Update on Magnetic Resonance Imaging and Ultrasound Evaluation of Crohn's Disease

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Abstract: Magnetic resonance enterography (MRE) and abdominal ultrasound are integral parts of multimodality assessments for patients with inflammatory bowel disease. Applications include assessing Crohn's disease (CD) extent and severity, differentiating CD from ulcerative colitis, detecting CD complications, evaluating response to therapy, and demonstrating postoperative recurrence. Magnetic resonance imaging protocols are being developed that may reduce or eliminate the need for intravenous contrast agents and better differentiate inflammatory from fibrotic strictures. MRE scoring systems have been created to objectively quantify disease activity and response to therapy. By utilizing advanced sonographic imaging techniques, including ultrasound contrast and Doppler assessments, the role of abdominal ultrasonography in the evaluation and management of CD continues to expand. Abdominal ultrasound may function as a low-cost, point-of care assessment tool, especially in CD restricted to the terminal ileum and ileocolic anastomosis.

Intestinal imaging continues to revolutionize diagnostic and management algorithms in patients with Crohn's disease (CD).[1] Cross-sectional imaging techniques are viewed as complementary to ileocolonoscopy, providing transmural assessments in regions inaccessible to standard endoscopic techniques. Applications include evaluating disease extent and severity; differentiating CD from ulcerative colitis; detecting disease complications such as strictures, fistulas, and abscesses; evaluating response to medical therapy; and surveilling postoperative recurrence.

Magnetic resonance enterography (MRE) and abdominal ultrasound have become key tools within the inflammatory bowel disease (IBD) imaging armamentarium. Recent MRE and ultrasound advances include the development of new techniques to enhance disease detection, attempts to estimate the degree of inflammation and fibrosis in CD strictures, the analysis of motility, the assessment of global intestinal damage, the evaluation of transmural response to medical therapy, and the creation of robust scoring systems that reflect

severity and burden of disease. This article summarizes the newer protocols, concepts, and scoring systems utilizing MRE and abdominal ultrasound in IBD patients.

Techniques and Concepts of Magnetic Resonance Imaging in Crohn's Disease

Standard MRE or enterocolonography imaging protocols include unenhanced, T2-weighted sequences and gadolinium-enhanced T1-weighted sequences. To create gadolinium-enhanced T1-weighted images, the patient ingests a large volume of oral contrast. Post–gadolinium contrast images are initiated during the enteric phase of enhancement, approximately 45 seconds after gadolinium injection, and are followed by several dynamic acquisitions to assess temporal enhancement of the bowel wall. Delayed imaging at 7 minutes can be performed to estimate inflammation and fibrosis in strictures.[2] Bowel wall enhancement characteristics, transmural ulcers, fistulas, sinus tracts, comb sign (dilated vasa recta), and perienteric abnormalities are well visualized in gadolinium-enhanced T1-weighted images. Bowel wall thickening and mural edema are better evaluated by T2-weighted images and diffusion-weighted imaging (DWI).[3,4]

Diffusion-Weighted Imaging

DWI protocols derive image contrast from the differences in the diffusion of water molecules between tissues based upon the Brownian motion of the spins in biological tissues.[5] DWI can provide information complementing T1- and T2-weighted images (Figure 1) with a decrease in a quantifiable parameter, the apparent diffusion coefficient, which indicates restricted diffusion and active inflammation.[6] In CD, this was initially explored in several retrospective studies demonstrating an ability to identify active disease in the small bowel.[6-9] Kim and colleagues showed that restricted diffusion reflects severe inflammation when CD is present and correlates with the presence of ulcers identified at endoscopy; however, diffusion-weighted images have a poor specificity for the detection of active inflammation, and the researchers concluded that the diagnosis of CD should rely on conventional imaging findings.[10] Seo and colleagues recently performed a prospective, noninferiority study in 44 patients with known or suspected CD, with pairwise comparisons between conventional magnetic resonance imaging (MRI) features of inflammation with gadolinium contrast vs precontrast sequences alone with DWI.[11] The researchers found a high correlation between estimations of disease severity with identical estimations of sensitivity and specificity for active inflammation in the terminal ileum of 93% and 67%, respectively. Additionally, the Clermont score uses DWI and can be obtained without bowel preparation or colonic enema.[12,13] High correlation (rho=0.99)

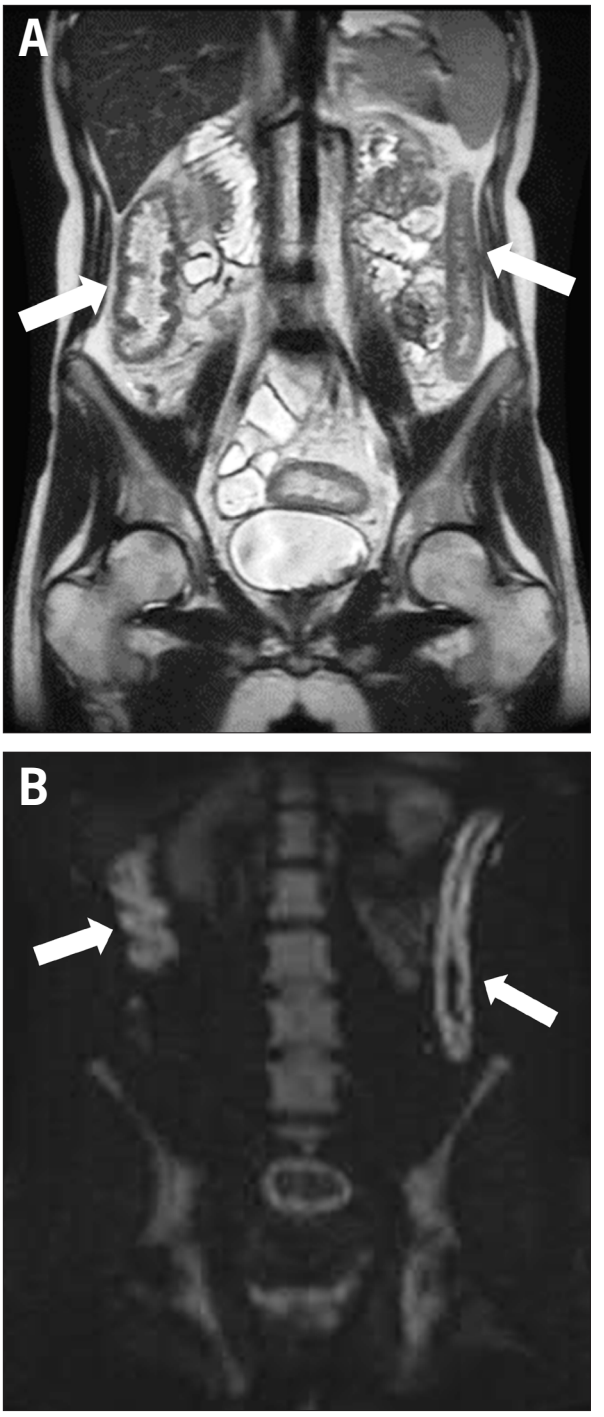

Figure 1. Single shot fast spin echo magnetic resonance (MR) sequence showing wall thickening (arrows) in the right and left colon of a patient with pancolonic Crohn's disease (CD; **A**). Diffusion-weighted imaging MR sequence showing restricted diffusion (arrows) in the right and left colon of a patient with pancolonic CD (**B**).

was noted in the validation study for the detection of active ileal disease between the Clermont score and the Magnetic Resonance Index of Activity (MaRIA) score (≥7).[13] As a

consequence of these studies, DWI is now generally performed at most institutions as part of MRE, and is used to identify bowel segments that have severe inflammation or may be inflamed (and correlated with imaging findings on other pulse sequences). In the absence of intravenous contrast, restricted diffusion is used to draw attention to bowel segments that may have inflammation so that these segments can be evaluated for findings of inflammation such as increased bowel thickness, intramural edema, ulcers, or penetrating complications. Recent studies have shown evidence of gadolinium accumulation in the brain of patients undergoing repeat imaging with gadolinium-based contrast-enhanced magnetic resonance (MR), even in the setting of normal renal function.[14,15] The risk of accumulation appears to be limited to linear gadolinium-based contrast agents (eg, gadopentetate dimeglumine; Magnevist, Bayer Healthcare) and not with macrocyclic gadolinium-based contrast agents (eg, gadoterate meglumine; Dotarem, Guerbet).[16] Despite the unclear clinical implications of this observation, the role of DWI may be expanding in CD patients who have to undergo repeat cross-sectional radiologic examinations.

Magnetization Transfer

Magnetization transfer (MT) in MRI utilizes the detection of energy transfers between protons in water molecules that are in the free state and protons that are bound to molecules such as collagen. Hence, MT has been the only MRI sequence sensitive to the changes in collagen content, potentially correlating with fibrosis, and enabling the differentiation of these tissues from edematous or inflamed bowel. In an animal model, the potential of MT was demonstrated, with the MT ratio showing good correlation with the quantity of type I collagen (r=0.74; *P*=.0003) and positive and negative predictive value ratios of 92% and 83%, respectively, for the prediction of fibrosis.[17] A subsequent study has shown that MT can detect a decrease in fibrosis induced by peptidoglycan-polysaccharide after anti-tumor necrosis factor (TNF)α therapy in the rat model.[18] Recently, a pilot human study has demonstrated the feasibility of incorporating MT into routine MRE in 31 CD patients (Figure 2), but it has not been validated prospectively in a larger number of patients.[19] Larger, prospective human studies are needed to confirm the ability of MT to differentiate on a continuous scale the level of inflammation and fibrosis compared to a histopathologic reference standard.

Small Bowel Motility

CD patients have been known to have altered small bowel motility, especially if the disease involves ileal or ileocolonic locations.[20,21] Advances in imaging technology allow detection of bowel motility by continuous acquisition of images on fast MR T2-weighted sequences in a

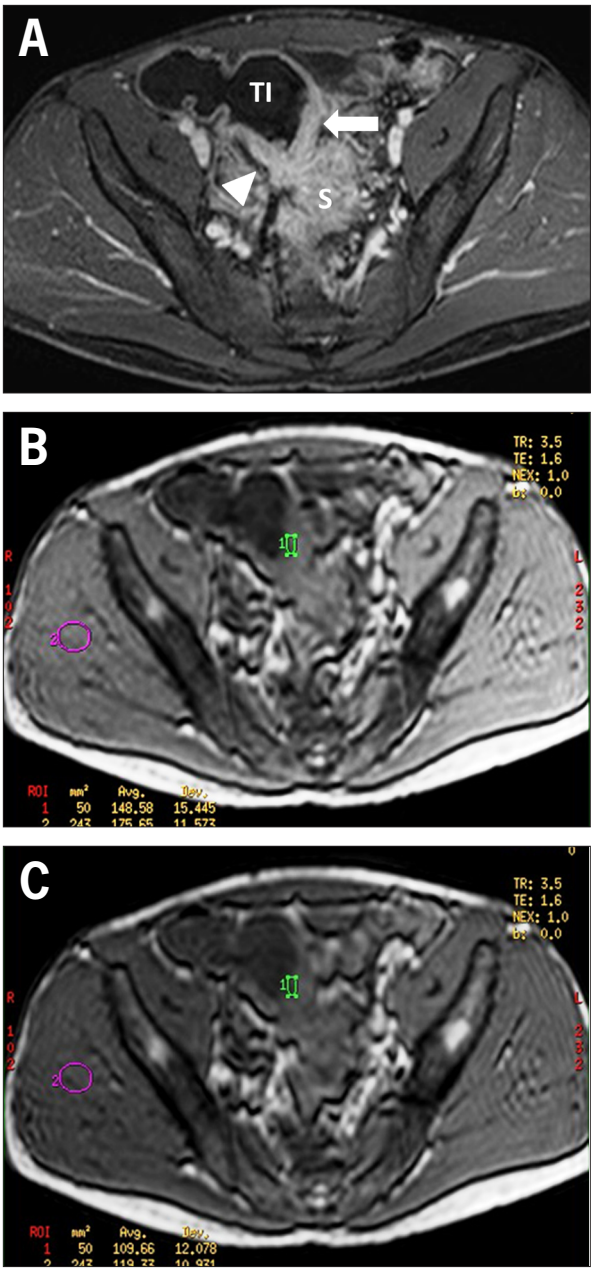

Figure 2. A 30-year-old patient with fistulizing terminal ileal and colonic Crohn's disease. Axial contrast-enhanced T1-weighted gradient echo image (**A**) demonstrates bowel wall thickening and mural enhancement (arrow) in the dilated terminal ileum (TI) secondary to inflammation in the small bowel. There is an enterocolic fistula (arrowhead) extending from the TI to the adjacent sigmoid colon (S). Axial T1-weighted gradient echo images without (**B**) and with (**C**) magnetization transfer (MT) show signal intensity measurements in the right gluteus muscle (purple circle, #2) and the diseased bowel segment (green oval, #1). The MT ratio is 32% in the muscle and 26% in the bowel wall.

Figure courtesy of Dr Mahmoud Al-Hawary, University of Michigan, Ann Arbor, MI.

single slice location during short breath holds, thereby generating cine-like images.[22] The ability to acquire these images has now also been reported during free breathing.[23] Motility abnormalities may improve detection for both inflammatory and fibrotic lesions.[24] In a study of 40 histologically proven CD patients with active disease (CD Activity Index [CDAI] ≥150), adding cine MRI to standard MRE detected CD-specific lesions in 9 additional patients (34 vs 25; *P*=.0007).[25] Menys and colleagues studied 28 CD patients who underwent coronal cine MRI motility sequences with true fast imaging with steady-state precession sequences.[24] Software-quantified terminal ileum motility index was significantly different between noninflamed and inflamed terminal ileum (mean, 0.37 and range, 0.13-0.55 vs mean, 0.19 and range, 0.06-0.44; *P*=.002). An analysis of 46 CD patients (35 retrospectively analyzed) showed improvement in small bowel motility with anti-TNFα therapy as early as 12 weeks after treatment.[26] These studies highlight the potential for incorporating cine MRI sequences as part of standard MRE protocol.[27] Potential limitations are the subjective nature of grading and comparing peristalsis and the inability to differentiate active from inactive CD without the use of other pulse sequences.[28]

Assessment of Response to Medical Therapy With Radiologic Targets

The Selecting Therapeutic Targets in Inflammatory Bowel Disease program of the International Organization for the Study of Inflammatory Bowel Diseases has identified several potential CD treatment targets.[29] Clinical remission has been defined as resolution of abdominal pain and diarrhea or altered bowel habit. Endoscopic remission has been defined as the absence of ulcerations at ileocolonoscopy. Imaging remission has been defined as the resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.[29] This latter definition has highlighted the importance of cross-sectional imaging modalities such as MRE. In a study of 153 CD patients, 53.7% of patients with normal ileoscopic findings had active small bowel disease.[30] Intramural disease was present in 63.9% of the patients, suggesting a potential need to extend the assessment of response to a transmural target. In a retrospective cohort of 63 CD patients receiving infliximab (Remicade, Janssen) therapy, transmural radiologic response was observed in up to 63.4% of patients.[31] A second study has suggested that radiologic response at the first follow-up cross-sectional scan (computed tomography enterography [CTE] or MRE) can predict the need for rescue corticosteroids, hospitalizations, or surgeries.[32] This finding may indicate that radiologic response as a treatment target can alter the natural history of CD similar to mucosal healing (MH). While the concept of radiologic targets appears to be logical, further studies are needed to ascertain whether MH or radiologic response is a more robust treatment target in patients with endoscopically accessible lesions.

Magnetic Resonance Severity Scoring Systems for Crohn's Disease

MRE scoring systems have been developed to allow quantitative assessments of lesions for target-directed medical therapy. The scoring systems could potentially also be used in clinical trials as an instrument to enrich enrollment with patients of appropriate disease severity, as well as to compare and quantify disease activity between patients and over time, similar to existing clinical scoring systems such as the CDAI and the Harvey-Bradshaw Index (HBI).[33] Three of the MR-based scoring systems that have been developed in comparison to an external reference are detailed in Tables 1 and 2 and include the MaRIA score, the Crohn's Disease MRI Index (CDMI) score, and the Nancy score.[34-36]

Magnetic Resonance Index of Activity Score

The MaRIA score was derived by correlating MR features of active inflammation with the Crohn's Disease Endoscopic Index of Severity (CDEIS) score.[34] In the derivation study, 50 patients with established CD underwent colonoscopy and 3-Tesla MRE within a 2-day period. The protocol required bowel cleansing with either endoscopic preparation (if performed on the same day as ileocolonoscopy) or 1000 to 2000 mL of polyethylene glycol (PEG) solution 4 hours before MRI. Adequate ileal distention was achieved with 1500 mL of PEG solution by mouth 45 minutes before MRI and colonic distention with 1000 to 2000 mL of saline instilled rectally. Independent predictors for segmental CDEIS were wall thickness (*P*=.007), relative contrast enhancement (RCE; *P*=.01), presence of edema (*P*=.02), and presence of ulcers at MR (*P*=.003). Using a regression model, the MaRIA score per segment was proposed as 1.5 × wall thickness (mm) + 0.02 × RCE + 5 × edema + 10 × ulceration.

RCE involves the calculation of pre- and postcontrast wall signal intensity in the bowel wall and the standard deviation of pre- and postcontrast signal intensity noise measured outside of the body. The segmental MaRIA score was shown to have good correlation with the segmental CDEIS score (r=0.82; *P*<.001). The overall MaRIA score was calculated by adding individual segmental scores similar to the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD). The MaRIA score also had a significant correlation with total CDEIS (r=0.78), C-reactive protein concentration (r=0.53), and

Table 1. Magnetic Resonance Enterography Scores for Crohn's Disease Based Upon Independent Predictors of Activity

	Derivation (patients/segments)	Validation[a] (patients/segments)	Therapeutic Response Assessment	Gold Standard
MaRIA Score[34,37]	50/213	48/258	Yes	Ileocolonoscopy (CDEIS)
CDMI Score[35]	16/44	26/26	No	Surgical specimen (AIS)
Nancy Score[36]	40/211	–	No	Ileocolonoscopy (SES-CD)

[a]An additional cohort of 30 patients also validated these indexes.[40]

AIS, acute inflammation score; CDEIS, Crohn's Disease Endoscopic Index of Severity; CDMI, Crohn's Disease Magnetic Resonance Imaging Index; MaRIA, Magnetic Resonance Index of Activity; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.

Adapted from Bruining et al[93] with permission.

Table 2. Magnetic Resonance Enterography Independent Predictors for Activity on Crohn's Disease According to MaRIA, CDMI, and Nancy Scores

	MaRIA Score[34,37]	CDMI Score[35]	Nancy Score[36]
Wall Thickening	Yes	Yes	Yes
Enhancement	Yes (quantification of relative contrast enhancement)	Qualitative (4 different categories)	Yes (qualitative evaluation)
High Signal on T2	Yes (qualitative evaluation)	Yes (4 different categories)	Yes (qualitative evaluation)
Ulcerations	Yes	–	Yes
T2 Perimural Signal	No	Yes (4 different categories)	No
Mural Stratification	–	–	Yes
Diffusion Weighting Imaging Hyperintensity	–	–	Yes

CDMI, Crohn's Disease Magnetic Resonance Imaging Index; MaRIA, Magnetic Resonance Index of Activity.

Adapted from Bruining et al[93] with permission.

HBI (r=0.56). The SES-CD score has been subsequently validated in a separate cohort of 48 patients, with a similar correlation of the global MaRIA score with the CDEIS (r=0.83; *P*<.001).[37] Further validation of the MaRIA score has been performed in a prospective, multicenter study, in which the score has been shown to be responsive and reliable in assessing the response to therapy in patients with CD.[38] The MaRIA score does not take into account the overall length of inflamed segments, even in the small bowel, where extensive disease can occur.

Crohn's Disease Magnetic Resonance Imaging Index Score

The Crohn's Disease MRI Index (CDMI) score was developed in 16 consecutive CD patients who underwent MRE within 2 weeks of elective small bowel surgical resection.[35] Transmural histopathologic scoring of acute inflammation was performed at all locations (score 0-13). Mural thickness (coefficient 1.34; 95% CI, 0.36-2.32; *P*=.007) and T2 signal score measured on a scale of 0 to 3 (coefficient 0.90; 95% CI, -0.24 to 2.04; *P*=.06) were the MRE parameters that best predicted acute inflammation. A simplified model was derived as CDMI = 1.79 + 1.34 mural thickness + 0.94 mural T2 score.

The CDMI score was validated in 26 CD patients and correlated to terminal ileal biopsy scores of acute inflammation (score 1-6). A score of 4.1 was shown to have a sensitivity of 81% and specificity of 70% for predicting acute inflammation at endoscopic biopsy.[35] The CDMI score is substantially faster to calculate than the MaRIA score because the former only requires a measurement of bowel wall thickness (with the estimation of T2 signal being visual), and does not need to take into account inhomogeneities in MR signal over the imaged volume. The CDMI score also reflects severity at a specific segment in the enteric tract and does not describe the length of bowel affected by CD inflammation.

Nancy Score

The Nancy score was developed in 40 CD patients who underwent a MR colonography (MRC) in combination with DWI and a colonoscopy within 48 hours of the DWI-MRC.[36] The scoring was recorded for the presence or absence (rated 1 and 0, respectively) of 6 different radiologic signs in 6 segments: rectum, sigmoid, left colon, transverse colon, right colon, and ileum. The scoring does not assign additional values for proximal small bowel inflammation. A total MR score was calculated by adding

the segmental scores with values ranging from 0 to 36. The severity and extent of endoscopic lesions were assessed per segment by the SES-CD. Both the segmental and total scores correlated with the SES-CD (r=0.57; *P*<.001 vs r=0.54; *P*=.001, respectively). The presence of a DWI hyperintensity (odds ratio, 2.67; *P*=.01) and bowel wall thickening (odds ratio, 10.03; *P*<.001) independently predicted the presence of endoscopic inflammation in the colon. A segmental score greater than 2 detected endoscopic inflammation in the colon with a sensitivity and specificity of 58.3% and 84.5%, respectively (area under the curve, 0.78; *P*<.001).

Scoring System Comparisons

Several key differences exist between the scoring systems. Only the MaRIA score provides a cutoff point for defining severe inflammatory lesions (segmental MaRIA ≥11, accuracy 96%).[37] Additionally, only the MaRIA score has data on detecting segmental MH (CDEIS <3.5), with a MaRIA score less than 7 consistent with MH (accuracy 83%, sensitivity 85%, specificity 78%). It should also be noted that the CDMI score was developed against a reference of transmural inflammation rather than mucosally based disease detected with endoscopy.[35]

The main concerns regarding MRI-based scoring systems are the limitations in describing overall disease burden and reproducibility. Because the MR severity scores have largely been modeled after and validated against endoscopic scoring systems, the relative weight given to small bowel inflammation can be modest (eg, only 1 of 5 bowel segments scored in the MaRIA score as part of the small bowel). Unlike ileocolonoscopy, MRE images the entire small bowel; thus, the potential estimation of overall burden is artificially underestimated by the way in which the scores rely on artificial constructions of bowel segments, rather than on estimating lengths of involvement. One of the potential benefits of cross-sectional enterography in general is that it identifies proximal and intramural small bowel inflammation not seen at ileocolonoscopy.[30,39] Hence, these scores may be improved in the future by incorporating methods that reflect the overall small bowel burden, and not by examining only the terminal ileum. Difficulties in reproducibility can arise from differences in patient preparation and image acquisition and from differences between readers. Unlike Rimola and colleagues who developed the MaRIA score,[34] most centers do not undertake the extensive bowel preparation with both oral contrast and a colonic enema. In terms of interobserver reproducibility, the CDMI and MaRIA scores were estimated in 33 consecutive CD patients undergoing 3-Tesla MRI examinations and ileocolonoscopy within 1 month by 4 readers.[40] The CDMI and MaRIA scores showed good reproducibility (intraclass correlation coefficient [icc], 0.78 and icc, 0.74, respectively) and moderate CDEIS correlation (r=0.59 and r=0.51, respectively).[40]

Further data are required to demonstrate outcomes while treating a radiologic target using 1 or more of these MRI scoring systems. These advances are important, as both clinicians and IBD researchers continue to seek objective estimations of disease severity and burden.

Lémann Index for Digestive Damage

CD is a chronic, progressive, and destructive disease. Recently, efforts have centered on the development of a scoring system that accounts for clinical, endoscopic, and radiologic information to assess the burden of disease. The Lémann Index was developed in 138 patients in a prospective, multicenter, cross-sectional study across 24 centers in 5 countries.[41,42] The entire digestive tract was divided into 4 organs and subsequently into segments. The disease damage (ie, previous operations, predefined strictures, and/or penetrating lesions of maximal severity) was graded per segment (1-3), and damage evaluation was calculated in a score ranging from 0 (no lesion) to 10 (complete resection). Overall level of organ damage was calculated as the average of segmental damage, and then a global damage evaluation was calculated (0-10) from the organ damage evaluations.[42] The Lémann Index could serve as an instrument to measure changes in disease burden with medical or surgical treatment in natural history studies.

Ultrasonography in Inflammatory Bowel Disease

Ultrasonography in IBD has been extensively studied in Europe and in select North American IBD centers. Sonographic technology has evolved over the past decade with high-frequency probes, harmonic imaging (with intravenous microbubble contrast), and the use of oral contrast agents. Advantages of ultrasound compared to MR-based imaging protocols include portability, availability, and lower cost. Ultrasound also allows real-time clinical assessment of IBD and is a radiation-free alternative to CTE. However, ultrasound is more operator-dependent than MRE and has limited utility in larger patients with deep lying segments of bowel. In some specialized IBD centers, ultrasound is being performed by gastroenterologists who have completed specialized training.[43] Ultrasound has also been used in the pediatric population for the assessment of IBD and may be especially suitable for these patients given their smaller size, lower body mass index, concern regarding lifetime radiation accumulation, and potential difficulty in performing lengthy MR examinations.[44,45]

Abdominal Ultrasonography for Inflammatory Bowel Disease

The unenhanced gray scale ultrasound protocol in IBD is often performed as a 2-step process using curvilinear probes of frequency similar to those used in liver evaluation (3-8 mHz), followed by higher-frequency linear probes (7-9 mHz).[46] In a meta-analysis of 7 ultrasound studies in IBD, a bowel thickness threshold value greater than 3 mm for CD diagnosis was associated with a high sensitivity (88%) and specificity (93%).[47] Using a threshold of 4 mm lowered the sensitivity (75%) but increased the specificity (97%). A more recent systematic review examined the use of ultrasound in various aspects of IBD diagnosis and management.[48] The pooled per-patient sensitivity and specificity for the diagnosis of CD (5 studies, 1029 patients) were 85% (95% CI, 83%-87%) and 98% (95% CI, 95%-99%), respectively.[48] Sensitivity varied by disease location, with the highest values at the terminal ileum, left colon, lower rectum, and upper small bowel. The diagnosis of postoperative recurrence was achieved with variable sensitivity ranging from 77% to 92% and specificity ranging from 20% to 95%. In a prospective study of 234 consecutive subjects with suspected small bowel CD, unenhanced ultrasound was compared with MRE (ileocolonoscopy as gold standard) and performed in random order by physicians who were blinded to test results.[49] Ultrasound was less accurate than MRE in defining CD extension with a diagnostic loss of 30% (mean extension at ultrasound 20 ± 11 cm vs MRE 28 ± 15 cm; r=0.69), especially with CD involvement of greater than 30 cm small bowel. MRE also was better at the detection of enteroenteric fistulas (Cohen's kappa coefficient, 0.67; $P<.01$).[49] Representative ultrasound images are shown in Figures 3, 4, and 5 with correlative computed tomography (CT) images.

Color Doppler

Color Doppler of the small bowel evaluates the amount of blood flow in the wall of the bowel and surrounding mesentery. The blood flow is quantitated by the absolute velocity of flow and density of mural blood vessels. The Limberg score has been used to semiquantify these findings.[50] These measurements, made with ultrasound contrast, have been used to assess response to medical treatment.[51] Color Doppler measurements have been shown to correlate histopathologically with lesions with greater vascularity and inflammatory cells.[52] Color Doppler has also been shown to increase the specificity of findings indicating recurrence after surgery.[53]

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) has been explored as a modification to IBD ultrasound protocols for assessing

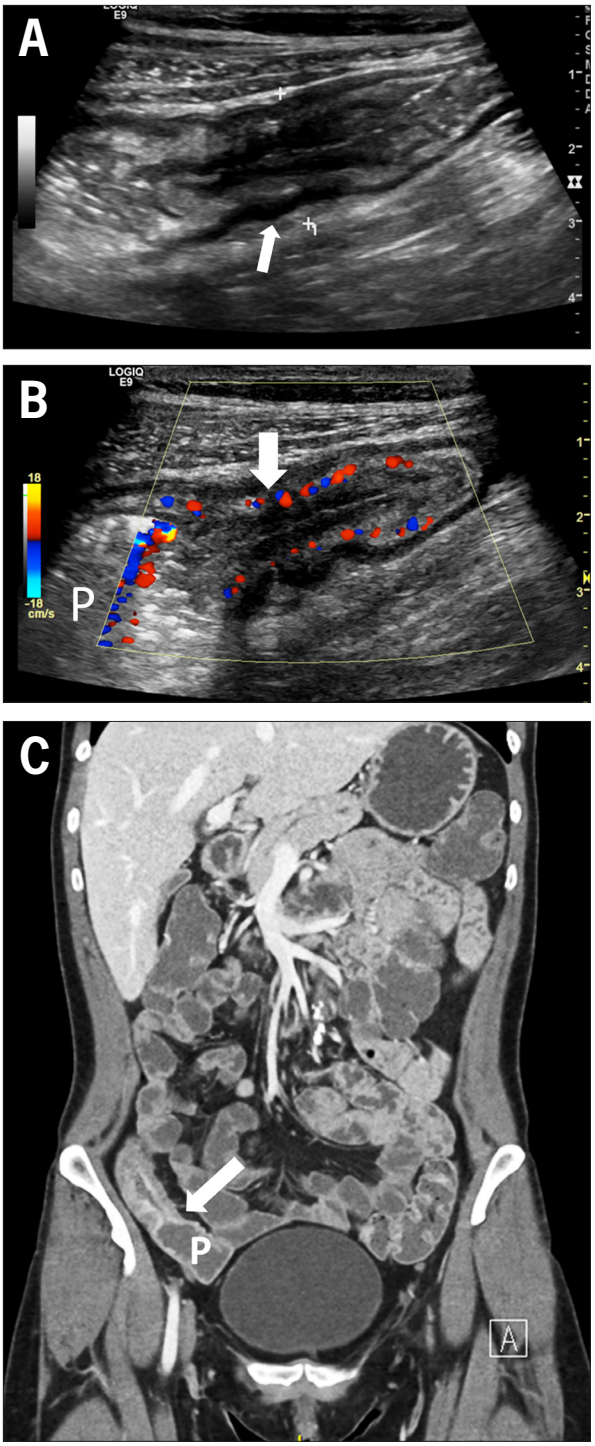

Figure 3. Terminal ileal inflammatory stricture seen on ultrasound with correlative computed tomography (CT) enterography. Ultrasound without color demonstrates a terminal ileal stricture (arrow; **A**). Ultrasound with color demonstrates increased vascularity in the terminal ileal stricture (arrow). Proximal small bowel dilation is seen (P; **B**). CT correlation demonstrates a typical Crohn's disease terminal ileal stricture with asymmetric inflammation and wall thickening (arrow) with mild proximal small bowel dilation (P; **C**).

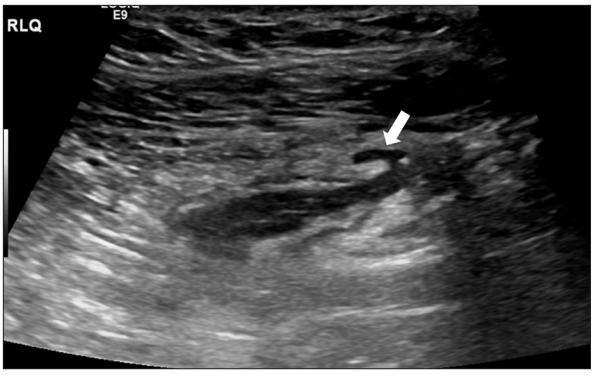

Figure 4. Gray scale ultrasound showing mural thickening and a penetrating ulcer in the terminal ileum (arrow).

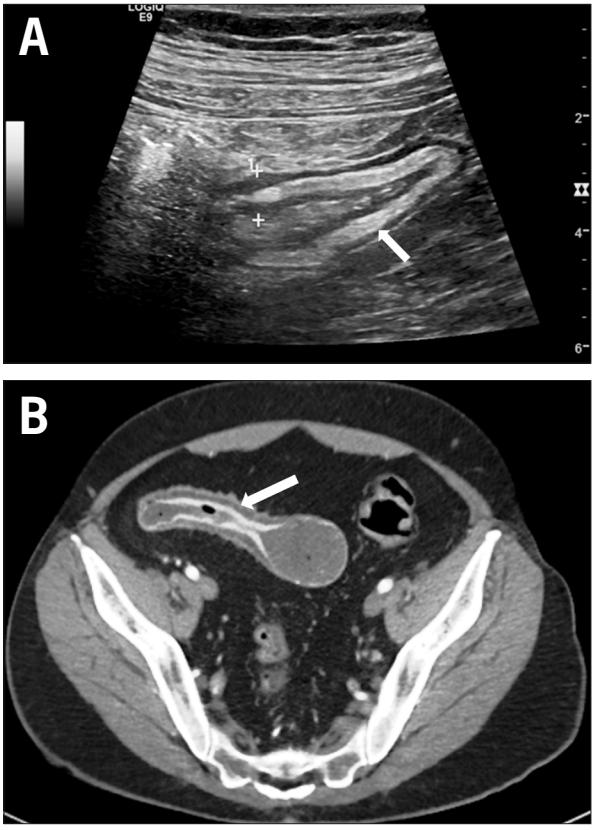

Figure 5. Fatty infiltration of the wall in the terminal ileum on ultrasound (**A**) and computed tomography (**B**).

disease activity in patients with CD.[54-56] CEUS involves the intravenous administration of microbubbles filled with sulfur hexafluoride (Lumason, Bracco Diagnostics), octafluoropropane, perflutren (Definity, Lantheus Medical Imaging), or perfluorobutane.[57] The contrast agents mentioned above have no risk of nephrotoxicity and are eliminated through the lungs approximately 10 to 15 minutes after injection. The microbubbles oscillate when exposed to a low-intensity ultrasound field and disrupt when exposed to a higher intensity. The contrast agents demonstrate tissue perfusion with real-time blood-pool imaging. Resolution is improved with harmonic ultrasound imaging and pulse inversion technology. These agents are very safe, with only 29 recorded adverse events and only 2 serious events in a multicenter study involving 23,188 examinations.[58] Lumason (known as SonoVue in Europe) is the only contrast agent that is currently approved by the US Food and Drug Administration. The only absolute contraindication for usage is in patients with suspected acute coronary syndrome, recent percutaneous coronary intervention, New York Heart Association class III/IV heart failure, or severe cardiac dysrhythmias.[54,56,59]

CEUS has been studied both in qualitative and quantitative analyses of CD inflammatory activity.[60-62] Migaleddu and colleagues conducted a study of 47 CD patients that compared conventional ultrasound, color Doppler, and CEUS using endoscopic findings (Rutgeerts score) and histologic findings as reference standards.[60] CEUS performed better than gray scale ultrasound or color Doppler, with 93.5% sensitivity, 93.7% specificity, and 93.6% overall accuracy.[60] Quantitative and semiquantitative analyses have been attempted based upon analysis of time-intensity curves using dedicated software, such as QLAB (Philips) and VueBox (Bracco Imaging).[62-69] The area under the time-intensity curve has been studied as a parameter to separate responders from nonresponders to medical therapy.[51,70] CEUS has also been studied in the assessment of MH, with an intestinal wall thickness less than 3 mm being the best predictor of healing (92.5%).[71] The performance of CEUS has been similarly studied in the diagnosis of postoperative recurrence in 60 CD patients who underwent a CEUS and colonoscopy within 3 days.[72] A thickness score greater than 5 mm or contrast enhancement greater than 46% resulted in a sensitivity, specificity, and accuracy of 98%, 100%, and 98.3%, respectively, for the diagnosis of endoscopic recurrence. The feasibility of using CEUS as a method to estimate inflammation and fibrosis in CD strictures has been investigated using percentage of maximal enhancement and area under the enhancement curve, but further validation is required.[73,74] A recent meta-analysis of 8 studies utilizing CEUS for the detection of active CD demonstrated a pooled sensitivity of 0.94 (95% CI, 0.87-0.97) and specificity of 0.79 (95% CI, 0.67-0.88). Relative intestine wall enhancement was shown to have the highest diagnostic value (area under the curve, 94%).[75]

Small Intestine Contrast Ultrasonography

Small intestine contrast ultrasonography (SICUS) is another modification of unenhanced gray scale ultrasound involving the ingestion of oral contrast (usually 250-800 mL of PEG) following an overnight fast.[76] SICUS has been shown to improve the performance of conventional ultrasound in detecting proximal small bowel inflammatory lesions and

strictures.[77,78] A quantitative sonographic lesion index for CD has been developed that accounts for transmural disease extent and severity assessed with SICUS using bowel wall thickness, lesion length, lumen narrowing, dilation, and CD complications.[79] This index has been shown to be responsive to medical therapy with anti-TNFα agents.[80] SICUS has also been shown to be superior to conventional ultrasound without oral contrast in detecting postoperative CD recurrence.[81,82] In a retrospective analysis of 59 patients with CD evaluated by SICUS and CT enteroclysis 3 months apart, SICUS was shown to have comparable performance for small bowel disease extent and presence of strictures, abscesses, and fistulas.[83] In a retrospective study of 67 CD patients (of whom 25 underwent both SICUS and MRE), both of these modalities were shown to be comparable in detecting small bowel complications of CD when correlated to the intraoperative findings.[84]

Sonoelastography

Ultrasound elasticity imaging, or sonoelastography, is a noninvasive method for the assessment of tissue mechanical properties to differentiate inflammatory from fibrotic tissue. Sonoelastography consists of a combination of application of controlled deformation of the study object and phase-sensitive, 2-dimensional ultrasound speckle tracking and evaluation of internal tissue motion, namely the measurement of displacement and strain components.[85] This method has shown promising results in animal models and ex vivo human specimens to differentiate normal from fibrotic tissue and low-grade from high-grade fibrosis.[86-88] A recent study correlated real-time sonoelastography performed before and during surgery and in ex vivo specimens with histologic findings.[89] These study results suggest the promising role of sonoelastography in detecting stricturing CD in real time to affect inpatient management decisions.

Future Ultrasound Directions

The role of ultrasound in IBD management appears promising.[43] Its performance appears to be similar to MRE for small bowel CD restricted to the terminal ileum, and it may have a role in the short-term assessment of response to anti-TNFα agents. Ultrasound has the unique advantage of avoiding radiation exposure, and some ultrasound protocols do not require oral or intravenous contrast. Ultrasound may also serve as a trigger for more extensive small bowel evaluation with MRE on follow-up visits.

Additional advancements and refinements are on the horizon for IBD ultrasonography. Molecular imaging with CEUS-tagged microbubbles is a technique still in preclinical studies with the potential for quantification of inflammation and targeted, acoustically activated platforms for drug delivery.[90-92]

Summary

MRE and ultrasound are revolutionizing CD assessments. Numerous novel approaches are being investigated to improve assessments of disease extent and severity while limiting the need for contrast agents. These new techniques may allow for better quantification of inflammatory and fibrotic components in CD strictures. Validated MR-based scoring systems are now available to standardize scoring and provide objective measurements of disease activity and digestive damage. The use of ultrasound in IBD will continue to expand as the technique is standardized and further refined.

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