Jejunal Inflammation in Crohn's Disease: Comparison Between Diffusion Weighted Magnetic Resonance Imaging and Video Capsule Endoscopy

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ABSTRACT **Background:** Jejunal disease is associated with worse prognosis in Crohn's disease. The added value of diffusion weighted imaging for evaluating jejunal inflammation related to Crohn's Disease is scarce.

Objectives: To compare diffusion weighted imaging, video capsule endoscopy, and inflammatory biomarkers in the assessment of Crohn's disease involving the jejunum.

Methods: Crohn's disease patients in clinical remission were prospectively recruited and underwent magnetic resonance (MR)-enterography and video capsule endoscopy. C-reactive protein and fecal-calprotectin levels were obtained. MR-enterography images were evaluated for restricted diffusion, and apparent diffusion coefficient values were measured. The video capsule endoscopy-based Lewis score was calculated. Associations between diffusion weighted imaging, apparent diffusion coefficient, Lewis score, and inflammatory biomarkers were evaluated.

Results: The study included 51 patients, and 27/51 (52.9%) with video capsule endoscopies showed jejunal mucosal inflammation. Sensitivity and specificity of restricted diffusion for video capsule endoscopy mucosal inflammation were 59.3% and 37.5% for the first reader, and 66.7% and 37.5% for the second reader, respectively. Diffusion weighted imaging was not statistically associated with jejunal video capsule endoscopy inflammation ($P = 0.813$).

Conclusions: Diffusion weighted imaging was not an effective test for evaluation of jejunal inflammation as seen by video capsule endoscopy in patients with quiescent Crohn's disease.

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Crohn's disease (CD) patients with jejunal involvement have a more stricturing disease. They also display higher rates of multiple abdominal surgeries compared to isolated distal CD [1]. Jejunal lesions are more fibrotic and thus exhibit reduced responsiveness to medical treatment and higher relapse rates [2].

MR-enterography (MRE) plays a role in the evaluation of CD patients [3]. Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) sequence based on differences of extracellular water molecule mobility in tissues [4]. It is a promising technique that has been shown to be beneficial for the detection and characterization of lesions in CD [5]. Until now, DWI studies have focused mainly on the distal ileum [6-8]. Detection of proximal inflammation on MRE is challenging, mainly due to inadequate delineation of mucosal ulceration. In addition, it is difficult to obtain adequate distention of the proximal small bowel [9].

Endoscopy is considered the gold standard for assessing intestinal mucosal inflammation [10]. While the jejunum is less accessible via conventional endoscopy, video capsule endoscopy (VCE) facilitates evaluation of the entire gastrointestinal tract [11-13]. Another important tool to evaluate CD is Inflammatory biomarkers, including C-reactive protein (CRP) and fecal calprotectin (FCP) [14].

The purpose of this study was to compare DWI, video capsule endoscopy (VCE), and inflammatory biomarkers in the assessment of CD involving the jejunum.

PATIENTS AND METHODS

STUDY DESIGN

We conducted a retrospective analysis of prospectively collected data. We evaluated quiescent CD patients using MRE, VCE, and tests for the inflammatory biomarkers CRP and FCP [15-18]. Our institutional review board approved the study. All patients signed an informed consent prior to enrollment.

Inclusion criteria were age older than 18 years, quiescent small bowel CD defined as CD activity index < 220, at least a 3-month period of steroid-free remission, and a stable medication dose. A stable dose was defined as 60 days of infliximab, a combination of thiopurines and methotrexate, 30 days of adalimumab, or 5-aminosalicylic acid (5-ASA) agents. All patients underwent patency capsule examination. Only patients who emitted the capsule intact within 30 hours were included in the study.

Exclusion criteria were unbalanced co-morbidities (e.g., kidney or liver failure, metabolic disorders, cardiorespiratory disorders, history of swallowing disorders, dysphagia, and high risk for aspiration), patients with suspected or observed severe strictures or obstruction of the intestine, and contraindications for MRI (e.g., pacemaker, metallic implant, claustrophobia).

Data collected on each patient included age, sex, disease duration, age at CD onset, and current treatment. At enrollment, all patients underwent blood (CRP) and stool (FCP) workup, VCE, and MRE. MRE and VCE examinations were completed within a maximum interval of 2 weeks in all patients.

MRE PROTOCOL

All MRE examinations were conducted on a 1.5T GE Optima MR 450w scanner with GEM Suite (GE Healthcare, Milwaukee, WI, USA). Oral contrast (360 ml osmitrol 20% diluted in water to create a solution of 1.5 L) was administered one hour prior to the examination. This protocol allowed small bowel distension. Patients were requested to drink four doses of 375 ml at 15-minute intervals before the MRE examination. A 150 ml of saline infusion with 0.5 mg of glucagon in slow drip was administered 15 minutes prior to the examination. All MRE scans were performed using standard T2- and T1-weighted images, as previously described [15].

All patients underwent coronal, axial and sagittal LAVA 3D gradient echoT1 examinations. They were taken before and 70 seconds after intravenous injection of gadolinium (0.5 mmol/ml by 0.2 ml/kg).

VIDEO CAPSULE ENDOSCOPY ANALYSIS

All patients underwent a patency capsule examination. Patients who emitted the patency capsule intact within 30 hours were included in the study and during the study they were given the VCE-SB-III capsule (Given Imaging, Yokneam, Israel). For 24 hours before the examination, patient intake was limited to clear fluids. In addition, they were requested to fast for 12 hours before undergoing the VCE. The VCE-based Lewis score [19,20] was used to quantify inflammation along the small bowel. Mucosal inflammation was evaluated. Lewis score < 135 was defined as mucosal healing, Lewis score of 135–790 was considered as mild to moderate inflammation, and a Lewis score ≥ 790 as moderate to severe inflammation.

DATA ANALYSIS

Two radiologists: MA with 11 years of experience and EK with 3 years of experience, separately evaluated MRE examinations of the jejunum. They evaluated DWI and apparent diffusion coefficient (ADC) maps. Images that acquired using more conventional sequences were not evaluated to avoid any influence on the interpretation. Both radiologists were blinded to the VCE results and the clinical symptoms of the patients.

Two parameters were used to evaluate MRE examinations: qualitative assessments (absence/presence) of restricted diffusion in the DWI sequence and quantitative assessment of ADC. A b value of 800 s/mm^2 was chosen for evaluation of the signal intensity on DWI sequence. This value showed highest specificity and sensitivity rate for detection of small bowel inflammation in previous studies [21]. The jejunum was examined for high DWI signal, which represented restricted diffusion. The signal was rated using a scale of 0–1 where 0 = low signal, no restriction and 1 = high signal, restricted diffusion.

ADC maps were constructed for each MRE-DWI examination. Three regions of interest (ROI) were placed on the jejunum wall in an area with the highest DWI signal. Each region had an area of 12–20 mm^2. The average intensity of the three ROIs was calculated to determine the ADC value.

STATISTICAL ANALYSIS

All reported *P*-values were 2-sided, and a *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA). Inter-rater agreement between the two study readers was calculated using Cohen's kappa coefficient for qualitative measurements and the intraclass-correlation (ICC) for quantitative measurements. Cohen's kappa coefficient was considered as slight agreement for kappa < 0.21, fair for kappa = 0.21–0.40, moderate for kappa = 0.41–0.60, substantial for kappa = 0.61–0.80, and almost perfect for kappa = 0.81–1.00. An ICC value of < 0.40 was considered as poor correlation, ICC = 0.40–0.75 was considered as fair to good, and ICC > 0.75 was considered as excellent reproducibility [22,23].

The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of restricted diffusion for endoscopic inflammation (defined as Lewis Score ≥ 135) were calculated. The association between restricted diffusion and endoscopic inflammation was assessed using the chi-square test.

The Pearson correlation coefficient was used to measure the correlation between ADC values and the Lewis score. In addition, receiver operating characteristic (ROC) curves were constructed to assess the accuracy of ADC to predict any mucosal inflammation (Lewis score ≥ 135) and moderate to severe inflammation (Lewis score > 790). Area under the curve (AUC) measures were calculated for the ROCs.

Correlations between ADC measurements and biomarkers (CRP and FCP) were evaluated with the Pearson correlation coefficient.

RESULTS

PATIENT POPULATION

Overall, 67 patients were recruited. Twelve patients were excluded from the study due to patency capsule retention. Four patients were excluded due to multiple artifacts in the ADC map. A total of 51 patients were included in the final analysis. Demographic data of the study population is presented in Table 1.

DIFFUSION WEIGHTED IMAGING (DWI) EVALUATION

Inter-observer agreement for the qualitative readings was substantial (kappa = 0.67, $P < 0.001$).

The first reader determined that 31/51 (60.7%) examinations showed evidence of restricted diffusion in the jejunum; however, only 16 of 31 (51.6%) examinations were confirmed by VCE to have inflammation. The second reader found that 33/51 (64.7%) examinations were consistent with restricted diffusion in the jejunum; 18 of 33 (54.5%) examinations were confirmed by VCE to have inflammation.

Figure 1 displays DWI images that did not coordinate with the VCE results [Figure 1 A to Figure E]. It also shows one example of a concordance between DWI image with restricted diffusion signal and VCE [Figure 1 F].

The sensitivity (59.26% and 66.67%), specificity (37.5% for both readers), PPV (51.61% and 54.55%), and NPV (45% and 50%) of restricted diffusion for VCE inflammation (Lewis score > 135), and the association between restricted diffusion and VCE inflammation are presented in Table 2.

APPARENT DIFFUSION COEFFICIENT (ADC) EVALUATION

Inter-observer agreement for the quantitative readings was fair to good (ICC = 0.723, $P < 0.001$).

The average ADC measurement for patients with restricted diffusion was $2144.3 \times 10^6 mm^2/s$. The average ADC measurements for those with normal diffusion signal was $3140.5 \times 10^6 mm^2/s$.

Table 1. Demographic data of the study population (N=51)

Characteristic	Value
Male, n (%)	27 (53%)
Female, n (%)	24 (47%)
Age, year ± SD	32.2 ± 11.35
Disease duration, year ± SD	6.02 ± 4.87
Age at onset, year ± SD	26.17 ± 11.16

SD = standard deviation

Table 2. Statistical analysis of the association of diffusion weighted imaging with the video capsule endoscopy Lewis score

	Reader 1	Reader 2
Sensitivity (%)	59.26	66.67
Specificity (%)	37.50	37.50
Positive predictive value (%)	51.61	54.55
Negative predictive value (%)	45.00	50.00
Chi-square (*P*-value)	0.831	0.986

ADC failed to predict active (Lewis score ≥ 135) or severe (Lewis score > 790) VCE mucosal inflammation [Figure 2A]. ADC's AUC for predicting active inflammation was 0.544. ADC's AUC for predicting severe inflammation was 0.382 [Figure 2B].

ADC did not correlate with either CRP (r = 0.088, $P = 0.570$) or FCP (r = 0.196, $P = 0.197$).

Figure 1. Diffusion weighted imaging of different cases taken from the cohort, all of them with quiescent Crohn's disease

VCE = video capsule endoscopy

[A] Restriction seen in the proximal jejunum with no VCE disease **[B]** Restriction seen in the distal jejunum with no VCE disease **[C]** Marked restriction with no VCE disease **[D]** No restriction seen in the mid jejunum with VCE disease **[E]** Poor restriction with VCE disease **[F]** Restriction seen in the proximal jejunum with VCE disease

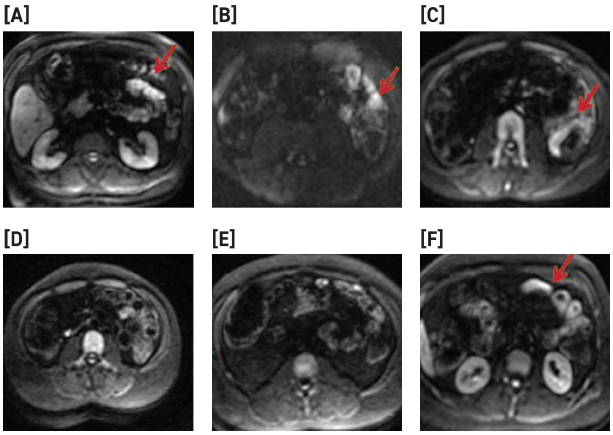
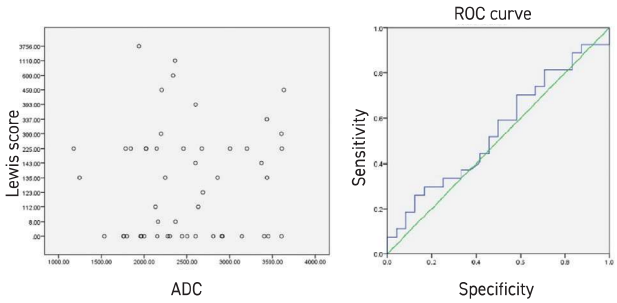


Figure 2. Apparent diffusion coefficient evaluation

ADC = apparent diffusion coefficient, AUC = area under the curve, ROC = receiver operating characteristic

[A] Scatter plot showing no correlation (r = -0.091) between the ADC and the Lewis score

[B] ROC curve presenting the inability of ADC to predict mucosal inflammation (Lewis score > 135) with an AUC of 0.544



DISCUSSION

Several studies have previously reported on the role of DWI for detection of inflammation and management of CD patients. Most of these studies were limited to the distal ileum and colonic segments [5,6,9] and only a few studies included jejunal segments [8,17].

In an earlier study [15], our team examined the role of DWI in quiescent disease. We compared findings on DWI with VCE inflammation in the distal ileum. We also compared it with the levels of inflammatory biomarkers. We found that the combination of high signal intensity on DWI and elevated FCP correlated to VCE mucosal inflammation.

Our current study demonstrates low sensitivity (59–67%) and lower specificity (38%) of restricted diffusion to the presence of VCE jejunal inflammation.

Unlike the distal ileum study, there was no correlation between ADC values and the Lewis score.

A previous study that included proximal bowel segments demonstrated different findings. There was a good correlation between findings at DWI and balloon enteroscopy [21]. That study included only 5 jejunal segments from a total of 100 evaluated bowel segments. In addition, statistical analyses were performed for both jejunal and ileal segments combined.

Two additional studies showed a good correlation between restricted diffusion on DWI and small bowel inflammation; however, they did not use endoscopy as a gold standard. One study compared the findings in DWI to qualitative MRI assessment [16] and the other to quantitative MRE MaRIA score [18].

Our research focused exclusively on the jejunum and included a larger number of segments.

The high signal in DWI in the inflammatory process is due to the hypercellularity caused by the presence of inflammatory cells, which leads to a decrease in the extracellular matrix. This result, in turn, leads to a decrease in the water molecule movement and restricted diffusion [24]. The jejunum has more circular folds compared to the ileum [25]. We think that these folds increase jejunal cellularity compared to the ileum. This finding could explain the false positive DWI signal in the jejunum.

In addition, achieving satisfactory distention of the jejunum in MRE is challenging and jejunal loops are often collapsed. These collapsed segments demonstrate a stronger diffusion signal. This result may be another possible explanation for the false positive DWI signal. Our hypothesis is supported by Seong's statement that false-positive results on DWI enterography tend to occur in bowel loops with inadequate fluid distention, particularly in the colorectum and jejunum [3].

Our study has several limitations. The VCE findings were compared to MRE despite the difficulty in correlating the exact anatomical location on the video capsule images and MRE. In the current VCE software, small bowel segments are defined by the transition time from pylorus to cecum. However, the transit speed is not constant. The capsule can be propelled forward in certain segments and be stalled in others. On MRE, the segments are established by their quadrant location. Another limitation is the relatively small group size, despite it being the largest series to be reported so far. All our patients were in clinical remission, although most of them had detectable endoscopic inflammation. It is possible that in clinically active patients the correlation would be clearer.

CONCLUSIONS

DWI was not an effective test for the evaluation of jejunal inflammation as seen in VCE in patients with quiescent CD.

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Capsule

Spatial dysregulation of T follicular helper cells impairs vaccine responses in aging

The magnitude and quality of the germinal center (GC) response decline with age, resulting in poor vaccine-induced immunity in older individuals. A functional GC requires the co-ordination of multiple cell types across time and space, specifically across its two functionally distinct compartments: the light and dark zones. In aged mice, there is CXCR4-mediated mislocalization of T follicular helper (TFH) cells to the dark zone and a compressed network of follicular dendritic cells (FDCs) in the light zone. **Silva-Cayetano** and colleagues showed that T_{FH} cell localization is critical for the quality of the antibody response and for the expansion of the FDC network upon immunization. The smaller GC and compressed FDC network in aged mice were corrected by provision of T_{FH} cells that colocalize with FDCs using CXCR5. This finding demonstrates that the age-dependent defects in the GC response are reversible and shows that T_{FH} cells support stromal cell responses to vaccines.

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Capsule

PLSCR1 is a cell-autonomous defense factor against SARS-CoV-2 infection

Understanding protective immunity to COVID-19 facilitates preparedness for future pandemics and combats new SARS-CoV-2 variants emerging in the human population. Neutralizing antibodies have been widely studied; however, based on large-scale exome sequencing of protected versus severely ill patients with COVID-19, local cell-autonomous defense is also crucial. **Xu** et al. identified phospholipid scramblase 1 (PLSCR1) as a potent cell-autonomous restriction factor against live SARS-CoV-2 infection in parallel genome-wide CRISPR-Cas9 screens of human lung epithelia and hepatocytes before and after stimulation with interferon-γ (IFNγ). IFNγ-induced PLSCR1 not only restricted SARS-CoV-2 USA-WA1/2020 but was also effective against the Delta B.1.617.2 and Omicron BA.1 lineages. Its robust activity extended to other highly pathogenic coronaviruses, was functionally conserved in bats and mice, and interfered with the uptake of SARS-CoV-2 in both the endocytic and the TMPRSS2-dependent fusion routes. Whole-cell 4Pi single-molecule switching nanoscopy together with bipartite nano-reporter assays found that PLSCR1 directly targeted SARS-CoV-2-containing vesicles to prevent spike-mediated fusion and viral escape. A PLSCR1 C-terminal β-barrel domain, but not lipid scramblase activity, was essential for this fusogenic blockade. These mechanistic studies, together with reports that COVID-associated *PLSCR1* mutations are found in some susceptible people, identify an anti-coronavirus protein that interferes at a late entry step before viral RNA is released into the host-cell cytosol.

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