REVIEW

Can faecal calprotectin predict relapse in inflammatory bowel disease: a mini review

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ABSTRACT

Crohn's disease and ulcerative colitis are chronic inflammatory disorders affecting the gastrointestinal tract. Faecal calprotectin is a protein complex of the S-100 family of calcium-binding proteins present in inflammatory cells that can be measured in stool samples, which act as a biomarker for bowel inflammation. Elevated faecal calprotectin has been shown to reflect the presence of ongoing mucosal inflammation, which improves with mucosal healing. The aim of this review was to evaluate the available evidence on the ability of faecal calprotectin to predict a relapse in inflammatory bowel disease. Multiple retrospective studies have shown that patients who relapse have significantly higher levels of calprotectin in their stool compared with non-relapsers, especially in ulcerative colitis. Elevated faecal calprotectin postoperatively in Crohn's disease was also shown to be indicative of a relapse. However, the association of a raised faecal calprotectin and relapse is not universal and may be explained by the different patterns of mucosal inflammatory activity that exist. In conclusion, we put forward our hypothesis that changes such as a rise in faecal calprotectin levels may be more predictive of a relapse than absolute values.

INTRODUCTION

Inflammatory bowel diseases (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders primarily affecting the gastrointestinal tract (GI).[1] Both CD and UC are distinguished by their different phenotypic expression of inflammation in the GI tract but share the pattern of activity common to many inflammatory disorders of a chronic-progressive or relapsing-remitting inflammation.

Faecal calprotectin (FC) is a protein complex of the S-100 family of calcium-binding proteins present in neutrophils, monocytes and macrophages. It is stable for measurement by quantitative assays in stool, which act as a biomarker for bowel inflammation that is non-invasive and cost-effective.[2] There is good evidence of its use to distinguish functional bowel symptoms from those with an inflammatory origin[3 4] as well as act as a surrogate biomarker of mucosal healing.[5] While FC has an established role in identifying the presence of bowel inflammation at the time of testing, its ability to predict future relapse in IBD is less clear. This review aims to look at the evidence of FC's role in predicting future relapse and challenge our perceived ideas about the pattern of inflammatory activity in the natural history of IBD.

A patient's bowel symptoms are often subjective and poorly reflect disease activity, which requires validation with objective tests such as serum inflammatory markers, faecal antigens, endoscopy and radiological imaging. However, even colonoscopic and histological evaluation of inflammation can be subjective and can be made more objective by using scoring systems such as the CD endoscopic index of severity[6] or one of the 22 known histological scoring systems.[7] These different markers of disease activity, that is, clinical, biochemical, endoscopic, histological and radiological, allow assessment of response and need for escalation of treatment, since individually each modality is susceptible to variability but collectively they present a more robust and objective assessment. There continues to be a drive to identify non-invasive, cost-effective and reliable biomarkers to assess ongoing bowel inflammation and FC has been seen by many to fulfil this role.

The concepts of relapse and remission in IBD are difficult to define strictly. There is a move away from using clinical symptoms to define remission to the use

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of *endoscopic* mucosal healing. However, some argue that mucosal healing should be assessed histologically, while others have even suggested the use of mucosal cytokine gene expression to define treatment success.[8] For now, the gold standard remains endoscopic mucosal healing, with good evidence that FC correlates well with endoscopic mucosal healing[9 10] as well as histological scoring of inflammation.[10 11] As such, since FC correlates with mucosal inflammation, does an elevated FC merely indicate the lack of complete mucosal healing, which would be associated with a clinical relapse in a model where inflammation is chronic and progressive? However, if mucosal inflammation is variable in a model of relapsing and remitting activity, then an elevated FC indicative of ongoing inflammation may not predict or progress to a clinical relapse in a particular individual. Conversely, a normal FC may not be protective by predicting a lower rate of clinical relapse.

USING FC TO PREDICT RELAPSE IN CD AND UC

Many different studies (table 1) have looked at the use of FC in predicting clinical relapse. The majority of studies investigated patients with CD and patients with UC in clinical remission, measuring their baseline FC and following them up for at least 12 months to identify patients who had a clinical relapse. Median FC levels were compared between relapsers and non-relapsers. The majority of studies found a statistically higher baseline FC level in patients with CD and patients with UC who subsequently relapsed compared with those who did not. The exceptions were the cohort of patients with CD studied by Costa *et al*[12] and D'Inca *et al*,[13] Sipponen's and Kolho's[14] paediatric patients with IBD and Laharie *et al*'s[15] patients with CD who newly achieved clinical remission with infliximab (IFX). These findings suggest that FC may be a better marker of colonic inflammation since all studies in adult patients with UC were significant in contrast to variably significant results in patients with CD. The findings by Laharie *et al*[15] is in contrast to a later study by Ferreiro-Iglesias *et al* of patients in remission on adalimumab (ADA)[16] and IFX[17] where a difference in FC levels was found between relapsers and non-relapsers. A crucial difference may be that the FC levels were done at week 14 of IFX treatment[15] in contrast to the patients who were in remission for at least 6 months on ADA[16] and IFX.[17]

The available studies (table 1) suggest a FC cut-off for UC ranging from 120 to 300 µg/g yielding a wide sensitivity of 31% to 100% and specificity of 63% to 98%. FC cut-offs for CD range from 130 to 340 µg/g with a sensitivity of 28% to 100% and specificity of 43% to 95%.

An ongoing study, *F*ecal marker of *I*ntestinal inflammation for *RE*lapse prediction in routine monitoring of patients with CD (FIRE) is prospectively trying to answer this particular question.[18] FIRE is a prospective, multicentre study in Germany that follows patients with CD in remission (Harvey–Bradshaw Index (HBI)<5) with 3-monthly FC and HBI for up to 2 years or when clinical relapse (HBI≥5) occurs. From the initial results presented in abstract so far, FIRE did not find a statistically significant difference in FC levels relative to HBI, treatment with immunosuppressants, anti-tumour necrosis factor and combination treatment or whether mucosal ulceration was present.[19] Further analysis found that relapsers had significantly higher median HBI, C reactive protein and FC levels at baseline compared with non-relapsers although on multivariate regression analyses only female gender and HBI≥1 but *not* FC were prognostic factors for a mild-to-severe relapse (HBI≥5).[18] These findings underpin the complexity of using FC to predict relapse in a multifaceted disorder such as CD.

USING FC TO DETECT POSTOPERATIVE RECURRENCE IN CD

In 2006, Orlando *et al*[20] investigated 39 patients with CD postoperatively with an FC at 3 months and colonoscopy at 1 year. A total of 19 patients had endoscopic recurrence at 1 year and with FC>200 mg/L, giving a sensitivity of 63% and specificity 75% for endoscopic recurrence. Of the 19 patients with endoscopic recurrence, 12 had FC>200 (true-positive), while 7 had FC<200 (false-negative). Of the 20 patients without endoscopic recurrence, 5 had FC>200 (false-positive), while 15 had FC<200 (true-negative). While these findings are useful, the interval time between FC collection at 3 months and colonoscopy at 1 year limits the applicability of these results.

Lamb *et al*,[21] in 2009, looked at CD recurrence in patients treated with an ileocaecal resection. It prospectively showed that in asymptomatic patients, FC levels resolved by 2 months and stayed low. However, in symptomatic patients, an early rise in FC at 1 month was related to postoperative complications while a late rise at 9 months was due to CD relapse. Additionally, this study showed that FC correlated significantly with HBI. Long-term follow-up of these patients showed that an elevated FC correlated significantly with escalation of treatment or further surgery over 5 years.[22]

More recently, Wright *et al*[23] also found that FC levels in patients with CD dropped postoperatively at 6 months, and that FC levels were higher in patients with endoscopic disease recurrence and correlated with severity of recurrence. Step-up treatment of those with endoscopic recurrence resulted in reduction of FC levels at 12 and 18 months.

CAN FC PREDICT RELAPSE IN IBD?

The answer to this question is not clear. While FC has been shown to correlate with CD Activity Index (CDAI) and HBI scores suggestive of clinical relapse

Table 1 Summary of studies looking retrospectively at baseline FC levels in patients who relapse or stay in remission

Year	Authors	Disease type	Patients (n)	Definition of relapse	Median FC levels		p Value	FC cut-off	Sensitivity (%)	Specificity (%)	Relapse risk
					Relapse/active disease group	Non-relapse/ remission group					
2000	Tibble *et al*[24]	CD	43	CDAI>150 and rise>100	122 mg/L	42 mg/L	<0.0001	50 mg/L*	90	83	
		UC	37	HBI>4 and rise>2	123 mg/L	29 mg/L	<0.0001				
2005	Costa *et al*[12]	CD	38	CDAI>150 and new Rx	220.1 µg/g	220.5 µg/g	0.395	150 µg/g	87	43	2
		UC	41	UCAI>4 and new Rx	220.6 µg/g	67 µg/g	<0.0001	150 µg/g	89	82	14
2008	D'Inca *et al*[13]	CD	65	CDAI>150 and rise>50	207 mg/kg	88 mg/kg	0.055	130 mg/kg	65	62	1.7
		UC	97	ET>4 and new Rx	190 mg/kg	49 mg/kg	0.02	130 mg/kg	70	70	2.4
2009	Gisbert *et al*[25]	CD	89	CDAI>150	266 µg/g	145 µg/g	0.002	150 µg/g	28	93	
		UC	74	Modified TWI>11	213 µg/g	126 µg/g	0.03	150 µg/g	31	91	
2010	Garcia-Sanchez *et al*[26]	CD	66	CDAI>150	524 µg/g	123 µg/g	<0.01	200 µg/g	80	65	4
		UC	69	Modified TWI≥11	298 µg/g	105 µg/g	<0.01	120 µg/g	81	63	6
2010	Kallel *et al*[27]	CD	53	CDAI>150 or rise>100	380.5 µg/g	155 µg/g	<0.001	340 µg/g	80	90.7	18.8
2010	Sipponen and Kolho[14]	IBD	72	PGA	409 µg/g	282 µg/g	0.44	108.5 µg/g	38	72	
2011	Laharie *et al*[15]	CD	50	CDAI>150 and rise>70	200 µg/g	150 µg/g	ns	130 µg/g	61	48	
2013	Lasson *et al*[28]	UC	69	New treatment	263 µg/g	102 µg/g†	0.009	262 µg/g	64.4	70.8	
2013	De Vos *et al*[29]	UC	87	New treatment, Mayo≥2	125 mg/kg‡	27 mg/kg‡	<0.001	300 mg/kg	58.3	93.3	
2014	Naismith *et al*[30]	CD	92	New treatment, surgery	414 µg/g	96 µg/g	0.005	240 µg/g	80	74.4	12.2
2015	Ferreiro-Iglesias *et al*[16]	CD	37	HBI>4	625 µg/g	45 µg/g	<0.005	204 µg/g	100	85.7	
2015	Ferreiro-Iglesias *et al*[17]	CD	33	HBI>4	287 µg/g	94 µg/g	<0.005	160 µg/g	87.5	84	
		UC	20	PMI>2	420 µg/g	136 µg/g	<0.005	198 µg/g	100	81.3	
2015	Scaioli *et al*[31]	UC	74	SCCAI>3	218 µg/g	48 µg/g	<0.01	193 µg/g	65	98	
2015	Mooiweer *et al*[32]	IBD	72	New Rx, admission and endoscopic activity	284 mg/kg	37 mg/kg	<0.01	56 mg/kg§	64	100	
2016	Delefortrie *et al*[33]	CD	29	Not stated	261.5 µg/g	37.6 µg/g	<0.05	106.5 µg/g	87.5	95.2	
2016	Zittan *et al*[34]	IBD	58	SES-CD≥3 and MES=0	1180 µg/g	100 µg/g	<0.0001	100 µg/g¶	71	91	

*Combined CD and UC.
†Mild disease activity.
‡Mean values.
§Predict absence of relapse.
¶Predict endoscopic remission.
CD, Crohn's disease; CDAI, Crohns Disease Activity Index; ET, Edwards and Truelove score; FC, faecal calprotectin; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; MES, Mayo endoscopic score; ns, non-significant; PGA, Physician's Global Assessment; PMI, partial Mayo index; Rx, treatment; SCCAI, Simple Clinical Colitis Activity Index; SES, simple endoscopic score; TWI, Truelove and Witt Index; UC, ulcerative colitis.

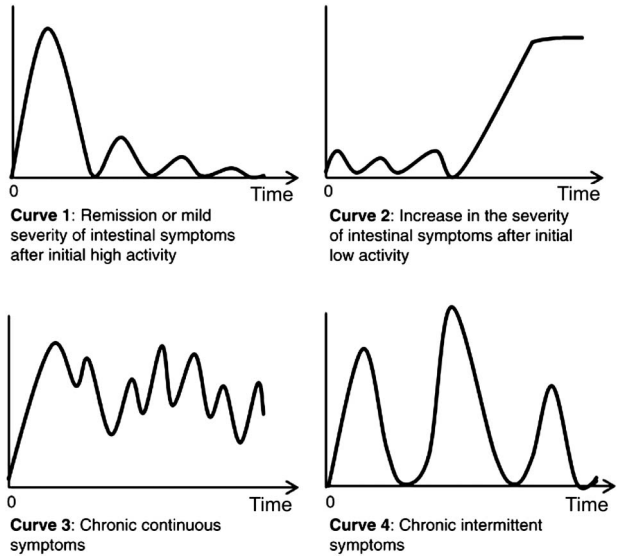

Figure 1 Graphical representation of possible patterns of mucosal inflammatory activity in inflammatory bowel disease; adapted from Solberg *et al*.

as shown above, this is not universal. FC also correlates with endoscopic and histological scores showing mucosal inflammation although again this is not universal. Additionally, there is no universal agreement or 'gold standard' of what constitutes a relapse, is it clinical, endoscopic or histological? We postulate that FC can identify but not necessarily accurately predict a relapse.

Part of the complexity in answering this question is the variable disease states that patients are in. These disease states include being in remission, subclinical or clinical relapse. Remission can be defined as clinical, endoscopic or histological remission, while relapse can be subclinical, with only histological changes or a 'full house' clinical relapse with clinical, endoscopic, histological and imaging changes. This complexity is further confounded by variability in the pattern of inflammatory activity, that is, whether it is chronic and progressive as is often the case in colonic inflammation in contrast to relapsing and remitting inflammation that is a feature of some of our patients with CD (figure 1).[35] In light of this, absolute FC values may be less predictive than ΔFC that is, change in FC levels. Deep remission with neither symptoms nor active inflammation is strongly associated with normal FC,[32] while active inflammation in a symptomatic individual is equally associated with very elevated FC levels. A moderately elevated FC level may be seen in patients with resolving inflammation (going into remission) or in patients heading for a flare or in patients who have ongoing elevated levels of inflammation. The direction and magnitude of changes in FC may be able to add better prediction to the use of FC, for example, a rise in FC may herald a pending relapse in contrast to a drop in FC that may be protective.

We suggest a schematic representation to understand this complexity (figure 2). In conclusion, the answer to the question of whether FC can predict a relapse in IBD is that it identifies inflammatory activity but is not able to accurately predict all individuals who will relapse. It remains to be seen whether identification of a rising FC (ΔFC) in patients who do not have symptoms of active disease is sufficiently predictive to use it clinically to direct pre-emptive treatment. Further research using the non-invasive property of serial FC may also allow identification of factors that

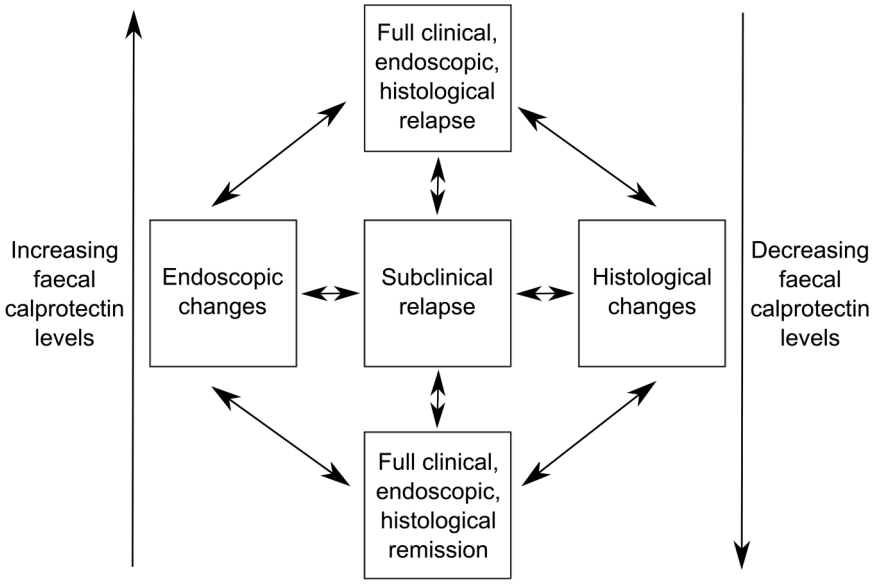

Figure 2 Schematic representation of pathways between full remission and complete relapse that faecal calprotectin may be able to predict.

provoke subsequent inflammatory relapses in patients in clinical remission.

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