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Is quantitative diffusion-weighted MRI a reliable method in the assessment of the inflammatory activity in ulcerative colitis?

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PURPOSE
We investigated the relationship between the apparent diffusion coefficient (ADC) values of the colonic wall and the pathologic pericolonic lymph nodes (PCLNs) and inflammatory activity in ulcerative colitis patients by diffusion-weighted magnetic resonance imaging (DW-MRI).

MATERIALS AND METHODS
A total of 28 ulcerative colitis patients (9 endoscopically active, 10 subacute and 9 in remission) were evaluated by DW-MRI with 0, 500 and 1000 s/mm^2 b-values. The ADC values of the rectum and sigmoid colon walls and the adjacent PCLNs were obtained for quantitative analysis. The DW-MRI findings were compared to the disease activity.

RESULTS
The ADC values of the sigmoid colon were similar in patients with active, subacute and remissive ulcerative colitis (P = 0.472). The ADC values of the rectum were different (P = 0.009) between patients in the active (1.08 ± 0.14×10^{-3} mm^2/s) and subacute phases (1.13 ± 0.23×10^{-3} mm^2/s) of disease and those in remission (1.29 ± 0.17×10^{-3} mm^2/s). The ADC values of the PCLNs (P = 0.899) did not differ with respect to disease activity.

CONCLUSION
DW-MRI is useful in identifying disease activity in ulcerative colitis patients, especially with respect to the rectum. The ADC values of the rectum increase during remission and decrease in patients with active distal colitis. The ADC values of the PCLNs were not useful in determining disease activity.

Key words: • *ulcerative colitis* • *inflammatory bowel diseases* • *diffusion magnetic resonance imaging*

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Ulcerative colitis is a chronic disease characterized by diffuse mucosal inflammation that is localized to the colon. In approximately 95% of cases, ulcerative colitis involves the rectum and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve part or all of the large intestine. Ulcerative colitis is usually associated with recurrent attacks, with complete remission of symptoms in the interim (1–4).

Disease activity indices are prediction rules that are used to objectively measure the activity of disease, to judge patients' responses to treatment in clinical trials and to choose which drug and dose to administer. Disease activity can be assessed clinically and endoscopically. Because the rectum is invariably involved in ulcerative colitis, flexible rectosigmoidoscopy is sufficient for depicting disease activity (1, 3). Despite its use as a gold standard, endoscopy is an invasive technique and has limitations. Due to the presence of severe inflammation in the colon, the use of colonoscopy in patients with active ulcerative colitis carries a high risk of perforation of the tissue. In addition, orientation cannot be ascertained in newly diagnosed patients with active ulcerative colitis. Furthermore, the view of the endoscopist is limited to the colonic lumen; the thickness of the colonic wall and the presence of lymph nodes cannot be assessed. Patient discomfort and the potential risks associated with obtaining biopsies via endoscopy have prompted the evaluation of various radiological imaging techniques to identify and quantify inflammatory bowel disease (IBD) activity in the colon (5).

The part of the gastrointestinal tract in which magnetic resonance imaging (MRI) studies have been the most successful is the rectum (2). MRI has been shown to be an excellent means of accurately assessing inflammatory diseases and congenital malformations following cancers in the rectosigmoid region (2–4). Several studies have reported MRI parameters that can be used to determine disease activity; these include increased contrast uptake in the colonic wall, thickening of the bowel wall, quantification of lymph nodes, and loss of haustral folds (5, 6). In addition, a non-invasive technique called diffusion-weighted MRI (DW-MRI), which was previously restricted to imaging of the central nervous system, has recently been implemented for the diagnosis and follow-up of various abdominal diseases. The purpose of this study was to determine disease activity in patients with ulcerative colitis by calculating the apparent coefficient values (ADC) of the colonic wall and pericolonic lymph nodes (PCLNs) using non-invasive DW-MRI.

Materials and methods

A total of 28 patients with ulcerative colitis (9 endoscopically active, 10 subacute and 9 in remission) were prospectively evaluated with DW-MRI

prior to endoscopy. The research protocol was approved by the local ethics committee, and written consent was obtained from all the patients prior to the study. Patients were excluded from the study if they presented contraindications to MRI such as the presence of a pacemaker, metallic implants in the central nervous system, or claustrophobia. All the patients were referred for MRI because of known ulcerative colitis affecting the distal large bowel. One patient was excluded from the study because endoscopic examination could not be performed.

The ADC values of the rectum and sigmoid colon walls and the adjacent PCLNs were measured for quantitative analysis. As controls for comparison, we also measured the ADC values of normal subcentimeter lymph nodes of the inguinal subcutaneous tissue in most subjects. These lymph nodes had a normal appearance, were ovoid-shaped and had sharp borders. The nodes were considered ovoid if the long axis/short axis ratio was greater than or equal to two. Short axis diameters were less than 7 mm. The DW-MRI findings in individual patients were compared with the disease activity in those patients. The MRI was performed on a 1.5 T scanner (Avanto; Siemens, Erlangen, Germany) with a 33 mT/m maximum gradient capability using an eight-channel phased-array body coil. The sequences used for pelvic MRI were as follows: axial, turbo spin-echo T2-weighted sequence repetition time (TR), 4320 ms; echo time (TE), 87 ms; axial fat-saturated 3D gradient-echo T1-weighted MRI sequence (VIBE) TR, 5.32 ms; TE, 2.53 ms; axial, turbo spin-echo T1-weighted sequence TR, 536 ms; TE, 11 ms; sagittal, turbo spin-echo T2-weighted sequence TR, 5030 ms; TE, 101 ms; coronal, turbo spin-echo TIRM sequence TR, 4980 ms; TE, 84 ms. This sequence was followed by a diffusion-weighted single-shot spin-echo echo-planar sequence using chemical shift selective fat-suppression technique; TR/TE, 4900/93; matrix, 192×192; slice numbers, 30; slice thickness, 6 mm; interslice gap, 35%; FOV, 45 cm; averages, 5; acquisition time, approximately 3 minutes; PAT factor, 2; PAT mode, GRAPPA with b factors of 0, 500 and 1000 s/mm^2.

Following the DW-MRI, contrast-enhanced imaging was performed using an axial 3D gradient-echo T1-weighted MRI sequence after intravenous administration of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at a dose of 0.1 mmol/kg of body weight as a bolus injection.

Within a period of two to seven days (mean, 5.2 days) following MRI, a colonoscopy was performed by an experienced gastroenterologist. After visual assessment, a biopsy of the colonic wall was obtained. The reports of the endoscopic examination and the results of the pathology report were reviewed. Visualization of an inflamed mucosa by endoscopy or evidence of bowel inflammation in the biopsy were accepted as proof of inflammation and noted for each segment. The quantitative DW-MRI findings were compared to the results of the traditional colonoscopy.

Image interpretation

The DW-MRI datasets were transferred to an independent workstation (Leonardo Console software version 2.0; Siemens) for post-processing. The MRI studies were interpreted, and measurements were performed by two radiologists experienced in abdominal radiology. The DW-MRI images were of diagnostic quality in all cases, and no cases were excluded from the study. The ADC maps were generated and mapped using the imaging software. For the measurement of the ADC values, the images were magnified, and oval region of interests (ROIs) were placed on the largest possible area covering the bowel wall. The measurements were made on the area of the bowel wall with the brightest signal. The ROI was then copied to the corresponding ADC map.

Colonoscopy

All the patients underwent an endoscopic colonoscopy two to seven days (mean, 5.2 days) following the MR examination. The patients consumed a low-fiber diet on the day prior to the colonoscopy. In addition, 3000 cc of an electrolyte solution (Golytely, Braintree Laboratories, Braintree, Massachusetts, USA) were ingested by the patients on the evening before the examination. All the procedures were performed by a gastroenterologist with 10 years of experience in conventional (video) colonoscopy using standard equipment (EC-250WL5 Fujinon, Japan). The attending gastroenterologist was blinded to the MR findings. Sedatives (midazolam hydrochloride/Dormicum, Roche, Germany) and/or analgesics (pethidin/Dolantin, Hoechst, Germany) were administered before the procedure. Inflamed segments of the colon were recorded, and we obtained endoscopic biopsies from the most inflamed segments of the colon in 21 patients. The biopsies were subsequently analyzed by histopathology. Upon endoscopic examination of the mucosa of the patients, we observed signs of inflammation and active disease, including the presence of hyperemia, edema, fragility, and superficial and deep ulcers, granular and atrophic appearance of the mucosa, and visualization of the vessel network. The endoscopic activity was evaluated using the Rachmilewitz criteria (7). Each patient was monitored in the endoscopy unit for at least 1 hour following the colonoscopy.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 software. The ADC values are reported as the mean ± standard deviation. The normality of distribution of the parameters was assessed using the Kolmogorov-Smirnov test. The Student's *t*-test was used to compare differences in the ADC values between groups. *P* values of less than 0.05 were considered to be statistically significant.

Results

The ADC values of the sigmoid colon were similar between patients in the active, subacute and remission phases of ulcerative colitis ($P = 0.472$). The ADC values of the rectum were different ($P = 0.009$) between patients in the active ($1.08 \pm 0.14 \times 10^{-3}$ mm^2/s), subacute ($1.13 \pm 0.23 \times 10^{-3}$ mm^2/s) and remission ($1.29 \pm 0.17 \times 10^{-3}$ mm^2/s) phases. The rectum ADC values of the patients in remission were higher than the rectum ADC values of patients in the active ($P = 0.009$) and subacute ($P = 0.007$) phases and were similar in patients in the active and subacute phases of the disease ($P > 0.05$). The average ADC values of the rectum+sigmoid colon were different between patients in the active, subacute and remission phases ($P = 0.047$), and the values were higher in patients in remission than in those with active disease ($P = 0.012$)

(Table 1). The ADC values of the PCLNs (P = 0.899) were not different with respect to disease activity. However, the ADC values of patients in the active and subacute phases were statistically different for the PCLNs and incidental reactive lymph nodes (IRLNs) ($P < 0.05$). The box plots of the ADC values of the rectum are shown in Fig. 1, and two sample cases are shown in Figs. 2 and 3.

To evaluate the contrast-enhanced images, we used the criteria published by Rimola et al (6). These criteria classify ulcerative colitis according to the alterations observed in the colon, as follows: 1) mild: mild thickening of the colonic wall and consistent infrequent mucosal alterations; 2) moderately active: moderate thickening of the colonic wall or mural edema, ulcers, blunting or loss of haustra, hyperenhancement after intravenous administration of contrast material, and vascular dilatation; and 3) chronic longstanding (remission): no mucosal alterations, loss

Table 1. Mean ± standard deviation of the apparent diffusion coefficient (ADC) values ($\times 10^{-3}$ mm²/s) of the sigmoid, rectum, sigmoid + rectum, incidental reactive lymph nodes (IRLNs) and the pathologic pericolonic lymph nodes (PCLNs)

	Sigmoid ADC	Rectum ADC	Sigmoid + rectum ADC	PCLN	IRLN
Active	1.30 ± 0.09	1.08 ± 0.14	1.19 ± 0.10	0.99 ± 0.09	1.11 ± 0.07
Subacute	1.45 ± 0.28	1.13 ± 0.23	1.29 ± 0.23	0.95 ± 0.11	1.13 ± 0.10
Remission	1.50 ± 0.24	1.29 ± 0.16	1.39 ± 0.17	1.00 ± 0.31	1.13 ± 0.10

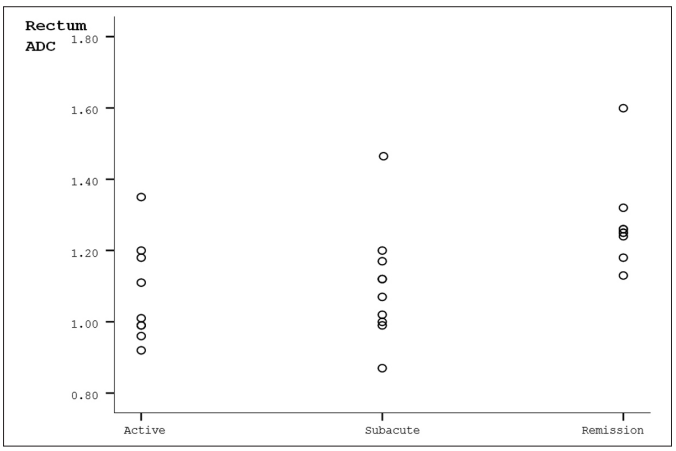
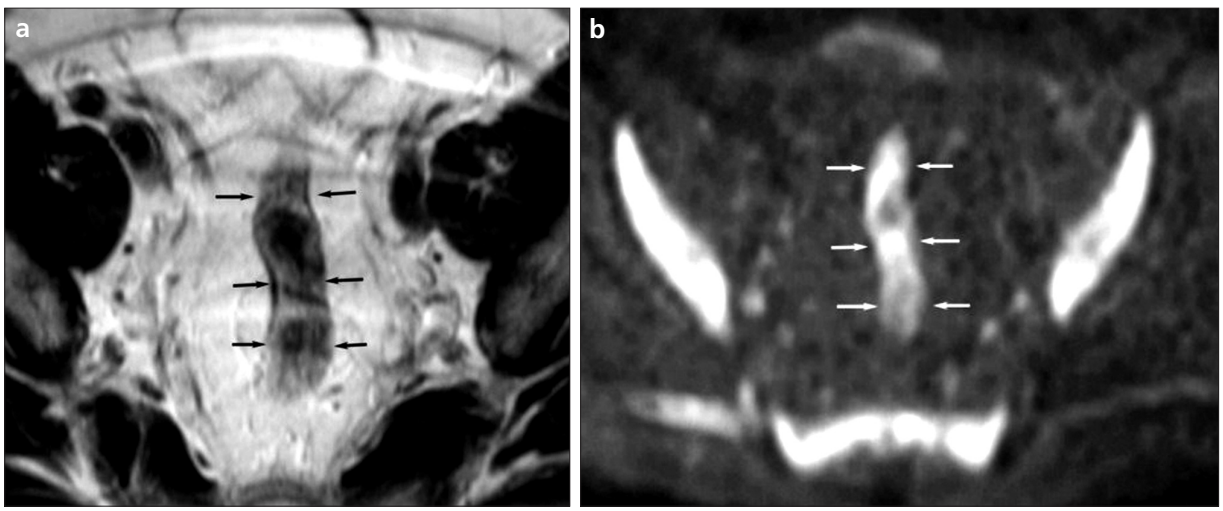


Figure 1. Scatter plot of the apparent diffusion coefficient (ADC) values of patients with different phases of ulcerative colitis involving the rectum.



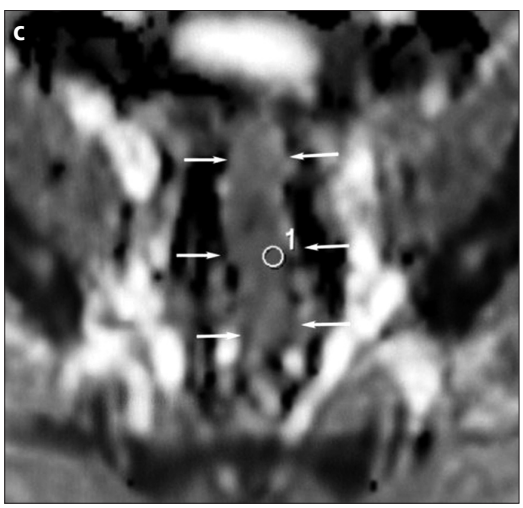


Figure 2. a–c. MR images of the rectosigmoid colon of a 34-year-old man with ulcerative colitis in the remission phase (*arrows*, distal sigmoid colon). T2-weighted MR image **(a)** shows mild thickening of the distal sigmoid colon wall. The diffusion-weighted MR image (b=1,000 s/mm^2) **(b)** shows the involvement of the colonic wall and hyperintensity. On apparent diffusion coefficient (ADC) map **(c)**, the colonic wall shows mild hypointensity (restricted diffusion). The region of interest (ROI) was placed on the colonic wall (ROI 1). The ADC value was 1.28×10^{-3} mm²/s.

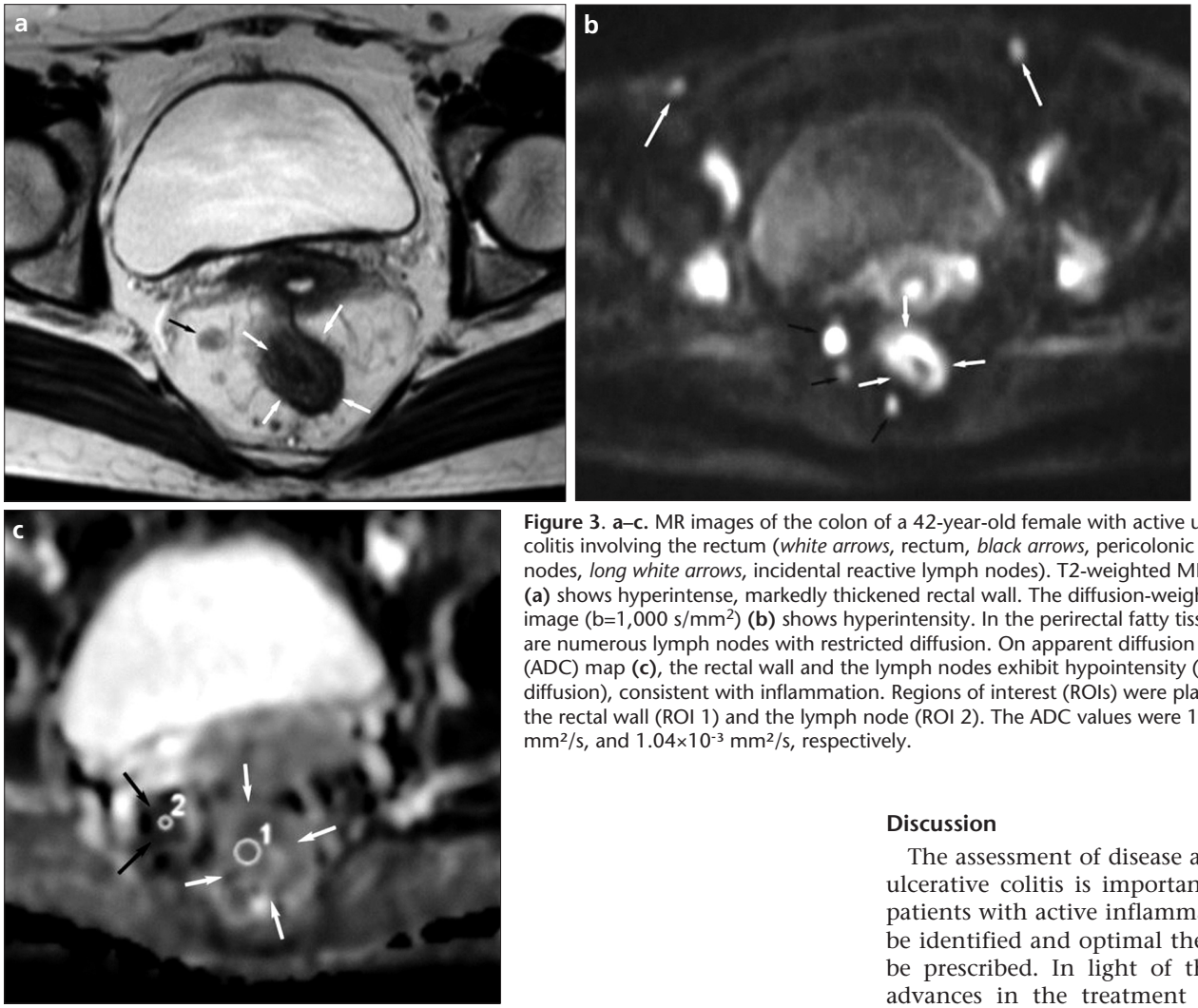


Figure 3. a–c. MR images of the colon of a 42-year-old female with active ulcerative colitis involving the rectum (*white arrows*, rectum, *black arrows*, pericolonic lymph nodes, *long white arrows*, incidental reactive lymph nodes). T2-weighted MR image **(a)** shows hyperintense, markedly thickened rectal wall. The diffusion-weighted MR image (b=1,000 s/mm^2) **(b)** shows hyperintensity. In the perirectal fatty tissue, there are numerous lymph nodes with restricted diffusion. On apparent diffusion coefficient (ADC) map **(c)**, the rectal wall and the lymph nodes exhibit hypointensity (restricted diffusion), consistent with inflammation. Regions of interest (ROIs) were placed on the rectal wall (ROI 1) and the lymph node (ROI 2). The ADC values were 1.16×10^{-3} mm^2/s, and 1.04×10^{-3} mm^2/s, respectively.

of haustra, smooth contours, tubular narrowing or rigidity. With the exception of one patient who exhibited only mild mural thickening and enhancement, all the patients with active ulcerative colitis (9 patients) presented moderate mural thickening, marked enhancement, submucosal sparing, and prominent vasa recta (Fig. 4). Of the patients with subacute colitis (10 patients), all but three exhibited mild mural thickening and enhancement. These three patients presented alterations that are characteristic of chronic longstanding ulcerative colitis. With the exception of one patient who presented with mural thickening and enhancement, the patients with chronic ulcerative colitis (9 patients) exhibited alterations that were consistent with their disease phase (Table 2). Enhancement was considered as positive when it was more intense than in the neighboring normal segment.

Discussion

The assessment of disease activity in ulcerative colitis is important so that patients with active inflammation can be identified and optimal therapy can be prescribed. In light of the recent advances in the treatment of active ulcerative colitis, the need for accurate assessment of disease activity has become even more important (8). Endoscopic biopsy is considered the gold standard for the detection and quantification of IBD. However, its invasiveness, discomfort for the patient, risk of perforation, and poor patient acceptance have prompted the exploration of alternatives for diagnosing and characterizing IBD (5, 9). To date, MRI and MR colonography have been used for this purpose. MRI has been shown to be an excellent means of accurately

Table 2. Assessment of the contrast-enhanced 3D GRE T1-weighted (VIBE) MR sequence

Subgroup	Number of cases	Hyperenhancement	Submucosal sparing	Vascular dilatation	Mean ADC ($\times10^{-3}$ mm^2/s)
Active	9	9 (100 %)	8 (88.8%)	9 (100 %)	1.080.14
Subacute	9	8 (88.8%)	4 (44.4%)	4 (44.4%)	1.13±0.23
Chronic	10	2 (20%)	0	1 (10%)	1.29±0.17

ADC, apparent diffusion coefficient.

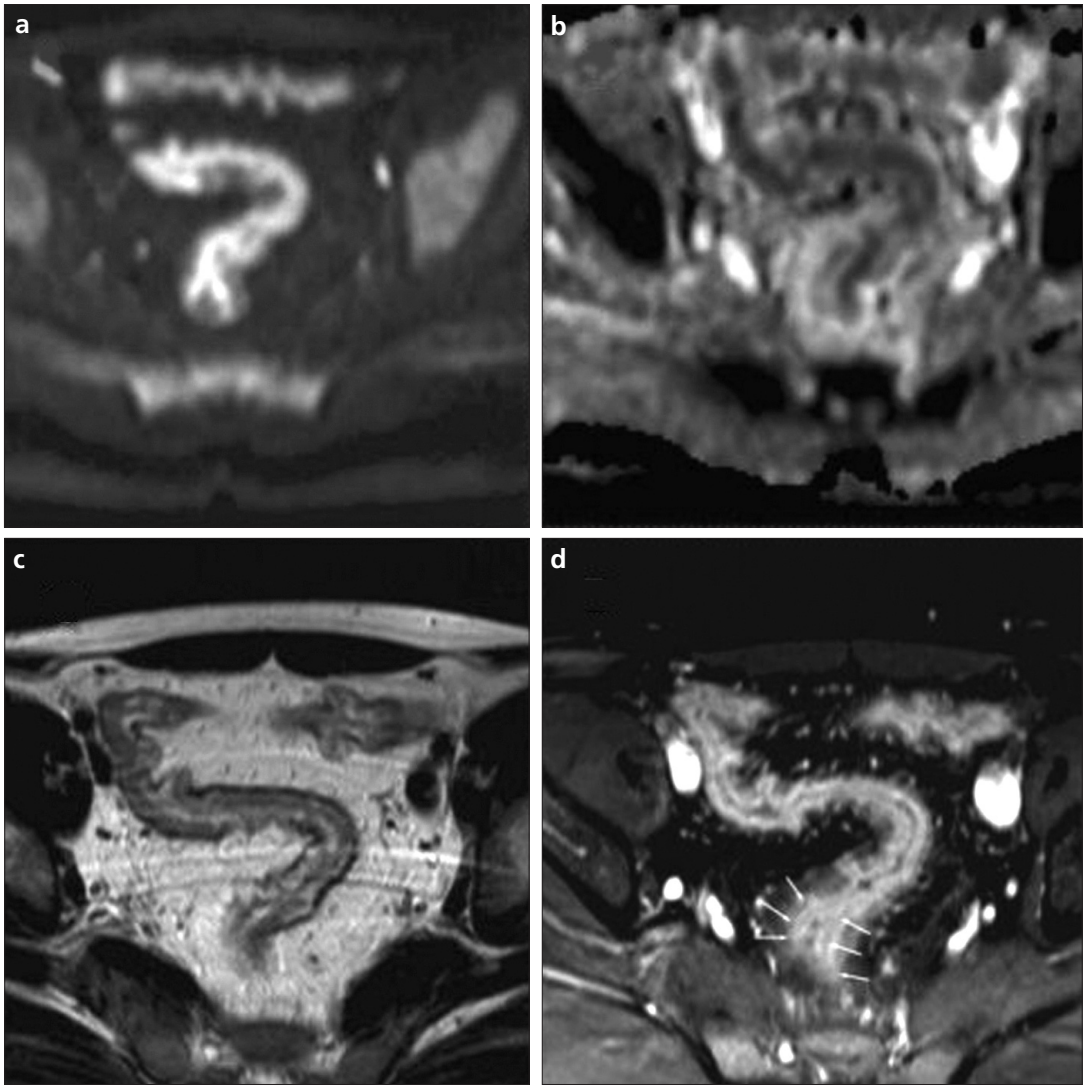


Figure 4. a–d. MR images of the colon of a 56-year-old female with active ulcerative colitis involving the rectum and sigmoid colon. The diffusion-weighted MR image (b=1,000 s/mm^2) **(a)** shows hyperintensity. On apparent diffusion coefficient (ADC) map **(b)**, the rectal wall exhibits hypointensity (restricted diffusion), consistent with inflammation. T2-weighted MR image **(c)** shows hyperintense, markedly thickened rectal wall. The post-contrast 3D GRE T1-weighted (VIBE) MR image **(d)** reveals hyperenhancement of the thickened rectal wall. However, there is a thin non-enhancing line (submucosa) between the enhancing inner (mucosa) and outer lines (muscularis propria). White arrows show the layered enhancement pattern-submucosal sparing in the rectum. Also, the pericolonic prominent vasa recta can be observed as enhanced small tubular structures.

assessing inflammatory diseases, especially in the rectosigmoid region (2).

DW-MRI, which is frequently used in neuroradiology, is a relatively new technique that can be used for the evaluation of abdominal diseases, especially in oncology (10). The diagnostic value of DW-MRI for hepatic, urinary, and pelvic malignancies (10–13) has been shown in multiple studies. In addition, the ADC values determined using this method were found to be lower in kidney and liver failure, concordant with the severity of the disease. DW-MRI has also been used in the evaluation of liver fibrosis and in the assessment of Crohn's disease activity (14–17).

In the present study, we aimed to evaluate the efficacy of DW-MRI in the assessment of disease activity in ulcerative colitis. Our results indicate that inflammation of the bowel wall causes restricted diffusion and that DW-MRI yields quantitative information (decreased ADC values) that can be helpful in the evaluation of bowel inflammation. To our knowledge, this is the first report showing that DW-MRI and the measurement of ADC values in the PCLNs can be used for the evaluation of bowel inflammation in patients with ulcerative colitis. In the patients in this study, the segments of the bowel with active inflammation were identified by their emission of a high-intensity signal detectable by DW-MRI. However, because normal bowel segments can also exhibit high intensity, we did not perform a visual assessment. A study by Kiryu et al. (16) based on visual evaluation, showed an overall accuracy of 82.4%, with an accuracy of 93.3% in the small bowel, where the assessment of disease activity is difficult because of poor accessibility. However, segments of the large bowel without active inflammation showed a high-intensity signal by DW-MRI in some patients, and this appeared to decrease the specificity in the evaluation of bowel inflammation. These authors attributed the high-intensity signal to the presence of viscous fluid. In another study by Oto et al. (17), which analyzed 53 segments (34 normal and 19 with inflammation), analysis by DW-MRI detected inflammation in 18/19 (94.7%) segments with inflammation and in 28/34 (82.4%) normal segments.

According to Oto et al. (17), quantitative assessment disease activity using the ADC is also feasible with the DW-MRI technique. In bowel segments with active disease, the ADC value is lower than in segments with inactive disease. On quantitative analysis, these authors found statistically significant differences between the ADC values of inflamed and normal bowel segments

of patients with Crohn's disease (0.47–2.60×10^{-3} mm^2/s and 1.39–4.03×10^{-3} mm^2/s for inflamed and normal, respectively; $P < 0.05$). A quantitative study by Kiryu et al. (16) also found that the ADC values for the small and large bowel in patients with active disease were lower than those in patients with inactive disease (1.61±0.44×10^{-3} mm^2/s vs. 2.56±0.51×10^{-3} mm^2/s for the small bowel and 1.52±0.43 ± 10^{-3} mm^2/s vs. 2.31±0.59 ± 10^{-3} mm^2/s for the large bowel, respectively; $P < 0.001$). Similarly, we found that increased disease activity correlates with decreased ADC values. It may be speculated that the possible causes of the restricted diffusion we observed in our patients may be related to inflammation, fibrosis and increased cell volume of the intestinal wall. Quantitative analysis may be useful in monitoring the status of a disease and the effects of therapy. However, the usefulness of the ADC for long-term follow-up of patients with ulcerative colitis warrants further investigation (16).

In patients with suspected or known IBD, the clinically important issues are diagnosis of the disease, determination of the extent and severity of the disease, discrimination between active inflammation and fibrosis, and monitoring the patient's response to treatment. DW-MRI of the bowel may provide information that is relevant to addressing these clinically important issues. The ability to use quantitative parameters such as ADC values to evaluate IBD can allow a more objective evaluation of the disease. Studies in which a larger number of patients are examined are needed in order to better understand the importance of DW-MRI in the evaluation of patients with IBD (1).

Our study has several limitations. First, the number of patients in our study was relatively low. Second, we attempted to magnify the images of the bowel as accurately as possible and to use an oval ROI to exclusively examine the bowel wall; however, we cannot completely exclude the possibility of a partial volume effect, especially from the normal bowel wall, on the ADC measurements. Third, we used free-breathing DW-MRI to evaluate the patients; however, breath-holding DW-MRI may provide better image quality.

It is important to note that the DW-MRI technique is completely non-invasive, does not require ionizing radiation or injection of contrast material, and does not cause discomfort to the patients. DW-MRI can be easily added to an MR examination protocol because it requires only a very short prolongation of the examination time. Thus, DW-MRI represents a useful evaluation technique to add to conventional evaluation protocols (12).

In conclusion, the ADC values of the distal colon wall and the PCLNs obtained using DW-MRI increased in ulcerative colitis patients on remission and decreased in patients with active distal colitis. Thus, DW-MRI is useful in evaluating disease activity in the rectum. However, the ADC values of the PCLNs may not be helpful in evaluating disease activity.

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