Is faecal calprotectin equally useful in all Crohn's disease locations? A prospective, comparative study

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Abstract

Introduction: There are data suggesting that the diagnostic usefulness of faecal calprotectin (FC) may vary depending on the Crohn's disease (CD) location. The aim of the study was to compare the diagnostic usefulness of FC in CD patients with different disease locations.

Material and methods: We prospectively enrolled 120 CD patients in the study. Disease activity was assessed by using Crohn's Disease Activity Index (CDAI), biochemical markers, and endoscopic and radiographic methods. Faecal calprotectin concentration was assessed in single stool samples by using the ELISA method.

Results: Among all patients, 54 (45%) had ileocolonic CD location, 44 (36.5%) had isolated small bowel location, and 22 (18.5%) had colonic CD location. FC correlated significantly with C-reactive protein concentration and endoscopic and radiographic activity among patients with isolated small bowel CD ($p = 0.03$, $r = 0.32$; $p < 0.0001$, $r = 0.78$; $p = 0.03$, $r = 0.35$; respectively) and with C-reactive protein and endoscopic activity in isolated colonic CD ($p = 0.0009$, $r = 0.7$; $p = 0.0002$, $r = 0.78$; respectively). CDAI and inflammatory biochemical markers did not correlate with endoscopic and radiographic assessment in small bowel CD. In patients with ileocolonic CD, FC correlated significantly with endoscopy ($p = 0.006$, $r = 0.5$), radiographic assessment ($p = 0.04$, $r = 0.3$), CDAI ($p = 0.0006$, $r = 0.5$) and the majority of biochemical markers.

Conclusions: Faecal calprotectin is a useful diagnostic marker in all CD patients. Although its usefulness in small bowel CD seems to be the lowest, it should be utilized particularly in this disease location because of the lack of other reliable, non-invasive diagnostic methods.

Key words: inflammatory bowel diseases, disease activity, endoscopy, magnetic resonance enterography.

Introduction

Faecal calprotectin (FC) measurement has become one of the most important novel biochemical methods in diagnosing and monitoring inflammatory bowel diseases (IBD) in recent years [1]. The diagnostic usefulness of FC has been proven in several studies. It can be helpful in differentiating functional from organic bowel disorders [2–4]. Thus it can

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serve as a screening method for patients who will need further invasive investigations. In patients with already diagnosed IBD, FC is a good method for monitoring the activity of the disease [1, 5, 6].

Crohn's disease (CD) is a chronic inflammatory disorder that can occur in any section of the gastrointestinal tract. Sipponen *et al.* showed that FC correlates better with CD endoscopic activity assessed by using the Simple Endoscopic Score for Crohn's Disease (SES-CD) and Crohn's Disease Endoscopic Index of Severity (CDEIS), than with C-reactive protein or the Crohn's Disease Activity Index (CDAI) [7–9]. Tibble *et al.* and Gisbert *et al.* suggested that FC is a reliable marker in predicting relapse of CD in patients who are in clinical remission [10, 11]. Others use FC in CD to predict endoscopic recurrence of inflammatory lesions after surgery [12].

In spite of the many advantages of this non-invasive diagnostic method, it may also have some faults. Crohn's disease is a very heterogeneous disorder in terms of disease phenotypes and the location of inflammatory lesions. In 40–50% of patients, CD occurs both in the small as well as the large intestine, with the ileocaecal location being the most common. In up to 30% of patients, inflammatory lesions are limited to the small intestine and in 20% of patients to the large intestine [13, 14]. Crohn's disease location in the stomach, oesophagus or oral cavity is rare. In the vast majority of studies on the usefulness of FC in CD, all the patients were analyzed together irrespective of disease location [5–12]. However, in studies carried out on small groups of patients, it was hypothesized that the diagnostic utility of FC in small bowel CD is much smaller or even questionable [8, 15]. Up till now a dedicated analysis concerning the usefulness of FC measurement in different disease locations in CD has not been performed. Such a comparative analysis would be essential in order to verify the reliability of FC in estimating CD activity, taking into account the heterogenicity of the disease location throughout the gastrointestinal tract.

Material and methods

The study group consisted of 120 CD patients. All of them were prospectively enrolled in the study between 2009 and 2012. All patients were hospitalized at the Department of Gastroenterology, Poznan University of Medical Sciences. The inclusion criteria were age ≥ 18 years and need for hospitalization because of CD exacerbation or in order to perform follow-up investigations. All patients had been on stable doses of their CD-related medications for at least 4 weeks while entering the study. The exclusion criteria were the presence of any other gastrointestinal pathology (malignan-

cies, infections, diverticula), any changes in the treatment regimens and/or use of non-steroidal anti-inflammatory drugs within the last 4 weeks before entering the study. Additionally, the use of proton pump inhibitors within the last 7 days before entering the study was not allowed. Patients were also ineligible if they had received biologics for 3 months before enrolment.

Informed consent was obtained from each patient before entering the study. Clinical activity was assessed by calculating the CDAI [16]. Each patient underwent magnetic resonance enterography (MRE). The CD activity in the small bowel was estimated by using the Simple Enterographic Activity Score for Crohn's Disease (SEAS-CD), which was assessed by an independent radiologist who was blinded to FC results and had more than 10 years experience in this imaging method. The SEAS-CD was formulated in our institution, and the usefulness of this score in determining the activity of CD was validated in an independent CD patient group by comparing it with endoscopic assessment, which was considered a diagnostic "gold standard" (Table I) [17]. Endoscopic CD activity was assessed by experienced endoscopists blinded to FC results (KL, IKK, LLS) in an ileocolonoscopic study by using SES-CD [18]. Biochemical inflammatory markers were also measured. Each patient also provided a single stool sample before undergoing MRE or ileocolonoscopy, which was used for the assessment of FC concentration by using the ELISA Immundiagnostik PhiCal Kit in accordance with the manufacturer's guidelines.

The following diagnostic "gold standards" for the assessment of CD activity in different CD locations were defined:
– in patients with isolated colonic CD – colonic SES-CD;
– in patients with isolated small bowel CD – SEAS-CD and ileal SES-CD;
– in patients with small and large intestine CD – SES-CD, SEAS-CD and the Global CD Activity Score (GCDAS) constructed by summing up SEAS-CD (assessing small bowel CD activity) and colonic SES-CD (assessing colonic CD activity).

The study has been approved by the Institutional Review Board at the Poznan University of Medical Sciences (decision no. 141/11).

Statistical analysis

Statistical analysis was performed using Graph Pad Prism Version 4.0. Results were presented as means with standard deviations (SD) or medians with 95% confidence interval (CI). The correlation analysis was performed by calculating Pearson's r or Spearman's rank coefficients depending on whether the data passed the normality test.

Table I. Simple Enterographic Activity Score for Crohn's Disease (SEAS-CD) [17]

MRE feature	Grading scale		
Bowel thickening	< 3 mm: 0 pts	3–7 mm: 1 pt	> 7 mm: 2 pts
Contrast enhancement	None: 0 pts	Homogeneous pattern: 1 pt	Layered pattern: 2 pts
Fat wrapping	None: 0 pts	Present: 1 pt	
Proliferation of mesenteric vasculature	None: 0 pts	< 5 vessels/3 cm^2 of mesenteric fat: 1 pt	≥ 5 vessels/3 cm^2 of mesenteric fat: 2 pts
Mesenteric lymphadenopathy	None: 0 pts	< 10 enlarged lymph nodes: 1 pt	≥ 10 enlarged lymph nodes: 2 pts
Ulcerations	None: 0 pts	At least one ulceration present, not exceeding 1/2 of bowel thickness: 1 pt	At least one ulceration present, exceeding 1/2 of bowel thickness: 2 pts
Stenotic complications	None: 0 pts	Stenosis without pre-stenotic dilatation: 1 pt	At least one stenosis with pre-stenotic dilatation: 2 pts
Intra-abdominal fistulae	None: 0 pts	At least one intra-abdominal fistula present: 5 pts	
Extent of disease in jejunum or ileum	< 30 mm: 1 pt	30–1500 mm: 2 pts	> 1500 mm: 3 pts

Statistical differences were assessed using the Welch test or Student's t test for independent samples in case of normally distributed data or by using the Mann-Whitney test when the data did not follow the normal distribution. A level of p less than 0.0500 was considered statistically significant.

Results

The characteristics of the whole study group and patients with different CD locations are presented in Table II. Among 120 patients, 44 (36.5%) had isolated small bowel disease, 22 (18.5%) had isolated colonic CD, and 54 (45%) patients had small bowel and colonic disease.

Faecal calprotectin concentration was highest among patients with combined small and large bowel involvement. It was higher when compared with both colonic CD (difference statistically not significant) and small bowel CD ($p = 0.0200$). C-reactive protein (CRP) and CDAI were highest among patients with combined small and large bowel involvement, but without statistical significance when compared with other disease locations.

Correlations of FC with defined "gold standards" of the disease activity assessment (SES-CD, SEAS-CD and GCDAS) and CRP are presented in Figures 1–3.

In the case of other biochemical markers (erythrocyte sedimentation rate – ESR, red blood count – RBC, haemoglobin – HGB, haematocrit – HCT, white blood cells – WBC, platelet count – PLT) we found statistically significant correlations between FC and:
– ESR ($p = 0.0400$; $r = 0.3$), PLT ($p = 0.0006$; $r = 0.5$) in ileocolonic CD,
– WBC ($p = 0.0300$; $r = 0.5$) in colonic CD.

None of the aforementioned parameters correlated with FC in patients with isolated small bowel CD.

The CDAI correlated significantly with FC in patients with ileocolonic CD ($p = 0.0006$; $r = 0.5$). We did not find any correlation between CDAI and FC in either small bowel ($p = 0.1600$; $r = 0.2$) or colonic CD ($p = 0.5000$; $r = 0.1$). We also compared FC concentrations in the study groups according to CDAI in order to assess the usefulness of FC in differentiating patients with different disease clinical activity (Table III).

Discussion

Crohn's disease is a heterogeneous disease in terms of the location of inflammatory lesions. In our study group, the proportions of patients with various disease locations accurately reflect the proportions reported in epidemiological studies [14, 19]. About 80% of patients have small bowel involvement, of which 37% have isolated small bowel locations and 45% of patients have inflammatory lesions in both the small and large intestine. About 20% of patients have isolated colonic CD.

Defining "gold diagnostic standards" in Crohn's disease

The most important question that needs to be answered when analyzing the usefulness of various diagnostic methods in CD (such as FC) is the issue of defining diagnostic "gold standards" for the assessment of disease activity that can be applied to a given method. The heterogenicity of CD clinical manifestations does not allow one method to be defined which could objectively reflect the activity of the disease in all cases. Moreover, it

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Table II. Patients' characteristics in the whole study group and in different disease locations

Feature	Whole study group (n = 120)	Patients with isolated small bowel CD (n = 44)	Patients with isolated colonic CD (n = 22)	Patients with small bowel and colonic CD (n = 54)
Age, mean ± SD	33 ±12	33 ±11	34 ±10	31 ±13
Male/female, n (%)	63/57 (52%/48%)	27/17 (61%/39%)	7/15 (32%/68%)	29/25 (54%/46%)
Disease phenotype, n (%):				
Inflammatory	117 (97)	43 (98)	21 (95)	53 (98)
Penetrating	40 (33)	12 (27)	9 (41)	19 (35)
Stricturing	11 (9)	1 (2)	3 (13)	7 (12)
Disease location, n (%):				
Ileal	34 (28.3)	34 (77)	–	–
Jejunal	1 (0.8)	1 (3)	–	–
Jejunal and ileal	9 (7.5)	9 (20)	–	–
Ileocolonic	49 (41)	–	–	49 (91)
Jejunoileocolonic	3 (2.5)	–	–	3 (5)
Jejunocolonic	2 (1.6)	–	–	2 (4)
Colonic	22 (18.3)	–	22 (100)	–
Medications used, n (%)				
Aminosalicylates	111 (92)	40 (91)	22 (100)	49 (91)
Azathioprine	72 (60)	24 (55)	16 (72)	32 (59)
Steroids	54 (45)	16 (36)	12 (56)	26 (48)
Antibiotics	42 (35)	13 (41)	10 (45)	19 (35)
Probiotics	49 (41)	16 (41)	9 (41)	24 (44)
Faecal calprotectin [mg/l]	147.6 ±121.6	114.9 ±77.4	162.2 ±158.9	167.4 ±130.2
Disease duration [years]	5 ±4	5 ±4	7 ±6	5 ±3
C-reactive protein [mg/l]	23.6 ±30.9	17.1 ±19.6	17.5 ±20.6	31.3 ±39.4
ESR [mm/h]	28 ±21	23 ±15	31 ±22	31 ±23
Red blood count [10^6/mm^3]	4.5 ±0.6	4.5 ±0.6	4.5 ±0.5	4.6 ±0.7
Haemoglobin [g/dl]	12.6 ±1.8	12.9 ±1.6	12.9 ±1.5	12.3 ±2.1
Haematocrit [%]	38 ±5	39 ±4	39 ±4	37 ±6
White blood count [10^3/mm^3]	7.8 ±3.4	7.1 ±2.9	8.2 ±3.6	8.2 ±3.6
Platelet count [10^3/mm^3]	359 ±130	356 ±120	323 ±88	376 ±150
CDAI	200 (188–229)	184 (159–221)	217 (152–257)	208 (188–252)
SES-CD	8 (8–12)	–	–	12 (11–18)
Ileal SES-CD	3 (3–5)	3 (2–5)	–	4 (4–6)
Colonic SES-CD	4 (4–7)	–	12 (8–15)	6 (6–10)
SEAS-CD	10 (8–10)	12 (11–15)	–	11 (9–12)
GCDAS	–	–	–	18 (15–20)

ESR – erythrocyte sedimentation rate, CDAI – Crohn's Disease Activity Index, SES-CD – Simple Endoscopic Score for Crohn's Disease, SEAS-CD – Simple Enterographic Activity Score for Crohn's Disease, GCDAS – Global Crohn's Disease Activity Score.
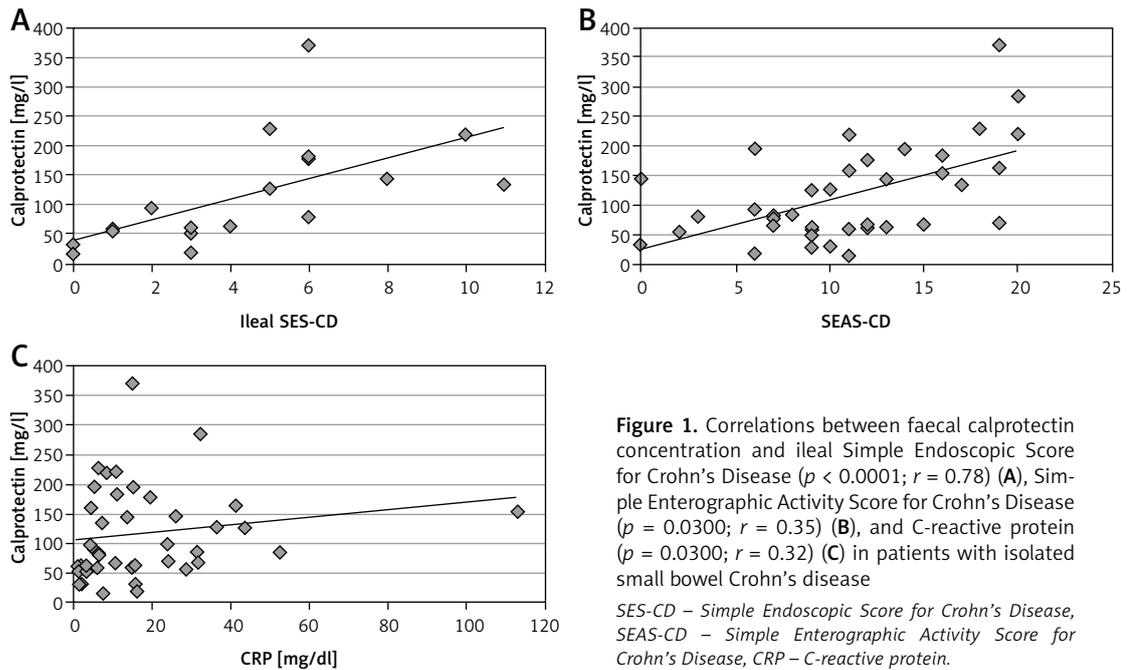
Figure 1. Correlations between faecal calprotectin concentration and ileal Simple Endoscopic Score for Crohn's Disease (*p* < 0.0001; *r* = 0.78) (**A**), Simple Enterographic Activity Score for Crohn's Disease (*p* = 0.0300; *r* = 0.35) (**B**), and C-reactive protein (*p* = 0.0300; *r* = 0.32) (**C**) in patients with isolated small bowel Crohn's disease

SES-CD – Simple Endoscopic Score for Crohn's Disease, SEAS-CD – Simple Enterographic Activity Score for Crohn's Disease, CRP – C-reactive protein.
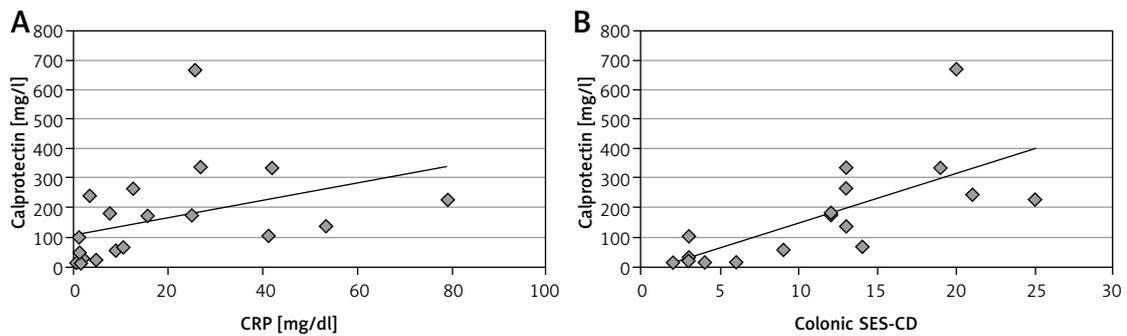

Figure 2. Correlations between faecal calprotectin concentration and C-reactive protein (*p* = 0.0009; *r* = 0.7) (**A**), and colonic Simple Endoscopic Score for Crohn's Disease (*p* = 0.0002; *r* = 0.78) (**B**) in patients with isolated colonic Crohn's disease

SES-CD – Simple Endoscopic Score for Crohn's Disease, CRP – C-reactive protein.

has been shown that for example clinical activity does not always correlate with biochemical markers or endoscopy. That is why it is still questionable whether it is possible to undoubtedly define the "gold diagnostic standards" in CD. However, in several studies performed in recent years, it has been demonstrated that the most sensitive and best diagnostic method from the clinical and prognostic point of view is endoscopy. The mucosal healing effect seen in ileocolonoscopy has a strong positive prognostic value in terms of the need for hospitalization and need for surgical treatment in long-term observation [20–22]. For the same reason also, endoscopic assessment is considered the method of choice in isolated colonic CD. Much more complicated is the assessment of CD activity in combined small and large bowel locations and in isolated small bowel CD. Endoscopy is still the method of choice; however, the ileal intubation rate, even in the best endos-

copy centres, is about 90% [23]. For this reason also, the global assessment of the inflammatory activity is technically not possible in some patients. Another limitation of classical ileocolonoscopy is that it does not allow for the visualization of the proximal part of the ileum and jejunum. The use of other endoscopic techniques is not always possible: capsule endoscopy is contraindicated in patients with bowel strictures, while enteroscopy techniques are not commonly available. That is why the development of imaging techniques such as MRE was crucial in enabling the assessment of CD involvement in the small bowel. Lately, in our institution, a score quantifying the inflammatory activity of CD in the jejunum and ileum has been proposed. This score has been called SEAS-CD, and its usefulness has been proved in a separate analysis comparing SEAS-CD results with endoscopic assessment, which stood for us as a "gold standard" [17]. That
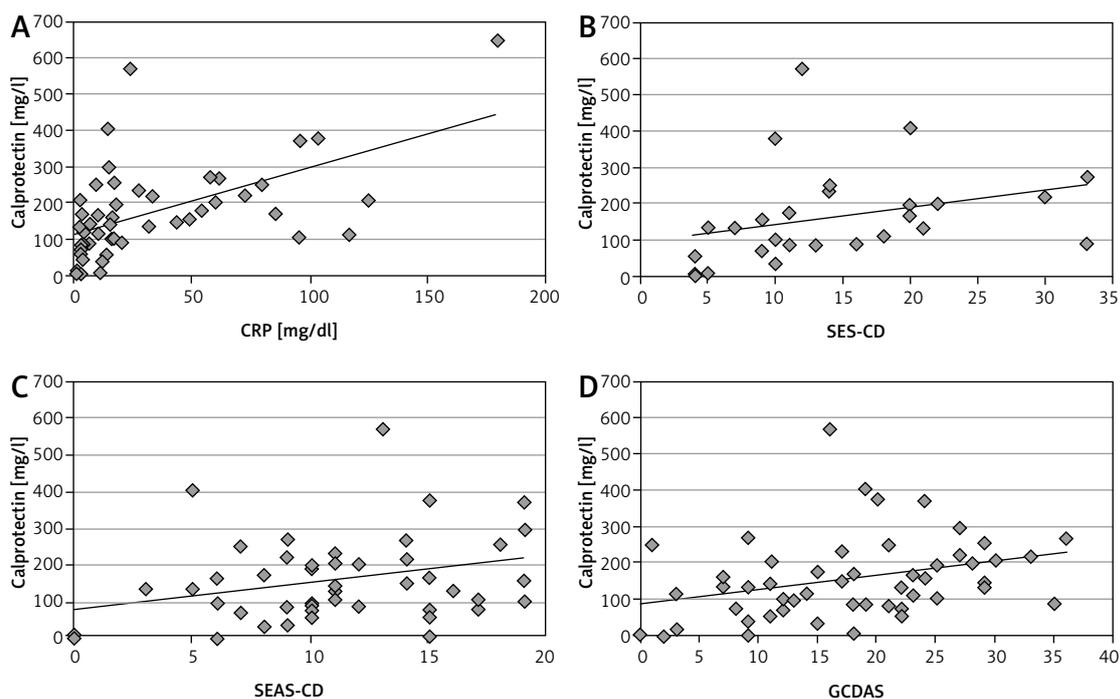
Figure 3. Correlations between faecal calprotectin concentration and C-reactive protein ($p < 0.0001$; $r = 0.62$) (**A**), Simple Endoscopic Score for Crohn's Disease ($p = 0.0060$; $r = 0.5$) (**B**), Simple Enterographic Activity Score for Crohn's Disease ($p = 0.0400$; $r = 0.3$) (**C**), and Global Crohn's Disease Activity Score ($p = 0.0030$; $r = 0.4$) (**D**) in patients with small and large bowel Crohn's disease

SES-CD – Simple Endoscopic Score for Crohn's Disease, SEAS-CD – Simple Enterographic Activity Score for Crohn's Disease, CRP – C-reactive protein, GCDAS – Global Crohn's Disease Activity Score.

Table III. Comparison of faecal calprotectin concentrations in patients in remission of Crohn's disease (Crohn's Disease Activity Index – CDAI < 150 pts), with mild (CDAI 150–219 pts) and moderate CD (CDAI 200–450 pts) clinical activity in different disease locations

Patients with isolated small bowel Crohn's disease			
CDAI	< 150	151–219	220–450
Calprotectin [mg/l]	91.5 ±64.9	139.3 ±100.2	121.2 ±64.3
CDAI < 150 vs. CDAI 150–219 → $p = 0.0700$ CDAI < 150 vs. CDAI 220–450 → $p = 0.2000$ CDAI 150–219 vs. CDAI 220–450 → $p = 0.5000$			
Patients with isolated colonic Crohn's disease			
CDAI	< 150	151–219	220–450
Calprotectin [mg/l]	117.5 ±69.1	118.4 ±110.4	216.3 ±209.8
CDAI < 150 vs. CDAI 150–219 → $p = 0.8000$ CDAI < 150 vs. CDAI 220–450 → $p = 0.2000$ CDAI 150–219 vs. CDAI 220–450 → $p = 0.1000$			
Patients with small bowel and colonic Crohn's disease			
CDAI	< 150	151–219	220–450
Calprotectin [mg/l]	97.6 ±80.1	160.1 ±132.4	212.5 ±140.5
CDAI < 150 vs. CDAI 150–219 → $p = 0.0500$ CDAI < 150 vs. CDAI 220–450 → $p = 0.0030$ CDAI 150–219 vs. CDAI 220–450 → $p = 0.0900$			

is why we decided to choose SEAS-CD, together with ileal SES-CD, as a method of choice in determining CD activity in small bowel CD. In patients with combined small and large bowel locations, we decided to use SEAS-CD and SES-CD. However, the usage of these indices separately can lead to underestimation of CD activity in this subgroup of patients. That is why we created the GCDAS

– a sum of colonic SES-CD (assessment of the colon) and SEAS-CD (assessment of the jejunum and ileum) – for analyzing the whole disease activity, taking into account inflammatory lesions in both the small and the large intestine.

Faecal calprotectin in small bowel Crohn's disease

The diagnostic usefulness of FC in patients with isolated small bowel CD seems to be the most controversial. It is generally believed that FC is a less sensitive method in detecting the inflammatory activity of CD in this subgroup of patients [8]. However, we still do not have enough studies to analyze this important clinical problem. Small bowel CD is the less characteristic in terms of symptoms, which are very often limited to mild or moderate severity. Small bowel CD is also difficult to diagnose. As mentioned above, endoscopy has limited application, and biochemical markers of inflammatory activity are often not elevated. That is why it is also difficult to monitor patients with already diagnosed small bowel CD. The only non-invasive and reliable method that can be performed repeatedly, which is MRE, is not generally available, and this investigation is expensive [24]. That is why FC would be an ideal marker for monitoring this group of patients, if its diagnostic usefulness for this disease location were confirmed.

Data from other studies, the number of which is limited, are conflicting. Koulaouzidis *et al.* demonstrated that elevated FC can predict the presence of inflammatory lesions in the small bowel assessed by capsule endoscopy in patients with prior negative bi-directional endoscopy. Moreover, the authors suggest that capsule endoscopy should not be performed in patients with negative bi-directional endoscopy who have a normal FC level [25]. In another study by Koulaouzidis *et al.,* it was found that FC correlated with the Lewis score, but not with the Capsule Endoscopy Crohn's Disease Activity Index in patients with CD who underwent small bowel capsule endoscopy [26]. Jensen *et al.* suggested in their paper that FC was equally sensitive in the detection of inflammatory lesions in patients with suspected small bowel as well as colonic CD [27]. On the other hand, in a more recent study by Sipponen *et al.,* the usefulness of FC in predicting small bowel CD detected by small bowel capsule endoscopy was estimated to be low. The authors conclude that FC cannot be used for screening or excluding small bowel CD [15].

However, the majority of aforementioned studies were planned to differentiate patients with CD from those without pathology in the small bowel, and none of them examined the possibility of differentiating the various levels of CD disease activity using FC measurement. To the best of our knowledge, our study is the first study to examine the usefulness of FC in quantifying disease activity in the small intestine in the largest CD patient group. We demonstrated that FC significantly correlated with both "gold standard" methods – endoscopic (ileal SES-CD) and MRE (SEAS-CD) assessment. Furthermore, we found a strong correlation between FC and CRP. On the other hand, we did not observe any correlation between FC and other biochemical inflammatory markers of CD, as well as with CDAI. However, further analyses showed that none of the investigated biochemical markers correlated with any of the "gold standard" methods. Moreover, CDAI correlated only with SES-CD and SEAS-CD, but there was no correlation with CRP (data not shown). In conclusion, it should be pointed out that only FC showed a significant correlation with CD activity assessed by SES-CD, SEAS-CD and CRP. Thus one can hypothesize that FC is more accurate in determining small bowel CD activity than other inflammatory biochemical markers and CDAI.

Faecal calprotectin in other Crohn's disease locations

We also found that in the other CD locations, FC correlated significantly with defined "gold standards" of disease activity assessment. Statistical analysis showed that FC reflected more accurately the inflammatory activity of CD in patients with lesions located both in the small and in the large intestine than in patients with isolated small bowel CD. Only in patients with small and large bowel involvement did FC correlate with endoscopic (SES-CD) and radiographic assessment (SEAS-CD), as well as with CDAI and with the largest number of inflammatory biochemical markers (CRP, ESR, and PLT). Additionally, only in this disease location did FC concentration allow for the differentiation of patients in remission from patients with moderate CD clinical activity assessed by CDAI. Thus, one can hypothesize that FC in patients with lesions in both the small and large intestine has the highest diagnostic value in determining CD activity. However, it should be mentioned that the use of CDAI has several limitations [28]. The most important of them is that some CD-unrelated factors can significantly influence the final CDAI result. For example, in a study carried out by Lahiff *et al.,* it was found that CDAI could be similarly elevated in patient with irritable bowel syndrome as in CD patients [29]. Also, symptoms of CD may vary in different disease locations. In colonic CD, the most common symptom is diarrhoea, very often accompanied by perianal complications. In ileocolonic location, abdominal pain and tenderness in the right lower abdomen are the most characteristic. Small bowel CD is very difficult to diagnose

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because symptoms can be very mild and/or less typical [14]. In our study, the highest CDAI scores (as well as the highest FC and CRP concentrations) were observed in ileocolonic CD patients, and the lowest among patients with isolated small bowel CD location. Therefore it seems that the heterogenicity of CD clinical manifestations may influence the final result of the CDAI scoring. One can also hypothesize that CDAI is most useful in the assessment of disease activity in patients with both small and large bowel CD locations. It is probably necessary to modify the CDAI score in the future and complement it with some more objective parameters, such as FC or CRP.

In conclusion, our study revealed that FC was an accurate tool in determining CD activity regardless of the disease location. However, comparative statistical analysis showed that FC was most useful in patients with combined small and large bowel CD. At the same time, the diagnostic usefulness of FC was lowest in isolated small bowel locations. Moreover, it was found that the significance of the correlation between FC and the global CD activity assessed by GCDAS in patients with small and large bowel disease location was lower than between FC and SES-CD. These results confirm that the accuracy of FC in reflecting the inflammatory activity of CD diminishes together with the "proximalization" of the disease location. Nevertheless, it should be emphasized that small bowel CD is the most difficult form of CD from the diagnostic point of view. Laboratory markers and CDAI can underestimate CD activity; a full endoscopic assessment is an invasive method and technically not always possible, and radiographic methods such as MRE are expensive and are not always accessible. That is why it seems that FC should particularly be used in small bowel CD in order to broaden the diagnostic possibilities in this CD location.

In summary, it should be pointed out once again that CD is difficult to diagnose and to monitor [30]. Several diagnostic methods (endoscopy, radiographic methods, laboratory markers, FC) have their limitations depending first of all on the CD location and disease extent, and they are not always useful when used separately. One can hypothesize that constructing an index, consisting of several parameters (including FC) assessed together, can lead to a better and more objective CD activity assessment.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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