ORIGINAL ARTICLE

Rapid fecal calprotectin test for prediction of mucosal inflammation in ulcerative colitis and Crohn disease: a prospective cohort study

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ABSTRACT

INTRODUCTION   Fecal calprotectin (FC) is a well-established biomarker of intestinal inflammation in Crohn disease (CD) and ulcerative colitis (UC). However, standard laboratory methods are time-consuming and not always useful in clinical practice.

OBJECTIVES   We analyzed the efficacy of a rapid bedside FC test to detect disease flares in a hospital setting. We also assessed the influence of disease location on the diagnostic accuracy of FC.

PATIENTS AND METHODS   This prospective study included 140 patients (46 with UC; 94 with CD). FC was measured by an enzyme-linked immunosorbent assay (ELISA) and by the rapid Quantum Blue® test. Endoscopic activity was assessed using the Mayo endoscopic subscore or the Simple Endoscopic Score for Crohn's Disease (SES-CD).

RESULTS   FC levels highly correlated with endoscopic activity in CD (area under the receiver operating characteristic curve [AUC], 0.83) and UC (AUC, 0.80), with the cut-off values of 238.5 μg/g and 499 μg/g, respectively. FC levels increased dynamically even with early signs of inflammation both in CD (SES-CD, 4–10 vs 0 points: 252 vs 100.0 μg/g; P = 0.02) and UC (Mayo subscore, 1 vs 0 points: 323.3 vs 100.0 μg/g; P <0.001). In UC, FC levels were lower in proctitis than in left-sided UC and pancolitis (340.0, 500.0, and 421.5 μg/g, respectively), but the differences were not significant. In CD, lower FC values were observed in isolated small bowel disease.

CONCLUSIONS   FC levels increased dynamically even with mild signs of intestinal inflammation. The rapid Quantum Blue® test presents a potential alternative to the time-consuming ELISA, because its diagnostic accuracy is not influenced by disease location. It may be useful in the hospital setting, providing faster diagnosis and allowing cost reduction by lowering the number of endoscopic procedures.

INTRODUCTION   Inflammatory bowel diseases (IBDs), which include Crohn disease (CD) and ulcerative colitis (UC), are a heterogeneous group of autoimmune disorders characterized by chronic inflammation in the gastrointestinal tract. Their clinical course consists of recurrent episodes of exacerbation and remission. Early detection of inflammation of the intestinal mucosa, before clinical symptoms occur, may help clinicians optimize treatment, thus preventing progressive damage to the gastrointestinal tract.[1,2]

One of the biggest challenges in IBD treatment is to develop new, noninvasive laboratory methods that would be highly sensitive and specific for mucosal inflammation, and that would be faster, easier, and cheaper than standard endoscopic procedures. Fecal calprotectin (FC) is widely used in the clinical setting as the most specific biomarker of intestinal inflammation.[3-5] Calprotectin is a cytosolic protein in neutrophils, excreted into the intestinal lumen by activated cells in inflammatory state.[6]

When making therapeutic decisions in a clinical environment, the time is crucial. An enzyme-linked immunosorbent assay (ELISA) remains the gold standard for the laboratory measurement of FC levels.[3] However, the assay is time-consuming, and recently, rapid semi-

TABLE 1 Characteristics of the study group

Parameter		Crohn disease (n = 94)	Ulcerative colitis (n = 46)
Age, y, mean (SD)		35.3 (13.5)	35.9 (13.6)
Sex (female), n (%)		52 (55.3)	25 (54.3)
CRP, mg/dl		2.4 (0.78–0.85)	2.0 (0.6–8.2)
WBC, $10^3/mm^3$		6.3 (5.0–8.02)	6.40 (5.05–9.95)
Hemoglobin, g/dl		13.0 (11.8–14.1)	12.9 (11.8–14.2)
Hematocrit, %		39.0 (36.6–41.8)	40.3 (36.8–42.4)
AST, UI/ml		19.0 (14.0–25.75)	16.0 (14.0–23.0)
ALT, UI/ml		15.0 (11.0–23.0)	13.0 (10.0–25.0)
Bilirubin, mg/dl		0.42 (0.27–0.64)	0.55 (0.37–0.88)
FC, µg/g		245.5 (100–1053)	490 (165–1014)
CDAI <150, n (%)		34 (36.2)	NA
SES-CD <4, n (%)		16 (28.1)	NA
Disease location (Montreal classification)		L1: 20 (21.3)	E1: 5 (10.8)
		L2: 16 (17.0)	E2: 15 (32.6)
		L3: 52 (55.3)	E3: 26 (56.5)
		L4: 6 (6.4)	–
Partial Mayo score ≤2, n (%)		NA	11 (23.9)
Mayo endoscopic subscore, n (%)	0	NA	9 (21.7)
	1	NA	13 (28.3)
	2	NA	12 (26.1)
	3	NA	11 (23.9)

Data are presented as median (interquartile range) unless otherwise indicated.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; E1, proctitis; E2, left-sided colitis; E3, pancolitis; FC, fecal calprotectin; L1, terminal ileum, with or without cecum involvement; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract, NA, not applicable; SES-CD, Simple Endoscopic Score for Crohn's Disease; WBC, white blood cell

-quantitative bedside tests have been developed that may play an important role especially in the hospital setting, as the results may be obtained already in 40 minutes. It has been proved that these rapid bedside tests highly correlate with ELISA results (87%–90%).[7,8] On the other hand, whether the diagnostic accuracy of FC is equally high with different locations of disease is still being debated.[5,9-12] Therefore, the aim of the current study was to prospectively assess the clinical usefulness of FC measured by a rapid bedside test in the detection of IBD flares. We also analyzed the influence of disease location on the accuracy of the biomarker.

PATIENTS AND METHODS A total of 140 patients with IBD, hospitalized in the Department of Gastroenterology with the Inflammatory Bowel Disease Subdivision at the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland, were prospectively enrolled in the study between 2013 and 2015. The exclusion criteria were as follows: the presence of *Clostridium difficile* infection, prior abdominal surgery, celiac disease or other concomitant autoimmune diseases, and disease duration of less than 6 months. Altogether, 94 patients with CD and

46 patients with UC were included in the study. The study design was approved by a local institutional review board.

The characteristics of the study group are presented in TABLE 1. All patients underwent a comprehensive diagnostic workup to maximize the homogeneity of the analyzed group. The laboratory panel consisted of full blood count, C-reactive protein, alanine transaminase, aspartate transaminase, γ-glutamyl transpeptidase, alkaline phosphatase (to exclude potential primary sclerotizing cholangitis), and antitissue transglutaminase antibodies with total immunoglobulin A count (to exclude celiac disease). Prior to endoscopic procedures, each patient provided a stool sample. In every sample, stool culture, glutamate dehydrogenase with *Clostridium difficile* toxin A/B and *Giardia lamblia* antigen tests were performed. FC levels were estimated within 48 hours with the Quantum Blue® Calprotectin High Range Test (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland). In the first 40 patients enrolled in the study, the gold-standard ELISA test was also performed (BÜHLMANN fCAL® ELISA). The range of FC values measurable by the semiquantitative Quantum Blue test ranged from 100 µg/g to 1800 µg/g (per gram of stool). Clinical disease activity was assessed using the Crohn's Disease Activity Index (CDAI) and the partial Mayo score.

In all 46 patients with UC and in 57 of 94 patients with CD, ileocolonoscopy was performed by a gastroenterology specialist. To assess the location of the disease, additional gastroduodenoscopy, abdominal ultrasound, or computed tomography with enteroclysis were performed in patients with CD. Both the location and extent of the disease were established in accordance with the Montreal classification.[13] Endoscopic activity of UC was graded in accordance with the Mayo score.[14] In patients with CD, endoscopic disease activity was assessed using the 4-grade scoring system: Simple Endoscopic Score for Crohn's Disease (SES-CD).[15]

Statistical analysis was performed using GraphPad Prism version 6.0 (GraphPad Software, Inc. La Jolla, California, United States). The results are expressed as the mean with SD or median with interquartile range (IQR), depending on the distribution. Variable distributions were tested with the Shapiro–Wilk test of normality. Bivariate correlations were assessed with the Pearson's or Spearman's test, as appropriate. To compare clinical indices between the 2 groups, the *t* test was used, and if the normality test failed, the exact Mann–Whitney test was performed. A 2-tailed *P* value of less than 0.05 was considered statistically significant. To assess diagnostic accuracy of FC in disease flare detection, the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were computed.

RESULTS A total of 140 patients with IBD were included in the study (64 men and 76 women;

FIGURE 1 Validation of the Quantum Blue® (QB) method with gold-standard enzyme-linked immunosorbent assay (ELISA) revealed no significant difference, with only 13.2% of the fecal calprotectin (FC) values being inconsistent (Wilcoxon signed rank test, P <0.001).
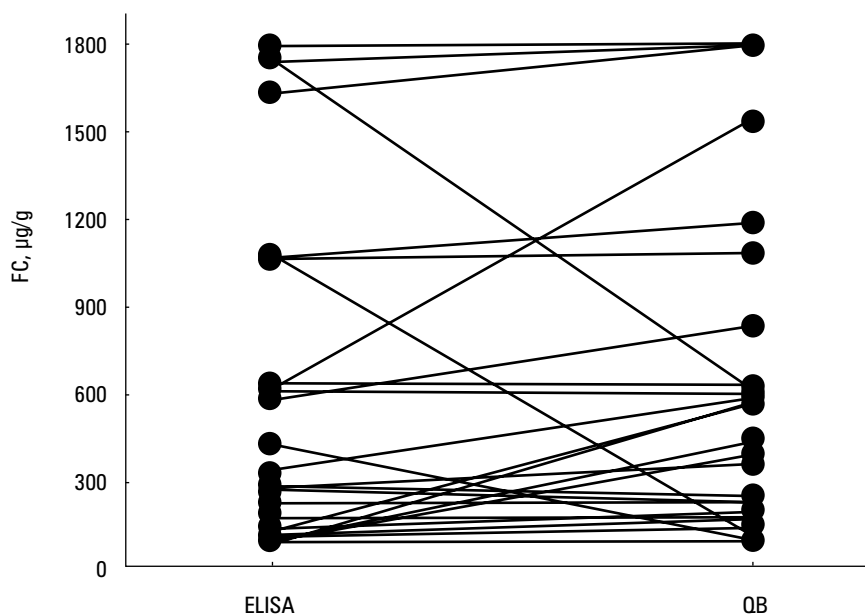
mean [SD] age, 36 [14] years). In 40 patients, a validation of the Quantum Blue method with the gold-standard ELISA was performed, revealing no significant difference, with only 13.2% of the values being inconsistent (Wilcoxon signed rank test, P <0.001; **FIGURE 1**).

In both subgroups, FC levels highly correlated with the endoscopic indices. In UC, median FC levels increased dynamically in the presence of a disease flare (**FIGURE 2A**). In patients with active

mucosal inflammation, median FC levels were 6-fold higher than in cases of full endoscopic remission (611.2 µg/g [IQR, 201–1301 µg/g] vs 100.0 µg/g [IQR, 100–454 µg/g], respectively; P <0.001). Even in cases of mild endoscopic disease activity (Mayo score 1), FC levels were 3-fold higher than the baseline value in comparison with cases of deep endoscopic remission (Mayo score, 0) (323.3 µg/g [IQR, 169–750 µg/g] vs 100.0 µg/g [IQR, 100–454 µg/g], respectively; P <0.001).

A

	Mayo endoscopic score, points			
	0	1	2	3
No. of patients	9	13	12	11
FC level, µg/g				
Minimum	100	100	100	316
25th percentile	100	169	111	500
Median	100	323	611	1119
75th percentile	454	750	1202	1800
Maximum	1083	1800	1800	1800

B

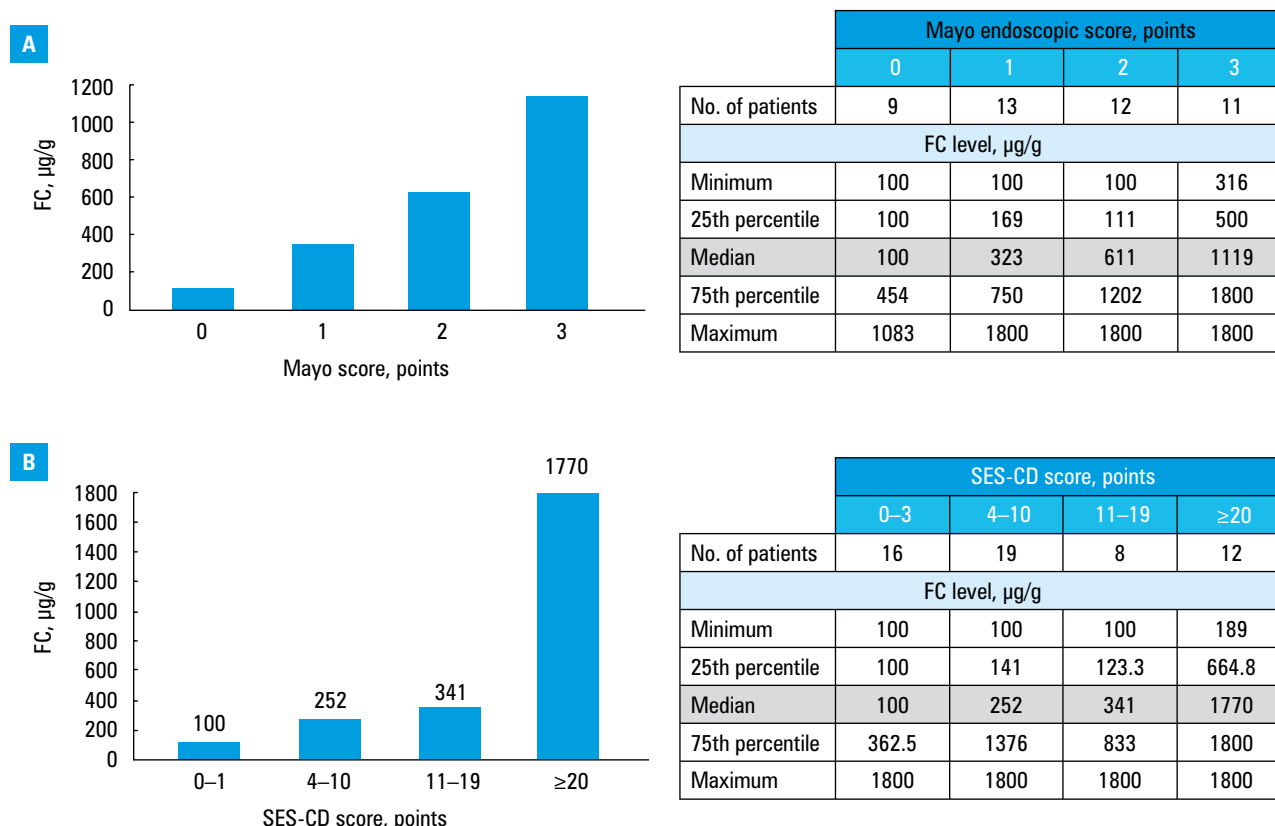|	SES-CD score, points			
	0–3	4–10	11–19	≥20
No. of patients	16	19	8	12
FC level, µg/g				
Minimum	100	100	100	189
25th percentile	100	141	123.3	664.8
Median	100	252	341	1770
75th percentile	362.5	1376	833	1800
Maximum	1800	1800	1800	1800

FIGURE 2 Median fecal calprotectin (FC) levels in patients with ulcerative colitis (**A**) and Crohn disease (**B**) depending on endoscopic activity score
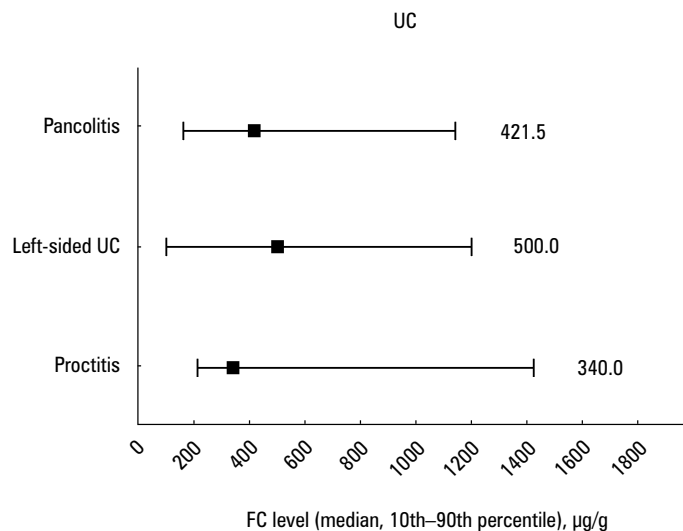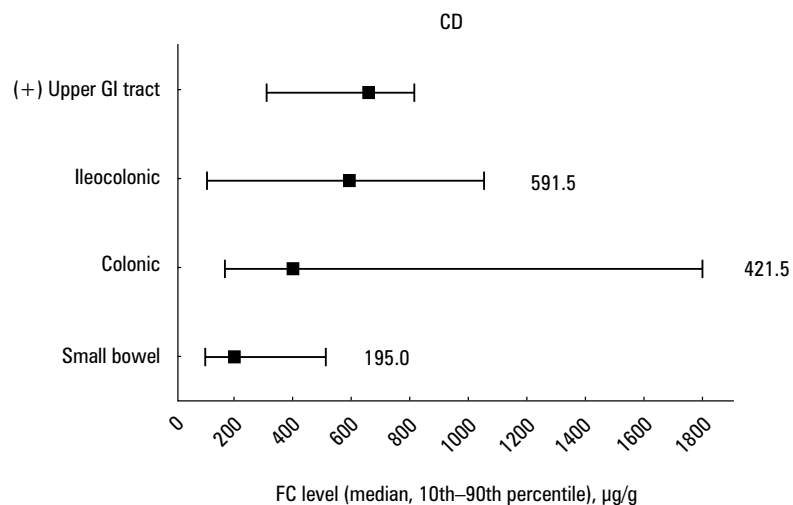
A

UC

Pancolitis   421.5

Left-sided UC   500.0

Proctitis   340.0

FC level (median, 10th–90th percentile), µg/g

B

CD

(+) Upper GI tract

Ileocolonic   591.5

Colonic   421.5

Small bowel   195.0

FC level (median, 10th–90th percentile), µg/g

FIGURE 3 Median fecal calprotectin (FC) level depending on disease location according to the Montreal classification; **A** – in patients with ulcerative colitis (UC), no significant difference was found between disease subtypes (Mann––Whitney test: E1 vs E2, $P = 0.98$; E2 vs E3, $P = 0.94$; E1 vs E3, $P = 0.70$). **B** – in patients with Crohn disease (CD), no significant difference was found between disease subtypes according to the Montreal classification (Mann–Whitney test: L1 vs L2, $P = 0.13$; L1 vs L3, $P = 0.08$; L1 vs L4, $P = 0.15$; L2 vs L3, $P = 0.83$; L2 vs L4, $P = 0.96$; L3 vs L4, $P = 0.93$). For explanation of E1–E3 and L1–L4, see **TABLE 1**. Abbreviations: GI, gastrointestinal

A similar relationship was found in patients with CD (**FIGURE 2B**). In the presence of mild endoscopic signs of disease flare (SES-CD, 4–10 points), median FC levels significantly increased when compared with remission period (252.1 and 100.0 µg/g, respectively; $P = 0.02$). In cases of active mucosal inflammation, the median FC level was 6-fold higher compared with full endoscopic remission (643.0 µg/g [IQR, 189–1800] vs 100.0 µg/g [IQR, 100–362.5 µg/g], respectively; $P <0.001$). Moreover, endoscopy revealed active lesions in half of the patients in complete clinical remission defined by the CDAI and partial Mayo score: 66.7% and 47.1% in patients with UC and CD, respectively.

In the ROC curve analysis, the calculated cut-off value for FC for the detection of active luminal CD was 238.5 µg/g, with high specificity and sensitivity (88.89% and 70.0%, respectively), and an AUC of 0.831. For UC, the cut-off value was higher: 499.0 µg/g, with a specificity and sensitivity of 88.89% and 60.0%, respectively, and an AUC of 0.80.

No association was found between C-reactive protein, white blood cell count, and clinical activity indices with endoscopic scores.

The extent of inflammation and its location in the gastrointestinal tract did not affect the final FC concentrations in any of the subgroups

(**FIGURE 3**). In UC, the median FC value was lower in patients with disease limited to the rectum (E1) than in left-sided colitis (E2) and pancolitis (E3), but the difference did not reach significance (340.0, 500.0, and 421.5 μg/g, respectively). In CD, a trend was observed towards lower median FC levels in small bowel disease (Montreal classification, L1) compared to extensive small and large bowel involvement (L3) (195.0 μg/g [IQR, 100–511.3 μg/g]) vs 591.5 μg/g [IQR, 105.5–1053 μg/g]), but the difference was not significant.

DISCUSSION One of the greatest challenges in IBD treatment is to develop more precise and less invasive diagnostic tests that could be useful in disease monitoring. Early detection of a disease flare can help optimize IBD care.[1,2] FC has already been adapted in clinical practice in Western Europe as a surrogate marker for intestinal inflammation. It highly correlates with endoscopic scores of activity,[5,16-20] and from an economic point of view, it is cheaper, faster, and more patient-friendly than the standard endoscopic procedures. This biomarker may be adapted in biological therapy monitoring, which is nowadays commonly used in IBD care in Poland.[21-23] It has been shown that FC elevation predicts short-term relapse after discontinuation of antitumor necrosis factor-α therapy in patients with IBD in deep remission.[24] Moreover, in the POCER study, Wright et al[25] found that FC elevation predicted early postoperative recurrence in patients with CD.

In clinical practice, timing is crucial when making therapeutic decisions for hospitalized IBD patients. As the gold-standard ELISA test is performed in the laboratory setting after at least several stool samples have been collected, a clinician may have to wait a few days to obtain the results. Recently, alternative rapid semiquantitative tests that can be performed in less than 30 to 40 minutes have been developed. More importantly, testing can be performed by a nurse directly on the ward without special infrastructure.[7,26] This was the rationale for conducting a prospective, clinically oriented study to determine how the rapid bedside FC test may be adapted to hospital settings.

The strength of our analysis is the inclusion of a highly homogeneous group of patients with IBD. By conducting a thorough diagnostic workup, we excluded celiac disease, diverticulosis, colorectal cancer, and gastrointestinal infections (such as *Clostridium difficile* infection and giardiasis), that is, any gastrointestinal disorders that may simulate IBD exacerbation and influence the final results.[27] In addition, the highly homogenous group included more than 130 patients, a notably higher number of patients than in previous publications.

The results of our study confirm the high correlation of the Quantum Blue method with the gold standard, ELISA, which was reported in a large analytical study that showed an agreement of 89.4%.[26] Moreover, the Pearson correlation coefficient (*r* = 0.868) that we observed is comparable to the results reported by Lobatón et al,[8] which included 115 ileocolonoscopies of patients with CD in clinical remission (*r* = 0.879, *P* <0.0001).[8]

The most clinically significant conclusion that we can draw from our analysis is that FC levels increase dynamically even in the presence of the mildest signs of endoscopic activity (**FIGURE 2**). While the FC level remains below 100 μg/g in full endoscopic remission in UC, its value triples (323 μg/g) even with the mildest endoscopic activity (Mayo score 1). Similarly, in CD, in the presence of mild mucosal inflammation (SES-CD, 4–10 points), the FC level rises to 252 μg/g. A relatively high specificity for the Qunatum Blue test is therefore crucial. This rapid bedside test can facilitate clinical decisions on hospital admission, such as deciding whether the IBD treatment should be intensified. Similarly, in the ambulatory setting, it is crucial when determining whether a patient should undergo endoscopy or not. On the other hand, as the ultimate goal of IBD treatment is to achieve full mucosal healing, the FC test may become an easy and practical tool to monitor fully asymptomatic patients, 50% of whom have endoscopically detectable disease activity (data not shown).

In previous studies that analyzed the calprotectin cut-off value for the detection of endoscopic flares in CD,[5,11,16,17] the value usually fluctuated between 50 and 250 μg/g, depending on the adapted endoscopic criteria and activity scores (SES-CD, CDEIS [Crohn's Disease Endoscopic Index of Severity]). Our cut-off value of 247 μg/g is towards the upper limit of this range, possibly because our cohort consisted of hospitalized patients, with some of them admitted for acute flare of CD. In the case of UC, the cut-off value was evidently higher (499 μg/g), which may be due to 2 factors.[18,19] First, the adapted criteria for disease flare included all 3 grades of the Mayo endoscopic score, and the majority of the participants gained 2 or 3 points. This may be because physicians were directing the patients to our department when they suspected a disease flare. Second, the Quantum Blue® method is semiquantitative and does not report results below 100 μg/g, so the final cut-off value may have been overestimated.

In summary, FC levels assessed by the rapid Quantum Blue® test highly correlated with endoscopic activity scores both in UC and CD (AUC, 0.80 in UC; 0.83 in CD), rising significantly even in the presence of minor signs of inflammation. Early detection of IBD flares, even before the occurrence of clinical symptoms, may be a useful tool in everyday practice, allowing a more rapid and accurate optimization of IBD treatment.

The second aim of the study was to evaluate the effect of disease location on FC levels. Data collected in our study showed a definite lack of correlation between the location of active inflammation throughout the gastrointestinal tract and the biomarker level. Nevertheless, FC levels

directly correlated with the intensity of mucosal inflammation.

In patients with UC, we observed slightly lower FC levels in proctitis compared with left-sided UC and pancolitis, but this finding was not significant. FC values highly correlated with the Mayo endoscopic score, rising nearly arithmetically with the severity of inflammation and reaching the upper limit of the Quantum Blue® test at grade 3. Presumably, FC levels increase rapidly both in proctosigmoiditis and extensive colitis, because the main sources of this protein are granulocytes and lymphocytes, which massively infiltrate the bowel wall during active inflammation. These findings partially confirm the results of Ricanek et al,[10] who reported no difference in FC levels between left-sided UC and pancolitis, while showing them to be significantly lower in proctitis.

Similarly, in CD, no significant difference was found with regards to disease location. Nevertheless, we did observe a trend towards higher FC levels in patients with ileocecal disease. Unfortunately, we could not include the L4 localization (upper gastrointestinal tract) in the statistical analysis owing to the low number of patients (n = 6). Previous publications in the field do not clearly answer the question as to whether FC can predict mucosal inflammation equally in different locations of CD. As CD can affect any segment of the digestive tract from the mouth to the anus, assessment of the location becomes more complex, and methods vary across studies. Sipponen et al[11] showed a higher FC level in colonic than in isolated small bowel disease in 77 patients with CD. Similarly, Schoepfer et al[5] suggested that FC was less reliable in patients with pure ileal CD, because the Spearman's rank correlation coefficient for endoscopic activity was lower than for colonic disease ($r = 0.65$ vs $r = 0.8$). Jensen et al[12] also included capsule endoscopy in their location assessment, showing equal accuracy of FC in the prediction of active disease in both isolated small bowel and colonic disease in 118 patients with CD. Our analysis confirms the results of a recent study by Goutorbe et al[9] on the utility of FC in the assessment of CD activity, as the authors also did not show any relationship between disease location and FC levels using the same Quantum Blue® method.

The most important conclusion we can draw from this subanalysis is an extremely practical aspect of FC measurement in CD monitoring, especially in isolated small bowel disease. Given its high diagnostic accuracy and low cost, this noninvasive test should also be implemented in routine ambulatory practice in Poland, where access to specialist imaging methods such as computed tomography or magnetic resonance imaging enterography is very limited.

In summary, the rapid bedside FC test is an adequate and effective alternative to the time-consuming ELISA method. FC levels increase rapidly even in the presence of the mildest signs of inflammation both in UC and CD. Moreover, this test may be considered an alternative to colonoscopy because of its high correlation with endoscopic activity scores. The rapid bedside FC test may play an important role both in the hospital and outpatient settings when it is crucial to promptly institute proper clinical treatment. This noninvasive diagnostic tool should be implemented in everyday clinical practice, because earlier detection of disease flares may help optimize the care of patients with IBDs.

REFERENCES

1 Froslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007; 133: 412-422.

2 Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010; 138: 463-468.

3 Sands BE. Biomarkers of inflammation in inflammatory bowel disease. Gastroenterology. 2015; 149: 1275-1285.

4 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: 2218-2224.

5 Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol. 2010; 105: 162-169.

6 Roseth AG, Fagerhol MK, Aadland E, et al. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol. 1992; 27: 793-798.

7 Wassell J, Wallage M, Brewer E. Evaluation of the Quantum Blue(R) rapid test for faecal calprotectin. Ann Clin Biochem. 2012; 49: 55-58.

8 Lobatón T, López-García A, Rodríguez-Moranta F. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. J Crohns Colitis. 2013; 7: 641-651.

9 Goutorbe F, Goutte M, Minet-Quinard R. Endoscopic factors influencing fecal calprotectin value in Crohn's Disease. J Crohns Colitis. 2015; 9: 1113-1119.

10 Ricanek P, Brackmann S, Perminow G, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. Scand J Gastroenterol. 2011; 46: 1081-1091.

11 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: 40-46.

12 Jensen MD, Kjeldsen J, Nathan T. Fecal calprotectin is equally sensitive in Crohn's disease affecting the small bowel and colon. Scand J Gastroenterol. 2011; 46: 694-700.

13 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005; 19: 5-36.

14 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987; 26: 1625-1629.

15 Daperno M, D'Haens G, van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004; 60: 505-512.

16 Eder P, Stawczyk-Eder K, Lykowska-Szuber L, et al. Association between disease duration and usefulness of fecal calprotectin measurement in patients with Crohn's disease. Pol Arch Med Wewn. 2014; 124: 51-57.

17 Moniuszko A, Wisniewska A, Rydzewska G. Biomarkers in management of inflammatory bowel disease. Prz Gastroenterol. 2013; 8: 275-283.

18 Schoepfer AM, Beglinger C, Straumann A, et al. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. Inflamm Bowel Dis. 2009; 15: 1851-1858.

19 Aomatsu T, Yoden A, Matsumoto K, et al. Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. Dig Dis Sci. 2011; 56: 2372-2377.

20 Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflamm Bowel Dis. 2013; 19: 332-341.

21 Eder P, Linke K, Witowski J. Update on the mechanisms of action of anti-TNF-α antibodies and their clinical implications in inflammatory bowel disease. Pol Arch Med Wewn. 2016; 126: 772-780.

22 Lykowska-Szuber L, Klimczak K, Eder P, et al. Diagnostic importance of faecal markers in long-term monitoring of anti-TNF-α therapy in primary responders with Crohn's disease. Gastroenterology Rev. 2016; 11: 232-238.

23 Szymanska E, Dadalski M, Szymanska S, et al. The impact of induction therapy with three doses of infliximab on deep histological healing in paediatric patients with active Crohn's disease. Gastroenterology Rev. 2016; 11: 176-180.

24 Molander M, Farkilla M, Ristimaki A, et al. Does fecal calprotectin predict short-term relapse after stopping TNFα-blocking agents in inflammatory bowel disease patients in deep remission? J Crohns Colitis. 2015; 9: 33-40.

25 Wright EK, Kamm MA, Cruz P, et al. Cost-effectiveness of Crohn's disease post-operative care. World J Gastroenterol. 2016; 22: 3860-3868.

26 Coorevits L, Baert FJ, Vanpoucke HJ. Faecal calprotectin: comparative study of the Quantum Blue rapid test and an established ELISA method. Clin Chem Lab Med. 2013; 51: 825-831.

27 Summerton CB, Longlands MG, Wiener K, et al. Faecal calprotectin: a marker of inflammation throughout the intestinal tract. Eur J Gastroenterol Hepatol. 2002; 14: 841-845.