Faecal calprotectin: a bright future for assessing disease activity in Crohn’s disease

Calprotectin is a calcium-binding protein with in vitro bacteriostatic and fungistic properties. It is found in abundance in neutrophils, where it accounts for 60% of the protein in the cytosol; lower concentrations are found in monocytes and reactive macrophages. It was hoped that measurement of faecal calprotectin would represent a surrogate marker of neutrophil influx into the bowel lumen and in turn act as a marker of intestinal inflammation. Studies to date support this hypothesis; increased levels of faecal calprotectin are found in inflammatory bowel disease, colonic cancer and non-steroidal anti-inflammatory drug (NSAID) treatment, suggesting it is a sensitive but non-specific marker of intestinal inflammation.

Clinical assessment of disease activity and laboratory indices of inflammation correlate poorly with endoscopic findings and histology in patients with inflammatory bowel disease. Faecal calprotectin, however, correlates well with endoscopic and histological grading of disease activity in ulcerative colitis. Moreover, it correlates more closely to histology than to macroscopic (colonoscopic) findings, suggesting it is more sensitive than endoscopy in inflammatory bowel disease.

Assessment of disease activity in ulcerative colitis is amenable to colonoscopic examination and subsequent histological analysis, as the disease is exclusively colonic. This is not always possible in Crohn’s disease, because of the variable location and patchy distribution of the disease; the small intestine, in particular, is not always accessible to endoscopic examination. In the absence of histology, an accurate measure of small-bowel inflammation in Crohn’s disease is controversial. Radiolabelled-white-cell scanning of the abdomen is the most popular method in current clinical practice, and offers information on distribution and severity of inflammation. Drawbacks, however, include cost, variable sensitivity, radiation dose and lack of availability in most district general hospitals. A four-day faecal excretion of indium-111-labelled granulocytes has been suggested as a ‘gold standard’ for assessing intestinal inflammation in Crohn’s disease. However, this test is costly to perform, requires sterile labelling facilities, exposes the patient to radiation and incurs all the practical problems of complete faecal collection over a four-day period. Hence its use is limited to only a few research centres. A strong positive correlation between faecal calprotectin and faecal excretion of indium-111-labelled neutrophils has been shown, which supports the hypothesis that faecal calprotectin reflects the migration of neutrophils through the inflamed gastrointestinal mucosa.

Hence faecal calprotectin has been proposed as an ideal marker of disease activity in Crohn’s disease; the test is cheap, and simple to perform (5 g spot stool sample with commercial ELISA kit), with a marker that is stable at room temperature for up to seven days (thereby permitting postage of samples). It correlates well with radiolabelled-white-cell scanning and is extremely sensitive.

Faecal calprotectin cannot replace invasive tests for the diagnosis of Crohn’s disease, as it is too non-specific. Histology will remain the gold standard for diagnosis, and a combination of endoscopic and imaging techniques will define disease distribution. However, faecal calprotectin has real potential to evolve as a simple, cheap, non-invasive and sensitive marker of disease activity and/or its response to treatment in those who already have a firm diagnosis of inflammatory bowel disease.

The Crohn’s disease activity index (CDAI) is a validated clinical/laboratory scoring system, used largely in trial settings, to assess the activity of the disease and the response of the score to treatment. Numerous problems exist with the CDAI. Firstly, substantial inter-observer variability exists when different observers review the same case notes to calculate the CDAI. Secondly, a large proportion of the score is subjective, depending heavily on the patient’s perception of the disease. Thirdly, the presence of draining fistulae may contribute...
disproportionately small number of points to the score. Finally, it is well known to underestimate Crohn’s disease activity, compared with excretion of autologous $^{111}$In-labelled granulocytes in faeces or with endoscopic evaluation. In Tibble’s study, there was a significant, albeit weak, correlation between faecal calprotectin and CDAI; the absence of a stronger correlation is not surprising, as symptoms in Crohn’s disease may derive from non-inflammatory processes such as fibrotic strictures and bile-salt-induced diarrhoea after previous ileal resection. One may question why, in the face of all the above disadvantages, the CDAI is used at all in such studies. Firstly, it has been widely used to evaluate drug efficacy in Crohn’s disease over a 25-year period, and secondly and perhaps more importantly, it does reflect patient wellbeing, which is the general basis on which treatments for Crohn’s disease are justified. Thus such indices will remain useful in clinical practice and at our institution we are currently comparing faecal calprotectin, radiolabelled-white-cell scanning and the CDAI in assessing disease activity in symptomatic patients with (histologically proven) Crohn’s disease.

Numerous other potential roles for faecal calprotectin appear to be evolving. These may involve differentiating between organic and functional bowel disease and assessing the toxicity of new NSAIDs. As shown by Schmidt et al., calprotectin measures will reveal treatment failure in Crohn’s and ulcerative colitis patients, thus avoiding prolonged ineffective steroid courses. Faecal calprotectin may be able to predict relapse in inflammatory bowel disease before this becomes apparent clinically; if treatment can then be targeted at such high-risk patients, one would hope that symptoms of a relapse could be avoided. This also raises the question of whether we should consider treating patients on the basis of the inflammatory component of Crohn’s disease, irrespective of symptoms, in order to alter the natural history of the disease, much as in the management of conditions such as Wegener’s granulomatosis and rheumatoid arthritis. However, we do not yet know if it would be in the patient’s best interests to treat asymptomatic bowel inflammation; for the foreseeable future, treatment decisions will remain symptom/sign-based.

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References