Impact of Gadolinium-Based Contrast Agent in the Assessment of Crohn's Disease Activity: Is Contrast Agent Injection Necessary?

Emilio Quaia, MD,[1]* Michele Sozzi, MD,[2] Antonio Giulio Gennari, MD,[1]
Michele Pontello, MD,[1] Roberta Angileri, MD,[1] and Maria Assunta Cova, MD[1]

Purpose: To determine whether magnetic resonance enterography (MRE) performed without intravenous contrast injection is diagnostically noninferior to conventional contrast-enhanced MRE (CE-MRE) in patients with Crohn's disease (CD).

Materials and Methods: This was an Institutional Review Board (IRB)-approved retrospective study. Ninety-six patients (52 male and 44 female; 47.18 years $\pm$ 13.6) with a diagnosis of CD underwent MRE at 1.5T including T_2-weighted single-shot turbo-spin-echo, T_2-weighted spectral fat presaturation with inversion recovery (SPAIR), T_1-weighted balanced fast-field-echo MR sequences, and CE-MRE consisting in T_1-weighted breath-hold THRIVE 3D MRI sequences after administration of gadobenate dimeglumine (0.2 mL/kg of body weight). Unenhanced MRE, CE-MRE, and unenhanced MRE plus CE-MRE were reviewed in separate sessions with blinding by two readers in consensus, and subsequently by two other readers independently considering a subgroup of 20 patients. Crohn's Disease Endoscopic Index of Severity (CDEIS) and/or histologic analysis of the surgical specimen were considered as reference standards for the assessment of inflammatory activity.

Results: Patients revealed prevalently active ($n = 55$ patients) or quiescent CD ($n = 41$ patients). The agreement between unenhanced MRE vs. CE-MRE in interpreting active bowel inflammation was 96% (123/128 bowel segments; one-sided 95% confidence interval [CI], >94.4%). Unenhanced MRE vs. CE-MRE vs. unenhanced MRE plus CE-MRE revealed a diagnostic accuracy of 93% [90/96] vs. 92% [88/96] vs. 97% [93/96] ($P > 0.05$) in the diagnosis of active CD. Interreader agreement was very good for all variables (κ value = 0.8–0.9) except for the measurement of the length of disease (κ value = 0.45).

Conclusion: Unenhanced MRE was noninferior to CE-MRE in diagnosing active inflammation in patients with CD.

The assessment of disease activity of Crohn's disease (CD) is based on clinical and laboratory findings, endoscopy with histology analysis, and imaging findings.[1,2] Clinical indices, including Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index,[3] are widely used both in clinical practice and experimental trials, even though they are based mainly on subjective symptoms with consequent variability in grading the inflammatory activity. Contrast-enhanced magnetic resonance enterography (CE-MRE) with gadolinium-based contrast agent injection has been used in the diagnosis and follow-up of patients with CD[4–9] and provides a good diagnostic accuracy (85–90%)[10–13] to identify patients with active CD based on bowel mural changes (eg, bowel wall enhancement, bowel wall thickening, wall edema, and stratification), lumen strictures, length of the involved segments, skip lesions, and complications (eg, fistulas). For this reason, different MRI scoring systems have been proposed.[14,15]

Diffusion-weighted MRI has more recently been used to assess CD activity[16–18] even though it may be limited by

*Address reprint requests to: E.Q., Department of Radiology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste, Italy, 34149. E-mail: quaia@units.it

From the [1]Department of Radiology, Cattinara Hospital, University of Trieste, Trieste, Italy; and [2]Department of Gastroenterology, Cattinara Hospital, Trieste, Italy.

TABLE 1. Patient Characteristics

Age, years, mean (range)	47.18 (22–78)
Gender, male/female	52/44
Disease duration, years	1–2 (mean, 1 year)
BMI	20–26 (mean 22, 5)
Nonstricturing, nonpenetrating disease	15
Structuring disease	63
Penetrating disease	18
Disease location	ileum, colon
Ileum (number of patients)	71
Ileo-colon	25
Crohn's diagnosis based on:	
1. Endoscopy with terminal ileal loop biopsy	85/96 (89%)
2. Surgical resection of ileal loop(s)	11/96 (11%)
Medication	
1. No medication	4
2. Sulphasalazine + corticosteroids	58
3. Methotrexate + corticosteroids	2
4. Corticosteroids only	14
5. Methotrexate only	0
6. Infliximab	18

artifacts due to bowel motion and to the air–mucosa interface. T_2-weighted imaging, especially with fat suppression, allows the identification of CD inflammatory activity,[19] even though it has been less extensively investigated than T_1-weighted gadolinium-enhanced imaging. Even though T_2-weighted MRI is essential in the evaluation of CD activity, it is usually considered complementary to T_1-weighted imaging, although it could potentially be used alone, without contrast agent injection. The aim of this study was to determine whether MRE performed without intravenous contrast injection is diagnostically noninferior to conventional CE-MRE in patients with CD.

Materials and Methods

Patients
This retrospective study was approved by the Institutional Review Board of (Cattinara Hospital), and informed consent for the study was obtained from all patients for the scientific use of their imaging and clinical records at the time of MRI examination according to the protocol used in our hospital.

Through a review of Radiology Department records of patients imaged between December 1st 2008 and December 31st 2014, we identified patients with a proven diagnosis of CD, based on endoscopy with deep mucosal biopsy or histologic analysis of the bowel resection specimen, who underwent MRE for symptoms including abdominal pain, fever, and leukocytosis to establish the activity of CD and the length of bowel involvement before or during medical treatment.

To be eligible for this study patients had to meet these inclusion criteria: 1) CD involving the terminal ileal tract with or without involvement of the colon as shown by endoscopy, or CD involving the rest of the ileum provided that the patient underwent elective small-bowel resection after MRI examination with histologic analysis of the surgical specimen; 2) a history of CD for a maximum time period of 2 years. Of the 127 patients who were deemed initially eligible for the study, 31 patients were excluded according to the following criteria: an interval of more than 30 days between endoscopy and MRE ($n = 4$ patients); visualization of the distal ileum not feasible at endoscopy ($n = 6$); MR image degradation due to artifacts from bowel motion ($n = 5$); absence of dosage of fecal calprotectin and C-reactive protein levels ($n = 16$).

Therefore, 96 patients (52 male and 44 female; 47.18 years ± 13.6) with a diagnosis of CD were finally included in our study (Table 1). Patients had a CDAI ≥150 ($n = 43$ patients, CDAI: 150–170) or <150 ($n = 53$ patients; CDAI: 10–140).

CE-MRI Examination
All patients underwent MRE within 30 days from endoscopy. After intestinal cleansing and preexamination fasting for 8 hours, each patient ingested 2000 mL of polyethilenglycol solution 1 hour before the examination in order to obtain an adequate distension of bowel loops. In addition, a 200–250 mL of water-soluble iodinated radiopaque contrast medium enema (diatrizoate meglumine and diatrizoate sodium solution, Gastrografin, Bracco, Milan, Italy) was administered for colon distension. Immediately before entering the MR unit room 40 mg of N-butylhyoscine (Buscopan; Boehringer Ingelheim, Germany) was administered intravenously to reduce bowel peristalsis during image acquisition.

MR images were obtained with a 1.5T whole-body MR system (Achieva, Philips, Best, The Netherlands), with gradients of 33 mT/m/s. The patient, with a 16-channel phased array coil covering the abdomen/pelvis, was placed in the prone position to reduce the breathing-dependent displacement of the small bowel. After standard localizer image, patients underwent coronal T_2-weighted single-shot turbo-spin-echo and spectral fat presaturation with inversion recovery (SPAIR) sequences, coronal and transverse T_1-weighted balanced steady-state fast field echo, and coronal T_1-weighted breath-hold resolution isotropic high volume (THRIVE) 3D with fat suppression before and after administration of gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco) at a dose of 0.2 ml/kg body weight by means of an automatic injector (Spectris MR Injector; Medrad, Indianola, PA), followed by a bolus of 30 mL of normal saline. The THRIVE sequence was acquired on arterial (40 sec after injection of the contrast material), portal venous (70 sec), and late equilibrium phase (3 and 5 min after injection of contrast material). The total scan time was 25–27

Sequence	T2-w TSE[a]	T2-w SPAIR[b]	T1-w FFE[c]	T1-w THRIVE 3D[d]
Fat saturated	No	Yes	No	Yes
Breath-hold	Yes	Yes	Yes	Yes
Acquisition time (sec)	120–180	120–180	18	18
Repetition time (msec)	593	448	332	3.2
Echo time (msec)	80	80	4.6	1.62
Flip angle (degrees)	90	90	80	10
Echo-train length	97	70	/	/
Parallel imaging factor	1.75	1.75	1.5	1.5
No. of signals averages	3	2	1	1
Field of view (mm)	(300–420) × (300–420) for all sequences			
Matrix	384 x 384	384 x 384	164 x 132	352 x 352
Section thickness (mm)	5	5	5	6
Intersection gap (mm)	1	1	1	− 3
Slice number	30	30	30	90
Voxel size (mm)	1.3 x 1.65	1.3 x 1.66	(2 x 2.5) / (1.72 x 2.16)	2 x 2
Acquisition time (sec)	126	96	23/20	18

TABLE 2. MRI Sequence Parameters

k-space sampling was linear-ordered except for THRIVE sequence where it was centric-ordered.
[a]T2-weighted half-Fourier single-shot turbo spin-echo respiratory-triggered or breath-hold.
[b]T2-weighted half-Fourier single-shot spectral presaturation with inversion recovery respiratory-triggered or breath-hold.
[c]T1-weighted balanced steady-state fast field echo.
[d]T1-weighted high resolution isotropic volume examination.

minutes. Table 2 shows the technical parameters of the different MRI sequences.

Image Visual Analysis

The MRE images of each patient were reviewed by two radiologists (10 and 12 years of experience on abdominal MR: A.G.G. and M.P.) during a consensus double-reading session. These readers were aware of the patients' identification and clinical histories but were blinded to endoscopy and biopsy results and other imaging findings. Unenhanced MRE (ie, T_2-weighted and T_1-weighted sequences), CE-MRE (ie, dynamic contrast-enhanced T_1-weighted sequences), and unenhanced MRE plus CE-MRE were reviewed in three separate sessions with a washout period (4 weeks between unenhanced MRE and CE-MRE, and 5 weeks between CE-MRE and unenhanced MRE plus CE-MRE) and simple randomization.

To assess interreader variability, two independent readers (experience, 10 and 20 years in abdominal imaging: R.A. and M.A.C.), who were different from the readers involved in the previous consensual reading sessions but also blinded to endoscopy and biopsy results and other imaging findings, repeated the subjective analysis in a subgroup of 20 patients, selected by simple randomization.

A total of 128 ileal segments, representing the whole spectrum of CD activity from normalcy up to severe inflammation, were selected by the study coordinator (E.Q.) provided that a reliable reference standard was available (see below). Different parameters were considered: 1) length of disease (cm); 2) the maximal bowel mural thickness (mm); 3) presence or absence of multiple loop/intestinal tract involvement; 4) creeping fat; 5) regional lymphadenopathy; 6) mural wall T_2 hyperintensity (at least in one involved loop in comparison to the subcutaneous fat); 7) comb sign during the arterial/portal venous phase after contrast injection; 8) mucosal only (with only the innermost wall layer enhancing), transmural (with all bowel wall enhancing equally), or layered avid enhancement (with both mucosal and serosal bowel wall layers enhancing, with a central band of relatively reduced enhancement) during the arterial and/or portal venous phase, or mural delayed enhancement after contrast injection on the late equilibrium phase.

We evaluated the following signs of activity: wall thickening >3 mm; submucosal edema (mural hyperintensity on fat-suppressed T_2-weighted sequences); ulcers; transmural enhancement, compared with a normal loop, mucosal or layered enhancement during arterial and portal venous phase; vascular congestion ("comb sign"); the presence of phlegmons, abscesses, sinus tracts or fistulas.[4–15] The evidence of only one of these imaging findings in one of the bowel tracts involved by CD determined the diagnosis of active inflammation of the bowel were scored in a binary fashion (absent = 0; present = 1). In those bowel segments in which unenhanced MRE or CE-MRE were not in agreement in the diagnosis of active inflammation, the disease was considered active

when unenhanced MRE or CE-MRE identified at least one sign of activity (eg, mural hypointensity on T_2-weighted images or evidence or transmural enhancement at CE-MRE). The length of disease (cm) and the maximal wall thickness (mm) of the whole bowel segment(s) involved by disease were measured by both radiologist readers in consensus. The presence of fistulas, sinus tracts, abscesses, and phlegmons were recorded and their appearance was analyzed at unenhanced MRE and CE-MRE.

Wall thickness was measured on T_2-weighted single-shot turbo-spin-echo sequence images on the coronal plane by using electronic calipers, while mural signal intensity was visually assessed on fat-saturated T_2-weighted images and compared to the signal intensity of the adjacent mesenterial fat. The total length of disease within each segment was measured via electronic calipers using the sequence and orientation that the observers felt best displayed the disease extent.

All readings were performed on a PACS-integrated workstation (Intel Core i7, Hewlett-Packard, Palo Alto, CA) on-screen (21.3-inch TFT display, resolution 2048 × 1536 pixels) at a central location by using a proprietary software package (Ebit Sanità AET, Genoa, Italy).

CDAI, C-reactive protein (mg/L), and fecal calprotectin levels (mg/g of feces) of each patient were also recorded.

Reference standards

Endoscopy (Olympus, probe CF-H180AI/L, Hamburg, Germany) included the examination of the large bowel and the distal part of the small bowel with deep mucosal biopsy of the involved loop(s). All patients had bowel preparation using polyethylene glycol administered the previous day and fasted overnight.

Immediately after the procedure, the endoscopic score was assigned according to the Crohn's Disease Endoscopic Index of Severity (CDEIS)[20] criteria, which include the presence of deep ulcerations (12 if present, 0 if absent in the segment), superficial ulcerations (6 if present, 0 if absent), and the surface involved by disease and by ulcerations (cm). Multiple deep mucosal biopsies from different colonic segments and the terminal ileal loop were performed in all cases. Using the histologic acute inflammatory score,[21] a score up to a maximum of 13 on the basis of grades for mucosal ulceration (grade 0–3), edema (grade 0–3), quantity (grade 0–3), and depth (grade 0–4) of neutrophilic infiltration was assigned. Mural fibrosis was defined as collagen fiber replacement involving at least one bowel layer.[21] The prevalence of the inflammatory findings over the fibrotic component was assessed by the gastroenterologist involved in the present study (M.S.) based on the acute inflammation score[21] higher than 7 combined with a CDEIS higher than 10.

In those patients ($n = 11$) who underwent elective small-bowel resection within 4 weeks from MRI, the histologic analysis of the surgical specimen including ($n = 5$) or not ($n = 6$) the terminal ileal loop was considered the reference standard based on the acute inflammation score. The study coordinator (E.Q., a radiologist with 5 years of experience in small-bowel MRI), reviewed the preoperative MR images to identify the exact location of each removed bowel segment for the subsequent correlation with the different MRI findings according to what was registered in the electronic record describing the surgical procedure. Note was made of the resected bowel length and of anatomic landmarks such as the ileocecal valve, mesenteric vessels, and lymph nodes that were visible on the presurgical MR images. The MRI findings were related to the histology of the resected specimen.

Statistical Analysis

The statistical analysis was performed with a computer software package (Stata, Statistical software, v. 13.1, StataCorp, College Station, TX).

The proportional agreement between unenhanced MRE and CE-MRE in diagnosing active bowel inflammation, and the overall diagnostic accuracy of unenhanced MRE vs. unenhanced MRE plus CE-MRE in diagnosing active inflammation were calculated. In the consensual analysis, the noninferiority margin was established if the agreement between unenhanced MRE and CE-MRE in interpreting active inflammation of the bowel was higher than 90%.

To assess the effect of the potential risk factors, separate univariate logistic regressions[22] were conducted. Overall model covariates included nine categorical variables: 1) presence or absence of multiple loop/intestinal tract involvement; 2) creeping fat; 3) regional lymphadenopathy; 4) mural T_2 hyperintensity; 5) comb sign; 6) mural mucosal-only enhancement; 7) transmural enhancement; 8) layered enhancement; and 9) delayed enhancement, and five continuous variables: 1) length of disease (cm); 2) maximal bowel wall thickness (mm); 3) CDAI; 4) C-reactive protein (mg/L); and 5) fecal calprotectin levels (mg/g of feces), considered as potential predictors (independent variables), and the probability of active bowel wall inflammation (dependent variable), selected as the outcome variable. The odds ratios (ORs) with 95% confidence intervals (CIs) and the P value for the chi-squared test with Yates correction were calculated.

Then multivariable stepwise logistic regression analysis was performed to identify findings that were potential independent predictors of Crohn's disease activity. The goodness of fit of the model was determined by the area under the receiver operating characteristic curve and the Hosmer-Lemeshow test,[23] which is a statistical test for goodness of fit for the logistic regression model. The Hosmer-Lemeshow test follows a chi-squared distribution with n-2 degrees of freedom. A large value of chi-squared (with small $P <$ 0.05) indicates poor fit and small chi-squared values (with larger P-value closer to 1) indicate a good logistic regression model fit. Those parameters that showed a significant correlation with active inflammation of the bowel wall were entered simultaneously into a multivariate analysis to assess how the different combinations predicted the probability of the active inflammation diagnosis.

The weighted κ statistic was calculated to assess interreader agreement among the two readers who performed the independent image analysis in the subgroup of patients. Agreement was graded as poor (κ value <0.20), fair ($\geq$0.20 and <0.40), moderate ($\geq$0.40 and <0.60), good ($\geq$0.60 and <0.80), and very good ($\geq$0.8 up to 1). For all tests $P < 0.05$ was considered statistically significant.

Results

Table 3 shows the distributions of parameters values and MRE findings according to the patient inflammatory activity in the bowel.

TABLE 3. Imaging Findings and Biomarker Value Distribution

Biomarkers	Active disease	Quiescent disease
CDAI	55 (12–99)[a]	41 (10–170)[a]
C-reactive protein	45 (22–85) mg/L	35 (10–55) mg/L
Fecal calprotectin	218 (12–634)[b]	116 (2–601)[b]
T2 hyperintensity	26	4
Total length of disease	8 (5–70) cm	3 (0–10) cm
Bowel wall thickness	6 (3–10) mm	2 (3–8) mm
Bowel tracts involved	1–3[c]	1[c]
Comb sign	38	2
Creeping fat	6	0
Loco-regional lymph nodes	20	8
Transmural enhancement	59	15
Layered enhancement	19	0
Mucosal-only enhancement	1	9
Mural delayed enhancement	14	18

Active and quiescent disease was diagnosed in 55 and 41 patients, respectively, based on the results of endoscopy with histologic analysis. Number are medians with the range between brackets. All numbers indicate patient number excluding: [a]Crohn's Disease Activity Index; [b]μg/g of feces; and [c]number of bowel tracts involved. The transmural, layered and mucosal-only enhancement were visualized on arterial and portal venous phase, while mural delayed enhancement was visualized on late equilibrium phase.

Patients revealed prevalently active ($n = 55$ patients) or quiescent CD with mural fibrosis ($n = 41$ patients). Patients with active CD revealed fecal calprotectin levels ≤ 100 μg/g ($n = 26$), >100 ≤ 200 μg/g ($n = 5$), or >200 μg/g ($n = 24$ patients). Patients with quiescent CD revealed a fecal calprotectin ≤ 100 μg/g ($n = 22$), >100 ≤ 200 μg/g ($n = 5$), or >200 μg/g ($n = 14$ patients).

Twenty-one ileal segments from 18 patients showed active penetrating CD, including 16 sinus tracts, two entero-enteric, and one entero-cutaneous fistulae, and two abscesses. All other ileal segments ($n = 107$) included in the visual analysis revealed nonstricturing and nonpenetrating disease ($n = 9$ in 15 patients) or stricturing disease ($n = 98$ in 63 patients).

In the consensus analysis, the agreement between unenhanced MRE and CE-MRE in interpreting active bowel inflammation (Fig. 1) was 96% (123/128 bowel segments; one-sided 95% CI, >94.4%).

In five ileal segments with active inflammation we found disagreement between unenhanced MRE and CE-MRE due to evidence of equivocal mural T_2 hyperintensity on fat-suppressed T_2-weighted sequences (Fig. 2) and layered or transmural enhancement after gadolinium injection, expressing CD activity, according to both readers. In these cases the mural T_2 hyperintensity was considered equivocal since it appeared quite similar to the subcutaneous fat at visual analysis according to both readers.

There was general agreement in the visualization of sinus tracts, fistulas, and abscesses between unenhanced MRE and CE-MRE (Fig. 3) except for three terminal ileal segments (Fig. 4) with sinus tracts which were identified by unenhanced MRE but missed by CE-MRE, due to diffuse contrast enhancement around fistula that concealed the sinus tract. Anyway, in all ileal segments in which disagreement between unenhanced MRE and CE-MRE was found, there was no final disagreement to diagnose active inflammatory activity of the bowel since the evidence of layered or transmural enhancement at CE-MRE allowed the diagnosis of active CD.

Unenhanced MRE when compared with CE-MRE, and compared with MRE plus CE-MRE, revealed a diagnostic accuracy of 93% [90/96] vs. 92% [88/96] vs. 97% [93/96] in the diagnosis of active disease with a not significant difference ($P > 0.05$).

Table 4 shows the results of univariate logistic regression. Neither CDAI nor C-reactive protein and fecal calprotectin were found predictors of active CD on univariate analysis. T_2 hyperintensity, total length of disease, more bowel tracts involved, comb sign, loco-regional lymph nodes, transmural and layered enhancement were found to be predictors of active disease on univariate analysis. Table 5 shows the results of multivariate logistic regression analysis. The mural wall T_2 hyperintensity and layered enhancement were found as the best independent predictors of active CD

FIGURE 1: A 45-year-old male patient with active CD. (a) T_2-weighted SPAIR MR images with fat suppression. Diffuse thickening of the ileal wall appearing hyperintense (arrows) with stricture of the bowel lumen. (b) THRIVE with fat suppression MR images acquired in the coronal plane after injection of gadobenate dimeglumine during the arterial phase. After contrast injection the involved ileal tract shows layered enhancement (arrows). T_2 hyperintensity of the bowel wall represents an independent predictor of CD activity. No further information is added by contrast agent administration. The patients presents active disease on endoscopy (CDEIS = 15).

on multivariate logistic regression. The logistic regression analysis revealed a significant goodness of fit of the model (area under the receiver operating curve: 0.932;95% CI: 0.84–0.96; Hosmer-Lemeshow test $P = 1$).

The interreader agreement was very good for all categorical variables (κ value = 0.8–0.9) and for the measurement of the maximal bowel thickness (κ value = 0.8) while it was moderate (κ value = 0.45) for the measurement of the total length of disease.

Discussion

In our study we found that unenhanced MRE is noninferior to CE-MRE in assessing CD activity. We found disagreement between unenhanced MRE and CE-MRE only in a few bowel segments with active inflammation due to equivocal mural T_2 hyperintensity at unenhanced MRE and layered or transmural enhancement after gadolinium injection. We also noted that unenhanced MRE vs. CE-MRE vs. unenhanced MRE plus CE-MRE did not differ in terms of diagnostic accuracy in the diagnosis of active disease since

all these combinations provided a diagnostic accuracy higher than 90%.

According to the results of our study, the use of intravenous contrast agent is probably not justified to assess disease activity in CD except for patients with equivocal mural T_2 hyperintensity. We found general agreement in the visualization of sinus tracts, fistulas, and abscesses between unenhanced MRE and CE-MRE. Anyway, even though the visibility of sinus tracts was considered poor in some patients after contrast injection, this did not reduce the detection of disease activity due to the evidence of additional imaging findings (transmural or layered enhancement) after gadolinium-based contrast injection, which allowed diagnosis of active disease as confirmed by endoscopy. These findings are important because it is reasonable to avoid the use of gadolinium-based contrast agent in most patients with CD, which suggests reduction of costs, examination time, and patient's exposure to potential adverse reactions, especially in patients with renal failure.

Moreover, we found that mural T_2 hyperintensity and mural layered enhancement are the best independent predictors
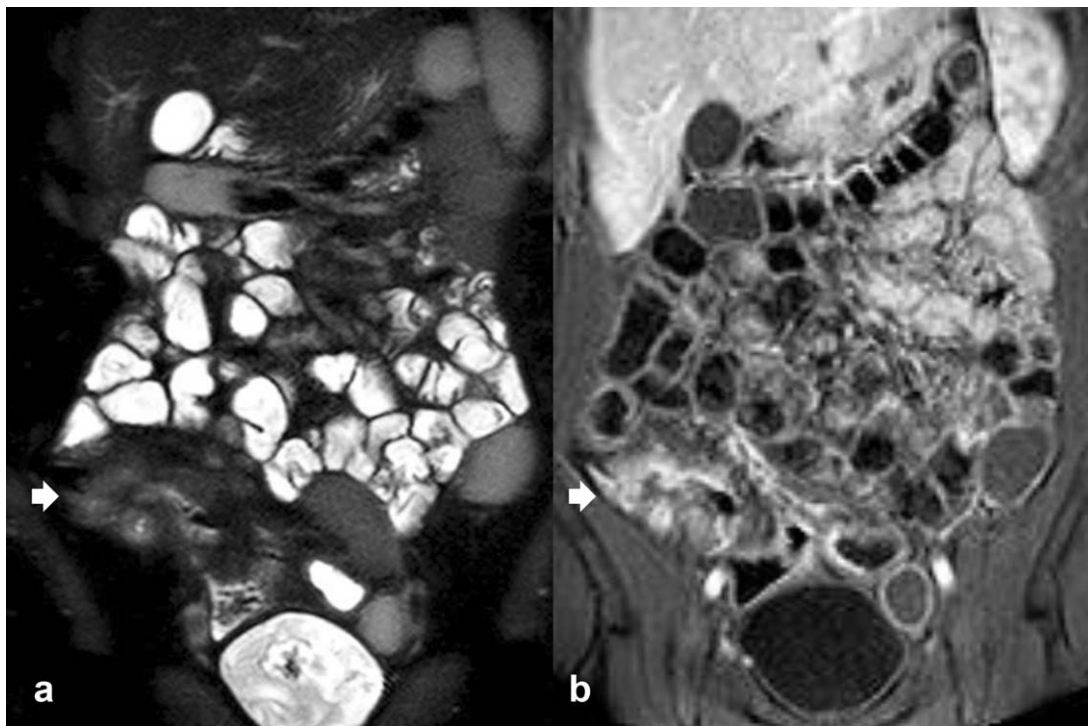
FIGURE 2: A 55-year-old woman with active CD. (a) T_2-weighted SPAIR MR images with fat suppression. (b) THRIVE with fat suppression MR images acquired in the coronal plane after injection of gadobenate dimeglumine during the arterial phase. (a) Focal thickening of the cecal and ileal wall (arrow) with stricture of the bowel lumen. The bowel wall appeared thickened but presented equivocal mural intensity (arrow) according to both readers, who were not able to define the presence or absence of disease activity. After contrast injection the involved ileal tract shows transmural enhancement corresponding to active inflammation which was confirmed at endoscopy (CDEIS = 14).

of active CD at MRE. Our results confirm previous studies that found that mural enhancement after gadolinium injection is a reliable sign of CD activity.[10–15,24–31] According to the results of our study the evidence of mural T_2 hyperintensity can be considered sufficient to diagnose active CD, without the injection of gadolinium, which can be avoided in most patients. We observed a very good interreader agreement, except for the measurement of the total length of disease, which shows the
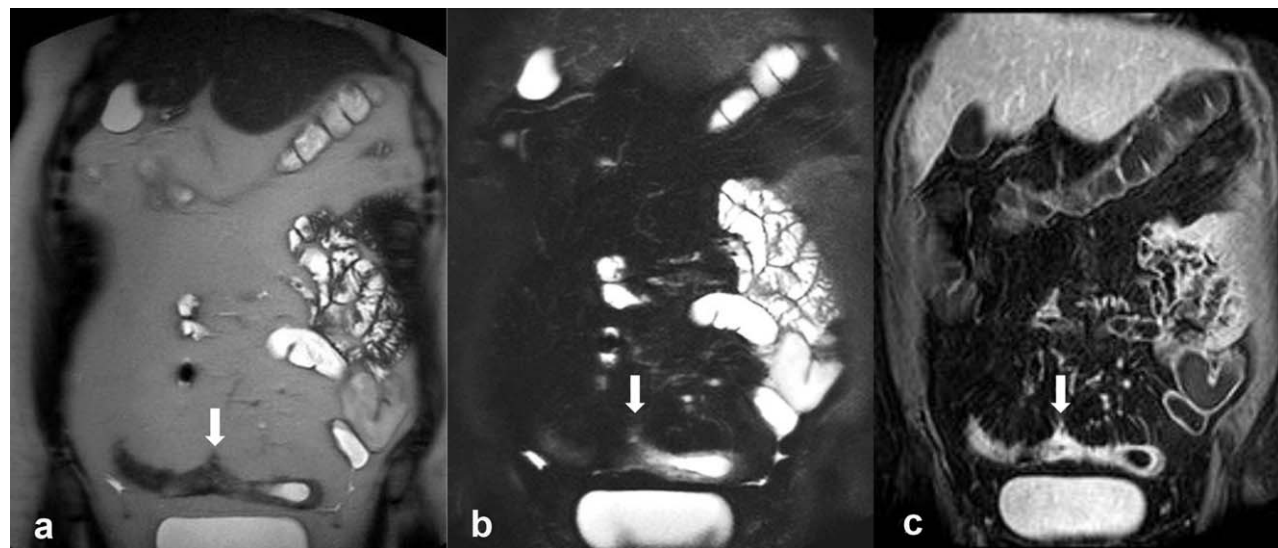

FIGURE 3: A 55-year-old woman patient with active CD. (a) TSE T_2-weighted MR images; (b) T_2-weighted SPAIR MR images with fat suppression; (c) THRIVE with fat suppression MR images acquired in the coronal plane after injection of gadobenate dimeglumine during the arterial phase. Diffuse thickening of the ileal wall with evidence of sinus tract (arrow) at unenhanced MRE both at TSE T_2-weighted (a) and T_2-weighted SPAIR MR images (b). The sinus is also clearly evident at contrast-enhanced MRE (c). There was agreement between unenhanced MR and contrast-enhanced MRE in defining active inflammation which was confirmed by endoscopy (CDEIS = 18).
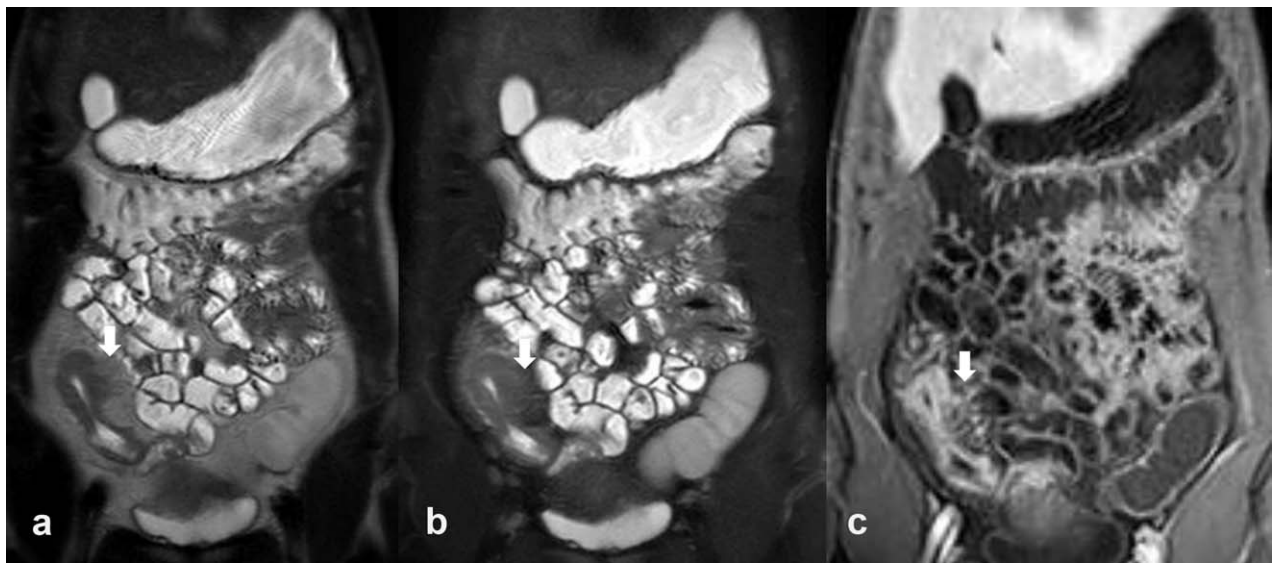
FIGURE 4: A 35-year-old woman patient with active CD. (a) TSE T_2-weighted MR images; (b) T_2-weighted SPAIR MR images with fat suppression; (c) THRIVE with fat suppression MR images acquired in the coronal plane after injection of gadobenate dimeglumine during the arterial phase. Diffuse thickening of the terminal ileal loop with evidence of sinus tracts (arrow) correctly identified at T_2-weighted images (a,b) by both readers but not clearly identified at contrast-enhanced MRE. Even though there was disagreement in identifying sinus tract, there was not disagreement between unenhanced and contrast-enhanced MRE in defining the presence of active inflammatory disease due to presence of transmural enhancement corresponding to active inflammation at endoscopy (CDEIS = 14)

reliability of visual analysis of MRE images. The body mass index (BMI) of patients included in the study is comparable to the general population and should not have any impact on image quality and on the results of the present study.

We also did not identify bowel wall thickening and transmural contrast enhancement as independent predictors of CD activity, even though they are considered as reliable imaging findings to identify and to grade the severity CD inflammatory activity.[24] In a study by Rimola et al,[32] a significant correlation with CD activity was demonstrated for bowel wall thickness, transmural contrast enhancement intensity, and wall T_2 hyperintensity on MRE. Our results

TABLE 4. Results of Univariate Logistic Regression Analysis

Parameter	Odds ratio (95% CIs)	P
CDAI	1.04 (1.01 - 1.06)	0.0001
C-reactive protein	1 (0.997–1.002)	0.742
Fecal calprotectin	1.002 (0.99–1.006)	0.104
T2 hyperintensity	7.43 (1.45–38)	0.016
Total length of disease	1.11 (1.03–1.20)	0.007
Bowel wall thickness	1.32 (0.99–1.75)	0.055
More bowel tracts involved	34.66 (6.85–175.4)	0.0001
Comb sign	8 (1.9–33.53)	0.004
Creeping fat	1.28 (0.10–15.23)	0.84
Loco-regional lymph nodes	5.6 (1.56–19.98)	0.008
Transmural enhancement	6.54 (1.45–29.35)	0.014
Layered enhancement	6.54 (0.74–57.33)	0.09
Mucosal-only enhancement	0.001 (0.0001–0.005)	0.99
Mural delayed enhancement	0.6 (0.18–1.91)	0.38

*P value < 0.05 selected as significant value. CIs, confidence intervals.

TABLE 5. Results of Multivariate Logistic Regression Analysis

Parameter	Odds ratio (95% CIs)	P
Mural T2 hyperintensity	78.79 (10.06–619.9)	< 0.001
Mural layered enhancement	21.84 (1.51–315.5)	0.02

CIs, confidence intervals. *P < 0.05 selected as significance value.

are explained by the increased mural thickening present both in patients with prevalent mural inflammation and patients with quiescent CD who were included in our study. As a matter of fact, transmural enhancement can represent active transmural inflammation, even though a less intense enhancement is also often seen in chronic disease without acute inflammation[27,28] with a consequent difficulty to differentiate active from quiescent CD based only on the visual analysis of contrast enhancement. Our results are probably due to the more comparable percentages of patients with active and quiescent CD in our study if compared to previous studies.[24–31]

In our study neither CDAI nor C-reactive protein nor fecal calprotectin levels were found as independent predictors of CD activity due to the high number of patients with quiescent CD who have normal or elevated of fecal calprotectin levels as reported in previous studies),[30] and by the large number of our patients with CD involving both the small bowel and colon who were previously shown to present significantly higher levels of fecal calprotectin than those in whom CD was limited to one or the other.[13]

The main limitation of this study was its retrospective nature. The second limitation is the absence of surgical specimen correlation in most of the patients included in our series, while the endoscopy with deep mural biopsy was considered the surrogate reference standard in the majority of patients included in our study. In those patients in whom endoscopy was the reference standard, the terminal ileum was the only bowel tract considered in the analysis and, therefore, it remains indeterminate whether unenhanced MRE is sufficient to assess the remainder of the bowel proximal to the terminal ileum. The third limitation was that in this study we did not perform diffusion-weighted MR sequences, which have been shown to improve the diagnostic accuracy and confidence in the diagnosis of active CD and to correlate with histopathological scores of surgical specimens.[33,34] However, diffusion-weighted MRI sequences are often penalized by bowel movements and air artifacts and may be penalized in CD in comparison to ulcerative colitis.[35] A further limitation of this study was the consensual reading of unenhanced and contrast-enhanced MR images.

According to these results, the administration of gadolinium-based contrast agents might be avoided in those patients who reveal T_2 hyperintensity of the bowel wall on fat-suppressed T_2-weighted images, while it could be considered in those patients with equivocal evidence of mural edema on fat-suppressed T_2-weighted images or with a mismatch between clinical/laboratory findings.

In conclusion, unenhanced MRE was noninferior to CE-MRE in diagnosing active inflammation in patients with CD.

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