

Editorial

Fecal calprotectin: towards a standardized use for inflammatory bowel disease management in routine practice.



The measurement of fecal calprotectin has now been studied in clinical research for more than 10 years. Its ability to differentiate Inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) patients and to predict clinical relapse in patients with Crohn's disease or ulcerative colitis in clinical has been extensively showed.¹ More recently, its correlation with endoscopic lesions of IBD and to endoscopic scores of activity in both Crohn's disease (CDEIS and SESCD) and ulcerative colitis (endoscopic Mayo score) has been demonstrated.^{2,3} Accordingly, a significant decrease of fecal calprotectin, after medical treatment, has been found in association with clinical response and also with mucosal healing.^{4,5} For all these aspects fecal calprotectin is superior to classically used blood biomarkers, such as C-reactive protein, erythrocyte sedimentation rate or fibrinogen. Hence, some IBD clinicians and centers across the world have used it for several years in their routine practice as a companion diagnostic tool to help to diagnose, monitor and adapt treatment in Crohn's disease and ulcerative colitis. More specifically, it is used by some as a first line test to help decide when and in whom a more invasive endoscopic or magnetic resonance imaging should be performed.⁶

Nevertheless, other less enthusiastic colleagues have not started yet and still advocate the need for more data, clarifying how to use this biomarker in routine practice. More particularly, the cut-off values that should be used in diagnosis and more importantly in patients follow-up and monitoring are not sufficiently defined; the intra-individual non specific variations and the best timing for stool sampling have not been enough characterized; finally the frequency at which fecal calprotectin should be measured in longitudinal follow-up of patients has not been determined. Four independent studies published in the present issue of Journal of Crohn and Colitis tackle these pending questions and help to progress on the road towards a more standardized and evidence-based use of fecal calprotectin in the management of IBD in routine practice.^{7–10}

The first data published on fecal calprotectin consistently showed a significant increase in IBD as compared to healthy controls and IBS.¹¹ Hence the first broadly approved application of fecal calprotectin measurement has been the differential diagnosis between IBS and IBD with a sensitivity and specificity higher than 90%, allowing to sparing a significant number of colonoscopies,⁶ although actually only a few small studies measured fecal calprotectin at the time of clinical presentation, before any diagnosis was made.^{12,13} In this issue of Journal of Crohn and Colitis, a retrospective study on a large Scottish population between 16 and 50 years of age, confirms a highly significant increase of fecal calprotectin at diagnosis in IBD patients.⁷ The reason to focus on patients younger than 50 years of age is the fact that beyond this age, due to the frequency of colorectal

cancer, a colonoscopy should be proposed to most of the patients with gastro-intestinal symptoms while in younger patients, a non invasive first-line testing may help to decide in which patients to perform a colonoscopy. What is particularly convincing in these data is the negative predictive value of a fecal calprotectin <100 microg/g to differentiate IBD from IBS, at 0.99. This study strongly confirms previous studies in this field and allows to claim that in a patient between 16 and 50 years of age and presenting with non specific gastro-intestinal symptoms, a fecal calprotectin as a unique first line test would be sufficient to decide in which patient to perform further endoscopic or medical imaging explorations. The presence of alarm symptoms was the second most informative parameter and even further increased the sensitivity and specificity for the detection of an IBD when added to fecal calprotectin. On the contrary, other classical biomarkers including C-reactive protein did not significantly improve sensitivity while they negatively impacted specificity. In their large series, only three patients finally diagnosed with IBD had a low fecal calprotectin, but all three had alarm symptoms: two with proctitis had blood in the stools and one with mild terminal ileal Crohn's disease had weight loss.

This study thus strongly validates the pivotal role of fecal calprotectin as a first-line test in patients presenting with non specific gastro-intestinal symptoms. As far as the optimal cut-off value, the authors seem to favor 50 microg/g, although their own data show very similar sensitivity and negative predictive value with 100 microg/g, while this level clearly has a better specificity and positive predictive value and would allow, according to a previous work, a larger colonoscopy sparing.¹⁴

Mucosal healing is now considered as the target to reach in IBD. Indeed, preliminary data in Crohn's disease and more consistent data in ulcerative colitis have showed the benefit of mucosal healing on short term and mid-term outcome.^{15–18} Fecal calprotectin is mainly considered as a non-invasive surrogate marker of mucosal healing. Nevertheless, several studies have showed the imperfect correlation between mucosal healing and fecal calprotectin on one hand and the added value of fecal calprotectin over mucosal healing in predicting disease relapse on the other hand. In the STORI trial, for example, the relapse rate in patients with mucosal healing stopping anti-TNF was around 30%, while it was between 10 and 20% in patients having both mucosal healing and low fecal calprotectin value.¹⁹ In the study by Mooiweer et al, in the present issue of Journal of Crohn and Colitis, assessing IBD patients in clinical remission and mucosal healing, an elevated fecal calprotectin was associated with an increased risk of relapse.⁸ This clearly confirms the added value of fecal calprotectin over mucosal healing in the prediction of clinical relapse. The optimal threshold to predict relapse was 56 microg/g,

which is lower than the previously proposed thresholds (130–340 microg/g).^{20–22} This may be due to the fact that the current study focused on patients being not only in clinical but also in endoscopic remission. There was no significant correlation between fecal calprotectin and histological inflammation. Nevertheless, fecal calprotectin was more strongly associated with the risk of relapse than histological inflammation. The absence of correlation between fecal calprotectin and histology in the present study is in contrast with previous studies^{13,23} and may be explained by the fact that none of the patients had endoscopic lesions and that only a minority had histological inflammation leading to a small range of histological inflammation grades. This may also explain the absence of predictive value of histology on clinical relapse, which has been previously well demonstrated, particularly in UC patients.^{24–26} There may also be a discrepancy between Crohn's disease and ulcerative colitis, which was not assessed in the present study, because both diseases were studied together.

This study thus confirms the added value of fecal calprotectin over mucosal healing in the prediction of relapse in patients in clinical remission. It also suggests its superiority over histological inflammation for this prediction.

In routine practice, when following up a patient in clinical remission, measuring fecal calprotectin just once to predict relapse is insufficient. Indeed, in several longitudinal studies measuring fecal calprotectin at baseline, the positive predictive value over one year or even longer period of time was actually linked to shorter term prediction, the majority of the patients with elevated calprotectin relapsing within the first 6 months after measurement.^{19–22} Serial measurements of fecal calprotectin are thus needed. However, very few data of this type are available²⁷ and the interpretation of such serial measurements of calprotectin is still a matter of debate. In the study by Molander et al, in the present issue of *Journal of Crohn and Colitis*, fecal calprotectin was measured every month for 6 months and then every other months in around 50 IBD patients having stopped anti-TNF after achieving deep remission (defined by clinical remission, mucosal healing and a fecal calprotectin <250 microg/g).⁹ Their main finding was that fecal calprotectin already significantly increased 6 months before a relapse, and that it was constantly increased in the relapsing patients a median of 94 days before the relapse while a constantly low fecal calprotectin was highly predictive of sustained remission. This suggests the fact that, when regularly monitoring fecal calprotectin after treatment de-escalation, a measurement every 3 months would be enough to capture the risk of relapse in half of the patients and react appropriately in a timely manner. However, in the other half of the patients, the timing between fecal calprotectin elevation and relapse is shorter and it should be measured more frequently. The problem is that we can't determine who are the patients requiring more frequent measurements. Beyond that, such frequently repeated measurement of fecal calprotectin would probably be difficult if the patient had to bring stools at the hospital for every measurement. This emphasizes the relevance of the Lasson's study, also published in this issue of *Journal of Crohn and Colitis*, which shows a good reproducibility of fecal calprotectin measurement when performed on several samplings in the same bowel movement by the patient himself, without previous stool homogenisation.¹⁰ This would allow the patient to extract the fecal sample himself, home, and send it to the laboratory. Globally, Lasson's study showed the good practicability for the patients of their own stool sample collection at home and the usefulness of complete faeces collection kits. It also showed a significant calprotectin concentration decrease when the stools were stored more than

3 days at room temperatures before measurements. This should thus be avoided and explained to the patients. All this also highlights the potential interest of developing devices that would allow the patient to measure fecal calprotectin himself at home.²⁸

Finally, if we want to use serial measurements of fecal calprotectin to manage the disease in routine practice and decide treatment changes, the existence of non specific variations is a major concern. In the study by Lasson et al, a significant variability was found in several stool samples collected over one day as well as collected over two consecutive days.¹⁰ Most often these variations, concerned values above and not across the classical thresholds for the prediction of mucosal healing and would thus mainly affect the ability to predict endoscopic severity of the disease but not the existence of an endoscopically active disease. A similar finding highlighting a lower variation in samples from Crohn's disease patients in remission was reported.²⁹ However in Lasson's paper, in one third of active ulcerative colitis patients, these fluctuations crossed the line separating active from inactive disease and may thus represent an important drawback for the use of fecal calprotectin in this setting.¹⁰ This non specific fluctuation is one important point that should be further studied. Another important aspect showed by this study is the significant variation along the same day. Fecal calprotectin concentration usually increased with time interval between stool collections. The interpretation is that calprotectin, released by the inflamed mucosa, tends to accumulate in the stools when they remain longer in the intestine. Therefore it would be wise to advocate the sampling of the first stool in the morning to try and uniform this sampling procedure.

Overall, the measurement of fecal calprotectin can thus now be considered as a powerful first line test to differentiate IBS from IBD. It also clearly correlates to endoscopic activity of both Crohn's disease and ulcerative colitis, and predicts clinical relapse over the short term even in patients with mucosal healing. To monitor IBD in routine practice, repeated measurements of this marker are necessary. These should be made on the first morning stool, kept no longer than 3 days at room temperature before measurement and performed more frequently than every 3 months in at least half of the patients, emphasizing the importance of the development of cost-affordable and patient-friendly methods of stool collection and even fecal calprotectin measurement. In this setting the most important issue to solve, requiring further studies, is the non specific variation of fecal calprotectin over time. Beyond these uncertainties and practical aspects, it also remains to be demonstrated that a change in medical treatment driven by fecal calprotectin measurement is able to impact on disease outcome. A recently published intervention study suggests that it may be the case.³⁰ In this study, increasing the dose of mesalazine in an ulcerative colitis patient in remission but having elevated fecal calprotectin was not only able to decrease fecal calprotectin but also to probably decrease the risk of relapse.³⁰

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