REVIEW

Practical guidance on the use of faecal calprotectin

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Received 26 October 2016

Accepted 30 January 2017

Published Online First

22 February 2017

ABSTRACT

Differentiation between inflammatory bowel disease (IBD) and functional gut disorders, and the determination of mucosal disease activity in established cases of IBD remain the cornerstones of disease diagnosis and management. Non-invasive, accurate biomarkers of gut inflammation are needed due to the variability of symptoms, the inaccuracies of currently available blood markers and the cost and invasive nature of endoscopy. Numerous biomarkers have been used and/or considered with some in current use. This article reviews the current evidence base around the indications for using biomarkers and their limitations, with a particular focus on faecal calprotectin.

BACKGROUND

Differentiation between inflammatory bowel disease (IBD) and functional gut disorders, and the determination of mucosal disease activity in established cases of IBD remain the cornerstones of disease diagnosis and management. Non-invasive, accurate biomarkers of gut inflammation are needed due to the variability of symptoms, the inaccuracies of currently available blood markers and the cost and invasive nature of endoscopy. Numerous biomarkers have been used and/or considered with some in current use.^{1–8}

CURRENT BIOMARKERS AND THEIR LIMITATIONS

Routinely used clinical activity indices alongside systemic markers of inflammation; C reactive protein (CRP), full blood count (FBC), platelet count, white blood count and erythrocyte sedimentation rate (ESR), lack sensitivity and specificity for differentiating between IBD and irritable bowel syndrome (IBS).^{8–11} Colonoscopy, perhaps the gold standard for diagnosis

and assessment of colonic IBD, is costly, invasive, time consuming and carries a degree of procedural risk.

These non-specific systemic biomarkers lead to a high number of negative endoscopic procedures.^{9 12} Additionally, the use of clinical indices is compromised by subjectivity and an over-reliance on patients' symptoms.^{13 14}

The above limitations emphasise the need for a sensitive and specific non-invasive marker of bowel inflammation, which could select patients for further investigation. Besides being non-invasive and less costly than endoscopy, faecal inflammatory markers are extremely sensitive to gut inflammation as well as being specific to its source.^{4 6 9} Thus, they can help reduce the numbers (and cost) of unnecessary endoscopies.^{12 15–18}

A number of proteins are released into the gut lumen by granulocytes infiltrating the mucosa as part of the pathogenesis of IBD, of these calprotectin, lactoferrin, matrix metalloproteinases and S100A12 can be measured in faeces.^{6 8 19} Of these, faecal calprotectin is currently the most widely used in the UK with the largest evidence-base.

CLINICAL USE OF FAECAL CALPROTECTIN IN THE ASSESSMENT OF PATIENTS WITH LOWER GASTROINTESTINAL SYMPTOMS TO DISTINGUISH BETWEEN IBD AND FUNCTIONAL GUT DISORDERS

Faecal calprotectin, in both adults and children, has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders.^{3 15–18 20–25} In this regard, National Institute of Health and Care Excellence (NICE) recommended its use in primary and secondary care in

To cite: Brookes MJ, Whitehead S, Gaya DR, et al. *Frontline Gastroenterology* 2018;**9**:87–91.

adults with recent onset lower gastrointestinal symptoms, where cancer is not suspected (considering factors such as age), and for whom specialist assessment is being considered.⁶ Usage was similarly recommended in paediatric cases, but only within secondary care institutions.⁶ In both of these situations, a caveat was that local laboratory quality assurance processes and care pathways should be established.⁶ Calprotectin assessment is cost-effective, and led to reduction in the need for colonoscopy by as much as 67% based on a previous meta-analysis,^{6 16} but the cost-savings are critically dependent on how widely the test is used in primary care, and what threshold is used for triggering a colonoscopy.

Intermediate range

When used in primary care to identify patients with altered bowel habit who require colonoscopy for possible IBD, it is clear that use of the upper limit of the 'normal range' for assays (usually 50 µg/g stool) as the threshold for referring for colonoscopy, will result in large numbers of unnecessary procedures. Several authors, including NICE, have proposed the role of an intermediate range of faecal calprotectin for values that are above the reference range, but not clinically significant in assessing possible IBD.^{6 18 26} There is a need to balance sensitivity and specificity. An indeterminate range could include values from 50, to as much as 200 µg/g stool.²⁶ The setting of a level above which colonoscopy is needed should be determined locally based on audit data, quality assurance processes and in conjunction with clinical assessment, as recommended by NICE. A higher threshold will result in fewer investigations, but more risk of missing IBD. A lower threshold will result in fewer missed diagnoses (increase sensitivity), but lead to more unnecessary investigations (reduced specificity). It has been suggested that specificity could be improved by repeat testing for patients with results in the indeterminate range, assuming that patients with IBD will have persistently raised or rising calprotectin.^{18 27} There is little or no evidence in the literature at present to support retesting for all patients with indeterminate values. Retesting is justified if the clinical picture changes.

Practical considerations

Calprotectin testing in primary care for patients with new symptoms should be undertaken in the context of a locally derived pathway. This should take into account the following:

- ▶ It is not necessary to test faecal calprotectin in all patients with clear-cut IBS. However, they should have a minimum of FBC, coeliac serology and blood inflammatory markers (CRP, ESR or plasma viscosity) checked as per the NICE guidance.
- ▶ Calprotectin is raised in patients using non-steroidal anti-inflammatory drugs (NSAIDs), in acute infective

diarrhoea (testing not indicated unless new gastrointestinal symptoms persist for at least 4 weeks) and in the presence of bloody diarrhoea.

- ▶ Calprotectin is not appropriate in older patients (aged >45–50 years), where other diagnoses including colonic polyps/malignancy are more common. The age cut-off should be determined on the basis of local audit data.
- ▶ In patients with diarrhoea only, a normal calprotectin does not rule out drug-induced diarrhoea (eg, metformin, proton-pump inhibitors), bile salt malabsorption or coeliac disease. Microscopic colitis may have raised calprotectin but to date there are few data,²⁸ and there is more likely to be overlap with normal or intermediate range.
- ▶ Point-of-care testing is not currently recommended, due to inadequate evidence to support its usage and further studies are required.
- ▶ For patients with values in the intermediate range, direct colonoscopy is not indicated, but if there is still a significant concern that they may have IBD, they should be assessed in a gastroenterology clinic.

Raised calprotectin and normal investigations

A small group of patients have significantly raised calprotectin but normal ileocolonoscopy and small bowel radiology. Many of these will go on to have small bowel video capsule endoscopy (VCE), and some will have mucosal ulceration consistent with Crohn's disease. It is important however to rule out occult NSAID use, and to note that minor mucosal lesions are present in a fifth of the normal population.²⁹ With normal VCE, Crohn's disease should not be diagnosed solely on the basis of a raised calprotectin, even if very high.

CLINICAL USE OF FAECAL CALPROTECTIN IN THE MANAGEMENT OF ESTABLISHED IBD

Faecal calprotectin is more sensitive and specific than systemic inflammatory markers,^{25 30 31} and correlates well with endoscopic and histological disease activity.^{30 32}

- i. *Surrogate markers for mucosal healing*—with increasing interest in the value of mucosal healing as a target of therapy, faecal calprotectin is a useful surrogate marker.^{11 30 32–35} Much of the evidence that mucosal healing predicts good long-term clinical outcomes is observational, but there is great interest in mucosal healing as treatment target.³⁶ A small controlled study in patients with ulcerative colitis in clinical remission, with faecal calprotectin levels >50 µg/g stool, showed that those randomised to an increased dose of mesalazine had lower calprotectin levels at 6 weeks, and that lower levels of calprotectin were associated with reduced relapse risk over 48 weeks.³⁷ This study was small, and further prospective studies are needed. We do not currently recommend escalating therapy for patients in clinical remission, on the basis of surrogate markers of incomplete mucosal healing.

- ii. *Decision-making in stopping IBD drugs*—the STORI study³⁸ showed that raised faecal calprotectin was a predictor of relapse, alongside clinical features, for patients in stable remission on combination therapy with thiopurines/methotrexate and infliximab who stop their infliximab. A low faecal calprotectin can be used to aid decision-making about stopping therapy, although once again there is little data on relevant calprotectin thresholds, which most likely vary between patients.
- iii. *Prediction of future relapse for patients in clinical remission*—a recent study of patients with endoscopic remission showed that faecal calprotectin was a better predictor of future relapse than microscopic inflammation in biopsies.³⁹ Serial measurement of faecal calprotectin in patients with IBD in clinical and endoscopic remission showed that levels rose before clinical relapse.⁴⁰ This study evaluated patients stopping anti-tumour necrosis factor- α therapy with an initial faecal calprotectin <100 $\mu\text{g/g}$, with monthly calprotectin for 6 months, and then bimonthly.⁴⁰ Calprotectin rose a median of 94 (13–317) days before clinical symptoms. This implies that early reintroduction of treatment could be made before symptoms recur, on the basis of rising calprotectin, but there is still inadequate data to support such use of faecal calprotectin.
- iv. *Assessment of symptoms which could be continuing IBD inflammation or other causes*—there are times when it is unclear whether ongoing symptoms are due to inflammatory disease activity or other causes (eg, coexisting IBS⁴¹ or bile salt malabsorption). Faecal calprotectin can be useful to confirm active inflammation, but there is no agreed threshold. If available, comparison of previous levels measured when disease is active is most likely to help. It is not helpful to measure calprotectin routinely in patients with clinically obvious relapse, as the degree of elevation makes no difference in treatment decisions.
- v. *Detection of postoperative relapse in Crohn's disease*—after uncomplicated ileocaecal resection, faecal calprotectin and lactoferrin normalise, but subsequent high levels have been strongly associated with clinical disease activity.^{42–43} In the POCER trial,⁴⁴ a prospective study to determine optimal medical management of postoperative Crohn's disease, a faecal calprotectin >100 $\mu\text{g/g}$ indicated endoscopic recurrence with a sensitivity 0.89 and negative predictive value 91%, potentially allowing avoidance of colonoscopy in 41% of patients.⁴³ In the TOPPIC trial however, faecal calprotectin performed poorly in prediction of endoscopic Rutgeerts score in subsequent colonoscopy.⁴⁵

SHORTCOMINGS OF FAECAL CALPROTECTIN

- *Variability between commercially available assays*—a number of different commercial calprotectin assays are available and some concerns have been raised about interassay variability in the literature, which is due, in part, to a lack of assay standardisation.^{46–47} The derivation of a nationally agreed normal range and an 'intermediate' level is thus an area of concern due to this

between-assay variability.^{3 16 20–23 48–50} Indeed, the NICE committee highlighted the different thresholds for interpreting faecal calprotectin results and concluded that there was a need to undertake further research before a recommendation on a particular cut-off could be nationally agreed.⁶

- *Intra-individual variability*—there is a degree of variability within patients over the course of a day and over the course of several days, but this is usually of no clinical significance.^{51–52} There is good reproducibility in multiple samples taken from different areas of the same stool sample.⁵¹ Levels measured after samples kept at room temperature for 3 days are similar to assays done the same day, but levels are significantly lower after 7 days.⁵¹ Calprotectin levels vary in stools passed in a single day, and levels appear to increase with interval between bowel actions. It is suggested that a standardised approach with sampling from the first bowel action in the morning would potentially reduce this variability.
- *Lack of specificity*—faecal calprotectin is not specific for IBD and can also be increased in stool in other gut pathologies, although its use is not recommended to identify these diagnoses, for example, infectious enteritis, colorectal neoplasia, polyps, diverticulitis and in patients using NSAIDs.^{53–56}

SUMMARY RECOMMENDATIONS

Faecal calprotectin is a sensitive and specific non-invasive marker of gastrointestinal inflammation.

- It is recommended that stool sample for calprotectin is collected from the first bowel action of the day, and kept for no longer than 3 days at room temperature.
- It is recommended that threshold values are determined on the basis of local audit data, and assay used.
- It is recommended that faecal calprotectin is used to discriminate between functional gastrointestinal symptoms and IBD in primary and secondary care in adults with recent-onset lower gastrointestinal symptoms, where cancer is not suspected and for whom specialist assessment is being considered. It should not be used in patients with acute diarrhoea, bloody diarrhoea or in older patients where the need to rule out polyps or cancer mandates colonoscopy anyway.
- It is suggested that faecal calprotectin measurement is useful in patients with IBD, in whom it is unclear whether symptoms are due to active inflammation, or other causes such as coexisting IBS or bile salt malabsorption.
- It is suggested that faecal calprotectin can be useful in decision-making regarding either stopping or increasing drug therapy for IBD. It is not recommended that faecal calprotectin is used *routinely* in the monitoring of all patients with IBD.

Contributors SJW and MJB performed the literature searches to prepare this manuscript. They prepared the initial document, which was extensively edited by DRG and ABH. The document has also been reviewed by the IBD section committee and we thank the committee for their insightful and helpful comments on this manuscript.

Competing interests MJB has received honoraria for advisory board membership to Shield Pharma and Vifor Pharma. He has received grant support from Vifor Pharma. He has been supported for conference expenses by MSD, Vifor, AbbVie, Warner Chilcott and Allergan. None of these was directly related to the preparation of this work. DRG is funded by a Senior NRS Fellowship Award.

Provenance and peer review Not commissioned; externally peer reviewed.

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