

## Current techniques and new perspectives research of magnetic resonance enterography in pediatric Crohn's disease

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### Abstract

Crohn's disease affects more than 500000 individuals in the United States, and about 25% of cases are diagnosed during the pediatric period. Imaging of the bowel has undergone dramatic changes in the past two decades. The endoscopy with biopsy is generally considered the diagnostic reference standard, this combination can evaluate only the mucosa, not inflammation or fibrosis in the mucosa. Actually, the only modalities that can visualize submucosal tissues throughout the small bowel are the computed tomography (CT) enterography (CTE) with the magnetic resonance enterography (MRE). CT generally is highly utilized, but there is growing concern over ionizing radiation and cancer risk; it is a very important aspect to keep in consideration in pediatric patients. In contrast to CTE, MRE does not subject patients to ionizing radiation and can be used to detect detailed morphologic information and functional data of bowel disease, to monitor the effects of medical therapy more accurately, to detect residual active disease even in patients showing apparent clinical resolution and to guide treatment more accurately.

**Key words:** Magnetic resonance imaging; Imaging; Pediatric; Enterography; Crohn's disease

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**Core tip:** Magnetic resonance enterography is an effective imaging modality to diagnosis, evaluating and

follow-up of Crohn's disease (CD) in pediatric patient and novel magnetic resonance imaging application, such as motility studies, spectroscopy, diffusion weighted imaging, molecular and hybrid imaging are extremely interesting and might contribute to diagnosis and management of CD.

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## INTRODUCTION

A recent study shows the increase of the incidence of Crohn's disease (CD) during childhood and adolescence<sup>[1,2]</sup>. In childhood, rates of CD increase from the first year of life, with highest rates in teenage years. The highest rate of CD occurs during adolescence. Between 11 to 30 years old, is registered the highest number of diagnosis.

The economic effects of pediatric and adult CD are staggering and are estimated to be between \$10.9 billion and \$15.5 billion per year in the United States alone<sup>[3]</sup>.

Diagnosis and follow-up of bowel CD in children and adults are typically based on a combination of patient history and physical examination, such as disease activity surveys [*e.g.*, the Pediatric Crohn's Disease Activity Index (CDAI)], laboratory assessment, endoscopy with biopsy, and imaging<sup>[4]</sup>.

Clinical subjective CD activity measurements, including the Physician Global Assessment, the Harvey-Bradshaw Index, CDAI and the Pediatric Crohn's Disease Activity Index (PCDAI), are predominantly subjective measurements<sup>[3-6]</sup>.

While several studies<sup>[7-10]</sup> have demonstrated no correlation between MRE (Magnetic Resonance Enterography) findings and the CDAI, other studies<sup>[11-13,14-18]</sup> have shown a correlation.

In particular, only two pediatric studies have compared MRE to PCDAI; Laghi *et al.*<sup>[14]</sup> demonstrated a statistically significant correlation between disease on MRE and PCDAI, instead Alexopoulou *et al.*<sup>[15]</sup> demonstrated no correlation between magnetic resonance (MR) percentage of CE (%CE) with pediatric CDAI.

These studies<sup>[14,15,19,20]</sup> showing discordance between inflammation on endoscopy and subjective activity index measurements and suggests that subjective clinical activity measurements do not essentially reflect mucosal findings with an intrinsic unreliability of subjective techniques for assessment of bowel wall and extra-enteric soft tissue pathology.

Various imaging modalities can be used to diagnose

and follow up pediatric patients with CD, including radiography, fluoroscopic studies, ultrasonography, CT, and MR imaging. Traditionally, pediatric CD has been diagnosed and monitored over time by using endoscopy and fluoroscopic endoluminal contrast material-enhanced studies (*e.g.*, upper gastrointestinal series, small bowel follow-through, and contrast enema).

Endoscopy with biopsy is considered as gold standard in diagnosis CD in particular in lesions localized in terminal segment of the ileum and for capability of obtaining samples for histopathologic assessment<sup>[3]</sup>.

However endoscopic techniques have some limitations including poor accessibility to remaining part of the small bowel (except for difficult and time-consuming enteroscopy), risk of bowel perforation and limited ability to evaluate extraluminal structures.

Therefore, these optical techniques alone may under-represent the extent of disease, particularly when considering that the mucosa has a high capacity for repair. Capsule endoscopy, although attractive, cannot be performed in very young children, does not allow for tissue sampling and is not reimbursed by national health service.

In the last ten years, the methods used to visualize the bowel, including computed tomography (CT) enterography and MR enterography in pediatric patients with CD, are increased. CT and MR enterography are similar imaging tests, both capable to identify CD in a sensitive and specific manner. The ECCO guidelines established the highest diagnostic accuracy of MR and CT enterography or enteroclysis imaging modalities. CT enterography, compared to MRE<sup>[21,22]</sup>, has a high diagnostic value and offers a lot of advantages as: Excellent spatial resolution, more willingness of CT scanner, low costs and shorter examination times.

However CT enterography, compared with MRE, have the major disadvantage of exposure to ionizing radiation, that's why it should not be routinely used in children. Even though the mean CT dose index has decreased in recent years with advances such as iterative reconstruction, it is still higher than ionizing radiation-free of MR enterography<sup>[23,24]</sup>.

In pediatric patients has been detected the similitude between the MR enterography and CT enterography, by the Appropriateness Criteria of the American College of Radiology. One recent study<sup>[25]</sup>, explained that the second technique was extremely accurate in detective active inflammation and in the absence of active inflammation, MR enterography showed high precision to detect the mural fibrosis<sup>[26]</sup>.

The progress in MR techniques and the development of new sequences with short exposition time, which are less sensitive to motion artifacts, has enabled acquiring good quality images of abdominal organs in children and currently it is considered the method of choice for the evaluation of CD severity and activity as well as for monitoring treatment effectiveness in children<sup>[3]</sup>.

The recent development of faster pulse sequences,

in fact, gives an opportunity to provide a movie cine images<sup>[27]</sup>. Cine imaging allows the observation of bowel movements in a short period and in real time. It provides high temporal, spatial and contrast resolution for monitoring bowel peristalsis<sup>[28]</sup>. MR enterography also allows for imaging that highlights multiple determinants of image contrast (e.g., T1 and T2 relaxivity, DWI, pre- and postcontrast imaging, etc.)<sup>[4]</sup>. New techniques as PET-MRI, molecular imaging and MR spectroscopy are trying out for improving diagnosis, management and treatment of CD. Aim of this review is to describe current techniques of pediatric MR enterography interpret bowel disease findings and propose new MR techniques regarding CD.

## DISCUSSION

### Examination technique

An important role is a proper patient preparation to guaranteed high-quality MR enterography images. The patients were instructed to eat light meals in the day before the examination and to be fasting in the day of the examination. To an adequate small bowel distension, are necessary large amounts of oral fluid intake and the oral contrast agents to provide the luminal distension. Contrast agents could give same collateral effects such as diarrhea, abdominal pain and nausea. The oral contrast agents can be divided into 3 groups<sup>[29,30]</sup>: Biphasic [e.g., water, polyethylene glycol (PEG) and others], negative (e.g., contrast media with iron particles), or positive (e.g., gadolinium) contrast agents<sup>[29]</sup>.

PEG is the most commonly used in MR enterography, appear as low signal intensity on T1 and high signal intensity on T2 images and these properties could supplies convenience in the detection of active inflammation (in particular on post-contrast T1W images)<sup>[30]</sup>. Ajaj *et al.*<sup>[31]</sup> developed a mixed solution with 4 different oral contrast agents (water, lactulose, low-dose barium sulfate with sorbitol and methylcellulose) with which the diagnostic quality of the MRE images was further superior respect to the MRE images obtained using lactulose solution in the adequate lumen distension of small bowels, is more tolerable and the adverse effects are less respect to the oral contrast agents routinely used<sup>[32-34]</sup>.

A study of Masselli *et al.*<sup>[35]</sup> has showed that intravenous glucagone, when administrated to children and adolescent undergoing MR enterography, improves visualization of the small and large bowel on post contrast T1 weighted 3D gradient Echo (GRE) images, including the terminal ileum. Small bowel distention in pediatric and young population was achieved by oral administration of 600-1000 mL (in general 900 mL) of PEG or water (when patients cannot tolerate the taste of consistency of VoLumen) during a 45-min period before the examination<sup>[29,30]</sup>.

Antiperistaltic agent such as hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Germany) or glucagon

(Glucagen, Novo Nordisk, Bagsvaerd, Denmark) are used intravenously in patients to improve visualization of the bowel at MR imaging.

There are few published data<sup>[36-40]</sup> about the use of these spasmolytic medications in pediatric patients undergoing MR enterography. 1-2 mL/s. of intravenous gadolinium chelates are administrated through a peripheral intravenous catheter by using a power injection; the amount of contrast material injected is based on patient weight (0.1 mmol/kg of body weight). Imaging procedure was performed with the patient lying prone or supine.

An information sheet is delivered to all patients, who may find the description of the procedure and any risks related to ingestion of PEG<sup>[41-43]</sup>.

### MR imaging protocol

MR imaging examination are performed with a 1.5 T MR imaging system and two six-channel phased - array abdominal coils. During the exam are used MR pulse sequences with insignificant sensibilities to motion artifacts (e.g., FISP, FFE, SSFP, FIESTA).

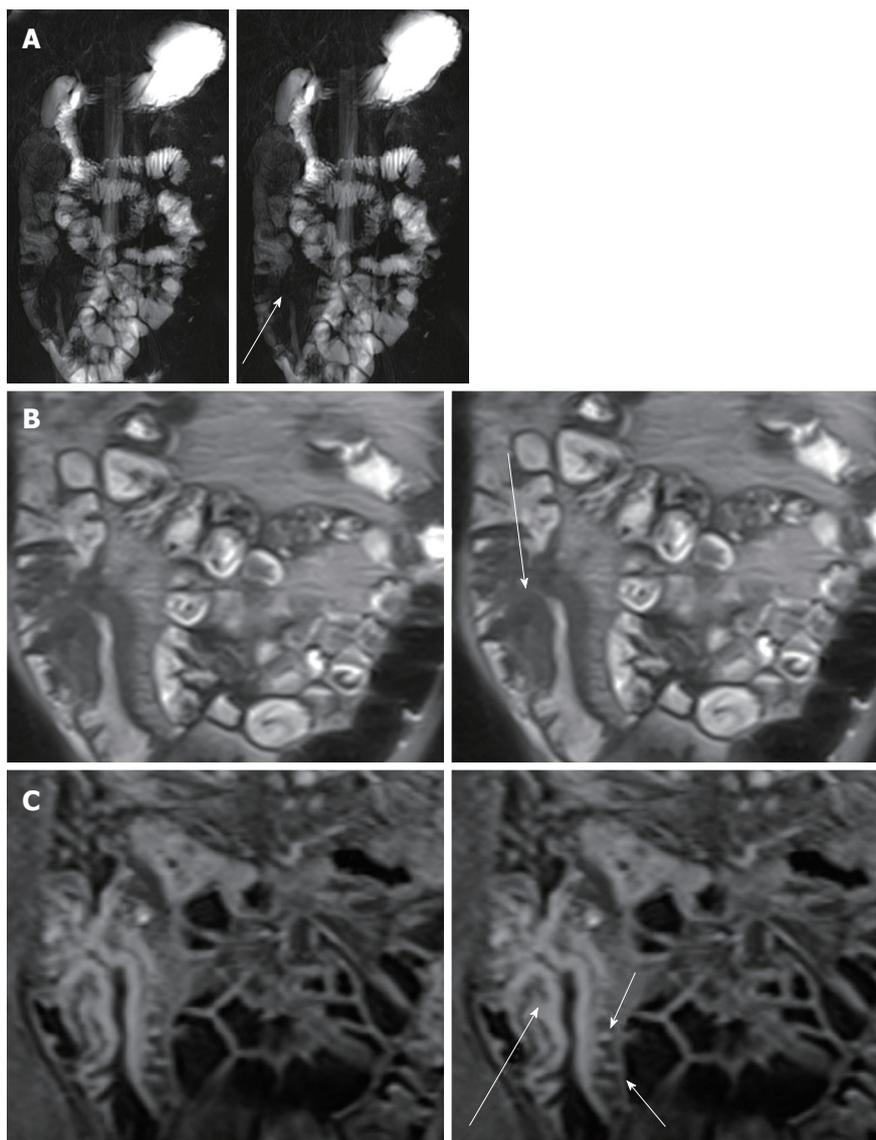
First of all, are acquired coronal and axial images (FISP) to evaluate adequate bowel distension with consecutive T2-weighted coronal and axial images (with half Fourier RARE sequences that minimize the artifacts due to small-bowel peristalsis), following by intravenously administration of Buscopan and after T1-weighted spoiled gradient echo and coronal T1-weighted fat-saturated sequences. Axial and coronal T1 GRE sequences, in arteria and portal phase, are obtained after giving gadolinium chelate (0.2 mg/kg with an injection rate of 3 mL/s) and the protocol is completed by diffusion-weighted study.

### Indications

Common indications for pediatric MR enterography involve evaluating suspected, following up known CD and appraising its complications. The first indication is identified CD and differentiate it from other small-bowel disease. Subsequently must determine the number, length and location of the segment involved; if a stenosis is present, must classify it as inflammatory (distinguishing between mild, moderate and severe disease) or fibrous subtypes.

Differentiation between the subtypes is clinically important because active inflammation is usually treated medically unless there are extramural complication, while fibrostenotic disease characterized by obstructive symptoms, often requires surgery<sup>[19,44-46]</sup>. Finally, it's important to assess the presence of mesenteric complication such as abscesses and fistulas and monitor response to medical therapy. There are many findings of CD at MR enterography that can be separated into intestinal and extraintestinal findings. Intestinal findings include bowel wall thickening, mucosal hyperenhancement, mural stratification, skip lesions, luminal narrowing, strictures and fistulas.

Masselli *et al.*<sup>[47]</sup> suggested an imaging-based



**Figure 1** Magnetic resonance enterography in 15-year-old patient with Crohn's disease. MR fluoroscopic ( $\infty/950$ ) image A shows luminal narrowing of the terminal ileum (arrow). Coronal half-Fourier RARE (1000/90, 150° flip angle) image; B shows wall thickening of the terminal ileum (arrow). Coronal contrast-enhanced fat-saturated T1-weighted VIBE (4.2/mini-mum, 10° flip angle) image; C shows stratified contrast enhancement with avid enhancement of mucosa relative to submucosal and muscular layers and layered appearance. Note high-signal-intensity linear structure due to increased vascularity close to mesenteric border of the small-bowel segment involved-the so-called comb sign (short arrows). These MR findings are indicative of active Crohn's disease. MR: Magnetic resonance.

classification of small bowel CD subtypes correlate with clinical classifications. They radiologically classified CD into four groups: Active inflammatory, fibrostenotic, fistulizing/perforating, and reparative or regenerative subtype that could be differentiated by MR imaging due to its accuracy for the detection of morphologic and functional abnormalities, early CD changes and help the clinical plan appropriate therapy. The visualization of early changes due to CD, such as ulcerations and subtle wall thickening, can be depicted by high-resolution (thin-section) true FISP and half-Fourier RARE images (Figure 1)<sup>[48,49]</sup>.

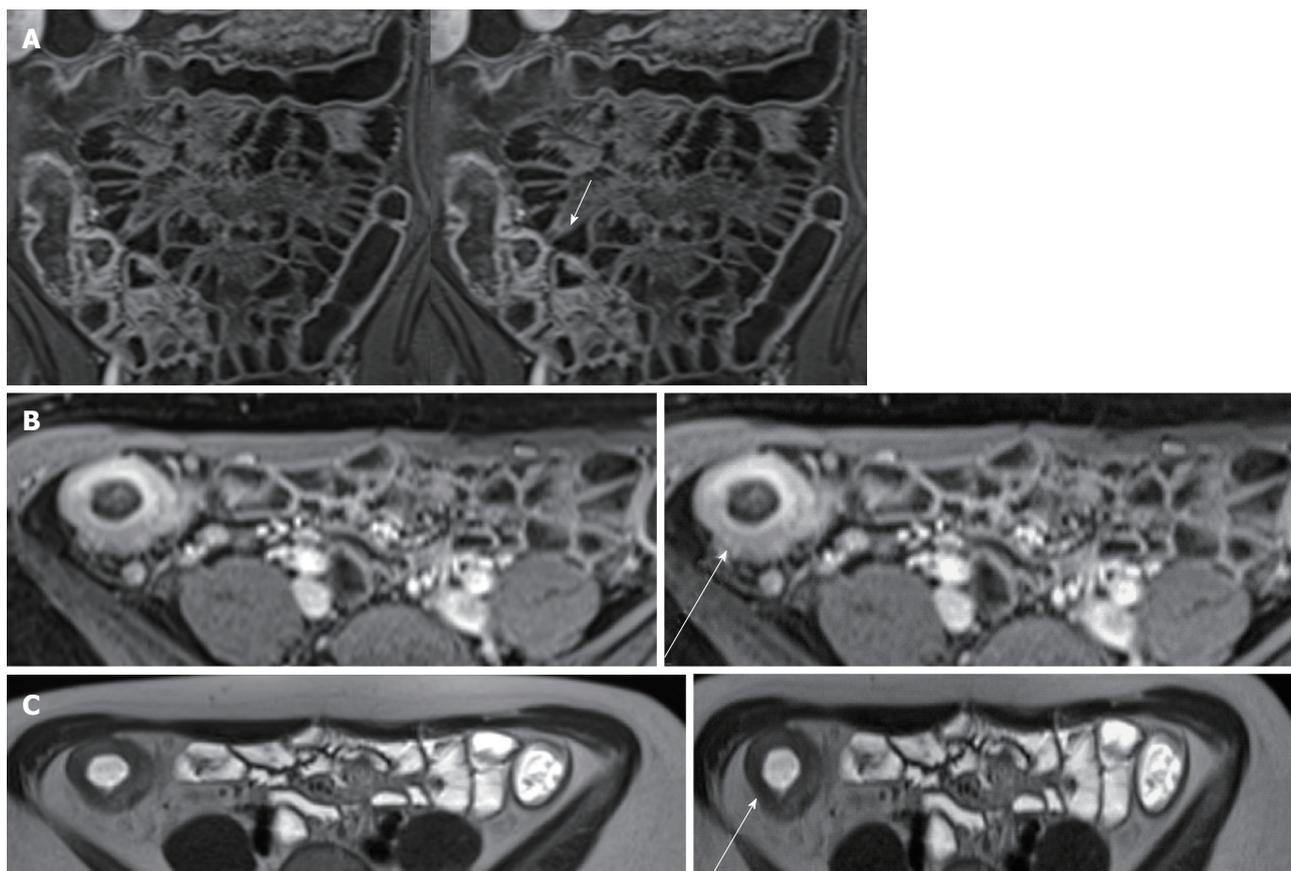
Bowel wall thickening is the common finding of CD with sensitivity of 83%-91% and a specificity of 86%-100% at MR enterography<sup>[50]</sup>. It is defined as a bowel wall thickness measuring more than 3 mm in

a distended loop and may be eccentric or concentric and smooth or nodular and several study<sup>[5,43]</sup>. Masselli *et al*<sup>[42]</sup> confirmed that the terminal ileum is the most common localization of bowel wall thickness (Figure 2).

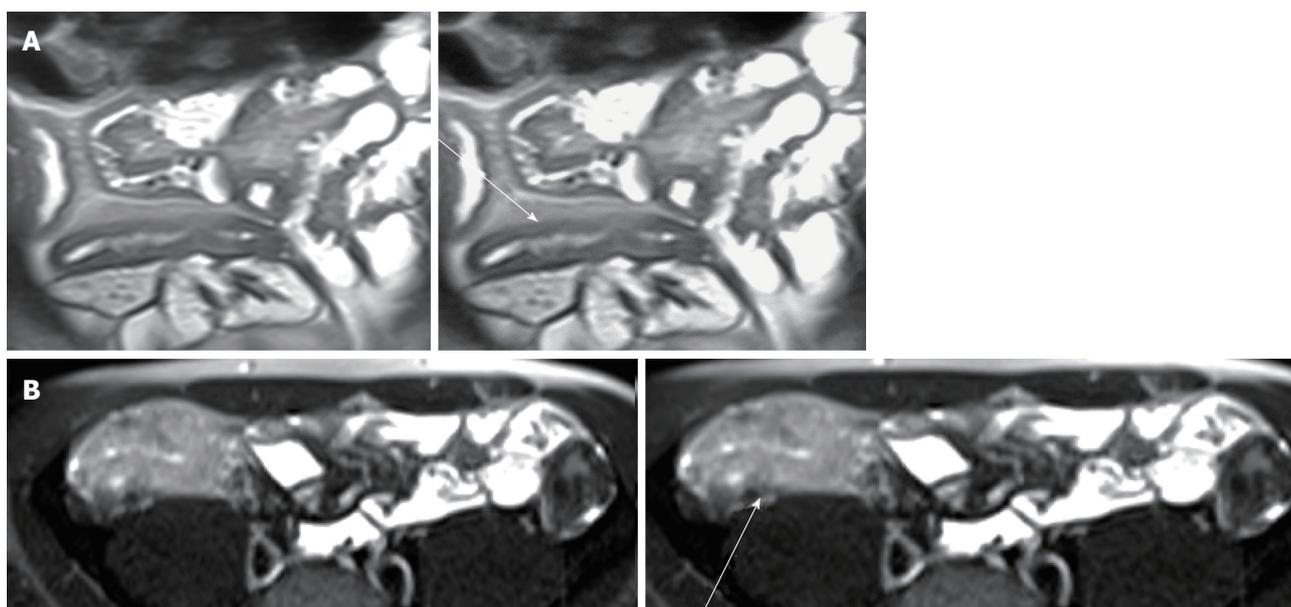
Stratified contrast enhancement with avid enhancement of the mucosa relative to the submucosa and muscular layers helps to confirm active CD<sup>[51]</sup> (Figure 1C). High signal intensity in T2-weighted images indicates wall edema and it is an acute inflammation's sign<sup>[52]</sup> (Figure 3).

Mucosal increased enhancement with submucosal edema is so-called "stratified type of bowel enhancement" and has been especially related to acute disease<sup>[53]</sup> (Figure 4).

Mural stratification with engorged vasa recta that penetrate the bowel wall perpendicular to the bowel



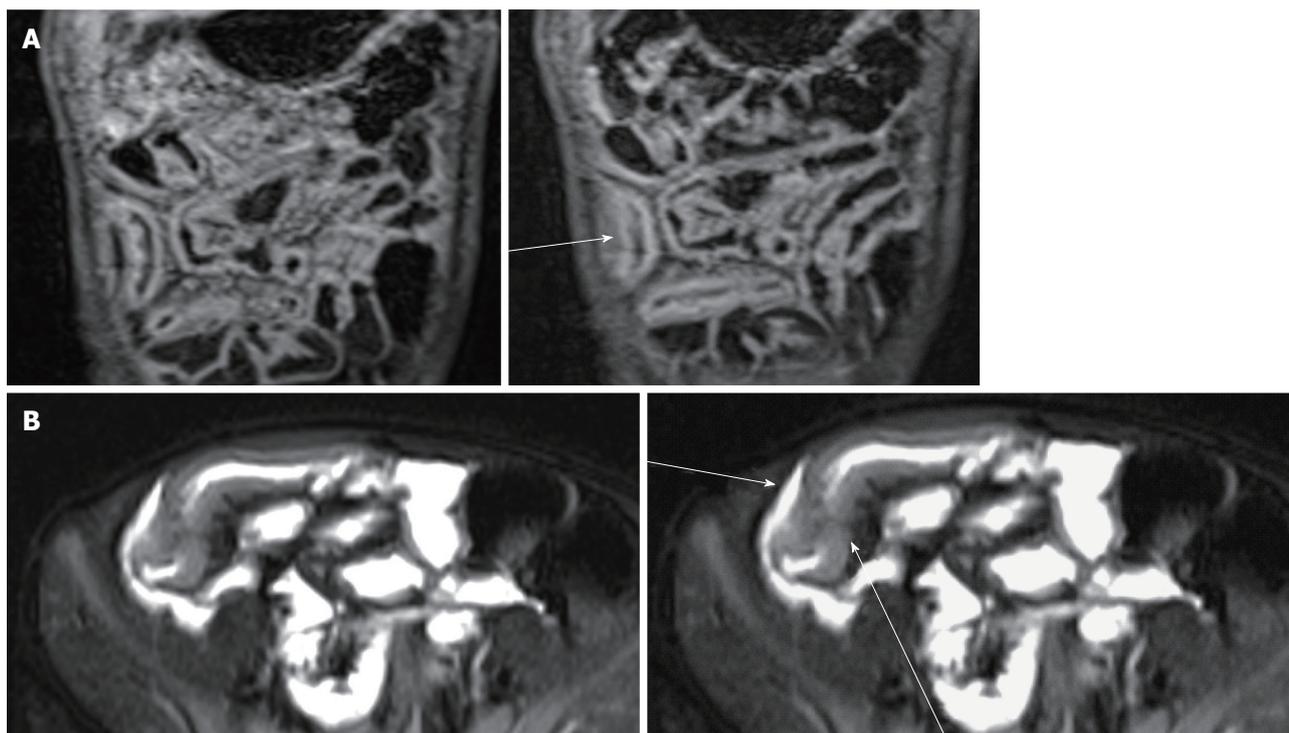
**Figure 2** Magnetic resonance enterography in 16-year-old patient with Crohn's disease. Contrast coronal T1 GRE A shows marked enhancement of wall of the terminal ileum (arrow). Axial contrast-enhanced fat-saturated T1-weighted VIBE (4.2/mini-mum, 10° flip angle) image; B shows stratified contrast enhancement with avid enhancement of mucosa relative to submucosal and muscular layers and layered appearance (arrow); axial HASTE image C shows wall thickening of the terminal ileum (arrow). GRE: Gradient Echo.



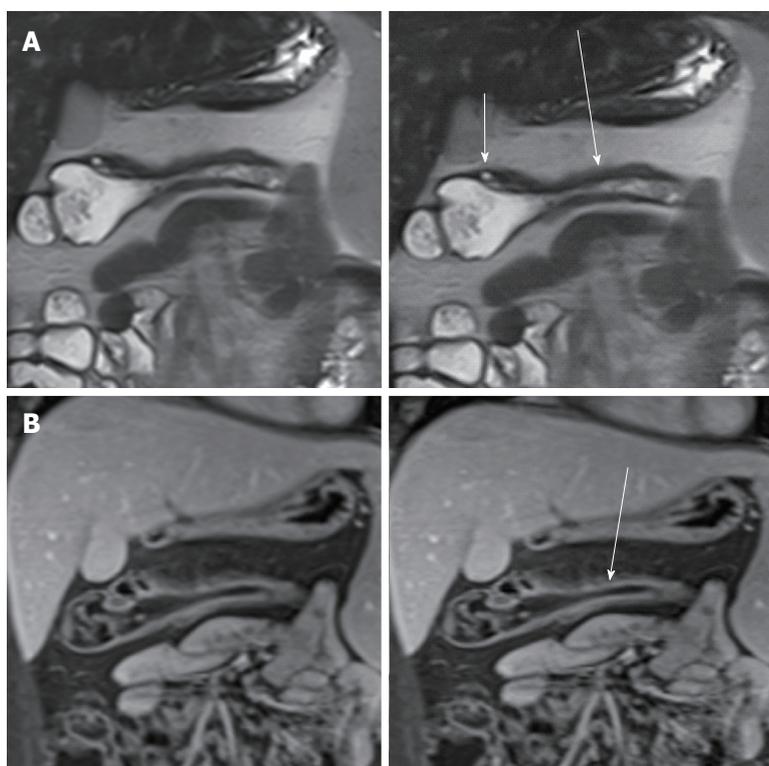
**Figure 3** Coronal T2 haste image. A: Marked thickening of wall of the terminal ileum (arrow). Axial T2 fat-saturated HASTE image; B: Marked hypersignal of wall of the terminal ileum due to edema (arrow).

lumen ("comb sign") which suggest that the disease is clinically active, advanced and extensive (Figure

1C)<sup>[49,54,55]</sup> and mesenteric lymphadenopathy, another finding in active disease<sup>[56]</sup>. On high-resolution SSFP



**Figure 4** Magnetic resonance enterography in 17-year-old patient with Crohn's disease. Coronal GRE image (A) shows marked enhancement of wall of the terminal ileum (arrows). Axial T2 fat-saturated HASTE image (B) (arrow) shows marked hypersignal of the wall due to edema (arrow) with adjacent fluid collection (short arrow). GRE: Gradient Echo.



**Figure 5** Magnetic resonance enterography in 15-year-old patient with Crohn's disease. Coronal half-Fourier RARE (1000/90, 150° flip angle) A and coronal contrast-enhanced fat-saturated T1-weighted VIBE (4.2/mini-mum, 10° flip angle) B show wall thickening lesions in the middle part of transverse colon (arrow). Coronal T2-w image A shows superficial ulcers that appears as a nidus of high signal intensity (short arrow in B surrounded by a rim of moderate signal intensity). Colonoscopy confirmed these findings.

image with fat suppression, it is possible to appreciate aphthous ulcers and transmural ulcers in the bowel

wall<sup>[57]</sup> (Figure 5).

In the fibrostenotic disease subtype, instead, small bowel obstruction is the principal clinical manifestation and it is characterized as a fixed narrowing of the bowel, wall thickening and marked prestenotic dilatation, the latter less likely responsive to medical therapy<sup>[58]</sup>.

Chronic fibrotic strictures have low intensity signal on T1 and T2 sequences with inhomogeneous contrast enhancement (lack of mural inflammation) edema and surrounding mesenteric hyperemia<sup>[59,60]</sup> and in many patients are likely due to a combination of active and chronic inflammation and fibrosis<sup>[61]</sup> (Figure 6) and on MR cine imaging, it appears as a peristaltic bowel segments with mural thickening and luminal narrowing<sup>[48,62]</sup>.

As pediatric CD, uncommonly manifests initially as a strictures<sup>[63]</sup>, the cumulative incidence of strictures increases with time, from 5.5% at 1-year following diagnosis to 20.5% at 10 years<sup>[64]</sup>.

In the fistulizing-penetrating subtype, involvement of bowel wall can range from superficial erosion and aphthous ulcers to fistula or perforation<sup>[61,65-67]</sup>.

These tracts develop in 8.2% of pediatric CD patients at 1 year after diagnosis and 24.5% at 10 years<sup>[64]</sup> and they are commonly associated with a stricture. By definition, sinus tracts are blind and may extend into adjacent structures (*e.g.*, mesentery, retroperitoneal musculature or abdominal wall), whereas fistula tracts communicate with a second epithelialized surface, as bowel, skin and genitourinary tract<sup>[67-69]</sup> (Figure 7).

These tracts are commonly recognized on single-shot FSE, balanced SSFE and fat-saturated T2-weighted FSE pulse images (with a sensitivity ranges from 83.3% to 84.4% and specificity of 100%<sup>[33,56,66,70]</sup>) as linear or stellate hypointense or hyperintense (if fluid-filled) abnormalities and also commonly enhance on post-contrast T1-weighted images<sup>[3]</sup>. Diagnostic advanced in CD: DWI, Perfusion, Motility Imaging, Magnetic Resonance Spectroscopy (MRS), and PET-MRI. Inflammatory process of the bowel wall in CD may be evaluated by most of these techniques that, as yet, have been applied to neurologic or oncologic disease.

However, over recent years, this imaging techniques showed great interest also in the evaluation and characterization of the bowel wall abnormalities of the CD and further developments, nowadays purely experimental (molecular imaging and PET-MRI), will provide relevant information on the status of inflammatory cells<sup>[71]</sup>.

Diffusion-weighted magnetic resonance imaging used the diffusion of water molecules in biological tissues (intracellular, extracellular and vascular space) to produce images by random translation motion, known as Brownian motion, that in cells is more restricted than in extracellular or intravascular spaces<sup>[72,73]</sup>.

The apparent diffusion coefficient (ADCs) is quantitative expressions of the diffusion characteristics of tissue. Its values decrease with increased tissue cellularity or cell density and may help in the quanti-

tative analysis of disease activity<sup>[74,75]</sup>. In inflammatory disease of the bowel<sup>[75,76]</sup> the increased cellularity lead to restrict diffusion (low ADC values) and high signal of DWI showed high sensitivity (86%-94%) and specificity (81.4%-84.8%) in inflammatory disease of the bowel with 94% of sensitivity and 88% of specificity by using an ADC threshold of  $2.4 \times 10^{-3} \text{ mm}^2/\text{s}$ <sup>[75,77-81]</sup>.

An observational prospective study<sup>[79]</sup> with 130 CD patients reported that, at certain apparent diffusion coefficient, sensitivity and specificity of discriminating active from non-active CD were 96.6% and 98.1% respectively, for the colon/rectum, and 85.9% and 81.6%, respectively for ileum. They also reported high interobserver agreement.

A recent study<sup>[80]</sup> involved 31 CD patients with ileal involvement, compared DWI with conventional MRE in estimating inflammation in small bowel CD; DWI hyperintensity was highly correlated with disease activity evaluated using conventional MRE.

Koh *et al.*<sup>[76]</sup> reported that a segmental magnetic resonance score (MR-score-S) based on DWI values and on other MRI parameters, detected endoscopic inflammation with a sensitivity and specificity of 58.33% and 84.48% in CD. In another study, Hordonneau *et al.*<sup>[78]</sup> compared the ADC values of inactive intestinal segments (from jejunum to rectum) with ADC values of active intestinal segments on the basis of signal intensity in DWI sequences (as expressed in the values of b equal to 800 s/mm<sup>2</sup>) and they found a restriction of diffusion at the level of active segments as compared to non-active ones, without use of oral contrast.

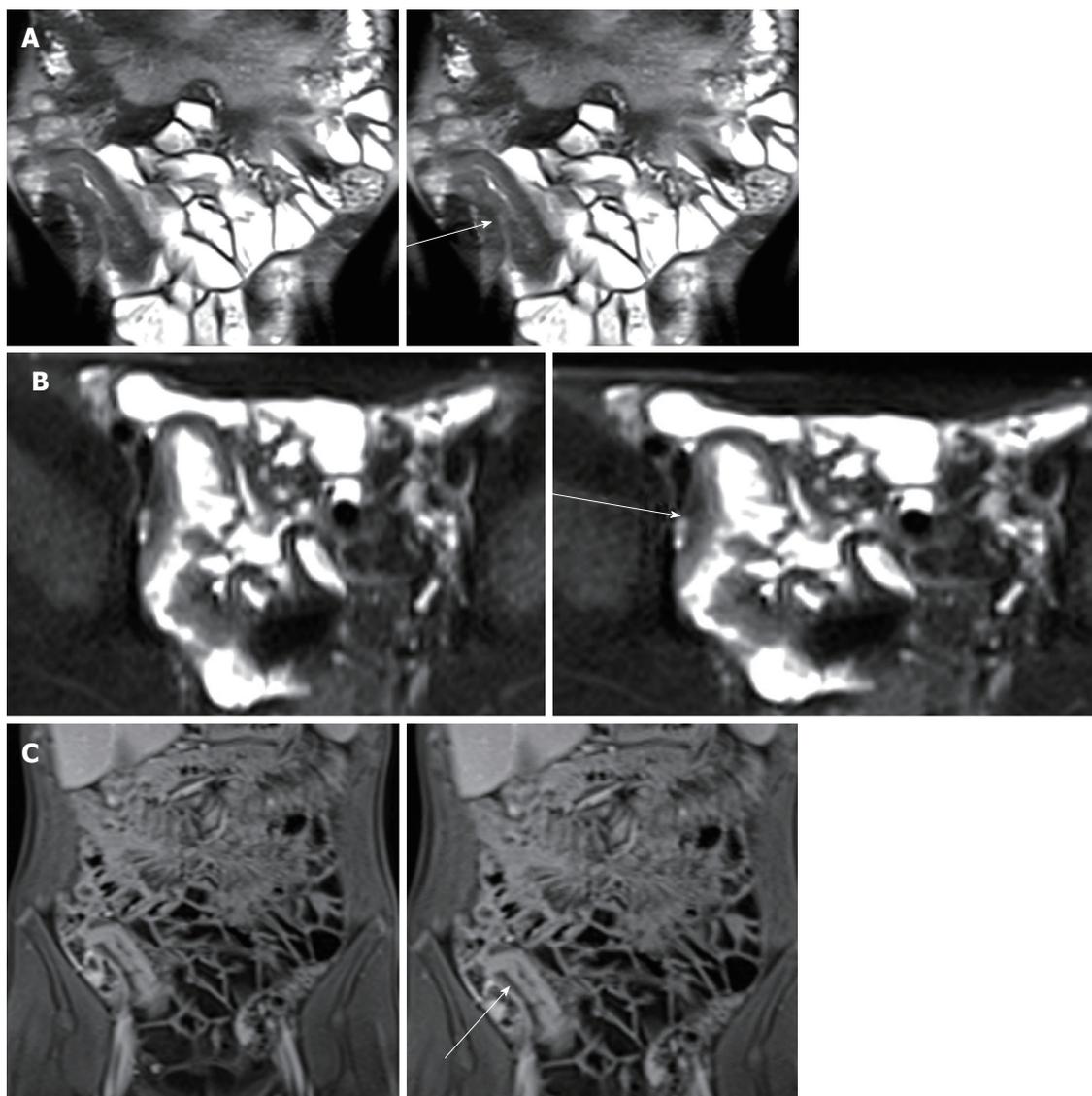
Preliminary studies<sup>[71,82]</sup> suggest that active wall inflammation in CD determines a restricted diffusion and it may be helpful in clinical practice to identify the sites of active CD, particularly when using biphasic intestinal contrast agents (Figure 8).

Although other studies are needed to define the practical clinical value of DWI; it is unclear if restricted diffusion is applied to acute wall inflammation (edema) only or wall fibrosis only or inflammation associated with fibrosis.

Dynamic contrast-enhanced MRI (DCE-MRI), gives information about physiological tissue characteristics and it is able to provide quantitative and semiquantitative measurements of perfusion, in this case, of bowel wall, on the bases of the kinetics of contrast media uptake and wash-out<sup>[83,84]</sup>.

In CD, acute inflammation, is characterized by an increase of vascular perfusion correlated with the activation of angiogenesis due to continuous epithelial damage and vascular remodeling of the intestinal mucosa.

This abnormal distribution of arteries increases the accuracy of DCE-MRI in the determination of disease activity through a quantitative or a semiquantitative approach. The first approach is based on the evaluation of two parameters (volume transfer coefficient  $K^{\text{trans}}$  and extracellular volume fraction  $V_e$ ) directly related to the uptake and wash-out of contrast, applying at



**Figure 6** Coronal half-fourier RARE and axial fat sat (1000/90, 150° flip angle) images. A and B shows wall thickening of the terminal ileum wall (arrows). Coronal contrast-enhanced T1-weighted fat-saturated VIBE (4.2/minimum, 10° flip angle) image C of terminal ileum shows uniform wall enhancement of terminal ileum with abnormal thickness a finding that indicates chronic inflammatory changes (arrow).

intravascular vs extravascular - extracellular space. The second approach, instead, assessed parameters directly derived by the time-enhancement curve, area under the curve, enhancement slope, time to pick enhancement and enhancement ratio, which are easier and faster to be calculated but are not directly related to pathophysiology<sup>[71]</sup>.

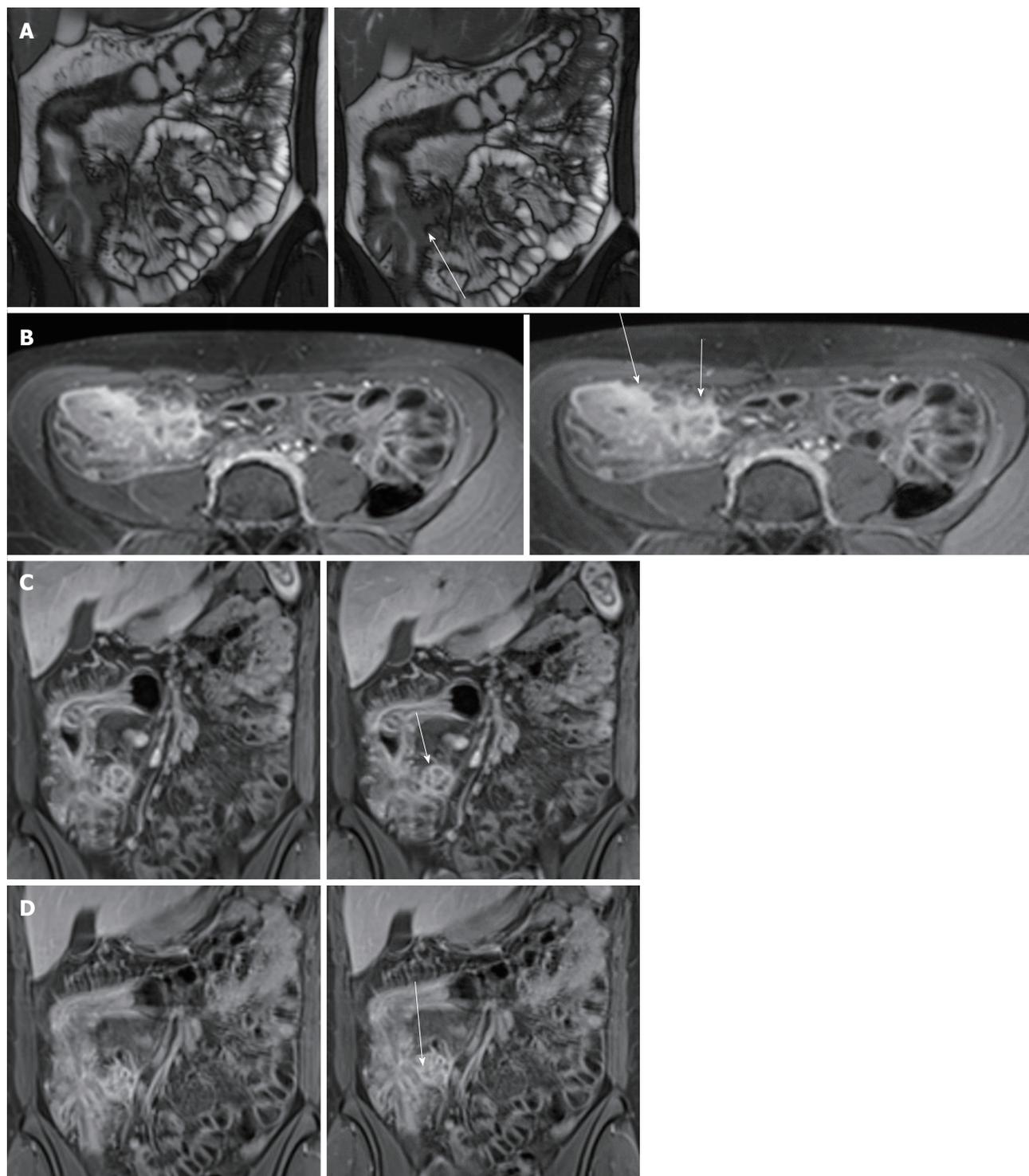
However, few study, performed on small series, have been published on the accuracy of DCE-MRI in CD diverging results mainly related to technical limitation (motion artifacts) resulting in measurements misregistration<sup>[81,85,86]</sup>.

Many pathologies affecting the small bowel such as diabetes, dyspepsia, irritable bowel disease and visceral neuropathies, can alter its motility. CD also affects motility of inflamed small bowel segments. The use of MRI could have an impact on the research of small bowel physiology and pathologies. MR motility imaging

used to evaluated CD related affected bowel segments showed an increase in the member of lesions in each patient and significant increase in the overall number of patients with CD lesions<sup>[87-90]</sup>.

The images must be acquired before the application of a spasmolytic drug such as glucagon or n-hyoscine<sup>[71]</sup>. The sequences to acquire small bowel motility is a fast cine sequences using T2-W SSFP or echo planar imaging sequences with a maximum repetition time of 1 s and slice thickness of 10 mm.

A retrospective study of Patak *et al*<sup>[91]</sup> correlated MR-detectable motility alterations of the terminal ileum with biopsy documented active and chronic changes in CD. It analyzed 43 patients and the evaluation was done between motility (classified as normal, hypomotility and complete arrest) and local biopsy. Histopathology correlated with grading of motility alterations in both active and chronic signs. It seems that the motility



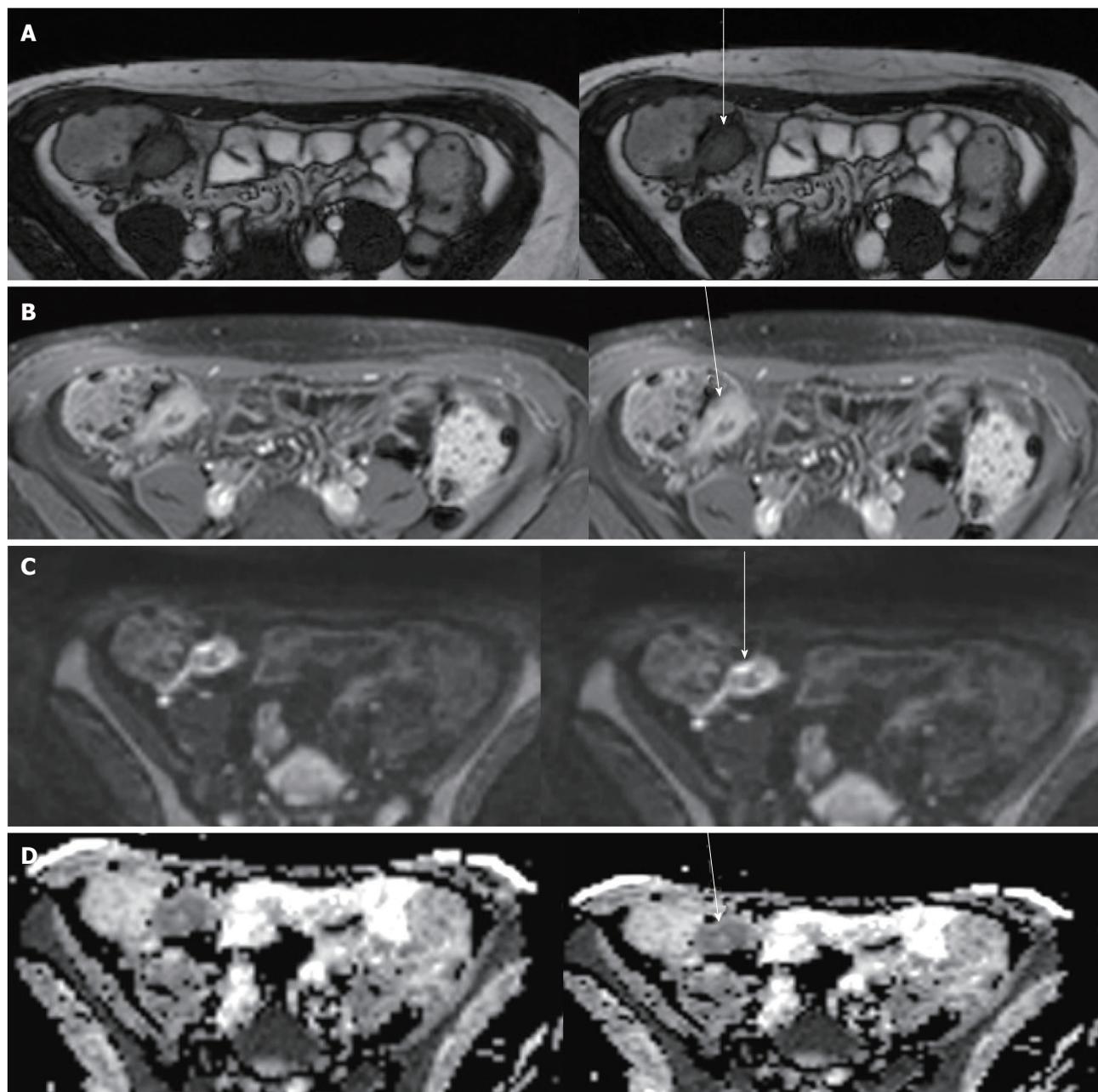
**Figure 7** Magnetic resonance enterography in 14-year-old with Crohn's disease. Coronal fat-suppressed T2-weighted half-fourier RARE A (1000/90, 150° flip angle) image shows high-signal-intensity edematous wall thickening of terminal ileum. Note inflamed adjacent tissue with hyperintense fluid collection with thick hypointense rim. Axial B and coronal C contrast-enhanced T1-weighted fat-saturated VIBE (4.2/minimum, 10° flip angle) images show marked enhancement of wall of the collection. D Coronal contrast-enhanced T1-weighted fat-saturated VIBE (4.2/minimum, 10° flip angle) image shows marked enhancement of wall of the collection. Note small fistula between the small bowel and the abscess (arrow).

changes are more a grading for severity of the disease than a predictor of activity. Another study of Maccioni *et al.*<sup>[71]</sup> showed an inverse correlation between the contraction frequency *via* MRI and both the blood levels of C-reactive protein and focal levels of calprotectin.

In conclusion, motility can be quantified by MR

imaging, but further studies are necessary to classify motility disorder assessed by MR.

MR molecular imaging and MRS are still two experimental techniques, have both the capability to study molecular composition of inflammatory bowel wall, identifying the metabolites involved in physiological



**Figure 8** Magnetic resonance enterography of 16-year-old with Crohn's disease. Axial true-FISP (4.3/2.2, 50° flip angle) A and contrast axial T1 VIBE B show marked thickening with evidence of enhancement of the wall of terminal ileum, that shows hypersignal on diffusion weighted Imaging (b = 800) image C and restriction of diffusion on ADC map D (arrows).

and pathological process<sup>[71]</sup>.

MRS is already routinely used in many malignant conditions such as brain, breast and prostate cancer and it provides to determine the distribution of metabolites associated with the relevant pathology producing predictive pattern of resonant frequencies corresponding to molecular arrangement of some atomic nuclei susceptible to perturbation, typically protons. The structural, or chemical information regarding the reaction of the nuclei can be obtained and after the examination is performed the data in a one-dimensional Nuclear MR (NMR) frequency spectrum<sup>[89,90]</sup>. Even though spectroscopy can be performed on different nuclei; the most common nuclei used are those that

not require exogenous label such as <sup>31</sup>P, <sup>1</sup>H and <sup>23</sup>Na which generate spectra from endogenous metabolites. Spectroscopy of hydrogenous nucleus (<sup>1</sup>H NMR) is the most widely studied in MRS and the feasibility of metabonomics in clinical studies was suggested by the analysis of <sup>1</sup>H NMR on plasma and urine samples obtained from healthy studies.

The <sup>1</sup>H NMR spectra obtained were analyzed using principal component analysis to generate metabonomic data. This approach has been suggested as a quantitative measurement of metabolic response in CD. Biochemical analysis of fecal extracts has been studied to reflect biochemical changes of bowel disease in patient with CD and by employing <sup>1</sup>H NMR

to spectroscopy multivariate pattern recognition techniques was reported to differentiate two IBD<sup>[91]</sup>.

Lately there was a rise of experimental studies regarding the research of small metabolites (as TCA) cycle intermediates for the screening of metabolic biomarkers in serum urine, fecal extracts and colon tissue in patients with IBD.

A study using *in vitro* <sup>1</sup>HNMR reported that patients with IBD showed similar metabolic profile in macroscopically involved and uninvolved colonic mucosa compared with that of control<sup>[92,93]</sup>.

In the mucosa of active phase of UC and CD, have been observed lower concentration of amino-acids, membrane components, lactate and succinate and an increase of alpha-glucose compared with normal mucosa of controls. Instead, during chronic inflammation there was a decreasing of levels of proteins and carbohydrate due to deterioration of mucosa integrity. An analysis of the fecal extract of both CD and UC patients, showed reduced levels of butyrate, acetate, methylamine and trimethylamine and a high amount of aminoacids, implying malabsorption. Metabolic difference in fecal profiles were more marked in the CD group because of the extent of the disease and the analysis reported that glycerol resonances were a feature of patients with CD<sup>[91]</sup>.

In a study based on urinary metabolomic, individual with IBD can be distinguished from healthy ones by difference on the levels of TCA cycles intermediates, aminoacid and gut microflora metabolites<sup>[94]</sup>.

NMR has also shown possibilities to differentiate between UC and CD, which is not always easy on clinical practice and <sup>1</sup>HNMR in particular could be used as part of metabolomics to diagnosis with other disease with similar signs and symptoms<sup>[19]</sup>.

A recent study, in fact, focused on findings of metabolic biomarkers and the correlation with serum zinc in CD patients, suggested two amino acid valina and isoleucina - as differentiating metabolites for CD diagnosis<sup>[95]</sup>. <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT depend on the accumulation of FDG in metabolically active cells and is used for detect active disease sites of CD through a standardized uptake values (SUV) that reveal areas of inflammation and it can be used also in the analysis of response to treatment<sup>[96,97]</sup>.

However <sup>18</sup>FDG PET has some limits to detect detailed morphologic information therefore benefits of combined use of CT and MR enterography. <sup>18</sup>FDG-PET/CT enterography (CTE) increases the sensitivity and specificity in the detection and monitoring of disease because provides morphological, physiological and metabolic information and may also allow distinction between active or fibrotic strictures<sup>[98]</sup>.

### <sup>18</sup>F-FDG PET scan protocols

Patients fast for 4-6 h before the scan and the blood glucose level is checked to detect hyperglycemia. A weight-based dose of 3.3 MBq/kg (0.09 mCi/kg) was

sufficient for diagnostic PET imaging in patients with CD. The patient should drink approximately 1350 mL of a refrigerated neutral oral contrast agent, such as VoLumen (Bracco Diagnostics, Inc., Princeton, NJ), for 45-60 min during the <sup>18</sup>F-FDG uptake period. For CTE protocols, 80-150 mL of non-ionic contrast material is injected at 3-5 mL/s and with a 70 s scan delay. PET acquisitions are usually obtained, beginning at the bottom of the pelvis and finishing at the top of the diaphragm.

Malham *et al.*<sup>[97]</sup> compared the measurement of disease activity with <sup>18</sup>F-FDG PET/CT with endoscopic biopsies and reported a sensitivity of 82% and specificity of 97%, using <sup>18</sup>F-FDG PET/CT and other studies have reported sensitivity of 85%-98% and specificity of 50%-89%<sup>[99-101]</sup>.

Combination of PET with FDG and MRI, have been shown to be useful for diagnostic evaluation of a variety of inflammatory processes and CD could be a candidate target of this novel technique<sup>[102]</sup>, with several advantages respect to PET/CT or SPECT/CT or MRI alone due to MRI excellent soft tissue contrast, diffusion weighted imaging, dynamic contrast enhanced imaging, fMRI and MR spectroscopy, improving the sensitivity and specificity of diagnosis and follow-up treatment monitoring the possibility of earlier response evaluation<sup>[64,103]</sup>.

PET/MRI system can be either simultaneous or sequential.

Simultaneous imaging systems have major advantages as compared to conventional PET/TC systems, due to an identical position of the patient during image acquisition, with a substantial reduction in motion artifacts due to heart beating. An important advantage of MRI compared to CT is its superior functional soft tissue analysis, for example for inflammation, dynamic perfusion, and identification of different tissue types, such as edema and fibrosis.

While MRI mainly provides exquisite morphological details in human tissue, PET investigates the human body at the molecular level enabling the acquisition of exquisite functional data in particular when PET is combined also with functional MRI like DWI, spectroscopy, and combined new paramagnetic nano-cell-contrast agent with radiolabelled probes for histological characterization of tissue.

However the major advantage compared with the clinical PET/CT systems of today is the absence of radiation burden, an important feature in pediatric patient. Molecular MRI allows a hybrid between PET and MRI with cells like lymphocyte/macrophage marked with radionuclides or fluorescent or MRI contrast agent.

Tracking of lymphocyte/macrophage migration could give important information about pathological processes and helping to monitoring response to treatment. The use of nuclear medicine techniques and MRI, nowadays purely experimental, is essential for detection of active inflammatory cells and cytokines in IBD. The primary target of PET-MRI in IBD must be to evaluate

if connected PET-MRI with targeted molecular imaging and various MRI techniques is able to find IBD with precision.

## CONCLUSION

MR enterography is an effective imaging modality to diagnosis, evaluating and follow-up of CD in pediatric patient while sparing children and adolescent from the potentially harmful effects of ionizing radiation exposure. Novel MRI applications such as motility studies, spectroscopy, DWI, molecular and hybrid imaging (PET-MRI), might contribute to diagnosis and management of CD but further studies are necessary to assess the diagnosis value of these newer MRI application which are not fully predictable but extremely interesting in the evaluation of CD.

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