Journal of the Egyptian Society of Parasitology, Vol. 53, No.1, April 2023
J. Egypt. Soc. Parasitol. (JESP), 53(1), 2023: 9 – 16
Online: 2090-2549

DIFFUSION WEIGHTED IMAGING VERSUS BOWEL SONOGRAPHY IN MONITORING THE RESPONSE TO BIOLOGICAL TREATMENT (ANTI TNF) IN CROHN'S DISEASE PATIENTS

By
AYAT ABDALLAH ABD-ELKHALIK[1], WALEED HAMED[1], RASHA HUSSEIN[2], ENAAM ALI AL MOWAFY[1], and SHIMAA Y. KAMEL[1]
[1]Department of Tropical Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain Shams University, Cairo 11566 and [2]Department of Radiology, Ain Shams University and MR Unit of Misr Radiology Center, Cairo, Egypt
(*Correspondence: ayat.abdallah@med.asu.edu.eg, mobile xx01004084362
ORCID: Ayat Abdallah 0000-0001-6595-9894)

Abstract

Crohn's disease (CD) is a chronic relapsing granulomatous disease. It is characterized by transmural inflammation of bowel walls and by skip lesions that may be found in any segment of the gastro-intestinal (GI) tract. Radiological imaging plays a major role in the initial diagnosis of small bowel Crohn's disease (CD) and assessing the response to medical therapy or planning for surgery, including the staging of complications of the disease.

This study assessed the value of diffusion weighted imaging (DWI) versus bowel sonography (BS) obtained before and after treatment in detecting of healing in patients with CD treated with biological treatment (anti-TNF). This study was conducted on 38 patients with active Crohn's disease who received anti-TNF in IBD clinic in Ain Shams University Hospitals. After obtaining informed consent from each patient, all were subjected to clinical assessment, laboratory investigations, bowel ultrasound and DWI before and after biological treatment

BS results showed that the DWI accuracy in assessment of disease response after biologics was 89.5% with 87.5% sensitivity & 100% specificity. Cut-off value of apparent diffusion coefficient (ADC) to detect bowel segment activity was <=1.6 with sensitivity 90% & specificity 85.71%

Key words: Diffusion weighted imaging, Bowel ultrasound, Colonoscopy; Crohn's disease, inflammatory bowel disease, apparent diffusion coefficient

Introduction

Crohn's disease is one of the inflammatory bowel diseases that may lead to progressive bowel damage and disability (Torres *et al,* 2017). Therapeutic lines to treat Crohn's disease (CD) was changed over years, shifting from simply resolving disease symptoms to profound bowel healing, with the aim not only treating short-term complications, but also affecting the natural history of disease by decreasing important outcomes (Pagnini *et al,* 2019). Bowel sonography (BS) is an easy, non-invasive, well tolerated and radiation-free imaging alternative in some situations (Pita and Magro, 2018). BS has a major role in diagnosing and monitoring many gastro-enterolic diseases with increasing IBD management (Kucharzik *et al,* 2017).

Nowadays DWI is routinely used in several clinical scenarios, besides still being a hot research topic: it was tested in almost all cancers to differentiate malignant from benign lesions, to distinguish different malignant histotypes or tumor grades, to predict and/or assess treatment responses, and to identify residual or recurrent tumors in follow-up examinations (Messina *et al,* 2020). It was a specialized MRI technique to map wter diffusion of molecules in biological tissues (Choi *et al,* 2016). DWI takes less time than other modalities and can be performed without intravenous contrast; a major advantage to avoid the risk of gadolinium-based contrast agents (Thomsen *et al,* 2013).

This study aimed to assess diffusion weighted imaging (DWI) value versus bowel sonography (BS) before and after biological treatment (anti-TNF) to detect healing in patients with CD.

Materials and Methods

Study population: The study was longitudinal observation study of 38 patients with

Crohn's disease selected from IBD Center, Ain Shams University Hospitals from June 2020 to June 2022. All were adults over 18 years old and accepted to receive biological treatment. Patients were excluded if they had severe or uncontrolled comorbidities, such as cardiorespiratory, liver, kidney diseases, cardiac pacemaker, or implanted metal objects that prohibited use of DWI.

Ethical approval: The study was approved by Ain Shams University, Faculty of Medicine, Research Ethics Committee Institutional Review Board, No. FWA000017585. All participants after explaining the study aim, signed an informed consent before taking any data or doing any investigations.

All patients reported a complete medical history, underwent thorough clinical examinations and laboratory investigations, including complete blood count, C-reactive protein, erythrocyte sedimentation rate, Stool analysis and culture.

All patients were subjected to colonoscopy up to terminal ileum with biopsies for histopathological confirmation, DWI and BS before biological treatment and 6 weeks later. The clinical activity score for Crohn's disease was assessed by the Crohn's Disease Activity Index (CDAI). Remission of Crohn's disease was defined as CDAI below 150, but severe one was defined as greater than 450 (Freeman, 2008).

Bowel ultrasound: BS was done by a well-trained examiner who had performed several general ultrasound examinations. He was trained for several BS exams at Sacco Hospital, Italy under supervision of an ultrasound gastroenterologist specialist.

BS assessment was reviewed blindly compared to DWI before biological treatment and 6 weeks later.

Patients were examined by BS after being fasting for six-hour period to minimize intestinal air contents by ultrasound machine (Toshiba Xeric, Japan).A low frequency curved-array transducer (2.5-4.5 MHz) was used to determine any pathological bowel motility or distension and any Para-intestinal findings, such as abscesses, in all abdominal quadrants. A high-frequency linear-array transducer (6.0-8.4 MHz) was used for bowel wall examination starting with the proximal colon followed with the distal one and then the small bowel. The BS examination assessed criteria of inflammation as wall thickness, vascularization of the wall using color doppler, with classification into: Grade 0: no vascularization, grade 1: barely visible vascularization, grade 2: moderately visible vascularization), and grade 3: markedly visible vascularization with abscess or fistulas.

DWI: On the DWI day, patients were fasting for at least 4hr and 1000mL of PEG solution (FORTRAN's, diluted manitol…etc.) was given 45 to 60 minutes before to achieve an adequate distension of the distal ileum. Patients were placed in supine (more comfortable) position in the MR imager.

In order to minimize motion artifacts secondary to bowel peristalsis, patients received spasmolytic medication at the beginning and again approximately half-way of the examination. The duration of DWI ranges from 3 to 5 minutes. Imaging began from the diaphragm and continued caudally to the ancutaneous line (Ewing, 1954).

The examination was performed on 1.5-T MR machine, Achieved, Philips Medical System, Best, Netherlands in MRI Unit, Ain Shams University Hospitals. Patient was laid in supine position using a multi-element phased array Torso coil (16 channels). Pixel-based apparent diffusion coefficient maps was generated on off-line workstation (extended workspace EWS), Pride software (Philips Medical Systems). Images were interpreted by a radiologist with 12 years of experts in pelviabdominal imaging and who was also blinded to the clinical and BS examination results.

DWI examination assessed the following: Qualitatively by restriction of the bowel, Quantitative by the degree of apparent diffusion coefficient (ADC) and presence of complications as bowel fistula and abscess.

Statistical analysis: Data was presented and

suitable analysis was done by using SPSS 23. Descriptive statistics included mean (±SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data.

Correlation analysis was done using Pearson's method to assess strength of associateon between two quantitative variables. Paired t-test assessed the significant difference between two means measured twice of the same group. ROC Curve (receiver operating characteristic) evaluated sensitivity and specificity. Wilcoxon signed rank test assessed significant difference of an ordinal variable (score) measured twice of same group. McNamara test assessed significant difference between a qualitative variable measured twice of same group.

Results

Patients mean ages were 27.1±8.29 years old, of whom 22 (57.9%) were males, and 16 (42.1%) were females. Patients 8(21.1%) were smokers and 30(78.9%) were nonsmokers. Besides, 24(63.2%) gave surgical history, of whom 18 underwent appendectomy. Symptoms were 29(76.3%) abdominal pain, 28 (73.7%), bloody diarrhea, two (5.3%), bleeding rectum, and 16 (42.1%). extra-intestinal manifestations. Patients 24 (63.2%) received infliximab® and 14 (36.8%) received adalimumab®. There were significant differences between BS in Crohn's disease patients before & after biological treatment as bowel thickness, bowel vascularity, or motility, fistula, proximal dilatation and abscess with P<0.001, <0.001, <0.013, <0.001, < 0.031 & <0.001 respectively, and significant differences between DWI in Crohn's disease patients before and after biological treatment as ADC score, fistula, abscess, stricture, lymphadenopathy and bowel restriction with P < 0.001, <0.002, <0.001, <0.001, 0.031 & < 0.001 respectively.

ADC score of DWI affected segment inversely correlated with thickness of the same segment by BS, with cut-off value to predict activity of bowel segment was <=1.6 with sensitivity 90% and specificity 85.71%. Also, there was inverse correlation between ADC value and CDAI with r -0.55.

Details were given in tables (1, 2, 3 & 4).

Table 1: Bowel sonography before and after receiving biologics for groups.

Bowel sonography		Before	After	Test of significance	
		N (%) M ± SD	N (%) M ± SD	P-value	Sig.
Site	Ileal	28 (73.68%)			
	Colonic	4 (10.53%)			
	Ileoclonic	4 (10.53%)			
	Ileocolic anastomosis	2 (5.26%)			
Thickness (mm)		5.06 ± 1.39	2.75 ± 1.43	<0.001*	Sig.
Vascularity	Absent	0 (0.0%)	12 (31.58%)	<0.001**	Sig.
	Moderate	26 (68.42%)	14 (36.84%)		
	Marked	12 (31.58%)	12 (31.58%)		
Motility	Diminished	34 (89.47%)	24 (63.16%)	0.013~	Sig.
	Normal	4 (10.53%)	14 (36.84%)		
Complications:	Yes	30(79%)	15 (39.5%)	<0.001~	Sig.
	No	8 (21%)	23 (60.5%)		
Fistula	Yes	28 (73.68%)	14 (36.84%)	<0.001~	Sig.
	No	10 (26.32%)	24 (63.16%)		
Stricture	Yes	10 (26.32%)	10 (26.32%)	1.00~	Not Sig.
	No	28 (73.68%)	28 (73.68%)		
Proximal dilatation	Yes	6 (15.79%)	0 (0.0%)	0.031~	Sig.
	No	32 (84.21%)	38 (100%)		
Abscess	Yes	20 (52.63%)	4 (10.53%)	<0.001~	Sig.
	No	18 (47.37%)	34 (89.47%)		

Table 2: DWI before and after receiving biologics for groups.

Variations	DWI		Before	After	Significance
			N (%) M ± SD	N (%) M ± SD	P-value
Location	Ileal	30 (78.95%)			
	Colonic	4 (10.53%)			
	Ileoclonic	2 (5.26%)			
	Ileal and small intestine	2 (5.26%)			
ADC (10^3 mm2/sec)		0.96 ± 0.16	1.62 ± 0.40	<0.001*	Sig.
Restriction	Yes	38(100%)	22 (57.89%)	<0.001**	Sig.
	No		16 (42.11%)		
Complication:	Yes	30 (79%)	16 (42.11%)	<0.001**	Sig.
	No	8 (21%)	22 (57.89%)		
1- Fistula	Yes	26 (68.42%)	16 (42.11%)	0.002**	Sig.
	No	12 (31.58%)	22 (57.89%)		
2- Abscess	Yes	20 (52.63%)	6 (15.79%)	<0.001**	Sig.
	No	18 (47.37%)	32 (84.21%)		
3- Stricture	Yes	24 (63.16%)	12 (31.58%)	<0.001**	Sig.
	No	14 (36.84%)	26 (68.42%)		
4- Restriction	Yes	36 (94.74%)	30 (78.95%)	0.031**	Sig.
	No	2 (5.26%)	8 (21.05%)		

Table 3: Correlation between bowel thickness by BS and ADC score by DWI after receiving biologics.

Variables		ADC (10^3 mm2/sec) After
Thickness after (mm)	Pearson Correlation	-0.6105
	P-value	<0.001
	0.932	0.801 to 0.988

Table 4: Roc curve of ADC (10^3 mm^2/sec) after biologics activity by DWI.

AUC	95% CI	Sig.	Cut-off value	Sensitivity	Specificity
0.932	0.801 to 0.988	<0.001	<=1.6	90%	85.71%

Discussion

Generally speaking, endoscopy plays a central part in the care for the IBD patient at multiple stages, providing diagnostic and prognostic data, guiding medical and surgical therapy, treating disease-related complications, and assisting in the early detection of dysplasia and prevention of colorectal cancer in the setting of IBD (Negreanu *et al,* 2019). However, ultra- sound examination is an easily accessible, non-invasive, radiation-free, and cheap imaging modality that preferred as the first diagnostic method in gastroenterology, but trans-abdominal ultrasound was rarely used to assess the intestines as to difficulty of visualisation, impaired by gas and other intestinal content (Andrzejewska and Grzymisławski, 2018). Loftus (2004) in USA reported high incidence and prevalence of ulcerative colitis and Crohn's disease in areas such as northern Europe and North America; they continue to rise in low-incidence areas such as southern Europe, Asia, and much of the developing world. Esmat *et al.* (2014) in Egypt reported a ratio of 6:1 for UC to CD, and that incidence of IBD is rising in Egypt.

In the present study, it was found that the DWI is a promising tool that can be used in disease management, including starting antibiotic therapy, stoppage of immunosuppressive therapy, performing percutaneous drainage, or surgical treatment.

In the present study, the parameters of BS were improved after receiving the anti-TNF agents as follow: a significant reduction of bowel wall thickness (BWT) as mean BWT reduce from 5.06±1.39mm to 2.75±1.43 mm (by 50%), vascularity of the bowel was improved in 68.42% and complications resolved in half of them as 60.5% of the patients didn't have complications after receiving biological treatment. This agreed with Paredes *et al.* (2019) in Spain who assessed benefits of transmural healing (TH) shown on intestinal ultrasound (IUS) after treatment with tumor necrosis factor-alpha antibodies in patients with Crohn's disease, reported that patients achieved TH on IUS with biological treatment have better clinical

outcomes, and Doppler flow grade was improved in 69.7%, and complications resolved in 66.7%.

In the present study, response to anti-TNF assessed by BS showed complete achievement in 55.26% of the patients, partial response in 28.95% and no response in 15.79%. This agreed with Zorzi *et al.* (2020) in Italy who reported that in 80 CD patients 51% responded to anti-TNF agents, 15% as non-responded and 34% as partial responders, and that ultrasonographic assessment gave a relatively non-invasive method for monitoring the treatment response. Moreover, Chen *et al.* (2022) in China in a pilot study on 30 cases reported that changes in bowel ultrasound behavior were assessed as early as 2 weeks after giving anti-TNF therapy, which together with elasticity imaging was significantly reduced compared that after anti-TNF therapy

In the current study, the restriction diffusion was found in 100% of patients with bowel inflammation before treatment. The vast majority of restricted-diffusion abnormalities caused by the acute stroke, and diagnosis may be problematic when this MRI feature resulted from other causes (Finelli, 2012). This agreed with Neubauer *et al.* (2013); Tielbeek *et al.* (2014) and Li *et al.* (2017).

In the present study, as to DWI, mean ADC value in 38 patients before and after biological treatment was 0.96±0.16 &1.62±0.40 respectively. ADC value change was negative as it increased after treatment, with significantly differed between improved and unimproved lesions ($P < 0.001$). DWI detected complications as bowel fistula, stricture and abscess in 79% of patients before treatment that was improved after treatment in half of them to be detected in 42%. This agreed with Huh *et al.* (2017) who reported that DWI proved to be a feasible tool to monitor quantitatively and qualitatively bowel inflammation of CD post treatment.

In the present study, there was strong inverse correlation between ADC value & bowel wa- ll thickness with correlation coefficient (r) -0.61. This more or less agreed with Neubauer *et al.* (2013) and Dillman *et al.* (2016) reported inverse correlation with r -0.72,-0.52 &-0.39 respectively. Moreover, Abd-El Khalek and Fahmy (2018) reported that the ADC value of affected segment by DWI inversely correlated with thickness of the same segment with r -0.73.

Also, the present study showed that the cut-off value of ADC to predict activity of bowel segment was $<=1.6\times10^{-3}mm^2/s$ with sensitivity 90% and specificity 85.71%. This agreed with Buisson *et al.* (2013); Dillman *et al.(*2016) and Huh *et al.* (2017), reported the ADC cut-off value of $1.6\times110^{-3}mm^2/s$ for differentiating active from non-active disease with sensitivity ranged from 82.4% to 88.7% and specificity from 80% to 100% Li *et al.* (2017) in China didn't find significantly, by using the ADC threshold value of $1.59\times10^{-3}mm^2/sec$ with sensitivity (97.2%) and specificity 84.3%. Besides, Tantawy and Algeball (2016) in Egypt found that by using cutoff point $1.65\times10^{-3}mm^2/s$ gave 88.7% sensitivity and 80% specificity. They concluded that DWI & quantitative ADC value study to MRI imaging detected inflammation in patients with Crohn's disease and differentiating between active and inactive diseased bowel segment. Oto *et al*. (2009) in USA reported a much higher cutoff value, on quantitative analysis, ADC values of inflamed and normal bowel were 0.47 -2.60 $\times10^{-3}mm^2$and 1.39 -$4.03\times10^{-3}mm^2/s$, respetively ($P < .05$). but, Abd-El Khalek and Fahmy (2018) in Egypt found that a mildly lower cutoff value of $1.35\times 10^{-3}mm^2/s$ with 80% sensitivity and 100% specificity. These differences in ADCs among different studies may be related to different samples and scan parameters, high variability of the selection of the segment of interest on the bowel.

In the present study, there was an inverse correlation between ADC value and CDAI with r -0.55 as ADC value decreased with increased disease severity assessed clinically by CDAI. This agreed with Li *et al.* (2015); and Wu *et al.* (2020) in China and Thormann *et al.* (2022) in Germany they found that the correlation coefficient between ADC va-

lue and the CDAI was -0.86, -0.80 & -0.71 respectively.

In the present study, that ADC values decreased with increasing severity of CD assessed by colonoscopy (SES-CD) which means there is inverse correlation between ADC value and severity by colonoscopy with r -0.453. This agreed with Buisson *et al.* (2013) in France, Caruso *et al.* (2014) in Italy, Li *et al.* (2017); Cheng *et al.* (2019) in China and Thormann *et al.* (2022), they found there was a negative correlation between ADCs in inflamed segments and severity by colonoscopy with r=−0.44, -0.63, -0.63, -0.66 & -0.88 respectively. These differences may be due to different scan parameters, different reference standard, or some studies used another imaging modality as MRE; others used endoscopic assessment, or used pathological specimens after surgery.

In the current study, as compared to colonoscopy, accuracy of DWI in assessment of disease activity after biologics was 84.6% with 100% sensitivity & 33.3% specificity. Huh *et al.* (2017) in Korea didn't find significant differences as they reported that the accuracy of DWI in assessment of improved inflammation after treatment was 81% with sensitivity and specificity 88% & 25% respectively compared to the colonoscopy. Durayski *et al*. (2019) in Brazil found the DWI gave an accuracy of 89.4% and sensitivity of 88.9%, but specificity was 90.0% in detecting colonoscopy-confirmed inflammation due to different scan parameters.

The present study showed that DWI is a good predictor to detect treatment response as compared to bowel US with accuracy, sensitivity and specificity of 89.5%, 87.5% & 100% respectively. This agreed with Choi *et al.* (2016) who found that the DWI diagnostic performance for active bowel inflammation in CD was very heterogeneous, with sensitivities & specificities ranged from 68% to 100% & 51% to 100%, respectively. Also, Kim *et al.* (2022) found that the pooled sensitivity and specificity of DWI-MRE to detect bowel inflammation were 93% & 96% respectively**.** The accuracy of DWI ranged from 90% to 100% with sensitivity 83% to 100% and specificity 89% to 100% (Oto *et al*, 2011; Hordonneau *et al*, 2014; Foti *et al*, 2015; Qi *et al,* 2015). This discrepancy in results may be due to the different scan parameters and different samples

The present study showed accuracy, sensitivity and specificity of DWI in detecting bowel fistula were 94.7% with 92.90% and 100% respectively. This agreed with Fahmy and Dawoud (2017) in Egypt who reported the DWI accuracy in detecting bowel fistula was 91.2% with sensitivity and specificity of 91.18 % & 100% respectively. Schmid-Tannwald *et al.* (2012) in USA evaluated 14 patients and found similar value for DWI in detecting bowel fistula compared with contrast-enhanced T1-weighted images, and concluded that DW-MRI was a useful adjunct, especially for patients with renal failure.
Dohan *et al.* (2016) in Canada reported that DWI value in CD to detect, characterize, & quantify disease activity and complications, gave 92% sensitivity and 100% specificity.

Conclusions

DWI is a growing tool to detect and localize active CD that attracted attention in clinical practice. DWI correlated well with disease activity by evaluation of restriction diffusion, ADC values and presence of complications. The ADC cutoff value to detect inflammation still needs to be more investigated. ADC value can reflect acute inflammatory reactions but not systemic inflammation.

To the present authors' knowledge none assessed the role of DWI in CD patients.

Authors' declaration: They declared neither have conflicts of interest nor received funds.

Authors' contributions: All authors equally contributed to the practical and theoretical study.

References

Abd-El Khalek, AA, Fahmy, DM, 2018: Diagnostic value of diffusion-weighted imaging and apparent diffusion coefficient in assessment of the activity of Crohn's Disease: 1.5 or 3 T. J. Comput. Assist. Tomogram 42, 5:688-96.

Andrzejewska, M, Grzymisławski, M, 2018: The role of intestinal ultrasound in diagnostics of bowel diseases. Prz. Gastroenterol. 13, 1:1-5. Published online 2018 Mar 26.

Buisson, A, Joubert, A, Montoriol, PF, *et al,* 2013: Diffusion-weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn's disease. Alim. Pharmacol. Therap. 37, 5: 537-45.

Caruso, A, D'Incà, R, Scarpa, M, *et al,* 2014: Diffusion-weighted magnetic resonance for assessing ileal Crohn's disease activity. Inflamm. Bowel Dis. 20:1575-83.

Chen,YJ, Chen, BL, Liang, MJ, *et al,* 2022: Longitudinal bowel behavior assessed by bowel ultrasound to predict early response to anti-TNF therapy in patients with Crohn's Disease: A pilot study. Inflamm. Bowel Dis. 28, 2:S67-75.

Cheng, J, Wang, K, Leng, X, *et al*, 2019: Evaluating the inflammatory activity in Crohn's disease using magnetic resonance diffusion kurtosis imaging. Abdom. Radiol. (NY) 44:2679-88.

Choi, SH, Kim, KW, Lee, JY, *et al,* 2016: Diffusion-weighted magnetic resonance enterography for evaluating bowel inflammation in Crohn's disease: A systematic review and meta-analysis. Inflamm. Bowel Dis. 22: 669-79.

Dillman, JR, Smith, EA, Sanchez, R, *et al,* 2016: DWI in pediatric small-bowel Crohn disease: Are apparent diffusion coefficients surrogates for disease activity in patients receiving infliximab therapy? AJR Am. J. Roentgenol. 207: 1002-8.

Dohan, A, Taylor, S, Hoeffel, C, *et al,* 2016: Diffusion-weighted MRI in Crohn's disease: Current status and recommendations. J. Magn. Reson. Imaging 44:1381-96.

Durayski, E, Watte, G, Pacini, GS, *et al,* 2019: Diffusion-weighted imaging and apparent diffusion coefficient values for evaluating terminal ileitis in patients with Crohn's disease. Radiol. Bras. 52, 6:361-7.

Esmat, S, El Nady, M, Elfekki, M, Elsherif, Y, Naga, M, 2014: Epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt. World J. Gastroenterol. 20, 3: 814-21

Ewing, MR, 1954: The white line of Hilton. Proceed. Roy. Soc. Med. 47, 7:525-30.

Fahmy, DM, Dawoud, MG, 2017: Value of diffusion weighted MRI in assessment of simple and complicated perianal fistula. Egypt. J. Radiol. Nucl. Med. 48, 3:553-62.

Finelli, PF, 2012: Diagnostic approach to restricted-diffusion patterns on MR imaging. Neurol. Clin. Pract. 2, 4:287-93.

Foti, PV, Farina, R, Coronella, M, *et al,* 2015: Crohn's disease of the small bowel: Evaluation of ileal inflammation by diffusion-weighted MR imaging and correlation with the Harvey-Bradshaw index. Radiol. Med. 120:585-94.

Freeman, HJ, 2008: Use of the Crohn's disease activity index in clinical trials of biological agents. World J. Gastroenterol.14, 26:4127-30.

Hordonneau, C, Buisson, A, Scanzi, J, *et al,* 2014: Diffusion-weighted magnetic resonance imaging in ileocolonic Crohn's disease: Validation of quantitative index of activity. Am. J. Gastroenterol. 109:89-98.

Huh, J, Kim, KJ, Park, SH, *et al,* 2017: Diffusion-weighted MR enterography to monitor bowel inflammation after medical therapy in Crohn's Disease: A prospective longitudinal study. Korean J. Radiol. 18, 1:162-72.

Kim, PH, Yoon, HM, Jung, AY, *et al,* 2022: Diagnostic performance of diffusion-weighted imaging for evaluation of bowel inflammation in paediatric inflammatory bowel disease: A systematic review and meta-analysis. J. Crohns' Colitis 16, 1:68-78.

Kucharzik, T, Kannengiesser, K, Petersen, F, 2017: The use of ultrasound in inflammatory bowel disease. Ann. Gastroenterol. 30, 2:135-44.

Li, XH, Sun, CH, Mao, R, *et al,* 2015: Assessment of activity of Crohn's disease by diffusion-weigh- ted magnetic resonance imaging. Med. Baltimore, 94, 43:e1819.

Li, XH, Sun, CH, Mao, R, *et al,* 2017: Diffusion-weighted MRI enables to accurately grade inflammatory activity in patients of ileocolonic Crohn's disease: Results from an observational study. Inflamm. Bowel Dis. 23:244-53.

Loftus, EV, 2004: Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 126:1504-17.

Messina, C, Bignone, R, Bruno, A, Bruno, F, *et al,* 2020: Diffusion-weighted imaging in oncology: An update. Cancers (Basel). 2020 Jun; 12(6): 1493. doi: 10.3390/cancers12061493

Negreanu, L, Voiosu, T, State, M, Voiosu, A, Bengus, A, *et al,* 2019: Endoscopy in inflammatory bowel disease: from guidelines to real life. Therap. Adv. Gastroenterol. 2019: Jul 24; 12: 1756284819865153

Neubauer, H, Pabst, T, Dick, A, *et al,* 2013:

Small-bowel MRI in children and young adults with Crohn's disease: Retrospective head-to-head comparison of contrast-enhanced and diffusion-weighted MRI. Pediatr. Radiol. 43:103-14.

Oto, A, Kayhan, A, Williams, JTB, *et al,* 2011: Active Crohn's disease in the small bowel: Evaluat- ion by diffusion weighted imaging and quantitative dynamic contrast enhanced MR imaging. J. Magn. Reson. Imaging 33, 3:615-24.

Oto, A, Zhu, F, Kulkarni, K, *et al,* 2009: Evaluation of diffusion-weighted MR imaging for detection of bowel inflammation in patients with Crohn's Disease. Acad. Radiol. 16, 5:597-603.

Pagnini, C, Pizarro, TT, Cominelli, F, 2019: Novel pharmacological therapy in inflammatory bowel diseases: Beyond anti-tumor necrosis factor. Front. Pharmacol.10:671-6.

Paredes, JM, Moreno, N, Latorre, P, *et al,* 2019: Clinical impact of sonographic transmural healing after anti-TNF antibody treatment in patients with Crohn's disease. Dig. Dis. Sci. 64, 9:2600-6.

Pita, I, Magro, F, 2018: Advanced imaging techniques for small bowel Crohn's disease: What does the future hold? Ther. Adv. Gastroenterol.11:1-15.

Qi, F, Jun, S, Qi, QY, *et al,* 2015: Utility of the diffusion-weighted imaging for activity evaluation in Crohn's disease patients underwent magn etic resonance enterography. BMC Gastroenterol. 15:12-5.

Schmid-Tannwald, C, Agrawal, G, Dahi, F, *et al,* 2012: Diffusion weighted MRI: Role in detecting abdominopelvic internal fistulas and sinus tracts. J. Magn. Reson. Imaging35:125-31.

Tantawy, HI, Algebally, AMW, 2016: Role of quantitative MRI diffusion-weighted imaging (DWI) in detecting lesion activity in patients with Crohn's disease. Egypt. J. Radiol. Nucl. Med. 47, 1:53-9.

Thomsen, HS, Morcos, SK, Almén, T, *et al,* 2013: ESUR contrast medium safety committee: Neph- rogenic systemic fibrosis and gadolinium-based contrast media, updated ESUR Contrast Medium Safety Committee guidelines. Eur. Radiol. 23, 2:307-18.

Thormann, M, Melekh, B, Bär, C, *et al,* 2022: Apparent diffusion coefficient for assessing Crohn's disease activity: a meta-analysis. Eur. Radiol. doi: 10.1007/s00330-022-09149-9.

Tielbeek, JA, Ziech, ML, Li, Z, *et al,* 2014: Evaluation of conventional, dynamic contrast enhanced and diffusion weighted MRI for quantitative Crohn's disease assessment with histopathology of surgical specimens. Eur. Radiol. 24:619-29.

Torres, J, Mehandru, S, Colombel, JF, *et al,* 2017: Crohn's disease. Lancet 389:1741-55.

Wu, YC, Lin, XH, Zheng, XY, *et al,* 2020: Dynamic contrast-enhanced magnetic resonance imaging and diffusion-weighted imaging in the activity staging of terminal ileum Crohn's dise ase. World J. Gastroenterol. 26:6057-73.

Zorzi, F, Ghosh, S, Chiaramonte, C, *et al,* 2020: Response assessed by ultrasonography as target of biological treatment for Crohn's disease. Clin. Gastroenterol. Hepatol. 18, 9:2030-7.