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MR-enterography with diffusion weighted imaging: ADC values in normal and pathological bowel loops, a possible threshold ADC value to differentiate active from inactive Crohn's disease

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Abstract. – OBJECTIVE: The aim of our study was to compare the apparent diffusion coefficient (ADC) values of pathological bowel loops wall (pADC) with the ADC values of normal appearing ones (naADC) and to determine a discriminating threshold.

PATIENTS AND METHODS: 60 patients were studied at our Institution through a MR-enterography that included free-breathing axial Diffusion Weighted Imaging (DWI) with two b (0 and 800 s/mm^2) after histological diagnosis of active Crohn's disease (CD). The one (when unique) or the best analyzable (when multiple) pathological bowel loop was identified in each patient, on the basis of the MRI features: wall thickness, presence of mural oedema and wall contrast enhancement after contrast medium administration. A normal appearing bowel loop was used for comparison. ADC values were measured in consensus by two radiologists, and they were compared with *t*-test. The ADC threshold value for the differentiation between pathological and normal appearing bowel loops was determined.

RESULTS: The pADC values were significantly lower than the naADC values (1.48 ± 0.058 x 10^{-3} mm^2/s versus 3.525 ± 0.07 x 10^{-3} mm^2/s; $p < 0.05$). A threshold of 2.416 x 10^{-3} mm^2/s showed 100% sensitivity and 100% specificity for the discrimination between normal and pathological bowel loops.

CONCLUSIONS: In patients with active CD the ADC values of the pathological bowel wall are significantly lower than those of normal appearing bowel loops. A threshold of ADC value of 2.416 10^{-3} mm^2/s could discriminate normal from pathological bowel loops.

Introduction

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract of unknown origin that can involve the entire length of the digestive tract.

This relapsing and destructing disorder affects both children and adults and can confer significant increased morbidity and mortality in affected patients. Its incidence and prevalence are increasing worldwide and it is a condition of social relevance.

Currently, colonoscopy is considered as the gold standard for colonic inflammatory activity assessment, but in most of the cases, it is inadequate for small bowel investigation and gives only information about superficial mucosal layers[1,2].

The small bowel can be investigated by both magnetic resonance imaging (MRI) and computed tomography (CT); in recent studies, they have shown similar accuracy and sensitivity for the detection of active inflammation[1].

Nevertheless, these patients need serial examinations because of the natural history of the disease, so MRI should be preferred to the CT, owing to its non-ionizing characteristics[3]. In addition, MRI has the potential advantage of providing both functional and quantitative information regarding the bowel wall such as diffusion, perfusion and motility that cannot be obtained by CT[4].

The correlation between MRI and indices of clinical severity of disease has been evaluated.

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MRI has been validated in comparison to alternative imaging modalities and correlated with histology[5]. Several authors reported the usefulness of T1-weighted (T1-w) after gadolinium MRI in the assessment of disease activity and recent studies support the role of Diffusion-weighted imaging (DWI) to differentiate active from inactive CD[1,6].

DWI sequence is a functional imaging technique that reflects molecular diffusion, which is the thermally induced Brownian motion of water molecules, without the administration of a contrast medium. Changes in proton diffusivity are an early indicator of alterations in cellular homeostasis in acute ischemic stroke and may also help in detecting inflammatory foci[1]. Restricted water motion on tissue is hyperintense on DWI sequence and this provides a very helpful instrument for the qualitative assessment of daily practice. From DWI acquisition an ADC value map can be generated; this adds quantitative information to the evaluation[7].

The aim of our study has been to compare the ADC values of pathological bowel loops wall (pADC) with those of normal appearing bowel loops wall (naADC) in patients with the previous histologically proven CD, in order to demonstrate the capability of this coefficient to discriminate these two conditions.

Patients and Methods

Study Population and Design

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional Review Board. Informed consent for the examination was obtained at the time of the procedure. Specific requirement for informed consent for the study was waived. This was a retrospective, single-centre study including 60 patients who underwent to MR enterography with DWI at our Institution after histological diagnosis of active CD from September 2012 to September 2013.

MRI technique

MRI was performed using a 1.5 Tesla (T) MR scanner (GE Healthcare, Milwaukee, WI, USA) and a 12 channels surface phased-array body coil. The standard imaging protocol included free-breathing axial DWI (b=800 and 0 s/mm^2).

No oral or rectal preparation was performed the days before the exam. Patients fasted 6 h before the examination and 1500 ml of polyethylene glycol electrolyte (PEG) solution (Isocolan, Giuliani S.P.A., Milan, Italy) was orally given to all patients 30-45 minutes before the MRI. Examinations were performed in the prone position. The details of the MRI protocol are described in Table I. Images were acquired during a time of breath holding and 0.5 mg of intravenous Glucagon (GlucaGen, Novo Nordisk A/s, Bagsvaerd, Denmark) was administrated before pre-contrast T1-w 3D-LAVA (3 Dimensional Liver acquisition with Volume Acceleration).

MRI data and Image Analysis

Visual assessment was performed by two trained radiologists, blinded of patients information in consensus, under the direction of an expert radiologist. All the images were reviewed on a picture archiving and communication system (PACS). One (when unique) or the best analyzable (when multiple) affected bowel loop was

Table I. MR-enterography basic protocol. CINE-FIESTA: Fast Imaging Employing Steady State Free Acquisition (balanced Steady State Free Procession sequence). 3D-LAVA: Liver acquisition with Volume Acceleration (3-Dimensional Fast Spoiled gradient echo sequence). SE/EPI: Spin Echo, Echo Planar Imaging. SSFSE: Single Shot Fast Spin Echo.

Sequences	FOV	Slice thickness	Matrix	NEX
Coronal CINE-FIESTA glucagone 5 mg injection	46	8	200x320	1
Coronal 3D-LAVA no contrast	48	3	245x182	0.78
Coronal 3D-LAVA after gadolinium injection	48	3	245x182	0.78
Axial 3D-LAVA	42	3	256x256	0.78
Axial SE/EPI (Diffusion) b:0, 800	40	8	9x128	6
Axial FIESTA	42	4	200x288	1
Axial T2-w SSFSE	42	4	200x288	1
Axial T2-w SSFSE with fat-saturation	42	4	200x288	1
Coronal SSFSE	48	4	252x244	0.57

identified in each patient, according to the MRI-derived features: wall thickening, presence of mural edema detected as hyperintensity on fat-suppressed T2-weighted (T2-w) images relative to psoas muscle and parietal enhancement after contrast medium administration. A normal appearing and well-distended bowel loop was used as internal control for comparison, defined as a segment with a normal parietal thickness, absence of edema on T2-w sequences or of relevant relative contrast enhancement at visual assessment, and necessarily not adjacent to pathological loop but in its same bowel's segment (Figure 1). The pADC and the naADC values were measured separately by the two radiologists, using an Advantage Workstation with Functool2 software (GE Healthcare, Milwaukee, WI, USA), drawing within the bowel wall a circular region of interest (ROI), whose area measured between 29 and 39 mm^2 (Figure 1). In cases where the difference be-

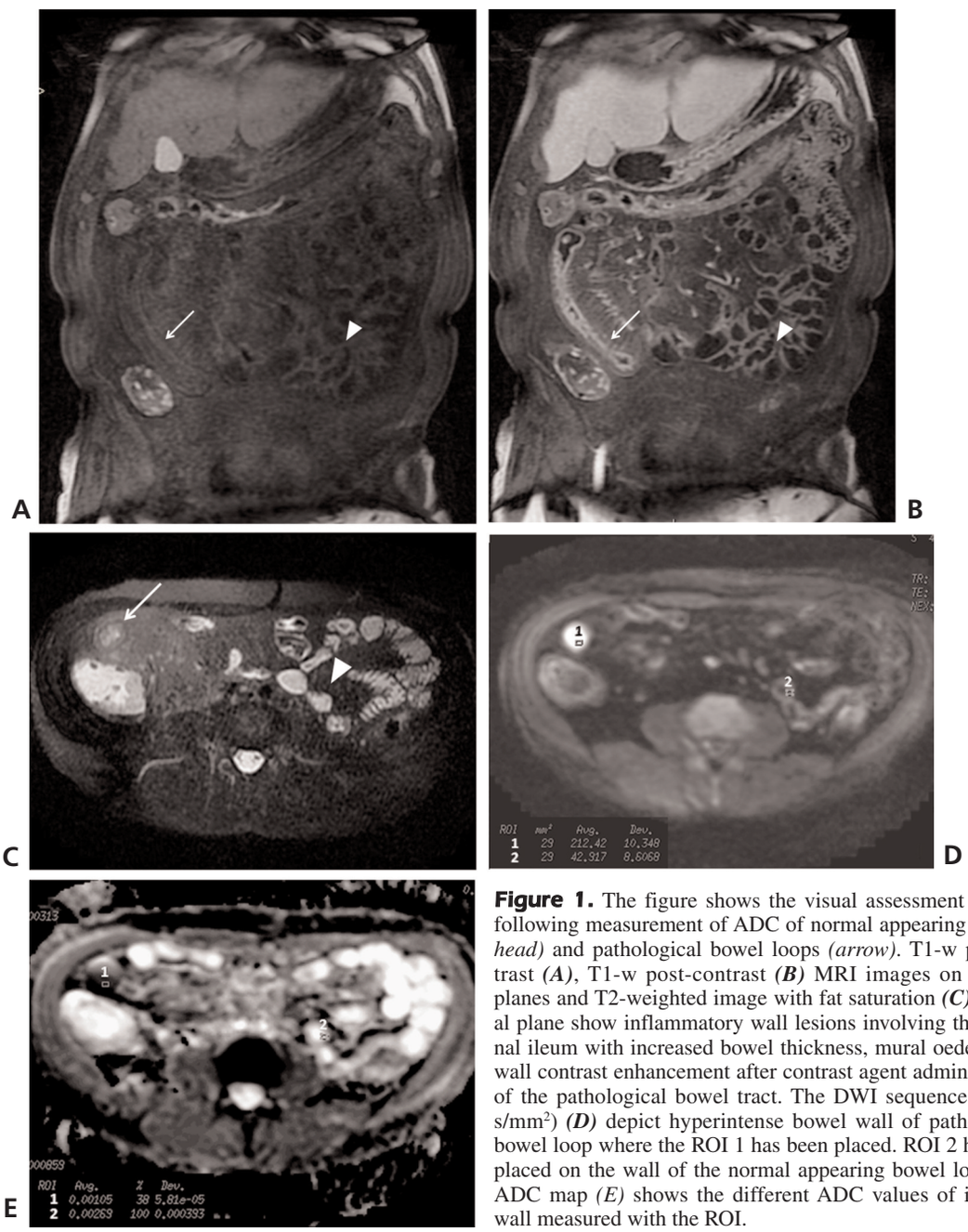

Figure 1. The figure shows the visual assessment and the following measurement of ADC of normal appearing *(arrowhead)* and pathological bowel loops *(arrow)*. T1-w pre-contrast ***(A)***, T1-w post-contrast ***(B)*** MRI images on coronal planes and T2-weighted image with fat saturation ***(C)*** on axial plane show inflammatory wall lesions involving the terminal ileum with increased bowel thickness, mural oedema and wall contrast enhancement after contrast agent administration of the pathological bowel tract. The DWI sequence (b=800 s/mm^2) ***(D)*** depict hyperintense bowel wall of pathological bowel loop where the ROI 1 has been placed. ROI 2 has been placed on the wall of the normal appearing bowel loop. The ADC map *(E)* shows the different ADC values of intestine wall measured with the ROI.

Table II. Statistical analysis.

	Pathological bowel loops	Normal appearing bowel loops
Mean ADC value (x10-3 mm2/s)	1.481983	3.525
Variance	0.051719	0.072123086
Observations	60	60
Pearson's correlation	-0.0115	

tween measurements was ≤5%, ADC values were averaged between the two observers, while in cases where the differences were greater than 5% another series of measurements were performed.

Statistical Analysis

The pADC and naADC values were compared with *t*-test. The calculation was done with SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). A *p*-value <0.05 was considered to be statistically significant.

Normal (or Gaussian) function was used to show the distribution of ADC values, in both normal and pathological bowel loops. The ADC threshold value (T_{ADC}) for the differentiation between pathological bowel loops and normal appearing bowel loops was determined, using the following formula: $T_{ADC}=(S_{na}M_p+S_pM_{na})/S_{na}+S_p$ (S_{na} and M_{na} are the standard deviation and the average ADC value of normal appearing bowel loops; S_p and M_p are the standard deviation and the average ADC value of pathological bowel loops)[8].

Results

A total of 60 patients were evaluated (33 male, 27 female; mean age 43.4 years, range 17-76 years). 60 pathological intestinal segments were evaluated (18 distal ileum segments, 42 terminal ileum segments). The mean value of wall thickness was 7.35 mm (range 4-11 mm). 60 normal appearing intestinal segments were also evaluated as internal controls.

The pADC values were significantly lower than the naADC values ($1.481\pm0.0517 \times 10^{-3}$ mm^2/s versus $3.525 \pm 0.072 \times 10^{-3}$ mm^2/s; $p<0.05$) (Table II).

Gaussian function showed that the distribution of ADC values in normal appearing and pathological bowel loops is different, without overlapping (Figure 2).

The ADC threshold value of 2.416 x10^{-3} mm^2/s showed a sensitivity and a specificity of 100% for discriminating normal from pathological bowel loops.

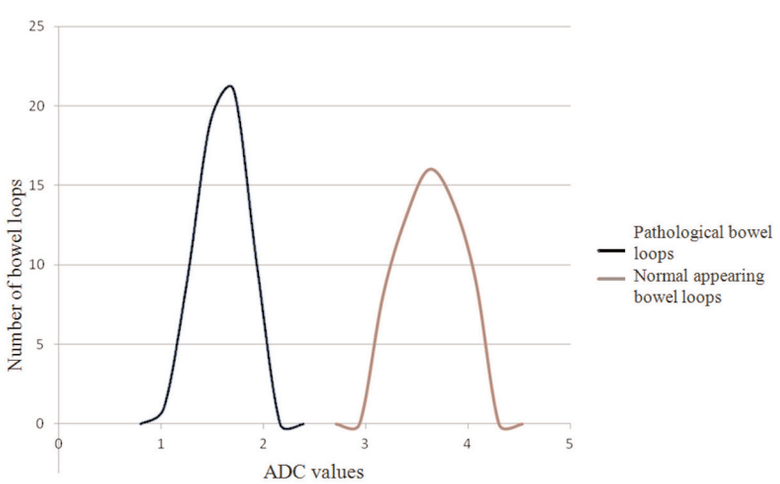

Figure 2. Normal distribution of ADC values measured on pathological and normal appearing bowel walls.

Discussion

Our results demonstrate that the wall of bowel segments affected by CD have significantly lower ADC value than the normal appearing ones. The explanation for this phenomenon is not clear and is still controversial.

Restricted diffusion has been reported in inflammatory processes of brain and abdomen, as in viral hepatitis in pyelonephritis and renal abscesses[9,10]. DWI qualitative evaluation has been investigated as a possible imaging biomarker for the assessment of intestinal bowel diseases activity.

The restricted diffusion could be related to an increased cell density and viscosity, typical of inflammation and other pathological changes observed in CD[4]. In early acute CD, lamina propria and submucosa are infiltrated by inflammatory cells and early lesions of active CD, such as aphthoid ulcers, are strongly associated with lymphoid aggregates that have restricted diffusion because of the increased cell density[6,11]. The association of other pathological changes such as increased number of inflammatory cells, dilated lymphatic channels, hypertrophied neuronal tissue, and the development of granulomas within the bowel wall can narrow the extracellular space and therefore can reduce the motion of water molecules. Changes of epithelial and inflammatory cells may also have an effect on the reduced diffusion[6]. Fibrosis of the bowel wall may be found in the fibrostenosing variant of the disease and it is also associated to the restriction of diffusion, as previously demonstrated in the liver by Taouli et al[9]. Tielbeek et al[12] in a study of 25 patients recently reported a significant correlation between low ADC values and extent of parietal fibrosis; no significant correlation was observed between ADC values and histopatological scores of inflammation but a trend was reported with high inflammation scores[12]. Moreover, inflammation and fibrosis can coexist in the same affected bowel loop, as demonstrated recently[13,14].

Quantitative evaluation of the ADC maps with measurement of ADC values could add precious information. It could complete the qualitative evaluation improving the diagnostic performance of MR-enterography. The mean pADC value, observed in our large series, is $1.481 \pm 0.0517\ 10^{-3}$ mm^2/s and appears similar to the values recently described by other scholars[1,4,15]. Kiryu et al[1] studied 31 patients and reported ADC values of $1.61 \pm 0.44 \times 10^{-3}$ mm^2/s and $2.56 \pm 0.58 \times 10^{-3}$ mm^2/s of active and inactive segments respectively, using b values[1] of 0, 50 and 800s/mm^2. Oto et al[4] in a group of 18 patients reported slightly higher pADC value (1.91×10^{-3} mm^2/s) and a similar naADC value (3.11×10^{-3} mm^2/s, b values 0, 600 s/mm^2) compared to our results[4]. Hordonneau et al[15] found on a larger group of 130 patients ADC values of $1.45 \pm 0.39 \times 10^{-3}$ mm^2/s of bowel walls of active disease segments and $2.62 \pm 0.46 \times 10^{-3}$ mm^2/s of bowel walls of inactive disease segments (b values: 0, 800s/mm^2)[15].

The ADC value threshold between CD pathological and normal bowel segments we found in our study (2.416×10^{-3} mm^2/s) shows high sensitivity and specificity; it is similar to the value of 2.47×10^{-3} mm^2/s previously described by Oto et al[4] (b values 0, 600 s/mm^2) in a smaller sample.

In our study, no oral or rectal preparation was performed the days before the exam, and this, as previously demonstrated[1], reduces the patients burden.

Before pre-contrast LAVA, we used an intravenous injection of glucagon to minimize motion artifact as reported in the literature and this is well tolerated by patients[16,17].

A high b-value (b=800 s/mm^2) was preferred because it improves the detection of inflamed bowel through the suppression of the background signal arising from body fluids and non-inflamed tissue surrounding the area, as confirmed in literature[18].

Our study has some limitations due to the retrospective design; no correlation was performed with histopathology after surgery or with clinical activity index. The identification of the bowel segments to be analyzed may have introduced some selection bias.

In spite of this, the study sample is one of largest in the literature and it is quite homogeneous because all patients have a previous histological diagnosis of CD, without previous surgical or medical treatment.

Furthermore, the high accurate threshold was found and it can be used to distinguish pathological from normal findings, even in order to avoid contrast agent i.v. injection[19]. Gadolinium injection is considered invasive and sometimes is not tolerated by patients, can induce nephrogenic systemic fibrosis and is contraindicated in case of severe renal failure. A high occurrence of renal insufficiency was found in patients suffering from intestinal bowel diseases (16%)[20]. Moreover, a MRI examination including DWI and without contrast medium administration would be shorter than a conventional contrast-enhanced

MRI, as long as DWI sequence requires a short time to be performed[3]. In a very recent study comparing DWI and post-contrast T1-weighed images the possibility of replacing post-contrast sequences with DWI is controversial, especially for the evaluation of penetrating complications[21].

In our work, we focused on finding a possible threshold ADC value to differentiate active from inactive

CD rather than a diagnosis of bowel inflammation or evaluation of penetrating complications. In our opinion, DWI could represent an alternative to post-contrast study in patients in which contrast medium administration is contraindicated.

Concerning these aims and in order to better understand the pathophysiology of restricted diffusion in CD of the small bowel further researches are needed, mostly to better correlate DWI findings to stages of bowel inflammation.

Conclusions

DWI is a very promising tool for the assessment of bowel inflammation and may improve MR-enterography diagnostic performance in patients affected by CD.

ADC values of the wall of affected bowel loops are found to be significantly lower than those of the normal bowel loops in patients with Crohn's disease. The ADC threshold value of $2.416X10^{-3}$ mm^2/s could be used to discriminate normal appearing from pathological bowel loops.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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