

# Magnetic resonance enterography for the evaluation of the deep small intestine in Crohn's disease

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For the control of Crohn's disease (CD) a thorough assessment of the small intestine is essential; several modalities may be utilized, with cross-sectional imaging being important. Magnetic resonance (MR) enterography, i.e., MRE is recommended as a modality with the highest accuracy for CD lesions. MRE and MR enteroclysis are the two methods performed following distension of the small intestine. MRE has sensitivity and specificity comparable to computed tomography enterography (CTE); although images obtained using MRE are less clear compared with CTE, MRE does not expose the patient to radiation and is superior for soft-tissue contrast. Furthermore, it can assess not only static but also dynamic and functional imaging and reveals signs of CD, such as abscess, comb sign, fat edema, fistula, lymph node enhancement, less motility, mucosal lesions, stricture, and wall enhancement. Several indices of inflammatory changes and intestinal damage have been proposed for objective evaluation. Recently, diffusion-weighted imaging has been proposed, which does not need bowel preparation and contrast enhancement. Comprehension of the characteristics of MRE and other modalities is important for better management of CD. (**Intest Res 2016;14:120-126**)

**Key Words:** Magnetic resonance enterography; Computed tomography enterography; Capsule endoscopy; Balloon-assisted enteroscopy; Diffusion magnetic resonance imaging

## INTRODUCTION

Appropriate therapy for a disease is based on its precise diagnosis and assessment. CD is a long-standing chronic IBD. With the recent advent of effective medications, "mucosal healing" is considered as the target of therapy for IBD;<sup>1</sup> this requires detailed disease assessment on the basis of not only clinical symptoms but also the findings of imaging modalities.

CD may affect any portion of the gastrointestinal tract. Three-quarters of patients with CD have small intestinal lesions.<sup>2</sup> However, due to the difficulties of endoscopic or cross-sectional approaches for imaging the small intestine, assessment of CD was mainly based on clinical symptoms use of scoring systems, such as the CDAI. Recent progress in modalities, such as capsule endoscopy (CE),<sup>3</sup> balloon-assisted endoscopy (BAE)<sup>4</sup> as well as cross-sectional imaging, such as CT enterography (CTE) and magnetic resonance (MR) enterography (MRE) enables direct assessment of the lesions deep within the small intestine that cannot be accessed by standard ileocolonoscopy. The cross-sectional imaging can acquire the information of not only the mucosal lesion but also the inflammation in the deep layers of the bowel wall and extraluminal complications, such as abscess and fistula.<sup>5</sup>

Hence, the joint European Crohn's and Colitis Organiza-

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tion (ECCO)/European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines in 2013 mentioned that MRE and CTE are important cross-sectional imaging techniques for the assessment of the small intestine.<sup>6</sup> These modalities are regarded as having the highest accuracy for evaluation of CD lesions. MRE is an excellent tool in diagnosing and monitoring CD in its daily course.<sup>7</sup> Recently, this journal reviewed CTE and MRE;<sup>8</sup> here, the recent advances in MRE for patients with small intestinal CD are reviewed.

**MRE AND MR ENTEROCLYSIS**

MRI, because of higher resolution and faster acquisition of images, has now become the modality of choice for imaging the small intestine. Contrasts are used for better imaging of the intestinal wall. Adequate distension of the small intestine is also important for images with good-quality and for accuracy of diagnosis.

There are two methods of imaging that fully distend the intestine. One is MR enteroclysis, in which the contrast is administered through a nasojejunal tube, and the other is MRE, in which the contrast is administered orally without tubing.<sup>9</sup> Several studies compared enteroclysis to MRE.<sup>10-12</sup> Proximal small bowel distension is frequently less optimal in MRE than in MR enteroclysis. However, both methods are equivalent for ileum distension and clinical information. MR enteroclysis requires insertion of a nasojejunal tube, which is often performed under fluoroscopy and, therefore, exposes the patient to ionizing radiation. Additionally, patients often find insertion of the tube to be unpleasant and even painful.<sup>13</sup> CD is a chronic disease that requires repeated examinations, and evading MR examinations due to an uncomfortable procedure may impede precise monitoring, especially in younger patients. MR enteroclysis is often not chosen as the first-line MRI because it has no overwhelming advantages compared with MRE. Many institutes prefer oral administration of contrast, especially for pediatric and adolescent patients;<sup>14</sup> we also use only MRE.

**MRE AND CTE**

On comparing MRE with CTE, both modalities show similar sensitivity and specificity. A recent meta-analysis of 290 patients with CD from 6 different studies showed that the pooled sensitivity and specificity for MRE in detecting active small bowel CD were 87.9% and 81.2%, respectively, with a weighted area under the curve (AUC) of 0.905. The pooled sensitivity and specificity of CTE in detecting active

small bowel CD was 85.8% and 83.6%, respectively, with an AUC of 0.898. AUCs of MRE in detecting fistula, stenosis, and abscess were 0.936, 0.931, and 0.996, respectively, compared with 0.963, 0.616, and 0.899 for CTE.<sup>15</sup> It was concluded that MRE is comparable to CTE and is a good alternative for evaluation of patients with CD. Patients with CD were frequently evaluated with imaging, such as CT and other radiological modalities during acute exacerbations.<sup>16</sup> Reducing the radiation exposure, as much as possible, is recommended; therefore, MRE has become the standard imaging modality at many pediatric institutions because it does not use ionizing radiation that may increase the possibility of malignancy, particularly in younger patients.<sup>17</sup> To this end, currently, the American College of Radiology recommends using both CTE and MRE for imaging of children and young adults with known CD and an acute exacerbation, but recommends using only MRE for the patients with stable, non-acute mild symptoms of CD.<sup>18</sup>

Another advantage of MRE over CTE is that it can acquire bowel images at multiple time-points and cinematic images to evaluate peristalsis. This cine MRI provides functional information of bowel movement. The visualization of peristalsis helps in the assessment of the bowel adhesions, fistula, and stenosis. Contrary to CTE, MRE provides both anatomic and functional information.<sup>19</sup> MRE also has better soft-tissue contrast resolution compared with CT and is superior in detecting fibrosis. It can help characterize bowel wall tissue composition and plan therapies based on this information. Newly developed medications, such as biologics, are very effective in treating inflammatory lesions. However, fibrotic strictures are not responsive to medical therapies; they require mechanical treatments, such as balloon dilation, strictureplasty, and bowel resection.<sup>20</sup>

There are some limitations of MRE compared with CT. CT has better spatial resolution and requires a significantly shorter acquisition time. Several sequences are used for MRE; therefore, longer examination time is needed. MRE is currently less accessible and significantly more costly,<sup>21</sup> and as a result, it is not used as often as other imaging modalities.

**ASSESSMENT OF DISEASE**

**1. Findings of CD Using MRE**

Several signs of inflammation and intestinal damage in the evaluation of CD can be assessed using MRE, such as abscess, comb sign, fat edema, fistula, lymph node enhancement, reduced motility, mucosal lesions, strictures, and

wall enhancement. A meta-analysis showed that the most important signs of inflammation are wall thickness and wall T2-hyperintensity. Sensitivities were >90% at the patient level and >65% at the bowel segment level. Motility is also a highly sensitive sign. The specific parameters were wall T2-hyperintensity and mucosal lesions, such as ulcers, fissuring, cobble-stoning, and pseudopolyps. The specificities are >90% at the patient level and >95% at the bowel segment level. As for intestinal damage, abscess, stricture, and fistula had consistently high sensitivity and specificity, especially at the patient level.<sup>22</sup>

MRE can detect lesions by providing images with high quality and reproducibility, even in a global multicenter setting.<sup>23</sup> It facilitates more objective assessment of disease and will be used as an important indicator for therapeutic intervention trial in future.

## 2. Assessment of Inflammation

Scoring of disease activity is important for objective assessment, and several indices for this have been proposed. The most widely used MRE score is the MR index of activity (MaRIA).<sup>24</sup> It is calculated as  $1.5 \times \text{bowel wall thickness in millimeters (mm)} + 0.02 \times \text{relative contrast enhancement} + 5 \times \text{edema} + 10 \times \text{ulceration}$ . MaRIA is strongly correlated with the Crohn's disease endoscopic index of severity (CDEIS).

Contrast enhancement of the bowel wall is necessary to calculate MaRIA. However, after removing the parameter relative contrast enhancement, which requires contrast enhancement, the modified formula ( $1.5 \times \text{wall thickening} + 5 \times \text{intramural edema} + 10 \times \text{ulceration}$ ) was comparable to MaRIA in the evaluation of disease activity in CD, with significant correlation. Therefore, MRE can be used without contrast enhancement for patients who are intolerant to gadolinium-based contrast or those with severe renal failure.<sup>25</sup> The global MaRIA score was calculated as the sum of the MaRIA in ileum, five colorectal segments: ascending colon, transverse colon, descending colon, sigmoid, and rectum.<sup>26</sup> However, allocation for the small bowel is relatively small; thus, Applied MaRIA can be used by dividing the small intestine into three segments: terminal ileum, proximal ileum, and jejunum. Applied MaRIA is well correlated to findings of BAE.<sup>27</sup>

The other proposed scoring system, Crohn's disease activity score (CDAS), is based on mural thickness and T2 signal on fat-saturated imaging. CDAS score is based on the following calculation:  $1.79 + 1.34 \times \text{mural thickness} + 0.94 \times \text{mural T2 score}$ .<sup>28</sup> CDAS showed a sensitivity of 81%, specificity of

70%, and AUC of 0.77 for predicting acute inflammation and was modified as a global assessment score called the MRE global score (MEGS), which is a sum of scores of qualitative and semiquantitative grading of bowel wall thickness, mural and peri-mural T2 signal, T1 enhancement, mural-enhanced pattern length of the diseased segment, and extramural features.<sup>29</sup> The bowel was divided into nine segments and each segment scored independently. The small bowel was divided into jejunum, ileum, and terminal ileum.

## 3. Assessment of Intestinal Damage

The clinical manifestations of CD consist of inflammation and accumulated intestinal damage. The Lémann index was proposed for the assessment of intestinal damage.<sup>30</sup> It assesses the upper tract, small bowel, colon/rectum, and anus, with three grades. The small bowel is divided into 20-cm segments. There are investigational methods designated for each area of the gastrointestinal tract. Strictures of the upper tract and the colon are assessed using endoscopy or MRI/CT. However, the small bowel is investigated using MRI/CT only. Direct comparison between MRE and enteroscopy revealed less sensitivity of MRE for strictures.<sup>31</sup> Evaluation of MRE in cases of surgery showed similar results.<sup>32</sup> Preoperative MRE for 43 patients with CD showed that sensitivity was 68% for stenosis and 60% for fistula. The negative predictive values of MRE were 65% for stenosis and 81% for fistula. MRE had 78% accuracy for stenosis and 85% for fistula. False-negative rates for MRE were 40% for fistula and 32% for stenosis. Assessment of stricture is important because it is a major cause of surgery in CD, although endoscopic balloon dilatation is effective in some cases.<sup>33</sup> Further research on the efficacy of investigational methods is needed.

## 4. Assessment of Therapeutic Effect

Several effective medicines for CD, such as anti-tumor necrosis factor (anti-TNF) antibody, have emerged. They are often costly, and the choice of treatment is sometimes difficult. MRE can assess current inflammation effectively and may guide the therapeutic decision. Some MRE findings will help predict outcome following commencement of anti-TNF antibody therapy. The strictures and penetrating complications detected using MRE often require future surgery.<sup>34</sup> MRE is a useful modality in monitoring the efficacy of treatment. Transmural and healing detected using MRE correlates with changes in CD clinical activity during anti-TNF therapy.<sup>35</sup> Bowel motility assessed using MRE is also

observed with response to anti-TNF antibody therapy. MRE may detect non-responsiveness to anti-TNF during early phases of treatment.<sup>36</sup>

Preoperative assessment of disease is crucial for better surgical outcomes. Laparoscopic surgery is commonly used for colorectal cancer resection, and its utility is increasing in the field of IBD. However, conversion from laparoscopic surgery to open laparotomy is not rare in IBD; the conversion results in longer operative courses, increased resource utilization, and increased morbidity than the complete laparoscopic and open surgery from the beginning. Unexpected intraoperative findings, such as large inflammatory mass, adhesions, ileosigmoid fistula, and pelvic abscess, are the causes of conversion. Cross-sectional imaging provides adequate information of disease extent and, thus, will help avoid conversion.<sup>37</sup> A retrospective analysis of 187 laparoscopic surgeries with preoperative CTE/NRE shows a negative correlation to conversion. However, the ability of MRE to detect stenosis is limited.<sup>31</sup>

**COMPARISON TO OTHER MODALITIES**

**1. CE**

CE noninvasively visualizes the entire small intestinal mucosa. A comparison between MRE and CE revealed that CE is more sensitive for detection of lesions at previously unrecognized locations, and MRE is superior for detection of the location of lesions.<sup>38</sup> The limitation of CE is retention due to strictures, which are often observed in CD; MRE may help predict such strictures.<sup>39</sup> However, it is recommended that investigation with a patency capsule should be undertaken before CE because the detection of strictures by MRE is only moderate.

**2. BAE**

It enables detailed, direct observation of mucosa; however, the invasiveness of endoscopy should not be ignored. The findings of MRE and ileocolonoscopy were compared; their inflammatory findings were correlated well.<sup>26</sup> A direct comparison between MRE and enteroscopy in 100 patients with CD has been reported. MRE detected ulcerative lesions in the small intestine with 82.4% sensitivity and 87.6% specificity. It detected major strictures with 58.8% sensitivity and 90.0% specificity. It was concluded that MRE had enough sensitivity for detecting active lesions; however, it was less sensitive in detecting intestinal damage, such as strictures.<sup>31</sup>

**3. Ultrasonography**

Ultrasonography (US) is a sensitive modality for diagnosis and evaluation of disease activity and is comparable to MRI. US is widely available and non-invasive; however, its accuracy depends on the examiner and is low in the proximal to terminal ileum region.<sup>40</sup> A comparison between US and MRE in 29 pediatric patients with CD showed an almost perfect agreement for abscess, substantial for maximum bowel wall thickness, stricture and penetrating disease.<sup>41</sup> A comparison in 120 adults showed comparable sensitivities and specificities for US and MRE.<sup>42</sup> The concordance of CD location was high; there was fair concordance in the detection of strictures and abscesses. However, US was less accurate compared with MRE for determining the extent of disease. MRE was more accurate for the detection of penetrating lesions, particularly in the deep pelvic region. A multicenter, non-randomized, single-arm, prospective comparison study is ongoing.<sup>43</sup> Further studies will clarify the proper use of such non-ionizing radiation techniques.

**NEW TECHNIQUES**

MRE uses several sequences and the technique is varied. Standardization enables comparison and assessment of techniques and facilitates the uptake of MRE. Recently, consensus for the optimal technique for MRE in CD was released with following recommendations:<sup>44</sup> patient preparation (fasting 2–4 hours prior to the procedure); oral contrast (>900 cc biphasic enteric contrast administered in divided doses 45–60 minutes prior to scanning); intravenous contrast (single dose of 0.1 mmol/kg extracellular space gadolinium agent or gadobenate dimeglumine injected at ≥2 cc/s); spasmolytics (recommended); coverage (from small bowel to perineum); required pulse sequences (T2-weighted sequence—axial and coronal, one plane with fat saturation, dynamic contrast-enhanced coronal T1-weighted fast spin three-dimensional gradient-echo—acquire at 45 seconds with two subsequent coronal acquisitions, axial contrast-enhanced T1-weighted fast spin three-dimensional gradient-echo); and contraindications for intravenous contrast (for noncontrast MRE, additional pulse sequences, such as diffusion and cine sequences may be added to T2-weighted imaging).

**1. Diffusion-Weighted Imaging**

Diffusion-weighted imaging MRE (DWI-MRE) does not

need bowel preparation and contrast enhancement. It is useful for patients who cannot receive contrast due to renal failure, pregnancy, or allergy. An early report on DWI-MR colonography reported that it was comparable to gadolinium enhancement for the detection of inflammation in CD.<sup>45</sup>

However, a recent meta-analysis of 1,515 bowel segments for diagnosis and 1,066 bowel segments for assessment of inflammatory severity showed sensitivity and specificity to be 92.9% and 91%, respectively.<sup>46</sup> It was concluded that DWI-MRE accuracy was heterogeneous among studies and was likely overestimated in some studies. On the other hand, an association between lower apparent diffusion coefficient (ADC) values and the presence of stricture on MRE were reported. A study of 5 pediatric patients with CD showed that ADC values were high in normal segments, moderate in segments with acute inflammation, and low in the presence of fibrosis.<sup>47</sup> There was a progressive decrease in ADC values during the clinical course. A longitudinal observation of 13 pediatric patients showed that ADC values changed with disease course.<sup>48</sup> ADC values of non-fibrostenotic imaging phenotypes increased, although those of fibrostenotic lesions did not change. These reports show the possibility of using DWI-MRE for the assessment of not only inflammation but also fibrosis. MR without contrast is not enough to replace MRE, and further studies are awaited.

## 2. Cine Motility

MRE can provide a quantitative assessment of small bowel motility. The motility of inflamed bowel segments decreases compared with non-inflamed segments. Hence, the decrease in motility can be used as a marker of inflammation. Furthermore, there are advantages of using cine MRE over static imaging to investigate the intestinal damage, such as adhesion, fistula, and stricture. Cine imaging does not require additional patient preparation and only short time is required for image acquisition and reading. There is a report comparing cine MRE to endoscopy in 28 patients with CD. Motility index was calculated and was significantly related to histological activity in the terminal ileum.<sup>49</sup> In 91 patients with stricturing CD, small bowel motility as indicated on MRE was shown to differ significantly among normal, prestricture, and strictured bowels.<sup>50</sup> There was a negative correlation between the prestricture bowel diameter and motility.

The 2013 ECCO/ESGAR guidelines mention that the inclusion of small bowel motility evaluation may increase lesion detection rate compared with static MRE alone.<sup>5</sup> The consensus statement from the Society of Abdominal Radiol-

ogy (SAR) Crohn's disease-focused panel published in 2015 mentioned that cine MRE can provide functional evaluation of small bowel peristalsis.<sup>44</sup>

## 3. Magnetization Transfer MRI

Magnetization transfer (MT) was proposed for detection of bowel fibrosis.<sup>51</sup> The MT ratio was significantly increased in the bowel wall with fibrotic scarring, although it was slightly decreased in the segments with acute inflammation. MT imaging may be useful for distinguishing inflammatory and fibrotic stenosis. Further research is needed to establish the value of MT MRI.

## CONCLUSIONS

The progress of MRE has changed the assessment of CD. Complete utilization of the recent advances in therapeutics requires more objective assessment and detailed information of the affected organs. The deep small intestine is a major segment affected by CD. Before the advent of MRE, it was difficult to assess the deep small intestine. MRE can provide information on the deep small intestine and extraluminal manifestations of CD. It helps monitor the effect of medicines and guides procedures for surgical treatment. MRE is not a mere substitute for CT, as non-ionizing radiation cross sectional imaging modality; it changes the static imaging into objective dynamic imaging. It is not restricted to anatomic diagnosis, but instead provides a wider, functional analysis.

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