

# Measuring disease activity in Crohn's disease: what is currently available to the clinician

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**Abstract:** Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by a relapsing-remitting clinical behavior and dominated by intestinal inflammation. Being a chronic disorder that with time develops into a disabling disease, it is important to monitor the severity of inflammation to assess the efficacy of medication, rule out complications, and prevent progression. This is particularly true now that the goals of treatment are mucosal healing and deep remission. Endoscopy has always been the gold standard for assessing mucosal activity in CD, but its use is limited by its invasiveness and its inability to examine the small intestine, proximal to the terminal ileum. Enteroscopy and the less invasive small bowel capsule endoscopy enable the small bowel to be thoroughly explored and scores are emerging for classifying small bowel disease activity. Cross-sectional imaging techniques (ultrasound, magnetic resonance, computed tomography) are emerging as valid tools for monitoring CD patients, assessing inflammatory activity in the mucosa and the transmucosal extent of the disease, and for excluding extra-intestinal complications. Neither endoscopy nor imaging are suitable for assessing patients frequently, however. Noninvasive markers such as C-reactive protein, and fecal biomarkers such as calprotectin and lactoferrin, are therefore useful to confirm the inflammatory burden of the disease and to identify patients requiring further investigations.

**Keywords:** activity, biomarkers, Crohn, endoscopy, imaging, monitoring

## Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by a relapsing-remitting clinical behavior. The main feature of CD is intestinal inflammation. Its site, extent, and severity influence the phenotype and natural history of the disease (together with factors such as age at onset, smoking habits, perianal disease, and the need for steroids at diagnosis).<sup>1,2</sup> It is not unusual to find intestinal inflammation (even without any gastrointestinal symptoms) leading to progressive bowel damage, increasing disability, and an impaired quality of life.<sup>3</sup> In recent years, the goals of treatment have gradually moved beyond clinical remission towards a new (and as yet poorly defined) concept termed "sustained deep remission", which means a condition of clinical, biological, endoscopic, and possibly, radiological remission.<sup>4,5</sup> Measuring clinical activity is consequently still important, but no longer enough, and the available symptom-based scoring systems (the Crohn's Disease Activity Index [CDAI], and the simpler Harvey Bradshaw Index) suffer from subjective interpretation.<sup>6-8</sup> The high rates of response to placebo (up to 33%) reported in randomized controlled trials using the CDAI to measure response to treatment justify the need for more objective methods for assessing the presence and severity of intestinal inflammation.<sup>9</sup> The ultimate goal

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of monitoring in CD patients is to modify the natural history of the disease, taking a “treat-to-target” approach.<sup>10</sup>

This review provides a brief, practical overview of the tools currently available to clinicians for objectively measuring disease activity in CD patients. In particular, we focus on the ability of endoscopy, cross-sectional imaging techniques, and biomarkers to detect intestinal inflammation.

## Endoscopy

Ileocolonoscopy is considered the gold standard for the diagnosis and assessment of disease activity and extent in CD patients. It has recently increased in importance with the use of biologics, and the growing awareness that mucosal healing may be the optimal treatment target with a view to changing the natural history of the disease.<sup>11–13</sup>

It is well known that clinical symptoms of CD seem to correlate little with the severity of endoscopic lesions,<sup>14</sup> while it has been demonstrated that the severity and extent of mucosal lesions influence the course of the disease. Allez et al reported that finding severe endoscopic lesions (deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colon) at colonoscopy in 102 patients with CD was a risk factor for penetrating complications and colectomy, with a probability of colectomy at 1, 3, and 8 years of 31%, 42%, and 62%, respectively.<sup>15</sup> In another study, a stricturing phenotype predicted a poor response to medical treatment and a greater need for surgery.<sup>16</sup> Complete mucosal healing in newly diagnosed CD patients after 2 years of medical treatment emerged as the only factor capable of predicting sustained, steroid-free remission for up to 4 years.<sup>12</sup> Similarly, in a large Norwegian population-based prospective cohort study, mucosal healing 1 year after the diagnosis of CD (in the prebiologic era) predicted a more limited subsequent disease activity and need for active treatment.<sup>17</sup>

Endoscopic remission should therefore be considered an early target of medical treatment. Af Bjorkesten et al showed that endoscopic remission after 3 months of anti-tumor necrosis factor alpha treatment strongly predicts endoscopic remission at 1 year.<sup>18</sup> The benefit of reaching mucosal healing is also confirmed by the effects of long-term maintenance infliximab treatment, with an improved long-term disease outcome, less major abdominal surgery, fewer hospitalizations, and fewer relapses.<sup>11,19</sup> Much the same can be said of adalimumab, judging from the results of the EXTEND trial.<sup>13</sup>

Endoscopy is thus a crucial step in assessing CD activity, but it has some limitations: it is invasive, poorly accepted by patients, and it can only examine the mucosa, not the deeper

layers of the intestinal wall, and it misses any extra-intestinal complications of the disease.<sup>20</sup> There is also some debate on the definition of mucosal healing, and how much a partial improvement in endoscopic disease activity in response to treatment suffices to improve clinical outcome remains to be seen.<sup>21,22</sup> In some studies, even a partial healing of the mucosa was enough to improve the course of the disease.<sup>11,18</sup> The most appropriate schedule for the endoscopic follow-up of CD activity also remains unclear. For the time being, it should be planned on a case by case basis, when the findings of an endoscopy might influence the management of a given patient's disease.

Endoscopic scoring systems have been developed to classify disease activity and they have been validated to enable a consistent and reproducible assessment of CD activity, minimizing interobserver variability. There are currently three endoscopic scoring systems for CD: the Crohn's Disease Endoscopic Index of Severity (CDEIS),<sup>23</sup> the Simple Endoscopic Score for Crohn's Disease (SES-CD),<sup>24</sup> and the Rutgeerts endoscopic grading scale.<sup>25</sup>

The CDEIS scores CD activity (from 0 to 44) in five bowel segments (terminal ileum, right colon, transverse, left colon and sigmoid, and rectum), considering specific mucosal lesions such as ulcers and stenosis, and extent of disease.<sup>21–23</sup> The CDEIS is complicated to use, requiring training and experience in estimating the extent of ulcerated or diseased mucosal surfaces, and expertise in distinguishing deep from superficial ulcerations. It is also time consuming. It has consequently not become routine in clinical practice and is used mainly in clinical trials.

To simplify the CDEIS and to make it easier to use in every day clinical practice, Daperno et al developed the SES-CD.<sup>24</sup> This system includes four variables, each considered in five segments of the bowel: ulcer size (0.1–0.5 cm; 0.5–2 cm; >2 cm), the extent of ulcerated surface (<10%; 10%–30%; >30%), the extent of affected surface (<50%; 50%–75%; >75%), and stenosis (single or multiple, and partially or totally occluded). Scores range from 0 to 60.<sup>21,22,24</sup> The SES-CD significantly correlates with the CDEIS (Spearman's  $r=0.938$ ,  $P<0.0001$ ), and this correlation is also maintained when the disease is graded from inactive to severe, and when changes in activity are compared between baseline and follow-up endoscopies.<sup>26</sup>

Endoscopic scores are useful objective tools for assessing the degree of CD activity, and should be used to monitor disease evolution and orient treatment decisions. The degree of mucosal improvement (endoscopic response) needed to alter midterm outcome is not known, however. Ferrante et al

recently performed a post hoc analysis on data from the SONIC trial addressing this specific issue.<sup>27</sup> In 172 patients they studied the minimum clinically important improvement in endoscopic disease activity at week 26 that reliably predicted corticosteroid-free clinical remission at week 50, and could therefore be proposed as an appropriate cutoff for endoscopic response. A reduction of at least 50% in the SES-CD or CDEIS score after 26 weeks of treatment identified the patients most likely to be in corticosteroid-free clinical remission at week 50.

The situation of CD patients after surgery deserves a separate discussion. Given the finding that almost 80% of patients have an endoscopically detectable recurrence within 1 year after surgery (even without clinical symptoms),<sup>28,29</sup> Rutgeerts et al developed a score for grading lesions in the neo-terminal ileum and anastomosis.<sup>25</sup> This score ranges from 0 to 4: 0, no lesions; 1, <5 aphthous lesions; 2, >5 more severe aphthous lesions; 3, diffuse inflammation with diffuse ulcers; and 4, nodules and/or narrowing. This score is considered the gold standard for establishing the prognosis in cases of postoperative recurrence: scores 3 and 4 are validated cutoffs for predicting clinical relapse, and should prompt medical treatment to prevent disease evolution and clinical relapse.

The goal of optimal treatment should be to stop the inflammatory process completely. Mucosal healing may not suffice and histological healing should be considered the final target, but there is currently no accepted definition of histological healing, or standardized histological scoring system. The presence of neutrophils in the lamina propria and epithelium, epithelial cell damage, and an increase in lymphocytes and plasma cells are considered features of disease activity, and their persistence may be associated with relapse.<sup>30</sup> It is important to bear in mind that histological healing does not necessarily coincide with mucosal healing: D'Haens et al showed that CDEIS and inflammatory infiltrate improved in patients treated with a single infusion of infliximab, but architectural glandular changes persisted in most patients.<sup>31</sup> Smith et al showed that CD patients on prolonged treatment with naltrexone further improved in terms of their endoscopic inflammation scores beyond the 12 week follow-up, but this was not associated with any further improvement in their histological scores.<sup>32</sup>

One of the limits of conventional endoscopy in CD is that the small bowel remains inaccessible. Small bowel endoscopy is defined as any endoluminal examination of the small bowel, including capsule endoscopy, push enteroscopy and balloon-assisted endoscopy.<sup>33</sup>

Small bowel capsule endoscopy (SBCE) enables the whole of the small bowel to be explored using a wireless capsule, which is swallowed and propelled through the gastrointestinal tract by gut motility. According to the recently published international OMED–ECCO consensus, there are no specific SBCE diagnostic criteria for CD: the method has a high diagnostic yield in terms of identifying small bowel mucosal lesions (even better than magnetic resonance imaging [MRI] or computed tomography [CT], judging from a few preliminary findings).<sup>34,35</sup> Such endoscopic lesions may not be specific for CD, however, and having no opportunity to perform a histological examination prevents any conclusive differential diagnosis. In patients with an established diagnosis of CD, SBCE should be reserved for cases with unexplained symptoms, when conventional ileocolonoscopy and imaging techniques prove inconclusive, and when identifying less obvious superficial lesions may have an impact on a patient's clinical management.<sup>33</sup>

Recent evidence has pointed to a role for SBCE in post-operative patient management to detect lesions in the small bowel overlooked by ileocolonoscopy after an ileocolic resection.<sup>36</sup> Ileocolonoscopy nonetheless remains the gold standard for assessing postoperative recurrences. The use of SBCE to monitor response to therapy is still controversial. As already established for conventional endoscopy, so too for SBCE, clinical activity does not correlate with mucosal healing. Efthymiou et al found clinical response apparently unrelated to mucosal healing as detected by capsule endoscopy, since only one of three variables (the number of large ulcers) improved significantly with treatment.<sup>37</sup> Similarly, Yang et al found that clinical and biological improvements after medical treatment were not consistently associated with any amelioration in the mucosal lesions seen at SBCE.<sup>38</sup>

Disease activity indices have been proposed for use with SBCE with a view to making the assessment and monitoring of mucosal healing more objective. The Capsule Endoscopy CD Activity Index ([CECDAI] or Niv score) was validated in a multicenter prospective study on 62 patients with isolated small bowel CD.<sup>39</sup> The three main parameters considered were inflammation, extent of disease, and presence of strictures. Then there is the Lewis score, which assesses villous edema, ulcer and stenosis, classifying CD activity from mild to severe.<sup>40</sup> When the performance of these two SBCE inflammation scoring systems (CECDAI and Lewis score) was tested by correlating them with patients' fecal calprotectin levels, the Lewis score correlated better with fecal calprotectin levels, providing they were below 100 µg/g.<sup>41</sup> These SBCE scoring systems have been

developed only recently, and their usefulness in clinical trials and clinical practice remains to be seen.<sup>21</sup>

Balloon-assisted enteroscopy (using double or single balloons) has largely replaced push enteroscopy because it enables the small bowel to be intubated completely via oral and anal routes and, unlike SBCE, it allows for tissue sampling and therapeutic procedures. The disadvantages of this technique lie in its complexity and the need for patient sedation and for specifically trained and experienced endoscopists to perform it. The method is not widely used.<sup>33</sup> A summary of advantages and disadvantages of endoscopy for the monitoring of CD is reported in Table 1.

## Cross-sectional imaging techniques

Although endoscopy remains the gold standard for assessing CD activity, it suffers from several limitations. Colonoscopy only explores the colon and a few centimeters of the terminal ileum. Gastroscopy is helpful in only a minority of patients. Double balloon enteroscopy is not widely available and rather invasive. As for SBCE, no biopsies can be obtained, it is not advisable in cases of stenosis, and it may provide suboptimal information on the small bowel if patient preparation is inadequate. In addition, endoscopic procedures can only examine the superficial layer of the intestinal mucosa, missing

transmural and extra-intestinal manifestations of the disease. Cross-sectional imaging techniques are therefore gaining in importance in a complementary role, especially to measure the cumulative intestinal damage and the interplay between inflammation and fibrosis. A summary of advantages and disadvantages of cross-sectional imaging techniques for the monitoring of CD is reported in Table 2.

## Ultrasound (US)

US is a noninvasive, radiation-free imaging technique that is particularly useful for examining the terminal ileum and colon, whereas the proximal ileum, jejunum, transverse colon, and rectum may be difficult to assess.<sup>42</sup> Visualization of the intestinal wall may be limited by gas-filled bowel and obesity, and the diagnostic accuracy of US is also influenced by the sonologist's experience.<sup>42,43</sup>

The main features detectable on US bowel studies are bowel wall thickness, loss of stratification, strictures, wall stiffness with a reduced or no peristalsis in the small bowel, and loss of haustra coli in the colon.<sup>44,45</sup> Other US findings correlating with CD include poor compressibility

**Table 1** Advantages and disadvantages of endoscopic techniques for monitoring Crohn's disease activity

Advantages	Disadvantages
<b>Ileocolonoscopy</b>	
<ul style="list-style-type: none"> <li>• Direct evaluation of mucosal healing</li> <li>• Possibility of mucosal sampling for histology</li> <li>• Validated scores of severity (CDEIS/SES-CD/Rutgeerts Score)</li> <li>• Predictive of risk of               <ul style="list-style-type: none"> <li>– Relapse</li> <li>– Refractoriness to medical therapy</li> <li>– Surgery</li> <li>– Postoperative recurrence</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Invasiveness</li> <li>• Bowel preparation</li> <li>• Costs</li> <li>• No transmural evaluation</li> <li>• No visualization of proximal ileum</li> <li>• Controversial definition of mucosal healing (partial versus complete healing of the mucosa)</li> </ul>
<b>Small bowel capsule endoscopy</b>	
<ul style="list-style-type: none"> <li>• Complete visualization of the small bowel mucosa</li> <li>• Less invasive than conventional endoscopy</li> <li>• High diagnostic yield for small mucosal lesions</li> <li>• Recent validation of scores of severity (Niv and Lewis)</li> </ul>	<ul style="list-style-type: none"> <li>• Scores of severity need further validation in larger cohort of patients</li> <li>• No mucosal sampling for histology</li> <li>• Costs</li> <li>• Bowel preparation</li> <li>• No transmural evaluation</li> <li>• Not widely available</li> </ul>

**Abbreviations:** CDEIS, Crohn's Disease Endoscopic Index of Severity; SES-CD, Simple Endoscopic Score for Crohn's Disease.

**Table 2** Advantages and disadvantages of cross-sectional imaging techniques for monitoring Crohn's disease activity

Advantages	Disadvantages
<b>MRI</b>	
<ul style="list-style-type: none"> <li>• Evaluation of small bowel and colon</li> <li>• Perianal evaluation</li> <li>• Assessment of transmural and extramural activity</li> <li>• Validated scores of activity (MaRIA/CDMI)</li> <li>• Radiation free</li> </ul>	<ul style="list-style-type: none"> <li>• Costs</li> <li>• Time consuming</li> <li>• Not widely available</li> <li>• Requires bowel distension with oral and/or rectal contrast</li> <li>• Requires intravenous contrast medium</li> </ul>
<b>CT</b>	
<ul style="list-style-type: none"> <li>• Evaluation of small bowel and colon</li> <li>• Assessment of transmural and extramural activity</li> <li>• Widely available</li> </ul>	<ul style="list-style-type: none"> <li>• Radiation exposure</li> <li>• No validated scores</li> <li>• Requires bowel distension with oral and/or rectal contrast</li> <li>• Requires intravenous contrast medium</li> </ul>
<b>US</b>	
<ul style="list-style-type: none"> <li>• Evaluation of terminal ileum and colon</li> <li>• Assessment of transmural and extramural activity</li> <li>• Radiation free</li> <li>• Noninvasive</li> <li>• Possibility to use Doppler and Contrast Enhanced techniques</li> </ul>	<ul style="list-style-type: none"> <li>• Limited assessment of proximal ileum, jejunum, transverse colon, rectum</li> <li>• Limited by gas filled bowel, obesity</li> <li>• Accuracy is dependent on the experience of the sonologist</li> <li>• Score of activity (SLIC) needs further validation</li> </ul>

**Abbreviations:** CDMI, Crohn's Disease MRI Index; CT, computed tomography; MaRIA, Magnetic Resonance Index of Activity; MRI, magnetic resonance imaging; SLIC, sonographic lesion index for CD; US, ultrasound.

of thickened bowel walls, narrowing of the lumen, conglomeration of loops, and extramural lesions such as fistulae or abscesses.<sup>43</sup>

Nonabsorbable oral solutions can be administered to increase the sensitivity of US in detecting segments with active disease, and using a luminal contrast in the colon can improve its accuracy in assessing colonic CD lesions.<sup>43,46,47</sup> In the systematic review conducted by Panes et al, the reported overall sensitivity and specificity of US in assessing CD activity were 85% and 91%, respectively.<sup>43</sup> Doppler US and contrast-enhanced US may feasibly help emphasize the vascularization pattern and thus increase the method's diagnostic accuracy in identifying CD activity, but they have demonstrated a similar sensitivity and specificity to conventional US.<sup>48</sup> On the other hand, contrast-enhanced US was able to classify the severity identified at endoscopy significantly better than Doppler US.<sup>49,50</sup> Calabrese et al developed a quantitative index for assessing CD-related small bowel damage as detected by small intestine contrast ultrasonography, called the sonographic lesion index for CD (SLIC).<sup>51</sup> The SLIC considers both the extent and the severity of small bowel damage (bowel wall thickness, lumen diameter, length of lesions, and number of sites involved), as well as fistulas, mesenteric adipose tissue changes, abscesses, and lymph nodes. It has the potential for scoring the progression of small bowel disease by means of serial assessments, and of quantifying any changes after treatments. It can therefore be a useful, noninvasive tool for gastroenterologists with sufficient expertise. This score needs to be validated on a larger cohort of patients, however, before it can enter clinical practice.

## CT

CT is a valid tool for examining luminal and extraluminal structures in CD patients, and it has the advantage of being widely available and standardized in its use.<sup>42,43</sup> Its major drawback lies in the related radiation exposure, especially in patients being assessed repeatedly.

CT enterography requires an adequate luminal distension obtained by means of oral contrast agents (such as polyethylene glycol solutions), and the intravenous administration of contrast medium is essential to assess bowel wall enhancement and mesenteric vessels.<sup>52</sup> Typical CT findings of active CD are mural hyperenhancement, bowel wall thickening (>3 mm), mural stratification due to intramural edema, engorged vasa recta (comb sign), and increased attenuation of mesenteric fat. The CT features that may be helpful in differentiating active inflammatory disease from

a fibrostenosing evolution of CD include strictures without mural hyperenhancement, submucosal fat deposition, and absence of mural stratification due to transmural fibrosis.<sup>52</sup> Drawing this distinction may be difficult, however, because active inflammation and fibrosis often coexist in the same patient, and even in the same bowel segment.

CT enterography is highly sensitive and specific in detecting intestinal lesions, especially in the ileum,<sup>53</sup> with an overall sensitivity and specificity of around 81% and 88%, respectively. It is less effective in detecting colonic lesions, and proper administration of the contrast is very important. An amelioration in the typical CT findings of active CD, or even their disappearance, after a course of treatment correlates with the achievement of a clinical remission, as demonstrated in a retrospective study on 50 CD patients.<sup>54</sup>

When CT and MRI were compared in terms of their diagnostic accuracy, neither proved significantly superior to the other. They both provide complementary information to ileocolonoscopy, especially when exploration of the ileum is not feasible.<sup>53,55–57</sup>

In the management of CD patients, it has been suggested that CT is more appropriate in acute cases and older patients, partly to contain radiation exposure, and partly because it requires fewer breath holds (than MRI), improving patient compliance. The use of the latest generation of multidetector CT scanning and low dose protocols has recently significantly reduced the radiation dose involved. Although these protocols produce lower quality images, this does not affect the technique's diagnostic value.<sup>58,59</sup>

Cipriano et al recently developed a model to compare the life time costs, benefits, and cost effectiveness of using MRI rather than CT for routine disease monitoring in young CD patients.<sup>60</sup> They demonstrated that although MRI is more costly than CT, it remains a cost effective alternative to CT for younger patients with CD who are likely to require multiple imaging procedures over the course of their disease. This result appeared to be related to a reduction in the cancer risk related to radiation exposure.<sup>60</sup>

## MRI

MRI is gaining a major role for its diagnostic accuracy in the management of CD patients. Using a radiation free method is particularly important in young patients needing numerous examinations during their life time. For assessing CD activity, there are specific MRI features that can be measured with standard protocols, acquiring fast, unenhanced T2-weighted and gadolinium-enhanced T1-weighted sequences.<sup>61,62</sup> These acquisition protocols enable images to be obtained



within a single breath hold, with limited motion and peristaltic artifacts, while an intravenous injection of contrast medium reveals the enhancement pattern of the bowel wall and mesenteric vessels. Adequate bowel distension is essential to obtain good quality images and to avoid missing less obvious signs, such as ulcerations. This distension can be achieved by administering enteric contrast agents either orally (magnetic resonance [MR] enterography) or through a nasojunal tube (MR enteroclysis).<sup>63,64</sup> Enterocolonography also demands colon distension with a water enema, and provides information on the whole gastrointestinal tract. Special MRI sequences and techniques can be used to further improve the quantitative and qualitative diagnostic capability of MRI in ascertaining CD activity and severity,<sup>65,66</sup> including diffusion-weighted imaging, motility imaging, and magnetization transfer imaging.

The MRI features measured to assess CD activity mainly concern mural and mucosal characteristics, including the presence of ulcerations, wall thickness, mural T2 signal intensity, and T1 contrast enhancement.<sup>65</sup> There are also extramural features of inflammation, such as a comb sign, lymph node enlargement, and fat wrapping.<sup>65</sup>

Combining certain MRI features into a scoring system may be the best way to improve the accuracy of MRI in measuring CD activity.<sup>67</sup> Rimola et al proposed and validated a simplified Magnetic Resonance Index of Activity (MaRIA) score that quantifies CD-related inflammatory activity in each ileocolonic segment ( $1.56 \times \text{wall thickness in millimeters} + 0.02 \times \text{relative contrast enhancement} + 5 \times \text{edema} + 10 \times \text{ulceration}$ ).<sup>68,69</sup> Wall thickness in millimeters ( $P=0.007$ ), relative contrast enhancement ( $P=0.01$ ), mural edema ( $P=0.02$ ), and ulceration at MRI ( $P=0.003$ ) emerged as independent predictors of segmental CDEIS ( $r=0.82$ ,  $P<0.001$ ).<sup>68</sup> It should be noted, however, that the MRI in the two above cited studies,<sup>68,69</sup> was performed with a 3.0 Tesla MR unit, and that the protocol required the use of both oral contrast and colon enema to distend the small bowel and colon, respectively. It is hard to say how reproducible the MaRIA score may be in patients undergoing only standard MRI without dedicated colon preparation.<sup>65</sup>

Another MRI score is the Crohn's Disease MRI Index (CDMI), which considers mural thickness, mural T2 signal, perimural T2 signal, and mural T1 enhancement. These features (scored from 0 to 3) have proved to be significantly correlated to a reference standard of transmural pathological activity grading in surgical resection specimens. When the score was validated vis-à-vis endoscopic biopsy in a cohort

of patients, its sensitivity was 81% and its specificity 70% for histopathological activity.<sup>70</sup>

For an imaging technique to be used routinely in the management of CD patients, reproducibility and a low interobserver variability are essential requirements. Tielbeek et al recently assessed interobserver variability across four readers for scoring MRI features and scoring systems (MaRIA and CDMI) in patients with CD, using CDEIS as the reference standard.<sup>71</sup> Wall thickness in millimeters, the presence of edema, enhancement pattern, and length of sites of disease in each segment showed good reproducibility, but for extramural MRI features (perimural T2 signal, comb sign, and lymph nodes) only fair reproducibility was observed (the absence of severe patients may have influenced the results). When individual features were combined with the scoring systems, the interobserver variability was good; the correlation with the CDEIS only moderate. The MRI protocol was different from the one used by Rimola, however.<sup>68,69</sup>

The way forward is to use MRI enterography to monitor treatment response after a flare of CD, aiming to achieve transmural healing as well as mucosal healing, which has been correlated with a better CD course, fewer hospital admissions, less surgery, and higher steroid-free remission rates.<sup>4,11,12</sup> This new treatment goal is particularly important because mural inflammation may persist even in cases of mucosal healing.

The study by Sempere et al found that a significant decrease in wall thickness and contrast enhancement of the affected bowel wall coincided with a change from the active disease phase to clinical remission.<sup>72</sup> In particular, once clinical remission had been achieved, there was no significant difference in the mean contrast enhancement between CD patients and controls, but intestinal segments remained thicker in CD patients in remission than in healthy controls. Ordàs et al used the MaRIA score to monitor response to therapy in 27 patients after 12 weeks of corticosteroid or adalimumab therapy (CDEIS was used as the reference standard).<sup>73</sup> A MaRIA score below 40 predicted endoscopic remission with a sensitivity of 82% and a specificity of 85%. Van Assche et al followed up 15 patients on infliximab therapy by performing MRI enteroclysis at weeks 2 and 26.<sup>74</sup> The inflammatory components of the MRI index had improved at week 2, correlating with the CDAI, but complete normalization of MRI findings was rare.

Assessing MRI features could also help to predict future response to treatment. Lawrance et al suggested classifying CD patients based on the following MRI findings: 1) fibrosis

(bowel wall thickening without contrast enhancement); 2) mild segmental hyperenhancement and mild wall thickening; 3) mild segmental hyperenhancement and marked wall thickening; and 4) marked segmental transmural hyperenhancement.<sup>75</sup> They demonstrated that female patients and those in the mild segmental hyperenhancement category were more likely to respond to medical therapy (based on the Harvey Bradshaw Index), while patients with luminal narrowing and hold up were less likely to do so ( $P < 0.05$ ). Inflammation and fibrosis are closely and positively related, however, sometimes making it difficult to distinguish between them and to exclude one or the other, as they often coexist.<sup>76,77</sup>

The panoramic view they provide of the whole abdomen makes cross-sectional imaging techniques important diagnostic tools for assessing complications in CD. MRI is considered slightly more sensitive and specific in diagnosing intestinal stenosis than CT or US.<sup>20,42,43</sup> Accuracy in diagnosing intra-abdominal fistulas and abscesses is comparable for MRI and CT, both achieving high levels of sensitivity and specificity.

Pelvic CD is one of the clinical settings in which the superiority of MRI is unquestioned. It is more effective than CT in detecting fistulizing tracts and elucidating their relationship with the anal sphincter and adjacent structures in the perianal soft tissues, especially in cases of complex fistulae.<sup>66</sup> Proper anatomical assessment of perianal disease is particularly important to orient the patient toward the best therapeutic approach, which is medical rather than surgical.

Van Assche et al developed an MRI-based score of perianal CD severity, based on the local extent of fistulae (number of tracks, location in relation to the anal sphincter, extension) and active inflammation (hyperintensity, presence of collections and rectal wall involvement), to assess the anatomical evolution of perianal fistulae.<sup>78</sup> This score was first applied to 18 patients before and after treatment with infliximab, and it proved reliable in assessing fistula tracks, with good interobserver agreement ( $P < 0.001$ ). The study showed that despite closure of draining external orifices after infliximab therapy, fistula tracks persisted with varying degrees of residual inflammation, causing recurrent fistulae and pelvic abscesses. Long-term monitoring of infliximab therapy for perianal fistulizing CD revealed that MRI can only be considered reliable for monitoring the first year of treatment; in the longer term, clinical assessment is equally reliable or even superior to MRI for the purpose of assessing the outcome of therapy, and it would save health care resources (given the cost of repeated MRI).<sup>79</sup>

## Biomarkers

Endoscopy and imaging techniques are the most objective methods for assessing CD activity, but they have their limitations and risks. Endoscopy is invasive and requires bowel cleansing, a procedure that is poorly accepted by patients and potentially harmful. MRI needs bowel distension and intravenous contrast, it is troublesome for claustrophobic patients, and it is expensive and not available at every hospital. Numerous biomarkers have been proposed as surrogate markers of intestinal inflammation, and therefore also as potential markers of CD activity, but there is still a paucity of scientific evidence to support their use in the management and monitoring of CD patients.

C-reactive protein (CRP) is an acute phase protein that has proved to be a sensitive marker of inflammation, infection, and tissue injury. CRP is produced almost exclusively in the liver on stimulation by interleukin-6 produced at sites of inflammation. Its short half-life makes CRP a useful marker for detecting and following up CD activity.<sup>80,81</sup> In patients with high CRP levels at diagnosis, it can be used as a very accurate marker of disease activity, and also as an independent predictor of short- and medium-term clinical relapse.<sup>82</sup> A retrospective review of the medical charts of 104 CD patients who had CRP assays, colonoscopy, and either small bowel follow through or CT enterography within 14 days showed that moderate–severe clinical activity (odds ratio [OR] 4.5), active disease at colonoscopy (OR 3.5), and histological evidence of severe inflammation (OR 10.6) were significantly associated with CRP elevation, whereas abnormal findings on small bowel radiographic images were not.<sup>83</sup> Since the introduction of anti-tumor necrosis factor alpha agents, it has been well established that patients with high baseline levels of CRP have greater chances of responding to medical treatment.<sup>84</sup> This was confirmed in a recent post hoc analysis of the ACCENT I trial: patients with high baseline CRP levels ( $\geq 0.7$  mg/dL) had a higher likelihood of remaining in remission during 1 year of infliximab maintenance therapy.<sup>85</sup> Conversely, in a Hungarian cohort of 201 CD patients treated with adalimumab, CRP levels at the start of the biological therapy were not associated with clinical response or remission at weeks 24 or 52, whereas early normalization of CRP (by week 12) was associated with clinical efficacy and mucosal healing.<sup>86</sup> The “real life experience” described by Magro et al of CD patients undergoing infliximab therapy emphasized the importance of an early drop in CRP levels after starting therapy (assayed at 14 weeks) as a predictor of sustained response in the first year, irrespective of baseline serum CRP levels.<sup>87</sup> The authors also found that patients with

more marked variations in CRP levels (CRP delta) were less likely to need further adjustments to their treatment, and that higher CRP values corresponded to a worse response. The authors judged this to be an expression of a more severe disease or a higher rate of infliximab clearance. We already know that some patients with clinically active CD (according to the CDAI) may have normal CRP levels, and that it may be difficult to know whether such patients really have active disease or only functional symptoms. Colonoscopy revealed endoscopic lesions in a sample of patients with a CDAI >150 and CRP <5 mg/L, although these lesions were only mild (CDEIS <6) in most cases.<sup>88</sup>

Fecal biomarkers, such as the neutrophil-derived calprotectin and lactoferrin, have proved useful for managing CD patients in several settings, as previously reported in two recent reviews.<sup>89,90</sup> Both fecal calprotectin and lactoferrin significantly correlate with endoscopic and histological scores of CD activity in ileocolonic or colonic disease, but not when the disease is confined to the ileum.<sup>91,92</sup> Calprotectin proved superior to CRP or the CDAI in discriminating between different degrees of intestinal inflammation (according to the SES-CD).<sup>93</sup> Once disease activity has been established, fecal calprotectin can also be used to monitor the course of the disease and response to medical therapy. Mao et al conducted a meta-analysis on the ability of fecal calprotectin to predict relapse in patients with inflammatory bowel disease, finding a pooled sensitivity and specificity of 78% and 73%, and comparable rates for ulcerative colitis and colonic CD.<sup>94</sup> The use of fecal calprotectin as a surrogate marker of mucosal healing has recently been introduced in clinical trials, with a recommended cut-off of 250 µg/g for predicting CDEIS ≤3 with 94% sensitivity and 62% specificity.<sup>95</sup> Normalization of fecal markers was also seen to correlate with endoscopic response after therapy enhancement in 19 CD patients, while these markers remained abnormal in the majority of endoscopic nonresponders.<sup>96</sup>

In preliminary reports on the STORI trial cohort, monitoring both CRP and calprotectin (in combination) has been suggested as a way to improve accuracy in predicting mucosal healing and establishing the risk of clinical relapse within 4–6 months.<sup>97,98</sup> Combining the two parameters also proved useful for identifying cases at higher risk of relapse within 1 year of discontinuing infliximab among patients on combined maintenance therapy with antimetabolites: CRP ≥5.0 mg/L and fecal calprotectin ≥300 µg/g (and also male sex, no surgical resection, leukocytosis, and anemia) could identify patients at higher risk.<sup>99</sup>

In conclusion, clinicians have numerous tools for assessing disease activity in CD patients. CD is a complex disease, with phenotypes that may differ significantly from one patient to another, and that may even change within the same patient over time, so an algorithm appropriate for the follow-up of all CD is unlikely. A patient-tailored strategy is needed, selecting a combination of tests and procedures that best assesses disease activity (in terms of the burden of inflammation), complications, and response to therapy.

Noninvasive markers such as CRP and fecal proteins can provide baseline information to confirm any presence of intestinal inflammation, and they should be used as a preliminary step to select patients requiring further investigations. Ileocolonoscopy (with histology) remains the gold standard for assessing mucosal disease activity in the majority of patients, while a complete examination of the small intestinal mucosa using SBCE and/or balloon-assisted enteroscopy is a complementary measure to be used when proximal intestinal involvement is suspected. Imaging techniques, especially MRI, can provide information on the transmucosal activity of the disease and rule out complications. Endoscopy and imaging techniques provide complementary information and are not mutually exclusive: they should be used when there is a clinical need to reassess CD activity and extent for the purpose of adjusting or changing a patient's treatment, or for referring a patient to the surgeon, as appropriate.

## Disclosure

The authors report no conflict of interest in this work.

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