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Faecal calprotectin – a useful tool in the management of inflammatory bowel disease

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Summary

Inflammatory bowel disease (IBD) should be suspected in any patient presenting with chronic or recurrent abdominal pain and diarrhoea. Current guidelines suggest performing invasive endoscopy with histological sampling for further diagnosis. Measuring calprotectin, a neutrophilic protein, in faeces has been proposed as a surrogate marker of intestinal inflammation. Calprotectin values have been shown to reliably differentiate between IBD and non-organic disease in symptomatic patients and, when elevated, warrant early endoscopic investigation to rule out IBD and other organic pathologies.

Endoscopy with histological sampling is also used to evaluate disease activity and here, too, faecal calprotectin values seem to correlate well. In a number of studies, faecal calprotectin values have consistently shown to better assess mucosal inflammation than clinical indices and serum markers. Calprotectin's advantage of non-invasive monitoring of disease activity is especially beneficial when considering the dynamics of repeated measurements.

Mucosal healing (MH) has been associated with sustained clinical remission, reduced rates of hospitalisation and of surgical resection, both in Crohn's disease and ulcerative colitis patients. Elevated faecal calprotectin levels in patients in clinical remission are associated with increased risk of disease relapse within 12 months follow-up. In most clinically quiescent IBD, residual mucosal inflammation is still present; it appears that faecal calprotectin can detect subclinical mucosal inflammation and thus might identify patients at risk for relapse.

In summary, measuring faecal calprotectin can be highly useful in the diagnosis and disease management of patients with IBD and could help predict disease course.

Key words: *inflammatory bowel disease; Crohn's disease; ulcerative colitis; faecal calprotectin; mucosal healing*

Introduction

Inflammatory bowel disease (IBD) is a life-long disorder that includes two major forms of chronic intestinal inflammation: Ulcerative colitis (UC) and Crohn's disease (CD) (table 1). The aetiology of IBD is not yet fully understood, but the disorder seems to arise from interactions between genetic and environmental factors [1–4]. IBD is more prevalent in developed countries, affecting approximately 1–2 per 1000 people, and its incidence is increasing both in adults and children [5–7]. UC occurs more frequently in men aged 30–40 years, whereas CD is most often seen in women between 20–30 years. Paediatric IBD accounts for 7–20% of all IBD cases and, here, CD seems to be more prevalent [8, 9].

UC and CD both have distinct pathological features. However, the clinical presentation of IBD depends on the disease location and its extent and can thus be inconsistent, showing symptoms that overlap with both disorders. Suspicion should be raised when patients present with chronic or recurrent episodes of abdominal pain and/or diarrhoea. The probability of IBD increases when alarm signs, such as rectal bleeding, fever, anorexia, or anaemia, are reported [10]. A single parameter or laboratory value for diagnosing UC or CD is not yet available; diagnosis is confirmed by clinical evaluation and a combination of biochemical, radiological, endoscopic and histological analysis [11, 12]. A change in diagnosis from UC to CD, or vice versa, occurs in 10% of UC patients and 5% of CD patients [13].

Some 10% of patients have CD of the small bowel and up to 15% may have penetrating lesions (fistulae, phlegmonous disease, or abcesses) at the time of diagnosis [14]. Extraintestinal manifestations in IBD are common and occur in up to 43% of patients [15–18]. However, this might be an over-estimation that arises from high-volume referral centre data. Community studies suggest a lower prevalence of extraintestinal manifestations [17]. Guidelines for the treatment of IBD have been published [19–23].

Diagnostic challenges

The clinical manifestations of IBD are not specific and no pathognomonic sign or symptom exists. In patients with chronic or recurrent abdominal pain and diarrhoea, suspicion of IBD should be raised, and endoscopy with histological sampling should be performed. Nevertheless, selecting patients for endoscopy solely based on symptoms is not reliable, and many patients with suspected IBD will have

negative findings on endoscopy [24]. A substantial portion of patients with negative findings will, suffer from functional gastrointestinal disorders, e.g., irritable bowel syndrome (IBS) (table 1) [25, 26]. Patients with IBS should be promptly identified, as they tend to undergo repeated endoscopies for abdominal complaints that are, in fact, unnecessary. On the other hand, diagnosing IBS using Rome criteria could lead to misdiagnosis. As many as 1/3 of patients with IBD also fulfil Rome criteria for IBS [27]. Although, in general, month-long diagnostic delays in IBD seem to be common, a considerable portion of patients experience long delays (>12 months), especially those with CD [28]. In children, timely diagnosis is of even greater importance as IBD may affect growth and sexual maturation [29].

The evaluation and risk stratification of patients using a simple, non-invasive and inexpensive test would be highly desirable. An ideal marker would be sensitive, thereby reliably detecting intestinal inflammation, yet still afford a good specificity that avoids unnecessary investigations. More than a decade ago, measurement of calprotectin in faeces was proposed as a surrogate marker of intestinal inflammation and has been extensively studied since.

Distinguishing organic disease from non-organic disorders

Several studies have investigated the value of faecal calprotectin in distinguishing organic from non-organic gastrointestinal disease in symptomatic patients [27, 29–43]. In a pioneer study, Tibble et al. measured the faecal calprotectin values of 602 patients with symptoms suggestive of IBS or organic intestinal disease who underwent invasive diagnostic imaging with barium enteroclysis, barium enema and/or colonoscopy [27]. Patients with non-organic disease, mainly IBS, had lower faecal calprotectin than did patients with organic disease, e.g., IBD, small bowel enteropathy, microscopic/collagenous colitis, infectious diarrhoea, diverticular disease, or cancer. The sensitivity and specificity of faecal calprotectin in identifying organic disease was 89% and 79%, respectively, and equally valid to Rome I criteria. In another study, Carroccio et al. investigated 120 patients with chronic diarrhoea [34]. Faecal calprotectin identified organic causes of diarrhoea with a 64% sensitivity and an 80% specificity. False positive results were associated with the use of aspirin or non-steroidal anti-inflammatory drugs while false negative results mainly included patients suffering from coeliac disease. In a recent prospective multicentre study by Meucci et al. including 870 unselected patients referred for colonocscopy, faecal calprotectin had an 89% sensitivity and a 62% specificity in identifying any organic disease. In the 416 patients with abnormal findings, colorectal cancer was found in 34, colorectal polyps in 244 (1 cm in 192, ≥1 cm in 52), inflammatory bowel disease in 102 (43 active UC, 30 UC in remission, 19 active CD, 10 CD in remission), diverticula with peri-diverticular inflammation in 12, ischaemic colitis in 2 patients, and miscellaneous diagnoses in the remaining 24 [42]. In a meta-analysis that included 2475 patients, Gisbert et al. calculated a mean sensitivity and specificity of 83% and 84%, respectively, for faecal calprotectin in distinguishing between organic and non-organic disease [44]. Faecal calprotectin's diagnostic accuracy has been reported as being higher than that of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or a combination of the two [27, 31].

In recent years, several studies have highlighted the importance of faecal calprotectin testing, not only for organic disease of the colon, but also of the small-bowel [45–47] and the upper gastrointestinal tract [43]. In the only study that systematically investigated the use of faecal calprotectin in the upper gastrointestinal tract, its diagnostic accuracy was reported as being highly valuable, though with a slightly lower sensitivity and specificity than for colonic inflammation [43]. In this lively field of research, more data on the diagnostic performance of faecal calprotectin will emerge and further define its role as a non-invasive test for the presence of gastrointestinal tract inflammation.

Key Message

Calprotectin in faeces is a reliable surrogate marker of intestinal inflammation throughout the gastrointestinal tract. It is useful in differentiating between organic and non-organic gastrointestinal disease.

Table 1: Definitions of Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS).

Inflammatory Bowel Disease
Inflammatory bowel disease encompasses a multisystem group of disorders of chronic inflammation with specific clinical and pathological features that primarily affect the gastrointestinal tract. Extraintestinal manifestations include: musculoskeletal (peripheral arthritis, sacroiliitis, ankylosing spondylitis, osteoporosis), dermatological (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis), and ocular (uveitis, scleritis, episcleritis) afflictions, as well as primary sclerosing cholangitis, thromboembolic events, and nephrolithiasis.
Ulcerative colitis (UC) is a chronic inflammatory condition causing continuous mucosal inflammation of the colon, without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterised by a relapsing and remitting course.
Crohn's disease (CD) is characterised by patchy, transmural inflammation, which may affect any part of the gastrointestinal tract. It may be defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by pattern of disease (inflammatory, fistulating, or stricturing).
Indeterminate colitis (IC): Because features of both conditions are present, about 5% of patients with IBD affecting the colon cannot be classified after considering clinical, radiological, endoscopic, and pathological criteria.
Irritable Bowel Syndrome
Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) at least 3 days/month in the last 3 months, with symptom onset at least 6 months before diagnosis, and associated with two or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool
Adapted from current guidelines [11, 12, 137].

Identifying inflammatory bowel disease

Consistently higher faecal calprotectin levels have been reported in both adult and paediatric patients with IBD compared to patients with IBS or healthy controls [27, 29, 31, 32, 34–37, 48–66]. Table 2 summarises all studies that investigated the diagnostic performance of faecal calprotectin in identifying patients with IBD. Tibble et al. first validated calprotectin in faeces as a marker of intestinal inflammation by comparing the faecal excretion of ^{111}indium-labelled leukocytes to faecal calprotectin in 22 patients with CD; they then assessed the sensitivity of faecal calprotectin in detecting established CD in 111 patients [31]. In the same study, they further investigated the diagnostic accuracy of faecal calprotectin in 220 consecutive patients who were referred for assessing whether they had IBD or IBS. Using a cut-off of 30 mg/l, calprotectin had a 100% sensitivity and a 97% specificity in discriminating between CD and IBS. In another study including 148 patients referred for lower gastrointestinal symptoms, Chung-Faye et al. found a slightly lower sensitivity and specificity (80% and 74%, respectively), for faecal calprotectin in identifying IBD [57]. Langhorst et al. assessed faecal levels of calprotectin in 139 (54 IBS, 42 UC, 43 CD) patients undergoing diagnostic ileocolonoscopy [62]. Calprotectin had a high sensitivity and specificity in identifying IBD (81.7% and 83.5, respectively), with a slightly superior diagnostic accuracy for CD (81.4%) compared to UC (78.6%). In a recent meta-analysis, von Roon et al. summarised data from 30 studies that included 5983 patients [27, 31–37, 48–51, 53–55, 67–76, 77]. Faecal calprotectin was higher in IBD patients than in non-IBD patients (by 219 µg/g), and showed excellent pooled sensitivity and specificity rates in distinguishing between these groups (95% and 91%, respectively). Other studies [27, 29] have reported higher faecal calprotectin levels for CD than for UC ($p = 0.04$), but the clinical value of this finding seems questionable as levels varied widely among patients and studies, and no clear-cut distinction between the two disorders were identified.

Most of these studies compared IBD patients with either IBS patients or healthy volunteers, i.e., the extremes of the clinical spectrum. This could overestimate the diagnostic accuracy of the test and impair its usefulness in clinical practice. Van Rheenen et al., in an excellent meta-analysis, compared the diagnostic accuracy of faecal calprotectin in the evaluation of patients with suspected IBD [78]. Thirteen studies summarising data of 1041 patients (670 adults, 371 children) were included [29, 31–33, 37, 56, 60, 61, 63–65, 79, 80]. Studies were selected for their methodological robustness and had to present a paired design where faecal calprotectin values were measured prior to endoscopy. Pooled sensitivity and specificity rates of calprotectin testing were 93% and 96%, respectively. The specificity in children and teenagers was significantly lower (76%). In adults, using faecal calprotectin as a diagnostic test in suspected IBD for deciding upon endoscopy would result in a 67% reduction in patients requiring endoscopy, but would also result in a delayed diagnosis for 6% of patients due to false negative test results.

The diagnostic accuracy of faecal calprotectin for IBD appears to be fairly similar to lactoferrin, another neutrophilic marker measured in faeces [59, 62], and is greatly superior to serum markers, such as CRP, ESR, anti-neutrophil cytoplasmatic antibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA). A number of studies have evaluated ESR and CRP [29, 31, 52] in the diagnosis of IBD and have reported high specificity, both for CRP (78–100%) and ESR (78–100%), though with a markedly lower sensitivity than faecal markers (35–40% and 18–52%, respectively). Schoepfer et al. prospectively compared faecal calprotectin levels with measurement of CRP and IBD antibodies (ANCA, ASCA) in 136 patients [63]. The goal of this study was the non-invasive discrimination between IBD and IBS patients. The overall diagnostic ability of CRP was only moderate (64%) and had a lower sensitivity for UC (52%) than for CD (73%). ANCA and ASCA were highly specific for the presence of IBD, but their diagnostic ability was limited by their low sensitivity. Even when IBD antibody and faecal calprotectin testing were combined, the overall accuracy in distinguishing between IBD and IBS patients improved only minimally.

Key Message
Faecal calprotectin levels are elevated in patients with active IBD. Calprotectin testing shows excellent diagnostic accuracy in patients with suspected IBD.

Monitoring disease activity

As the clinical course of these chronic, remitting and relapsing conditions often changes, the assessment of the severity of IBD and the monitoring of disease activity are important issues, both in CD and UC [81]. Symptoms of colonic inflammation are often unspecific, complicating the evaluation of IBD's clinical activity. A variety of activity indices, such as the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw index, have been developed [82, 83]. These scores use a combination of symptoms, clinical examination results, and laboratory values to quantify IBD activity, but they have two major drawbacks: First, the collection of data is tedious and, second, they depend strongly on subjective patient symptoms. Accordingly, they are used in clinical studies, but rarely in clinical practice. Laboratory values measuring systemic inflammatory parameters (leukocytes, CRP, ESR) to detect IBD show a low sensitivity and specificity and the correlation with symptoms and activity indices is poor [62, 75, 84–89]. Currently, endoscopy with biopsy is still considered the gold standard for the evaluation of mucosal inflammation [11, 12], and a number of scores exist to assess endoscopic activity in CD [90–92] and UC [93–102]. However, endoscopy is invasive, costly, and uncomfortable for patients. To overcome these limitations, a non-invasive marker to monitor activity of intestinal inflammation in IBD patients would be welcome.

In recent years, growing interest in the value of faecal calprotectin for disease monitoring has led to a number of studies investigating its correlation with the degree of IBD activity, as measured by endoscopy (summarised in table 3) and histology [31, 33, 35, 38, 49, 51, 59, 62, 85–89,

103–113]. Langhorst et al. reported faecal calprotectin to be valuable in differentiating between active and inactive IBD, and between IBD and IBS patients [62]. Calprotectin was able to identify active IBD and was superior to CRP and activity indices in detecting endoscopic inflammation. The location of colonic inflammation seems to be irrelevant, though the correlation is better for colonic than for ileal disease activity [49, 108, 109]. In a recent study by Ricanek et al., faecal calprotectin levels correlated highly with endoscopic activity scores in patients with suspected IBD, but correlated inconsistently with clinical activity scores, especially in CD [89]. Schoepfer et al. reported similar results in patients with UC [88]. Using the Rachmilewitz index [99], endoscopic disease activity correlated best with faecal calprotectin (R = 0.834), followed by the Clinical Activity Index (R = 0.672), CRP (R = 0.503), and blood leukocytes (R = 0.461). The overall accuracy for calprotectin in detecting endoscopically active disease was 89%, and was the only marker to discriminate inactive, mild, moderate, and highly active disease. In another study, Sipponen et al. investigated 77 patients with CD who underwent colonoscopy, and compared endoscopic disease activity, as scored by the Crohn's Disease Index of Severity (CDEIS), with a clinical index (CDAI) [109]. Faecal calprotectin correlated well with CDEIS (R = 0.729) and had a 70% sensitivity and a 92% specificity in predicting endoscopically active disease (CDEIS ≥3), whereas the sensitivity of CDAI ≥150 was only 27%, but with a somewhat higher specificity (94%). In general, faecal calprotectin values correlate better with endoscopic findings than with clinical activity. Accordingly, this sensitive marker may detect residual inflammatory activity in patients with presumably quiescent disease [114].

Key Message
Faecal calprotectin levels correlate well with endoscopic and histological disease activity. In CD, the correlation is better for colonic than for ileal disease.

Monitoring response to treatment

The evaluation of treatment response in IBD has been based primarily on symptoms, clinical scores and serum markers of inflammation. Data on the value of faecal calprotectin in this setting have long been scarce [103, 115] and are, only now, becoming evident [110, 116–120]. Wagner et al. investigated 38 (11 CD, 27 UC) patients with active IBD and measured their response to treatment using the Harvey-Bradshaw clinical activity index for CD, and for UC, a semi-quantitative four-grade (normal, mild, moderate and severe) scale to assess endoscopic activity [116]. Patients were treated with 5-aminosalicyclic acid (5-ASA) or various combinations of 5-ASA, prednisone, and azathioprine. None received anti-tumour necrosis factor alpha (TNFα) agents. After 8 weeks, 82% of patients had normal endoscopy and normalisation of calprotectin levels were 100% predictive for complete response to treatment.

The response of CD patients to anti-TNF agents was investigated by Sipponen et al. [110]. In 15 patients from a previously-published cross-sectional study [109] who were considered in need of anti-TNF treatment for acute flare-ups (N = 6), chronic active disease (N = 6) or rapid reccurrence of the disease postoperatively (N = 3), colonoscopy was performed at baseline and 12 weeks after induction treatment with 5 mg/kg intravenous Infliximab (week 0 and week 8) in 14 patients, and 40 mg Adalimumab subcutaneously (week 0, 2, 4, 6, 8) in 1 patient. The endoscopic post-treatment activity (by CDEIS) correlated highly with

Table 2: Diagnostic precision of studies investigating the use of faecal calprotectin in distinguishing inflammatory bowel disease (IBD) from non-IBD.

Author	No. of patients	Patient population	Cut-off value (µg/g)	Sensitivity	Specificity	PPV (%)	NPV (%)
Adult patients							
Tibble, JA [31]	220	CD	30	1.00	0.97	86	100
Limburg, PJ [32]	110	UC/CD	100	0.94	0.83	63	93
Carroccio, A [34]	70	CD	170	1.00	0.95	75	100
Costa, F [35]	239	UC/CD	50	0.81	0.82	88	74
Wassell, J [54]	50	CD	90	0.85	100	100	87
Chung-Faye, G [57]	148	UC/CD	25	0.80	0.74	87	65
Kaiser, T [58]	171	UC/CD	50	0.63	0.86	90	51
D'Incà, R [59]	144	UC/CD	80	0.79	0.74	92	53
Schroder, O [60]	88	UC/CD	15	0.93	1.00	100	91
Schoepfer, AM [61]	74	UC/CD	50	0.83	1.00	100	77
Langhorst, J [62]	139	UC/CD	50	0.82	0.84	89	74
Schoepfer, AM [63]	136	UC/CD	50	0.83	1.00	100	74
Paediatric patients							
Canani, RB [29]	49	UC/CD	95	0.93	0.89	91	91
Fagerberg, UL [37]	36	UC/CD	50	0.95	0.93	95	93
Bunn, SK [51]	68	UC/CD	50	0.65	1.00	100	71
Kolho, KL [56]	57	UC/CD	50	100	0.48	69	100
Sidler, MA [64]	61	UC/CD	50	1.00	0.64	72	100
Ashorn, S [65]	73	UC/CD	100	0.89	0.90	97	67
Diamanti, A [66]	626	UC/CD	160	1.00	0.80	54	100

For each study, the number of included patients (No. of patients) and the type of inflammatory bowel disease (IBD) is given: Ulcerative colitis (UC) or Crohn's Disease (CD), or both (UC/CD). Cut-off values for the following are given to distinguish between IBD and non-IBD: calprotectin, sensitivities, specificities and positive (PPV, %) and negative predictive value (NPV, %).

faecal calprotectin values (R = 0.831). Using 200 µg/g as a cut-off value, calprotectin had an 87% sensitivity and a 100% specificity in predicting endoscopically active disease (CDEIS ≥3). In 90 patients with acute severe ulcerative colitis, Ho et al. studied how well faecal calprotectin could predict those patients requiring colectomy and those who would not respond to corticosteroid or Infliximab treament [118]. Calprotectin levels were higher only in patients requiring colectomy (P = 0.04), but not in corticosteroid (P = 0.08) and Infliximab non-responders (P = 0.06). In two studies involving paediatric patients with UC (N = 24 and N = 128), the Pediatric UC Activity Index (PUCAI), a clinical score, predicted treatment response and long-term outcome more accurately than did faecal calprotectin [119, 120]. However, in these studies by Turner et al., treatment decisions might have been guided by symptoms also assessed by the PUCAI, and it might therefore be difficult for calprotectin to outperform the prognostic value of clinical symptoms. This contrasts with results cited by Langhorst [62] from adult patients where calprotectin better identified active vs inactive IBD than did activity indices.

Key Message
Low faecal calprotectin levels after treatment indicate response of endoscopic disease activity better among adult than paediatric patients.

Establishing mucosal healing

Growing evidence suggests that MH indicates controlled IBD activity with a more favourable course; surprisingly, episodic clinical remission is a poorer marker of clinical outcome [121–125]. Baert et al. showed that, after 2 years of treatment, endoscopic activity of mucosal inflammation in CD could predict the clinical course for the next 2 years [126]. The relapse rate in patients with MH was lower than in patients with residual mucosal inflammation (32% vs 65%, P = 0.004). In 214 patients with CD (31 (14.5%) primary non-responders excluded) receiving anti-TNFα therapy, MH (achieved in 68%) predicted long-term sustained clinical benefit (65% of the 68% achieving MH vs 40% of those who did not, P <0.001 by logrank), reduced the need for major abdominal surgery (14% among those patients with MH vs 38% of those without MH, P <0.001) and hospitalisation (42% with MH vs 59% of those without MH, P = 0.002) during a median of 69 months follow-up [127]. In a large population-based, cohort study with 495 (354 UC, 141 CD) patients who had endoscopy at baseline and after 1 and 5 years, MH was associated with a 60% reduction in surgery among CD patients, and with a lower rate of colectomy among UC patients (2% vs 7%, P = 0.02) [128]. As explained above, faecal calprotectin correlates highly with endoscopic activity of IBD, especially when calprotectin values are normal. Accordingly, it might be considered a surrogate marker of MH. Røseth et al. performed colonoscopies in IBD patients in clinical remission that had normal faecal calprotectin values and found normal mucosal histology, eg, mucosal healing, in 38 of 45 [103]. Similarly, Sipponen et al. showed that faecal calprotectin values normalised in CD patients who achieved endoscopic remission after anti-TNFα treatment [110, 117].

Key Message
Mucosal healing seems to indicate controlled IBD activity. It has been associated with sustained clinical remission as well as reduced rates of hospitalisation and surgical resection. Data on faecal calprotectin as a surrogate marker of MH are emerging, but the evidence is not yet conclusive.

Table 3: Studies investigating the correlation between faecal calprotectin levels and endoscopic IBD activity.

Author	No. of patients/ endoscopies	Patient population	Endoscopic Activity Index	Correlation with calprotectin
Bunn, SK [33]	22/22	UC/CD	Saverymuttu score	0.75
D'Incà, R [59]	46/46	UC	Mayo score	0.51
D'Incà, R [59]	31/31	CD	SES-CD	0.48
Langhorst, J [62]	42/42	UC	Rachmilewitz index	0.49
Langhorst, J [62]	43/43	CD	SES-CD	0.35
Røseth, AG [49]	62/64	UC	Mayo score	0.57
Jones, J [87]	164/164	CD	SES-CD	0.72
Schoepfer, AM [88]	140/140	CD	CDEIS	0.75
Denis, MA [85]	28/28	CD	CDEIS	not significant
Xiang, JY [86]	66/66	UC	Sutherland criteria	0.87
Hanai, H [104]	31/31	UC	Matts' index	0.81
Aomatsu, T [112]	17/17	UC	Matts' index	0.84
Aomatsu, T [112]	18/18	CD	SES-CD	0.76
Langhorst, J [106]	31/31	UC	Rachmilewitz index	0.51
Sipponen, T [108]	61/87	CD	SES-CD	0.64
Fagerberg, UL [107]	39/39	UC/CD	Study score *	0.52
Sipponen, T [109]	77/106	CD	CDEIS	0.73
Schoepfer, AM [111]	134/134	UC	Rachmilewitz index	0.83
Sipponen, T [110]	15/15	CD	CDEIS	0.83

For each study, the number of included patients and the number of endoscopies (No. of patients/endoscopies), the type of inflammatory bowel disease (IBD), the endoscopic activity index (for UC: Mayo score [97], Matts' index [94], Sutherland criteria [98], Saverymuttu score [138], Rachmilewitz index [99]; for CD: Crohn's Disease endoscopic index of severity [CDEIS] [90], simple endoscopic score for Crohn's Disease [SES-CD] [92]), and the correlation coefficient (Spearman's correlation, R) are given. *Colonoscopy scoring system of macroscopic inflammation in 8 colonic segments. Adapted from [139].

Prediction of IBD relapse

The natural course of IBD is typically characterised by recurrent episodes of disease relapse with exacerbated intestinal inflammation and remissions. However, the disease course may vary substantially and include patients suffering from chronic active disease, patients with recurrent episodes of disease relapse, and even patients who remain in remission. Most IBD patients with clinically quiescent disease seem to have some degree of residual mucosal inflammation [129] and elevated faecal calprotectin levels have been detected in patients in clinical remission [114]. Several other studies have shown that values of faecal calprotectin predict relapse in patients with IBD within 12 months (table 4) [68, 74, 114, 130–134]. In a pioneer study, Tibble et al. demonstrated that, among 80 IBD (43 CD, 37 UC) patients in clinical remission, faecal calprotectin levels of patients who experienced clinical relapse (as measured by clinical activity scores) were higher than those who remained in remission [68]. Calprotectin predicted clinical relapse with a 90% sensitivity and an 83% specificity. In a prospective multicentre study, Gisbert et al. included 163 (89 CD, 74 UC) IBD patients in clinical remission [133]. Sixteen patients (9.8%) experienced a clinical relapse within the 12 months follow-up, and faecal calprotectin values at inclusion were higher in those patients with clinical relapse later on (239 µg/g vs 136 µg/g, p <0.001). The risk of relapse was 30% if calprotectin levels were >150 µg/g and 7% if values were <150 µg/g (p <0.001). In a study by Costa et al., median faecal calprotectin levels were higher only in UC patients who relapsed, but not in those with CD. Accordingly, the risk of relapse within 12 months was increased 14-fold in UC patients with faecal calprotectin levels >150 µg/g but only two-fold in CD patients [74]. Results from another study by D'Incà et al. report that median faecal calprotectin levels in CD patients experiencing a clinical relapse within 12 months did not differ from non-relapse patients (P = 0.055) [130]. Only in the subgroup of patients with colonic CD were calprotectin levels significantly different (177 mg/kg vs 75 mg/kg, P = 0.04). Recently, Kallel et al. studied 53 CD patients in clinical remission, specifically excluding patients with small-bowel CD [134]. Within 12 months follow-up, 18% developed clinical relapse. Calprotectin values were higher in the relapse group (381 µg/g vs 155 µg/g, respectively, p <0.001). Using 340 µg/g as the cut-off, faecal calprotectin provided an 80% sensitivity and a 91% specificity in predicting clinical relapse, which corresponded to an 18-fold risk increase.

Key Message

Faecal calprotectin levels <150 µg/g indicate IBD remission with a low risk of relapse. Reports from prospective intervention studies using calprotectin-guided therapy strategies to investigate the long-term outcome of IBD are not yet available.

Discussion

Measurement of faecal calprotectin has been shown to differentiate IBD from IBS. Its high sensitivity and high negative predictive value have proven especially useful in ruling out IBD in undiagnosed, symptomatic patients with abdominal pain or diarrhoea. Unfortunately, the specificity of faecal calprotectin testing in identifying IBD is lower than desirable, as several other organic intestinal disorders can also show increased calprotectin levels. Difficulties in

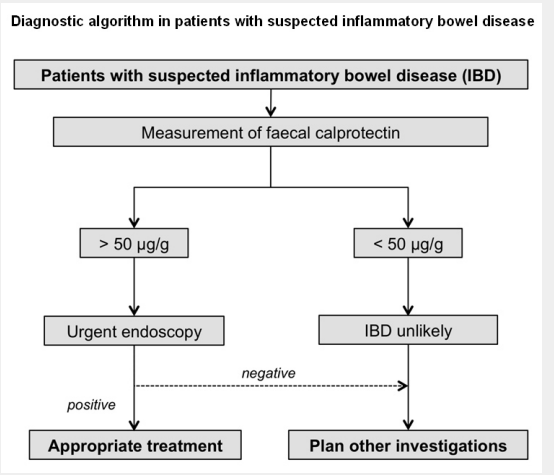

Figure 1

A diagnostic algorithm for the evaluation of patients with suspected inflammatory bowel disease that includes faecal calprotectin measurement before endoscopy.

Table 4: Studies investigating the use of faecal calprotectin to predict relapse of IBD activity.

Author	No. of patients	Patient population	Calprotectin cut-off (µg/g)	Relapse rate below cut-off (%)	Relapse rate above cut-off (%)
Costa, F [74]	41	UC	>150	10	81
Costa, F [74]	38	CD	>150	57	87
Tibble, J [68]	37	UC	>50	10	85
Tibble, J [68]	43	CD	>50	15	85
Sipponen, T [114]	72	UC/CD	>100	25	39
D'Incà R [130]	97	UC	>130	21	59
D'Incà R [130]	65	CD	>130	20	43
Gisbert, JP [133]	163	UC	>150	9	31
Gisbert, JP [133]	163	CD	>150	8	30
Diamanti, A [132]	73	UC/CD	>275	1	84
Walkiewicz, D [131]	32	CD	>400	11	56
Kallel, L [134]	53	CD	>340	5	67

For each study, the number of included patients (No. of patients), the patient population (ulcerative colitis [UC], Crohn's disease [CD], or both [UC/CD]), the calprotectin value (µg/g) used as cut-off, and relapse rates (%) of patients below and above the calprotectin cut-off are given. Adapted from [139].

comparing results from published studies about the diagnostic value of faecal calprotectin arise from different limits for defining a positive test. Most studies used 50 µg/g as a cut-off, as recommended by the test manufacturers [35, 37, 51, 56, 58, 61, 63, 64], while others based their cut-off on receiver operating characteristics analysis [31, 32, 34, 57, 59, 66], on the 95th percentile of values in healthy subjects [29, 60], or on previous investigations [65]. Most recent studies [58, 61–64] have used 50 µg/g as the cut-off to define a positive test result and to decide on endoscopy in patients with abdominal discomfort to rule out IBD or other organic pathologies. It has been calculated that the use of faecal calprotectin as a diagnostic test in suspected IBD would result in a 67% reduction in patients requiring endoscopy. However, the consequences of misdiagnosis leading to a delayed start of appropriate treatment must be balanced against the number of ultimately unnecessary invasive endoscopic procedures. Figure 1 offers an algorithm to investigate patients with suspected inflammatory bowel disease that includes faecal calprotectin measurement before endoscopy.

To date, data on the use of faecal calprotectin in IBD diagnosis are almost exclusively gathered from studies carried out in large GI clinics and referral centres. Data on the value of calprotectin testing in primary care are scarce, and can only be extrapolated from data available from tertiary care facilities. In primary care, the emphasis is on ruling out IBD and test characteristics focus on sensitivity. Estimating a lower disease prevalence in primary care than in referral centres, the negative predictive value of normal calprotectin values would significantly increase and allow one to rule out IBD or to adopt a strategy of watchful waiting. Recently, the cost-effectiveness of faecal calprotectin testing to rule out IBD has been demonstrated in hypothetical economic models [135, 136]. Using cut-off values of 50 µg/g and 100 µg/g, the estimated demand for colonoscopies was reduced by 50% and 67%, respectively [135]. However, these data need confirmation from large multicentre studies including primary care populations.

The correlation between faecal calprotectin levels and endoscopic and histological IBD disease activity has been well established. Calprotectin consistently performed better than clinical indices and serum markers in assessing mucosal inflammation. Currently, endoscopy with mucosal biopsy is considered the gold standard for evaluating the extent and severity of disease activity. However, endoscopy is an expensive and invasive procedure that is onerous to the patient. Faecal calprotectin allows a non-invasive monitoring of disease activity, especially advantageous when the dynamics of repeated measurements are considered. Recently, symptom-based clinical activity indices for defining IBD remission have been challenged and, among both CD and UC patients, MH has been proposed as better identifying controlled disease activity. MH has been associated with sustained clinical remission, as well as reduced rates of hospitalisation and surgical resection. Several smaller studies have shown normal faecal calprotectin values in patients with endoscopic remission. Nevertheless, the current data are not yet conclusive enough to establish faecal calprotectin as a surrogate marker for MH.

It has also been shown that elevated faecal calprotectin levels in patients in clinical remission increase the risk of disease relapse within 12 months follow-up. In most clinically quiescent IBD, residual mucosal inflammation is still present to some extent. When disease activity increases, clinical symptoms are usually not present during the early relapse stage, and patients become symptomatic only later, when intestinal inflammation has been well established. Faecal calprotectin seems to be able to detect subclinical mucosal inflammation, and thus might earlier identify those patients at risk for IBD relapse.

In conclusion, measurement of faecal calprotectin is highly useful for the diagnosis and disease monitoring of patients with IBD, and might additionally predict disease outcome. Future studies should evaluate the value of faecal calprotectin testing to guide treatment decisions and assess their effect on long-term outcome. Precisely this topic is currently being investigated with the CALM Study, a 56-week randomised, open-label, multi-centre efficacy and safety study that evaluates two treatment algorithms in subjects with moderate to severe Crohn's disease. Patients are treated with prednisone, azathioprine and adalimumab using tight control management, including measurement of faecal calprotectin, or a clinically-driven management route. The primary endpoint of the study is MH after 56 weeks. Pending results from this and similar studies likely to be carried out in the near future, faecal calprotectin awaits confirmation of its value in changing disease outcome through earlier recognition, and treatment monitoring.

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Figures (large format)

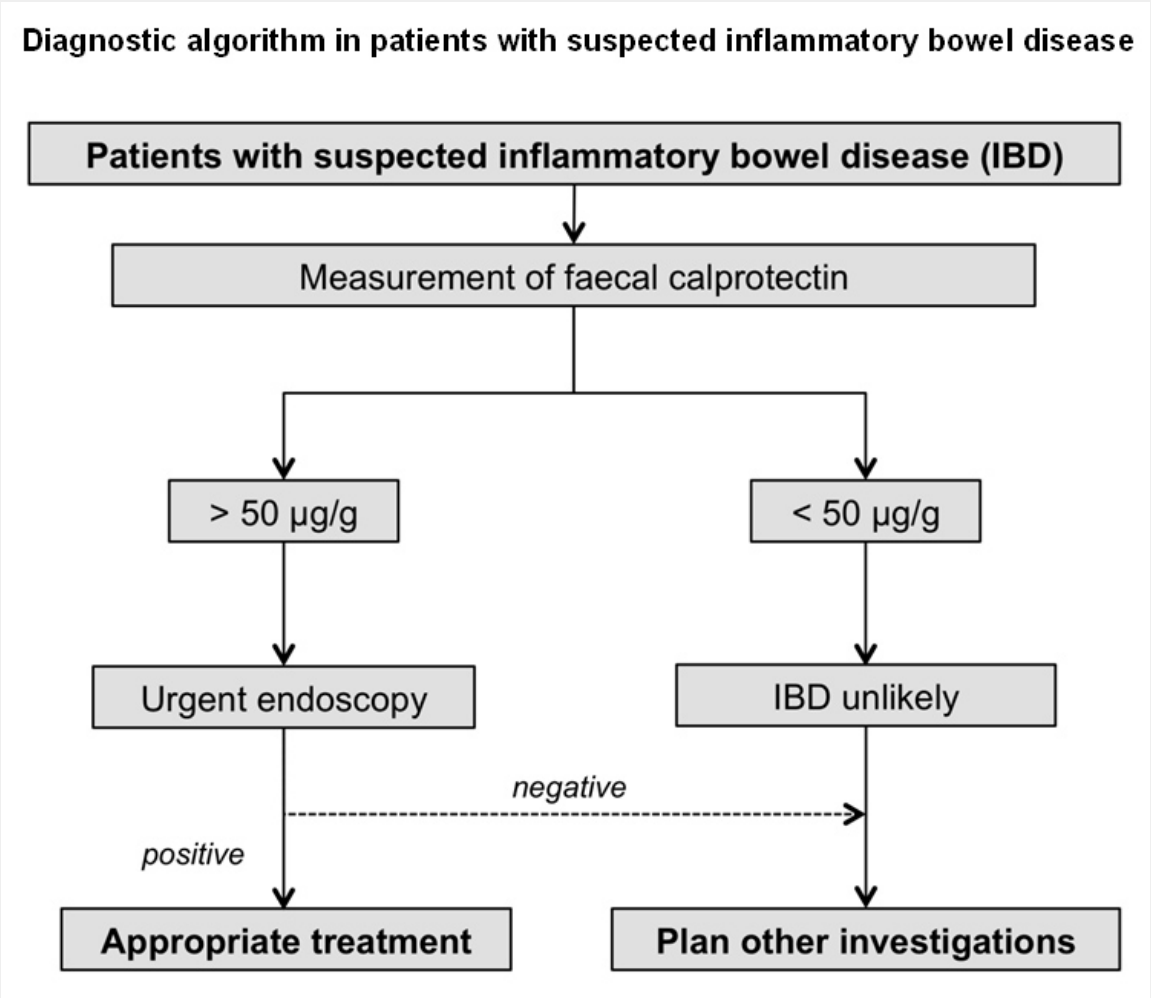

Figure 1

A diagnostic algorithm for the evaluation of patients with suspected inflammatory bowel disease that includes faecal calprotectin measurement before endoscopy.