Inflammation

Faecal calprotectin in the diagnosis of inflammatory bowel disease

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Abstract

Suspicion of inflammatory bowel disease should be raised in any patient with chronic or recurrent abdominal pain and diarrhoea. However, symptoms of inflammatory bowel disease (IBD) overlap with functional gastrointestinal disorders and those patients may not need endoscopy. Currently, colonoscopy with multiple biopsies is considered the gold standard to establish the diagnosis of IBD. Unfortunately, patient selection for endoscopy based on symptoms is not reliable. The use of guidelines of appropriateness for endoscopy yields significantly more significant findings but the selection criteria suffer from low specificity.

Calprotectin is a calcium binding protein of neutrophil granulocytes that correlates well with neutrophil infiltration of the intestinal mucosa when measured in faeces. In the last decade, a large body of evidence on the diagnostic value of faecal calprotectin has accumulated and measurement of calprotectin in faeces has been suggested as a surrogate marker of intestinal inflammation. Testing of faecal calprotectin has been highly useful to distinguish organic from functional intestinal disorders in patients with abdominal complaints. Additionally, faecal calprotectin has reliably identified colonic inflammation in patients with suspected IBD. The use of this inexpensive and widely available test in the evaluation and risk stratification in patients with abdominal complaints is likely to increase in the future.

Key words: inflammatory bowel disease; faecal calprotectin; diagnostic accuracy

Introduction

Abdominal discomfort is a common complaint and presents a clinical challenge even for experienced physicians (1,2). Discomfort may arise from a variety of organic diseases, e.g. inflammatory bowel disease (IBD), and establishing a prompt diagnosis is crucial. However, many patients will suffer from non-organic intestinal disorders, e.g. functional disorders, as it is estimated that 10-20% of the general population suffer from irritable bowel syndrome (IBS) (3). Accordingly, endoscopy might not be necessary in some patients and the selection of those who should receive prompt endoscopic investigation is crucial in the diagnostic process. The abuse of expensive invasive tests must be balanced against the under-diagnosis of potentially harmful diseases (4,5). Symptoms of

IBD are not exclusive and show a considerable overlap with symptoms of IBS. Therein lays the diagnostic difficulty (6). Suspicion of IBD should always be raised, when patients present with chronic or recurrent episodes of abdominal pain and diarrhoea, especially when alarm signs (rectal bleeding, anorexia, anaemia) are reported (7).

Two major clinical forms of IBD with distinct pathological features exist: ulcerative colitis (UC) and Crohn's disease. The aetiology of the disease is far from being understood but seems to occur mostly in patients in the second to fourth decade with a rising incidence in developed countries. The rapid identification of IBD is crucial as up to 15% of patients with CD have penetrating lesions (fistulas, phlegmonas, or abcesses) at the time of diagnosis

(8). The time to diagnosis in general seems to be acceptable, but long delays (> 12 months) exist for a considerable part of patients, especially in CD (9). In children, prompt diagnosis is of special importance as IBD may affect growth and sexual maturation (10).

Currently, colonoscopy with multiple biopsies both from the terminal ileum and the colon, is considered the gold standard to establish the diagnosis of IBD. Unfortunately, patient selection for endoscopy based on symptoms is not reliable (11,12). Both the *American Society for Gastroenterological Endoscopy (ASGE)* and the *European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE)* have released guidelines to optimize patient's selection for endoscopy (13-15). In several studies, applying these guidelines significantly yielded more endoscopic findings for appropriate than for inappropriate investigations, but the selection criteria suffered from low specificity (16,17). The evaluation and risk stratification of patients using a simple, non-invasive, and cheap test would therefore be highly desirable. An ideal marker should be sensitive to reliably detect intestinal inflammation and should have reasonable specificity to avoid unnecessary investigations. In fact, measuring calprotectin levels in faeces could fulfil some of these criteria.

Mechanisms of calprotectin during innate immune response

Calprotectin is a calcium binding protein that is found mainly in neutrophils and to a lesser extent in monocytes and reactive macrophages (18). It belongs to a subgroup of proteins of the S100 family (calgranulin A, S100A8; calgranulin B, S100A9 and calgranulin C, S100A12) that is associated with acute/chronic inflammatory disorders and a number of malignancies (18,19). As part of the innate immune system, they provide intra- and extracellular protection during infection and inflammation. Apart from anti-infective host defence mechanisms of S100 proteins, the phagocyte-specific calgranulins have important proinflammatory properties and high concentrations can be found during inflammation both at the sites of infection and

in the serum (20). Their release is activated through interaction of activated monocytes with endothelial cells that bind calgranulin on their surface and increase leukocytes recruitment (21). Additionally, proinflammatory chemokines by which phagocytes further promote extravasation of leukocytes to the sites of inflammation are released (22). For a detailed insight on the molecular functions of S100 proteins, we refer to the excellent reviews by Hsu (23) and Manolakis (24).

Distinguishing organic disease from non-organic disorders

Roesth *et al.* first reported elevated faecal calprotectin levels in patients with colonic inflammation and colorectal neoplasm almost 20 years ago (25,26). Since then, increased levels of calprotectin have been described in various gastrointestinal diseases: microscopic colitis (27), infectious diarrhea (28), peptic lesions of the upper intestinal tract (29,30), gastric cancer (26,30), and after the use of non-steroidal anti-inflammatory drugs (31). In patients treated for extraintestinal disorders, e.g. rheumatological disorders, the use of corticosteroids or anti-TNF-alpha inhibitors may also influence faecal calprotectin levels through their systemic effect on the intestinal mucosa. It has been shown that in IBD, faecal calprotectin levels dramatically decrease after treatment with either one of these drugs when the intestinal inflammation is restored (32,33).

In recent years, a number of studies have investigated the diagnostic ability of faecal calprotectin to reliably distinguish organic from non-organic gastrointestinal disease in symptomatic patients with lower abdominal complaints (6,10,29,34-57). Table 1 summarizes all studies that evaluated the diagnostic accuracy of faecal calprotectin to identify organic disease. Initially, Tibble *et al.* investigated 602 patients with symptoms suggestive of IBS or organic intestinal disease that underwent invasive diagnostic imaging with barium enteroclysis, barium enema and/or colonoscopy, as was considered appropriate. Median faecal calprotectin values in patients with organic disease were significantly higher than in patients with non-organic di-

TABLE 1. Diagnostic accuracy of faecal calprotectin to distinguish between organic and non-organic gastrointestinal disease.

Author	No. of patients	Patient population	Cut-off (µg/g)	Sensitivity (%)	Specificity (%)
Limburg (2000) (35)	110	IBD, HC	100	83	83
Tibble (2000) (36)	220	IBD, HC	50	82	83
Kronborg (2000) (37)	814	CRC, HC	50	74	64
Bunn (2001) (41)	22	IBD, HC	31.5	100	86
Kristinsson (2001) * (40)	237	CRC, HC	50	47	56
Tibble (2001) † (39)	391	IBD, CRC, HC	50	79	72
Summerton (2002) (29)	116	IBD, CRC, IBS, HC	50	82	73
Tibble (2002) (6)	602	IBD, IBS, HC	50	89	79
Costa (2003) (42)	239		50	83	82
Carroccio (2003) (43)	120	IBD, CRC, IBS, HC	50	66	84
Limburg (2003) (45)	412	CRC, HC	50	37	63
Thjodleifsson (2003) (44)	65	IBD, HC	50	86	88
Dolwani (2004) (46)	148	IBD, IBS, HC	60	100	79
Hoff (2004) (47)	1534	CRC, HC	50	27	76
Berni Canani (2004) (48)	281	IBD, IBS, HC	100	74	98
Fagerberg (2005) (50)	36	IBD, HC	50	95	93
Bremner (2005) (52)	100	IBD, IBS, HC	50	92	85
Canani (2006) (10)	357	IBD, IBS, HC	100	73	98
Garcia Sanchez (2006) (53)	190	IBD, CRC, HC	217	85	81
D'Inca (2007) (54)	144	IBD, HC	50	78	88
Chung-Faye (2007) (55)	131	IBD, CRC, IBS	25	80	74
Jeffrey (2009) (56)	199	IBD, IBS	50	93	92
Meucci (2010) (57)	870	IBD, CRC, IBS,	50	82	62

For each study the number of included patients (No. of patients), the patient population and the respective faecal calprotectin cut-off used to define an abnormal test result are given. Sensitivity and specificity indicate the diagnostic ability to distinguish between organic and non-organic intestinal disorders. Sensitivity and specificity to identify colorectal adenoma (*) and any colorectal neoplasm (†).
Adapted in parts from Gisbert *et al*. (58).
IBD - inflammatory bowel disease; CRC - colorectal cancer, IBS - irritable bowel syndrome; HC - healthy controls

sorders (50 mg/L *vs*. 4 mg/L, P < 0.001). To distinguish between the two groups of patients, faecal calprotectin had 89% sensitivity and 79% specificity (23). In a recent meta-analysis combining data from 2475 patients, these initial results by Tibble *et al*. were again confirmed. Gisbert *et al*. calculated a mean sensitivity of 83% and mean specificity of 84% for faecal calprotectin to distinguish organic and non-organic disease (58). The diagnostic accuracy was higher than for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or a combination of both (6,36). A recent prospective multi-center study by Meucci *et al*. expanded the use of faecal calprotectin to a population with unselected patients (57). The study included 870 consecutive patients referred for colonoscopy for any reason to one of five participating centres. In this unselected group of patients, mean sensitivity of faecal calprotectin to detect any organic disease remained high (89%) but specificity (62%) was somewhat lower than previously published. When subgroups of patients were analyzed, test sensitivity and specificity varied considerably: To detect any organic disease in patients with chronic diarr-

hea (N = 43, 100% and 79%, respectively), to detect any organic disease in patients with lower gastrointestinal bleeding or abnormal barium enema (N = 156, 81% and 60, respectively), to detect colorectal cancer in patients with altered bowel habits (N = 135, 100% and 57%, respectively), and to detect colorectal cancer or polyps > 0.9 cm in diameter in patients referred for screening colonoscopy (N = 247, 56% and 67%, respectively).

Diagnostic value of faecal calprotectin to identify IBD

Measuring leukocytes in faeces has long been the only available non-invasive stool biomarker to assess colonic inflammation, but the technical difficulties of the test hindered its widespread use. Stool samples had to be analyzed immediately to avoid cell dissolution and furthermore, measuring leukocytes in faeces provided only semi-quantitative test results. The clinical utility of this stool marker has therefore been limited. Faecal calprotectin on the other hand correlates well with neutrophil infiltration of the intestinal mucosa and is resistant to enzymatic degradation both *in vivo* and *in vitro* (59). The distribution of calprotectin is homogenous within stool samples (60,61) and concentrations from single samples correlate well with those from corresponding four days collections (36,62). Dietary restrictions are not necessary prior to collecting a sample (60). There is only limited data on the effect of intestinal blood loss on calprotectin values, but data suggest that in the absence of overt hematochezia, faecal calprotectin values are not significantly increased by intestinal blood (39,63). Calprotectin is resistant to proteolytic degradation and is stable at room temperature for up to seven days in stool samples (25).

A number of studies have reported higher faecal calprotectin levels in patients with IBD compared to IBS patients or healthy controls (6,10,25,29,35, 36,38,41-44,46,48,51,54,55,59,64-74). Table 2 summarizes all studies that investigated the diagnostic performance of faecal calprotectin to detect IBD. Gisbert *et al*. calculated a pooled sensitivity and specificity of 80% and 76%, respectively, to identify IBD from data of 754 patients. From this data,

slightly higher diagnostic accuracy was calculated for CD (sensitivity 83%, specificity 85%) than for UC (sensitivity 72%, specificity 74%). Recently a meta-analysis by von Roon *et al*. (19) summarized data of 5983 patients from 30 studies (25,26,29,35-52, 59,62,64,75,76). In IBD patients, higher faecal calprotectin levels was reported than in non-IBD patients, which translated into an excellent mean sensitivity and specificity of 95% and 91%, respectively, to distinguish between them. Higher calprotectin levels were reported for CD than for UC (P = 0.04), but the difference did not allow separating the two disorders (6,10,51).

To determine, if the use of faecal calprotectin may reduce the number of endoscopies in patients with suspected IBD, data from 13 studies (10,35,36, 41,50,68,69,71-74,77,78) including a total of 1041 patients (670 adults, 371 children) were recently summarized in an excellent meta-analysis by van Rheenen *et al*. (79). All studies prospectively investigated the diagnostic accuracy of faecal calprotectin in patients with clinically suspected IBD that had to be confirmed histopathologically. Pooled sensitivity and specificity of calprotectin testing was 93% and 96%, respectively. Specificity in children and teenagers was significantly lower (76%). In adults, using faecal calprotectin as a screening test in suspected IBD to decide upon the need for endoscopy would result in a 67% reduction of patients requiring endoscopy, but would result in delayed diagnosis of IBD in 6% of patients because of false negative test result.

C-reactive protein has long been the best-established biomarker in IBD (80) and other serum-based biomarkers (α1-acid glycoprotein, serum amyloid A-protein (SAA), α_2-globulin, thrombopoietin) appear to be inferior to, or less validated, than CRP (81). Serum calprotectin seems to correlate with active IBD (82) and elevated serum and mucosal calprotectin values have been reported in patients with active disease (83,84). However, the diagnostic accuracy of faecal calprotectin to diagnose IBD is superior to CRP and ESR, to serological markers such as anti-neutrophil cytoplasmatic antibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) and also to serum measurement of calprotectin (72). The main advantage of faecal bio-

TABLE 2. Diagnostic accuracy of faecal calprotectin to distinguish inflammatory bowel disease (IBD) from non-IBD.

Author	No. of patients	Patient population	Sensitivity (%)	Specificity (%)
Limburg (2000) (35)	110	UC/CD	94	83
Tibble (2000) (36)	220	CD	100	97
Bunn (2001) (41)	68	UC/CD	65	100
Summerton (2002) (29)	116	UC/CD	79	n.a.
Costa (2003) (42)	239	UC/CD	81	82
Carroccio (2003) (43)	70	CD	100	95
Langhorst (2005) (66)	31	UC	92	63
Silberer (2005) (51)	119	UC/CD	61	n.a.
Canani (2006) (10)	27	UC/CD	93	89
D'Inca (2007) (54)	144	UC/CD	78	83
Chung-Faye (2007) (55)	148	UC/CD	78	90
Kaiser (2007) (67)	171	UC/CD	63	86
Schroder (2007) (68)	88	UC/CD	93	100
Langhorst (2008) (70)	139	UC/CD	100	37
Otten (2008) (71) *	114	UC/CD	100	n.a.
Schoepfer (2008) (72)	136	UC/CD	83	100
Sidler (2008) (73)	61	UC/CD	100	64

For each study the number of included patients (No. of patients) and the type of inflammatory bowel disease (IBD) of the patient population is given: Ulcerative colitis (UC) or Crohn's disease (CD), or both (UC/CD). Sensitivity and specificity indicate the diagnostic ability to distinguish between IBD and non-IBD.
*A rapid test for calprotectin measurement was used.
Adapted in parts from Gisbert *et al*. (58).
n.a. – not available

markers is that the faecal stream is in direct contact with the mucosa and therefore, when measured in faeces, calprotectin detects inflammatory conditions far more precisely than biomarkers measured in serum (25,85).

Clinical use of faecal calprotectin

When using faecal calprotectin in clinical practice, it is important to understand, that it is not a disease-specific marker for IBD but rather a marker of mucosal damage. Elevated values have been described in a number of clinical conditions other than IBD (25-31) and to rely solely on faecal calprotectin to diagnose IBD would prove misleading. Important biological variability has been reported for faecal calprotectin measurements on different days (86,87) and calprotectin levels seem to fluc-

tuate depending on disease location (67). In Crohn's disease the release of calprotectin from site of ileal inflammation has been greater than from the inflamed colon (88). Furthermore, it should be mentioned, that in several important gastrointestinal disorders, such as small bowel bacterial overgrowth, celiac disease, or lactose intolerance, calprotectin levels will be normal (89,90). Although faecal calprotectin has been established as a valid marker of intestinal inflammation in recent years, these limiting factors have to be kept in mind when investigating a patient with suspected IBD.

When comparing data from different studies investigating the diagnostic ability of faecal calprotectin in IBD, the use of the same cut-off to allocate a "positive" or "negative" test results would be preferable. Among the available literature, published cut-off concentrations for faecal calprotectin

vary from 18.6 to 250 μg/g (51,62). Currently, the recommended cut-off level provided by manufacturers indicating an abnormal test results is 50 μg calprotectin *per* gramm of faeces. However, it might be useful to use different cut-offs depending on the clinical situation that the test is being applied. Higher values have been suggested for patients with known inflammatory conditions while lower values might be appropriate to rule out patients with IBS (42,54). The use of a low cut-off would assure clinicians in their decision to avoid unnecessary endoscopies in the evaluation of patients with abdominal complaints (42).

Summary

Inflammatory bowel disease is a lifelong disorder of chronic inflammation that should be suspected in all patients with chronic or recurrent episodes of abdominal pain. The clinical features of UC and CD are distinct, but symptoms may not only overlap among them, but also with other non-IBD disorders, such as IBS.

Endoscopy with histopathological confirmation is the current gold standard for the diagnosis of IBD.

However, endoscopy is invasive, costly, and often not much appreciated by patients. Measurement of faecal calprotectin has been shown to reliably differentiate IBD from IBS and has been proven especially useful in ruling out IBD in undiagnosed, symptomatic patients. The use of faecal calprotectin as a screening test in suspected IBD would result in a considerable reduction of patients requiring endoscopy.

More work needs to be done to further define the value of faecal calprotectin measurement as a diagnostic test in different clinical settings, e.g. asymptomatic patients vs. symptomatic patients, and to establish clinically useful cut-off levels to define an abnormal test result for a given setting. Furthermore, the short- and long-term outcome as well as the cost-effectiveness of a faecal calprotectin-based diagnostic approach to patients with abdominal complaints has to be further investigated.

In conclusion, measurement of faecal calprotectin is highly useful for the diagnosis of IBD and may serve as a surrogate marker of mucosal inflammation throughout the intestinal tract.

Potential conflict of interest

None declared.

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Fekalni kalprotektin u dijagnozi upalne bolesti crijeva

Sažetak

Kod svakog bolesnika s kroničnom ili rekurentnom abdominalnom boli i proljevom potrebno je posumnjati na upalnu bolest crijeva. Međutim, simptomi upalne bolesti crijeva (engl. *inflammatory bowel disease*, IBD) preklapaju se s funkcionalnim gastrointestinalnim poremećajima te je moguće da ti bolesnici ne trebaju endoskopiju. Trenutno se kolonoskopija s višestrukim biopsijama smatra zlatnim standardom u postavljanju dijagnoze IBD. Nažalost, odabir bolesnika za endoskopiju temeljen na simptomima nije pouzdan. Smjernice za određivanje primjerenosti endoskopije daju statistički značajno više značajnih rezultata, međutim primjena ovih kriterija ima nisku specifičnost.

Kalprotektin je protein neutrofilnih granulocita koji veže kalcij te je pri određivanju koncentracije iz stolice u dobroj korelaciji s neutrofilnom infiltracijom crijevne sluznice. U zadnjih je deset godina sakupljen veliki broj dokaza o dijagnostičkoj vrijednosti određivanja koncentracije fekalnog kalprotektina te je ono predloženo kao zamjenski biljeg crijevne upale. Određivanje koncentracije fekalnog kalprotektina vrlo je korisno u razlikovanju organskih od funkcionalnih crijevnih poremećaja kod bolesnika s abdominalnim tegobama. K tome se još određivanjem koncentracije fekalnog kalprotektina pouzdano otkriva upala debelog crijeva kod bolesnika za koje se sumnjalo da su oboljeli od IBD. Primjena ovog ekonomski povoljnog i vrlo dostupnog testa pri procjeni i stratifikaciji rizika kod bolesnika s abdominalnim tegobama vjerojatno će porasti u budućnosti.

Ključne riječi: upalna bolest crijeva; fekalni kalprotektin; dijagnostička točnost