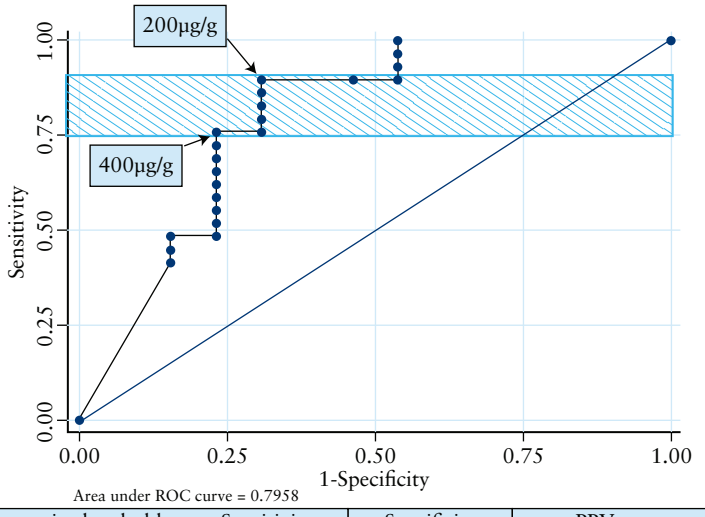
	Regression coefficient	*p*-value	95% confidence interval	
Affected surface	0.0211	0.010	0.0053	0.0369
Ulcerated surface	0.0203	0.897	-0.0296	0.0337
Non-ulcerated lesions	1.1501	0.039	0.0642	2.2360
Superficial ulcerations	1.1237	0.004	0.3823	1.8652
Deep ulcerations	1.2569	0.035	0.0928	2.4209
Crohn's disease location	0.387	0.239	-0.2693	1.0450

Use of fecal calprotectin level to monitor CD activity in daily practice has been widespread since mucosal healing has been considered as the therapeutic target in IBD. However, regarding the curves illustrating the correlation between endoscopic scores and fecal calprotectin level published so far,[11,14,22,23] one can observe that several points highlight conflicting data [ie low endoscopic score with high fecal calprotectin value or high endoscopic score with low fecal value]. Best knowledge of these situations in which fecal calprotectin results might less reliable is a key requirement in daily practice.

In our cohort, the CDEIS was correlated with the fecal calprotectin levels [0.66, $p < 0.001$], which is in line with previous studies[11,14,22,23] reporting correlation coefficients ranging from 0.48 to 0.73 between fecal calprotectin levels and endoscopic scores [CDEIS or SES-CD]. The two main endoscopic scores, CDEIS and SES-CD, depend on the affected area, the ulcerated area, the presence of stenosis, the ulceration size [only for SES-CD], and the ulceration depth [only for CDEIS]. Although the correlation between CDEIS and calprotectin value has been previously demonstrated, we advocate that the lack of reliability of fecal calprotectin in some situations could be linked to the different impact that each item composing the endoscopic scores has on fecal calprotectin level.

In our study, the first point is that the presence of CD lesions, even non-ulcerated, did increase the fecal calprotectin level. In addition, we reported that fecal calprotectin values were significantly associated with ulceration depth, especially in the case of deep ulcerations. Our results complete the data from D'Haens *et al.*[23] suggesting, in a univariate analysis, a correlation between fecal calprotectin levels and the presence of ulcerations larger than 5 mm. Recently the same team confirmed the impact of the ulceration size on fecal calprotectin value [27]. We reported also that the fecal calprotectin value depends on the affected surface but not on the ulcerated surface in multivariate analysis. From a statistical point of view, we hypothesise that the non-significance of the ulcerated surface might be related to the weak variation of this item in our population.

We investigated the role of disease location on fecal calprotectin values. First, we showed that the location of the most distal segment involved [eg right colon vs rectum] did not impact the calprotectin level, confirming that the calprotectin is a very stable protein in the lower gastrointestinal tract, with negligible loss during the ileocolonic course. The question of the reliability of calprotectin measurement in pure ileal CD remains debated. Shoepfer *et al.*[14] reported that ileocolonic CD was associated with significantly higher mean calprotectin level compared with ileal CD, in a univariate analysis. Regarding our multivariate analysis, we consider that this difference is more likely to be linked to the affected surface or the ulceration depth rather than the CD location. They also suggested that fecal calprotectin was less reliable in patients with pure ileal CD as the correlation seemed to be decreased in the subgroup of pure ileal CD compared with the subgroup of ileocolonic CD [0.649 vs 0.795].[14] Other authors reported the same trend.[16,23] Recently, the D'Haens team reported in a smaller cohort [$n = 44$] than ours that fecal calprotectin value was lower in ileal CD compared with colonic or ileocolonic CD, even in case of large ulcerations.[27] However, they did not take into account several potential confounding factors, especially the affected area, as their statistical analysis did not include a multivariate analysis. In our study, fecal calprotectin levels were not different according to CD location, either in the univariate or in the multivariate analysis. Our results are consistent with those published by Jensen *et al.* who found that fecal calprotectin was equally sensitive in colonic and small-bowel CD.[15] As suggested by this present study, we believe that the supposed decreased accuracy of fecal calprotectin in ileal CD could be related to the impact of the affected surface. In addition, the accuracy of endoscopic scores to assess pure ileal CD is a key point when discussing the performances of calprotectin. Indeed, endoscopic scores are known to underestimate endoscopic severity in pure ileal CD, in particular because a colonoscopy allows only few centimetres to be explored.



Fecal calprotectin thresholds	Sensitivity	Specificity	PPV	NPV
≥200µg/g	0.86 [0.68-0.96]	0.69 [0.39-0.91]	0.86 [0.68-0.96]	0.69 [0.39-0.91]
≥400µg/g	0.76 [0.53-0.87]	0.77 [0.46-0.95]	0.88 [0.67-0.97]	0.56 [0.31-0.79]

[95% confidence interval]: PPV: positive predictive value: NPV: negative predictive value

Figure 3. Receiver operating curve [ROC] illustrating the performances of fecal calprotectin value to detect the presence of superficial or deep ulcerations in Crohn's disease.

An ongoing issue is the fecal calprotectin cut-off value that should be used in practice to predict mucosal healing or endoscopic remission. Although several trials have defined mucosal healing with different thresholds of CDEIS or SES-CD,[28,29] large trials like ACCENT-1, EXTEND, and SONIC[2,30,31] used 'absence of ulcers' as the main endoscopic endpoint, which seems to be a more consistent marker of lesion severity.[2,30,31] We found that fecal calprotectin ≥ 400 µg/g was the best compromise between sensitivity and sensitivity [using positive likelihood ratio] in detecting the presence of superficial or deep ulcerations, whereas a cut-off value ≥ 200µg/g showed a high sensitivity [0.86]. Calprotectin ≥ 250 µg/g is, to date, the most acceped value to detect significant endoscopic activity defined as presence of ulcerations larger than 5 mm.[23,32] The authors have chosen this point with low sensitivity [= 51.6%] and high specificity [= 82.6%] to avoid performing useless endoscopy in CD patients. Our daily experience and our results led us to consider that between 200 and 400µg/g remained a grey zone where fecal calprotectin value should be interpreted with caution and in which measurements should be repeated, owing to the intra-individual variability due to the time and the technique of stool collection.[8] The stool collection should be performed preferably during the first morning stool to reduce intra-individual variability, and the sample should kept no longer than 3 days before dosage.[17] These cut-off values could be discussed and should be confirmed in other studies. Therefore, we encourage IBD physicians to be cautious in interpreting intermediate calprotectin values in daily practice.

IBD physicians should be aware that the variation of calprotectin value under therapy is probably more informative than the absolute value. In addition, several factors could influence calprotectin values in daily practice, for example bacterial or drug-induced enterocolitis could increase calprotectin level.

Our sample size could be considered as a limitation, although it was large enough to provide widely significant results. Our study has also several strengths such as the prospective design and the use of multivariate analysis, which was not performed in the studies published so far.

In conclusion, fecal calprotectin is an effective surrogate marker of CD activity, which depends on the presence of CD elementary lesions [even non-ulcerated] and the affected surface but not the ulcerated surface or disease location. Moreover, fecal calprotectin increases with ulceration depth, especially in case of deep ulcerations. Although fecal calprotectin is very reliable to detect superficial or deep ulcerations, the best threshold remains a grey zone ranging from 200 to 400 µg/g. These intermediary values warrant repeating measurements before performing morphological examination, to confirm CD activity in daily practice.

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None.

Conflict of Interest

None.

Authors' Contributions

F. Goutorbe: acquisition of data; analysis and interpretation of data; drafting of the manuscript. M. Goutte: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. R. Minet-Quinard: acquisition of data [biochemistry]; analysis and interpretation of data. A-L. Boucher: acquisition of data. B. Pereira: statistical analysis. G. Bommelaer: study concept and design; critical revision of the manuscript for important intellectual content. A Buisson: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; guarantor of the article.

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