Conclusion The occurrence of IF and IF-related death in CD patients is not rare over the long term. There is a pressing need to develop strategies for the prevention and management of IF.

Keywords Crohn's disease · Intestinal failure · Short bowel syndrome · Home parenteral nutrition · Surgery

Introduction

Crohn's disease (CD) is a chronic inflammatory gastrointestinal disorder with a high recurrence rate. It is estimated that up to 80 % of patients with CD will require at least one intestinal surgery during their course [1–4]. The rates of recurrence requiring re-operation from the first surgery are reported to range from 16 to 36 % at 5 years and from 28 to 55 % at 10 years [3–6]. Although medical and surgical management aims to prevent recurrence and minimize the extent of resection [7], CD patients often require multiple surgeries, which increases the risk for intestinal failure (IF).

The term IF was originally defined by Fleming and Remington as a reduction in functioning gut mass below the minimum necessary for adequate digestion and absorption of nutrients [8]. Initially, this definition was often used to describe patients who require home parenteral nutrition (HPN) to survive, without taking into account the patients who simply require fluid [9]. Recently, the definition has been broadened, and an international consensus group proposed that IF be characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance, which results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption [10].

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Among patients with CD who receive long-term treatment, IF is one of the most serious complications. However, there have been few reports concerning the occurrence rate and characteristics of IF in CD patients. The aim of the present study was to clarify the risk and characteristics of IF in CD patients after intestinal surgery.

Methods

Participating hospitals

This retrospective study was performed at the following 12 Japanese hospitals, which were participants in the study group of inflammatory bowel disease, sponsored by the Japanese Ministry of Health, Labour and Welfare: Tohoku University Hospital, Fukuoka University Chikushi Hospital, Hyogo Medical University Hospital, Yokohama Municipal Citizen's Hospital, Osaka Rosai Hospital, Osaka University Hospital, Tokyo Women's Medical University Hospital, Mie University Hospital, Kansai Medical University Hirakata Hospital, Tohoku Rosai Hospital, Teikyo University Hospital, and Nara Medical University Hospital.

Definition of IF

The definition of IF in the present study was based on the proposed definition by the international consensus group [10]. CD patients who required intravenous infusion therapy at least twice per week for a period of more than 1 year because of inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance, which resulted from surgical resection, were defined as having IF in the present study. Patients who received intravenous infusion therapy for bowel inflammation, bowel stenosis, fistula, abscess, and/or anal disease were excluded. In terms of the type of infusion fluid, both high-calorie fluid and crystalloid fluid were included in the study.

Patients and methods

A retrospective review of medical records from the 12 hospitals was conducted. CD patients who underwent initial intestinal surgery (bowel resection, strictureplasty, and/or stoma construction) at any of the 12 hospitals between January 1970 and December 2009 were collected ($n = 1{,}703$). Of the 1,703 patients, patients who developed IF by December 2010 were reviewed ($n = 68$), and the cumulative risk for developing IF after initial intestinal surgery was evaluated. In addition, CD patients with IF who underwent initial intestinal surgery at other hospitals and were then treated at any of the 12 hospitals were also reviewed ($n = 41$). Of the 41 patients, eight were excluded

Table 1 Number of CD/IF patients who underwent initial intestinal surgery at the 12 participating hospitals by decade

	Time of initial intestinal surgery				
	1970–1979	1980–1989	1990–1999	2000–2009	Total
CD patients	37	139	511	1,016	1,703
CD patients with IF	2 (5.4 %)	12 (8.6 %)	33 (6.5 %)	21 (2.1 %)	68 (4.0 %)

CD Crohn's disease, *IF* intestinal failure

from the present study because of insufficient clinical data. Hence, a total of 101 CD patients with IF were collected, and their characteristics were reviewed. The cumulative risk for IF-related death by the time from the occurrence of IF was evaluated.

The following clinical data were collected in patients with IF: age at diagnosis of CD, age at initial intestinal surgery, age at the occurrence of IF, age at the time of the study, number of surgeries to the occurrence of IF, bowel disease location, length of remnant small intestine at the occurrence of IF (which was evaluated by the findings at the surgery), medical therapies, and complications after the occurrence of IF.

Statistical analysis

The cumulative risks of IF after initial intestinal surgery and IF-related death by the time from the occurrence of IF were evaluated using the Kaplan–Meier method. CD patients without IF were regarded as censored cases. Quantitative and qualitative variables were compared using the Mann–Whitney U test. Values of $P < 0.05$ were considered significant. All statistical analyses were performed using SPSS® version 13.0J software (SPSS Japan, Tokyo, Japan).

Results

Cumulative risk of IF

A total of 1,703 CD patients underwent initial intestinal surgery at any of the 12 hospitals between 1970 and 2009 (Table 1). Of the 1,703 patients, 68 (4.0 %) developed IF. The cumulative risk for developing IF after the initial intestinal surgery was 0.8 % (5 years), 3.6 % (10 years), 6.1 % (15 years), and 8.5 % (20 years) (Fig. 1a).

In consideration of the historical bias, the cumulative risk of IF was also evaluated excluding 176 patients who underwent initial surgery between 1970 and 1989. A total of 1,527 CD patients underwent initial intestinal surgery at any of the 12 hospitals between 1990 and 2009. Of the 1,527 patients, 54 (3.5 %) developed IF. The cumulative risk of IF after the initial intestinal surgery was 0.6 % (5 years), 2.8 % (10 years), and 4.9 % (15 years) (Fig. 1b).

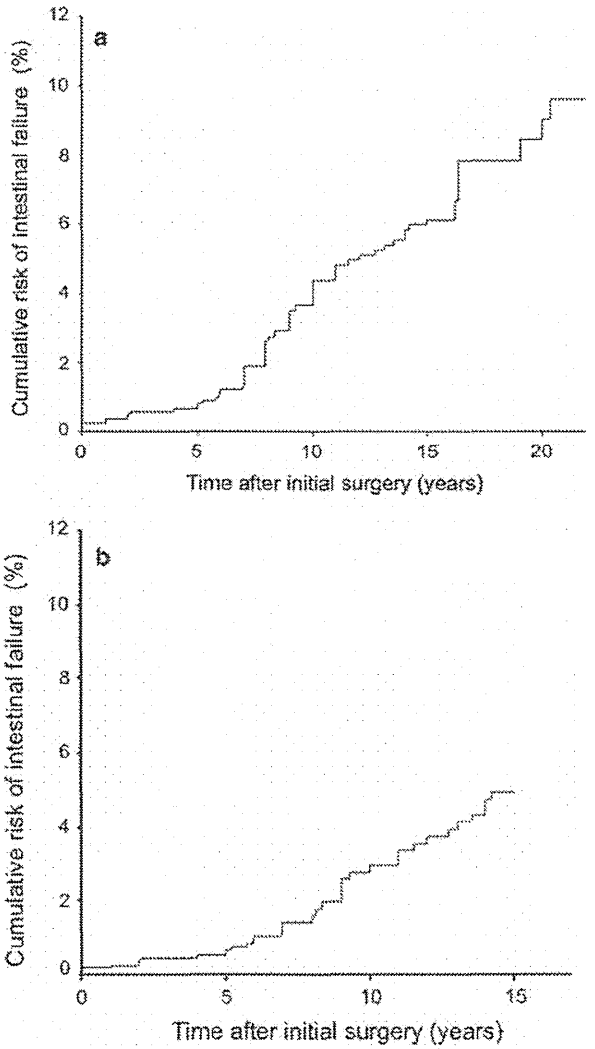

Fig. 1 Kaplan–Meier curve for the cumulative risk of intestinal failure in CD patients who underwent initial surgery between 1970 and 2009 ($n = 1,703$) (**a**) and between 1990 and 2009 ($n = 1,527$) (**b**)

Characteristics of CD patients with IF

The characteristics of the 101 CD patients with IF are shown in Table 2. The mean duration between CD diagnosis and the initial intestinal surgery was 6.4 years, and the mean duration between the initial surgery and the

Table 2 The characteristics of CD patients with IF ($n = 101$)

Age at (years)	
Diagnosis of CD	21.8 ± 8.8
Initial intestinal surgery	28.2 ± 9.3
Occurrence of IF	38.2 ± 10.7
Present (or age at death)	46.1 ± 11.4
No. of intestinal surgeries (times)	3.3 ± 1.7
Length of the small bowel (cm)	162 ± 64
Stoma	
Present (jejuno- or ileostomy/colostomy)	65 cases (64 %) (45/40)
Absent	36 (36 %)
Ileocecal valve	
Preserved	15 (15 %)
Resected	86 (85 %)

Mean ± SD

CD Crohn's disease, *IF* intestinal failure

Table 3 The characteristics of CD patients with IF who underwent initial surgery between 1990 and 2009 ($n = 63$)

Age at (years)	
Diagnosis of CD	21.1 ± 7.9
Initial intestinal surgery	29.1 ± 7.9
Occurrence of IF	35.8 ± 8.9
Present (or age at death)	42.0 ± 9.1
No. of intestinal surgeries (times)	3.1 ± 1.8
Length of the small bowel (cm)	176 ± 65
Stoma	
Present (jejuno- or ileostomy/colostomy)	46 cases (73 %) (36/10)
Absent	17 (27 %)
Ileocecal valve	
Preserved	8 (13 %)
Resected	55 (87 %)

Mean ± SD

CD Crohn's disease, *IF* intestinal failure

occurrence of IF was 10.0 years. The mean number of intestinal surgeries to the occurrence of IF was 3.3, and the mean length of remnant small intestine at the time of IF was 162 cm. The mean duration of follow-up after the occurrence of IF was 7.9 years. Sixty-five patients (64 %) had a stoma (jejuno- or ileostomy, $n = 45$; colostomy, $n = 20$), and 86 patients (86 %) had a resected ileocecal valve at the time of IF occurrence.

The characteristics of the 63 CD patients with IF who underwent initial surgery between 1990 and 2009 are shown in Table 3. Comparing the 38 CD patients with IF who underwent initial surgery before 1990, the mean length of remnant small intestine was significantly longer (176 vs. 138 cm, $P = 0.002$) and more patients had a stoma (73 vs. 50 %, $P = 0.022$).

Table 4 Medical treatments for CD patients with IF ($n = 101$)

	Before IF	After IF
HPN alone	–	4 cases (4 %)
5-ASA or sulphasalazine	76 cases (75 %)	74 (73 %)
Enteral nutrition	68 (67 %)	62 (61 %)
Steroid	48 (48 %)	28 (28 %)
Antimicrobial agent	29 (29 %)	31 (31 %)
Anti-TNF therapy	11 (11 %)	30 (30 %)
Immune-regulating agent	9 (9 %)	21 (21 %)
Cytapheresis	1 (1 %)	2 (2 %)
Intestinal surgery	101 cases	20 (20 %)
Unknown	11 cases	2 cases

CD Crohn's disease, *IF* intestinal failure, *HPN* home parenteral nutrition, *5-ASA* 5-aminosalicylic acid

Table 5 Medical treatments for CD patients with IF who underwent initial surgery between 1990 and 2009 ($n = 63$)

	Before IF	After IF
HPN alone	–	2 cases (3 %)
5-ASA or sulphasalazine	51 cases (81 %)	51 (81 %)
Enteral nutrition	44 (70 %)	41 (65 %)
Steroid	33 (52 %)	22 (35 %)
Antimicrobial agent	20 (32 %)	23 (37 %)
Anti-TNF therapy	7 (11 %)	21 (33 %)
Immune-regulating agent	5 (8 %)	12 (19 %)
Cytapheresis	1 (2 %)	1 (2 %)
Intestinal surgery	63 cases	13 (21 %)
Unknown	5 cases	1 cases

CD Crohn's disease, *IF* intestinal failure, *HPN* home parenteral nutrition, *5-ASA* 5-aminosalicylic acid

Medical treatments

The medical treatments for the CD patients with IF are shown in Table 4. Enteral nutrition was used in 68 patients (67 %) before the occurrence of IF and 62 patients (61 %) after the occurrence of IF. Twenty patients (20 %) underwent intestinal surgery during the mean 7.9 years of follow-up after the occurrence of IF. No patient underwent small bowel transplantation. The medical treatments for the CD patients with IF who underwent initial surgery between 1990 and 2009 are shown in Table 5. There were no significant differences in terms of medical treatment comparing the CD patients with IF who underwent initial surgery before 1990.

The intravenous infusion therapy given to the CD patients with IF is shown in Table 6. Excluding cases who died ($n = 12$) and weaned-off cases ($n = 16$), 73 IF

Table 6 Intravenous infusion therapy for CD patients with IF ($n = 73$)

Frequency of infusion (per week)	
7 times	58 cases (78 %)
4–6 times	4 (5 %)
3.5 times	7 (10 %)
2–3 times	4 (5 %)
Volume of infusion (per one time, mL)	
<1000	6 (8 %)
1000–2000	37 (51 %)
2000–3000	24 (33 %)
≥3000	6 (8 %)
Type of infusion	
High-calorie infusion	70 (96 %)
Crystalloid infusion	3 (4 %)

Excluding cases who died ($n = 12$) and weaned-off cases ($n = 16$), 73 IF patients were reviewed

patients were reviewed. Sixty-nine patients (95 %) used intravenous infusion therapy at least every second day, and 58 patients (79 %) used intravenous infusion every day. The median volume of infusion per time was 1500 mL. Seventy patients (96 %) used high-calorie infusion. The median number of calories by infusion was 1160 kcal/day.

Complications

Complications after the occurrence of IF are shown in Table 7. Seventy-nine patients (78 %) had at least one complication during the mean 7.9 years of follow-up after the occurrence of IF. Central venous catheter-related bloodstream infection (CRBSI) was the most frequent complication ($n = 58$, 57 %). Of the 58 patients, four died due to CRBSIs (Table 8). The frequency of CRBSI in CRBSI-related death cases ($n = 4$) was 2.4 times per 1000 days (mean), which was not significantly different from the other CRBSI cases ($n = 54$; 1.8 times per 1000 days) ($P = 0.636$). Liver dysfunction was the second most frequent complication ($n = 32$, 32 %).

Outcomes

The outcomes of CD patients with IF are shown in Table 8. Twelve patients (12 %) had died at 7.0 ± 4.0 years (mean ± SD) of follow-up after the occurrence of IF. The durations from the occurrence of IF to death were 4.5 ± 2.4 years (CRBSI), 7.4 ± 5.2 years (anorectal cancer), and 10.9 ± 4.5 years (liver cirrhosis). The ages at death were 37.5 ± 8.5 years (CRBSI), 59.4 ± 14.7 years (anorectal cancer), and 59.7 ± 14.6 years (liver cirrhosis). The cumulative risk of IF-related death (CRBSI or liver cirrhosis; $n = 6$) by the time from the occurrence of IF was

Table 7 Complications after the occurrence of IF ($n = 101$)

Complications			
Yes	79 cases (78 %)		
No	16 (16 %)		
Unknown	6 (6 %)		
CV catheter-related complication		Metabolic complication	
CRBSI	58 cases (57 %)	Liver dysfunction	32 cases (32 %)
Catheter obstruction	16 (16 %)	Mineral deficiency/excess	14 (14 %)
Loss of venous access	7 (7 %)	Vitamin B12 deficiency	12 (12 %)
Skin trouble at CV port	6 (6 %)	Renal dysfunction	12 (12 %)
CV port broken	4 (4 %)	Dehydration	11 (11 %)
Subcutaneous infection	3 (3 %)	Gall bladder stone	6 (6 %)
Infection		Renal stone	5 (5 %)
Infective endocarditis	2 (2 %)	Hyperuricemia	2 (2 %)
Fungal endophthalmitis	1 (1 %)	Electrolyte abnormality	2 (2 %)
Cerebral meningitis	1 (1 %)	Amyloidosis	1 (1 %)
Brain abscess	1 (1 %)	Growth disorder	1 (1 %)
Splenic abscess	1 (1 %)	Osteoporosis	1 (1 %)
Others		Renal anemia	1 (1 %)
Skin trouble	4 (4 %)		
Thrombosis	3 (3 %)		
GI hemorrhage	3 (3 %)		
Depression	2 (2 %)		

IF intestinal failure, *CV* central venous, *CRBSI* catheter-related bloodstream infection, *GI* gastrointestinal

1.1 % (3 years), 3.7 % (5 years), 6.5 % (7 years), and 8.9 % (10 years) (Fig. 2). Sixteen patients (16 %) were weaned from IF status after 4.1 ± 2.1 years from the occurrence of IF.

Discussion

The present study showed that the cumulative risk of IF in CD patients, who underwent initial intestinal surgery between 1970 and 2009, was less than 1 % at 5 years after the initial surgery, but the risk increased over 5 % at 15 years after the initial surgery. Because medical treatments and surgical techniques have changed, the authors also evaluated the risk of IF excluding patients who underwent initial surgery between 1970 and 1989 to avoid the historical bias. The cumulative risk of IF was still nearly 5 % at 15 years after the initial surgery. To the best of our

Table 8 Prognosis of CD patients with IF ($n = 101$)

Deaths	12 cases (12 %)
CRBSI	4 (4 %)
Anorectal cancer	4 (4 %)
Liver cirrhosis	2 (2 %)
Suicide	1 (1 %)
Intestinal perforation	1 (1 %)
Weaned off cases	16 (16 %)

CD Crohn's disease, *IF* intestinal failure, *CRBSI* catheter-related bloodstream infection

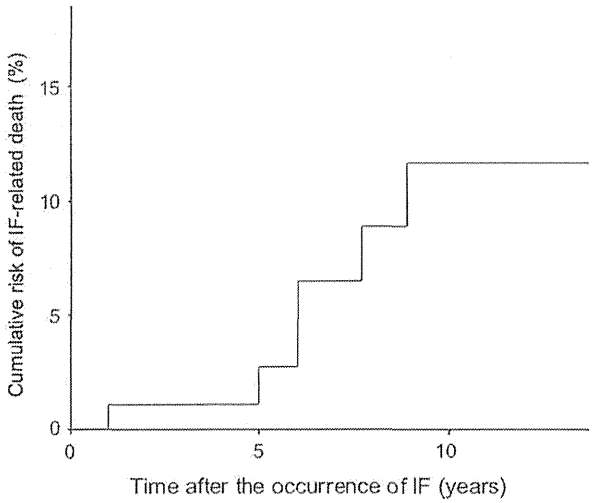

Fig. 2 Kaplan–Meier curve for the cumulative risk of IF-related death in CD patients with IF ($n = 101$)

knowledge, the present study is the first to estimate the cumulative risk for developing IF in patients with CD using the Kaplan–Meier method. To date, there has been a very limited number of studies concerning the incidence of IF in patients with CD. Most of these studies were population-based studies or small-sized studies, and they only assessed the incidence of IF at one time point [11–15]. Hurst et al. [13] reported that four (0.8 %) of 513 CD patients who underwent surgery between 1985 and 1996 developed IF, which was a short-term result, because the study was published in 1997. Dietz et al. [14] reported that 23 (10 %) of 219 CD patients developed IF at a median follow-up of 7.8 years after the initial operation. Yamamoto et al. [15] reported that two (4.5 %) of 44 CD patients developed IF at a median follow-up of 15 years after the initial operation. These studies support the present results; the occurrence of IF in CD patients is rare in the short-term period after initial surgery, though it is not rare over the long term.

In the present study, the term "intestinal failure (IF)" was used instead of the term "short bowel syndrome (SBS)" because the term "SBS" seems to indicate that the degree of malabsorption only depends on the length of the residual bowel itself [16]. However, both intestinal length and intestinal function affect the severity of malabsorption [17]. The term "IF" is a more general expression and refers directly to the intestinal function itself [16]. In CD patients, the intestinal absorptive function may be affected by the disease activity, as well as the bowel length; therefore, the present study used the term "IF" from the clinical standpoint. From the standpoint of intestinal length, in the present study, the mean length of remnant small intestine was 162 cm. The American Gastroenterological Association Clinical Practice Committee stated that SBS can occur when there is less than 200 cm of small bowel [10]. Hurst et al. [13] noted that 5 % of patients with CD were left with intestinal remnants of less than 180 cm after multiple resections, and were at risk for the development of SBS. These findings were consistent with the present study.

The present study showed that death was not rare in CD patients with IF. Several studies have reported that the overall 5-year mortality in HPN-treated patients (including CD and other diseases) ranged from 2 to 28 %, though most of these studies were population-based studies, and the precise mortality of CD patients with IF was still unclear [18–21]. To the best of our knowledge, the present study is the first to have estimated IF-related death in CD patients using the Kaplan–Meier method. The poor prognosis was mainly due to complications of HPN (CRBSI, liver dysfunction) and anorectal cancer. Since CRBSI and liver dysfunction were the most frequent complications in CD patients with IF, it is very important to prevent and/or manage these complications. In terms of CRBSI, previous studies reported that the occurrence rate of CRBSI in HPN patients (including CD and other diseases) ranged from 0.44 to 3 times per 1000 days [22–24]. The Center for Disease Control and Prevention (CDC) guideline recommended the use of a prophylactic antimicrobial lock solution in patients with long-term catheters who have a history of multiple CRBSIs despite optimal maximal adherence to aseptic technique [25]. In terms of liver dysfunction, parenteral nutrition–induced liver disease varies from steatosis due to excessive caloric administration to severe cholestatic injury with irreversible cirrhosis [26]. Optimal methods for preventing or retarding the development of liver dysfunction have not been established, although several have been proposed. A few recent studies indicated that substituting fish oil-based lipid solutions (rich in omega-3 fatty acids) may improve parenteral nutrition-associated cholestasis [27, 28]. Intestinal and/or liver transplantation is an option for some patients for whom other treatments have failed and who have complications from long-term parenteral nutrition. These patients are typically considered for transplantation as a result of the loss of venous access sites, recurrent and

persistent episodes of sepsis, and development of liver failure.

Finally, the limitations of the present study must be considered. Because the present study is a long-term study, there is a bias in terms of medical treatments. Recent studies showed that anti-TNF therapy was effective in maintaining remission in Crohn's disease [29, 30]and reduced the rate of surgery [31]. Another recent study showed that teduglutide, a glucagon-like peptide-2 (GLP-2) analogue, reduced volumes and numbers of days of parenteral support for SBS patients with IF (including CD and other diseases) [32]. There is a possibility that recent medical treatments including anti-TNF therapy and teduglutide reduce the occurrence of IF and/or prompts weaning from IF status in CD patients, though another long-term study is essential to clarify the issue. Similar to medical therapy, factors such as materials (e.g., central venous catheter) and infection countermeasures have changed over time. These factors may improve the managements of the IF patients and may reduce late complications, though further study is also needed to clarify the issue.

In conclusion, the present study showed that the incidence of IF in CD patients was not low over the long-term after initial surgery. CRBSI and liver dysfunction were the most frequent complications, and the poor prognosis was mainly due to these complications. To date, there are few treatments for SBS patients with IF [33]. There is a pressing need to develop strategies for the prevention and management of IF.

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Conflict of interest This work was supported in part by Health and Labour Sciences Research Grants for research on intractable diseases from the Ministry of Health, Labour and Welfare of Japan.

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Comparison of Magnetic Resonance and Balloon Enteroscopic Examination of the Small Intestine in Patients With Crohn's Disease

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See Covering the Cover synopsis on page 257.

BACKGROUND & AIMS: Magnetic resonance (MR) enterography is a recommended imaging technique for detecting intestinal involvement in Crohn's disease (CD). However, the diagnostic accuracy of MR enterography has not been compared directly what that of enteroscopy of the jejunum and proximal ileum. We evaluated the usefulness of MR enterocolonography (MREC) by comparing its findings with those from balloon-assisted enteroscopy. **METHODS:** In a prospective study, MREC and enteroscopy were performed within 3 days of each other on 100 patients. Ulcerative lesions and all mucosal lesions were evaluated. Physicians and radiologists were blinded to results from other studies. Findings from MREC were compared directly with those from enteroscopy; the sensitivity and specificity with which MREC detected CD lesions were assessed. **RESULTS:** MREC detected ulcerative lesions and all mucosal lesions in the small intestine with 82.4% sensitivity (95% confidence interval [CI], 75.4%–87.7%) and 67.5% sensitivity (95% CI, 63.1%–70.0%); specificity values were 87.6% (95% CI, 83.7%–90.6%) and 94.8% (95% CI, 90.1%–97.5%). MREC detected major stenosis with 58.8% sensitivity (95% CI, 37.6%–77.2%) and 90.0% specificity (95% CI, 88.4%–91.5%) and all stenoses with 40.8% sensitivity (95% CI, 30.8%–49.4%) and 93.7% specificity (95% CI, 91.1%–95.9%). **CONCLUSIONS:** MREC is useful for detecting active lesions in the small intestine. However, MR imaging is less sensitive for detecting intestinal damage, such as stenoses. Enteroscopy is preferred for identifying intestinal damage. Suitable imaging approaches should be selected to assess CD lesions in deep small intestine.

Keywords: IBD; Diagnosis; Ulcer; Intestinal Damage.

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that is associated with abdominal symptoms such as diarrhea, abdominal pain, and bloody stools. Management of CD largely depends on the location and severity of inflammation and tissue damage. CD lesions can involve the entire gastrointestinal tract, particularly the small intestine, and the assessment of active lesions is important for CD patients because mucosal healing has been reported to be associated with better long-term prognosis.[1,2] In addition, significant clinical improvement and disappearance of endoscopic lesions have been observed with biologic agents such as infliximab, natalizumab, and adalimumab.[3–6] Conventionally, imaging of CD lesions has relied mainly on ileocolonoscopy (ICS) and small-bowel follow-through (SBFT). ICS is useful for the detection of inflammation in the colon and the distal end of the ileum; however, it is impossible to access the deep small intestine using this procedure. Because small-bowel lesions are present in 4%–65% of CD patients,[7–10] conventional ICS has limitations in detecting CD lesions. SBFT is used to detect the presence of fistulae or mucosal damage in CD. However, the detection of small erosions or aphthae depends on the skill of the examiner. The range of diagnostic and therapeutic investigations for the small intestine in CD patients has widened considerably with recent technical advances such as wireless capsule endoscopy (WCE),[11–13] high-resolution computed tomography (CT),[14] and magnetic resonance (MR) enteroclysis or MR enterography (MRE).[15–18] Sensitivity values for the detection of extra-enteric complications in CD were significantly higher for CT and MRE than for SBFT.[19] In addition, balloon-assisted enteroscopy such as double-balloon endoscopy (DBE)[20,21] and single-balloon endoscopy (SBE)[22] are new techniques. An advantage of enteroscopy is that it enables concise assessment of the mucosa and acquisition of histopathologic specimens. In addition, endoscopic therapeutic procedures such as balloon dilatation of stenoses can be performed. Enteroscopy is expected to become an integral procedure for CD assessment.

The European Crohn's and Colitis Organisation guideline recommends MR or CT enterography or enteroclysis as imaging techniques with the highest diagnostic accuracy for the detection of intestinal involvement in CD, including extramural complications.[23] However, a recent study emphasized the high cumulative radiation dosages imparted to patients with CD.[24] MR imaging overcomes this limitation.[25] MRE is particularly useful in providing tissue-specific information on CD at its various stages, from the acute inflammatory, regenerative, fistulizing, and perforating stages

Abbreviations used in this paper: AMLs, all mucosal lesions; CDAI, Crohn's disease Activity Index; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; DBE, double-balloon endoscopy; ICS, ileocolonoscopy; MR, magnetic resonance; MRE, MR enterography; MREC, MR enterocolonography; R, correlation coefficients; SBE, single-balloon endoscopy; SBFT, small-bowel follow-through; SES, simple endoscopic score; ULs, ulcerative lesions; WCE, wireless capsule endoscopy.

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to the fibrostenotic stage, because of its excellent soft-tissue contrast for not only inflammatory changes but also stenoses or fistulae.[26–30] Conventional ICS and WCE are problematic in patients with CD complications such as stenoses and fistulae, and MRE is expected to be useful in such cases. We developed MR enterocolonography (MREC) without rectal contrast to simultaneously image the small intestinal and colonic CD lesions.[31] In this study, however, we performed only 10 DBE procedures for endoscopic assessment (in contrast, 24 ICS procedures were performed). MR findings in the proximal small intestine have not been compared with endoscopic findings. Therefore, the present study aimed to evaluate the efficacy of MREC for CD lesions in the small intestine by comparing its findings with those of enteroscopy. This study compared CD lesions on MREC with those on enteroscopy, with a special focus on small intestinal findings. CD lesions are categorized into 2 types: (1) active lesions such as ulcers or erosions and (2) intestinal damage such as scars, stenoses, and fistulae. MREC is an additional imaging technique that may be selected and used according to individual patient requirements.

Patients and Methods

Patients

From July 2009 to November 2013, a total of 100 patients who already were diagnosed with ileal or ileocolonic CD from the inpatient and outpatient departments of Tokyo Medical and Dental University Hospital were enrolled in this prospective study. All the patients were diagnosed according to the criteria of the Research Committee on Inflammatory Bowel Disease in Japan.[32] We excluded patients who had purely colonic CD, who had colostomy/ileostomy, who had an abdominal abscess, or who had severe or fulminant disease. Severe or fulminant disease was defined as a Crohn's Disease Activity Index (CDAI) score greater than 450 or serum C-reactive protein (CRP) level greater than 10 mg/dL. Patients with purely colonic CD were excluded because we intended to focus on CD lesions in the small intestine. Patients with severe or fulminant disease were excluded because they obviously required immediate strong medical therapeutics, hospitalization, or surgical procedures. In contrast, the assessment of CD lesions in patients with mild or moderate disease is important for determining their treatment; therefore, we evaluated MR and endoscopic findings in this patient group.

MREC was performed initially, with enteroscopy (SBE/DBE) subsequently performed within 3 days because of the slight possibility that it could affect and change the identified mucosal lesions. MREC and enteroscopy were performed on the same day in most patients (n = 87).

On the day MREC was performed, the age, sex, duration of CD, disease type, presence of perianal involvement (defined as anal fistula or perianal abscess), number and type of surgical interventions, CDAI, CRP level, and current and former treatments were recorded. The patients' clinical characteristics are shown in Table 1. Twenty-six patients (26.0%) had the ileal type and 74 patients (74.0%) had the ileocolonic type. Thirty-two patients (32.0%) had clinically active disease, and the serum CRP level of 43 patients (43.0%) was greater than 0.3 mg/dL. The pain scores in CDAI (graded from 0 to 3 each day for 7 days) were associated with the presence of stenoses, and the mean pain score was 4.9 (Supplementary Table 1). Written informed consent for undergoing the diagnostic procedures and for study participation was obtained from all patients. The study was approved by the Ethics Committee of Tokyo Medical and Dental University.

Table 1. Clinical Characteristics of 100 Patients on the Day of Examination

Female, n (%)	36	(36.0)
Median age at examination, *y* (range)	31	(16–71)
Median disease duration, *y* (range)	4	(0–32)
Disease type, n (%)		
Ileal	26	(26.0)
Ileocolonic	74	(74.0)
Perianal involvement, n (%)	27	(27.0)
Previous surgery, n (%)	30	(30.0)
Median CDAI score (range)	105	(0–382)
CDAI > 150, n (%)	32	(32.0)
Median CRP level, *mg/dL* (range)	0.20	(0.02–7.23)
CRP level > 0.3 mg/dL, n (%)	43	(43.0)
Concomitant treatments		
Mesalamine, n (%)	64	(64.0)
Steroids, n (%)	2	(2.0)
Immunosuppressants, n (%)	31	(31.0)
Anti-TNF antibodies, n (%)	36	(36.0)
Elementary diet, n (%)	25	(25.0)

TNF, tumor necrosis factor.

Enteroscopy and Endoscopic Segmentation

Ninety SBE procedures and 10 DBE procedures were performed by experienced endoscopists. DBE was performed before July 2012 and SBE was performed after July 2012. Hospitalization was required for DBE, whereas SBE was performed on an outpatient basis for many patients (n = 62 [68.9%]). We used a retrograde approach and advanced the enteroscope as deep as possible. If stenoses inhibited the path of the scope or overtube, a contrast study from the scope and endoscopic balloon dilatation was performed. With a contrast study from the scope, we confirmed that it was not a sharp angulation that could be misinterpreted as a stenosis, and we recorded the diameter and length of stenosis. In our protocol, we limited the total insertion time to 90 minutes. After every stroke of the endoscopic overtube, we made a mark with 0.3% crystal violet, measured the length between each marking, and calculated the sum total to determine the length of the small intestine.

The large and small intestines were divided into 7 distinct anatomic sections according to the modified simple endoscopic score (SES) for CD.[33] The rectum was defined as the portion distal to the rectosigmoid junction. The left colon included the descending colon and the sigmoid colon up to the rectosigmoid junction. The transverse colon was defined as the segment between the hepatic and splenic flexures. The right colon included the cecum with the ileocecal valve and the ascending colon to the hepatic flexure. The terminal ileum was defined as the section 10 cm or less from the ileocecal valve because this is the part of the bowel that can be observed by ICS. In addition, in case of an ileocolonic anastomosis, the terminal ileum included lesions less than 10 cm from the anastomotic site. The proximal ileum was defined as the part of the bowel extending between the proximal end of the terminal ileum 300 cm or less from the ileocecal valve.

Table 2. Classification and Evaluation of CD Lesions for Enteroscopy

Variables	0	1	2	3
A: size of ulcers	None	Aphthous ulcers (φ 0.1–0.5 cm)	Large ulcers (φ0.5–2 cm)	Very large ulcers (φ > 2 cm)
B: ulcerated surface	None	<10%	10%–30%	>30%
C: affected surface	Unaffected segment	<50%	50%–75%	>75%
D: presence of stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed
E: presence of scars	None	Single	Multiple	Convergence of mucosa or longitudinal scar
Active lesions			Intestinal damage	
All mucosal lesions: A + B + C ≥ 1 Ulcerative lesions: A + B + C ≥ 5			All stenotic lesions: D ≥ 1, all scar lesions: E ≥ 1 Major stenotic lesions: D = 3, major scar lesions: E = 3	

φ, diameter of ulcers.

The jejunum was defined as the proximal part of the small bowel, excluding the section defined as the proximal ileum. The length of the entire small intestine was approximately 600 cm when measured as previously described, and the borderline between the ileum and the jejunum was defined as the midpoint.

MREC and Segmentation

The MREC protocol used in the present study has been described previously.[31] Bowel cleansing was performed by oral ingestion of 50 g of magnesium citrate with 200 mL of water at 7 PM on the day before MR imaging. Within 60 minutes before MR imaging, all patients were instructed to drink 1000 mL of polyethylene glycol. MR imaging was performed using a 1.5-T scanner (Excelart Vantage powered by Atlas; Toshiba Medical Systems, Tokyo, Japan). All MR images were acquired with the patient in the supine position. We first confirmed the adequate distention of both the small and large intestine by MR imaging using True Steady State Free Precession (True SSFP; Toshiba Medical Systems, Tokyo, Japan). If the distention was insufficient, the patient was required to drink additional polyethylene glycol. We performed a coronal balanced sequence that was True SSFP and a cine coronal single-shot fast-spin echo sequence, termed *fast advanced spin echo*. After intravenous injection of 20 mg of scopolamine butylbromide, a coronal True SSFP and a coronal 3-dimensional T1-weighted, gradient echo sequence, termed *quick dimensional dynamic diagnostic scan*, were acquired. After 60 seconds of manual intravenous administration of gadolinium chelate at a dose of 0.2 mL/kg body weight, a quick dimensional dynamic diagnostic scan was performed in axial and coronal orientations. Finally, transverse diffusion-weighted imaging (spin-echo echo planar imaging) was performed. All imaging covered the entire small and large intestines.

The small intestine was divided into 3 segments using the same technique as that used for endoscopic segmentation. These segments were determined relative to the position of the small intestine in the abdominal cavity. The terminal ileum extended 10 cm from the ileocecal valve or the anastomotic site, the proximal ileum was located in the left lower quadrant, the segment corresponding to the bowel loops was located in the right upper and lower quadrants, and the jejunum was located in the left upper quadrant. The large intestine was divided into 4 segments on the basis of endoscopic segmentation: the rectum, left colon, transverse colon, and right colon.

Classification and Evaluation of CD Lesions for Enteroscopy and MREC

All 7 segments were scored and evaluated separately. To assess the severity of CD lesions in each segment, the most severe lesion in each was selected to be scored by enteroscopy and MREC. Two physicians performed endoscopy and assessed the endoscopic findings, and 2 board-certified radiologists assessed the MREC findings. Both the physicians and radiologists were blinded to the patient's clinical presentation and results of other studies.

First, the endoscopic findings of each segment for each patient were scored as shown in Table 2 according to the modified SES-CD.[33] To assess active lesions in CD, we summed the scores A, B, and C. The active lesions were defined in the following manner: no endoscopic changes (A + B + C = 0), all mucosal lesions (AMLs; A + B + C ≥ 1), and ulcerative lesions (ULs; A + B + C ≥ 5). To assess intestinal damage, we defined all stenotic lesions (score D ≥ 1) as stenoses that the scope could pass, and major stenotic lesions (score D = 3) as stenoses that the scope could not pass. Similarly, we defined all scarred lesions (score E ≥ 1) as the lesions in which the regenerating epithelium completely covered the ulcer floor, the white coating had disappeared, and the redness of the regenerating region was reduced to the color of the surrounding mucosa. Major scarred lesions (score E = 3) were defined as absolute convergence of mucosa or a longitudinal scar over 5 cm.

In contrast, MREC findings of each segment were evaluated as positive/negative criteria. The presence of at least one of the following criteria was required to diagnose active lesions: increased contrast enhancement, wall thickening, submucosal edema, deep mucosal fissures, or extramucosal hypervascularity. The criteria for stenosis required luminal narrowing of less than 11 mm and agreement from the evaluating radiologist.

Statistical Analysis

Continuous variables are shown as means and SDs for normally distributed data; if not, they are presented as medians and ranges. The Mann–Whitney test was used to compare continuous variables. The chi-square test or the Fisher exact test was used to analyze categoric data, as appropriate. The level of statistical significance was set at a P value less than .05. Sensitivities and specificities are shown with their 95% confidence intervals (CIs). The Spearman rank

correlation coefficients (R) were determined and used for evaluating endoscopic findings in the small intestine. IBM SPSS Statistics 19 (Tokyo, Japan) was used to perform all statistical analyses.

Results

Enteroscopy and MREC were performed on the same day in most patients (87 of 100). There were no severe complications with enteroscopy, such as perforations or bleeding requiring transfusion. Balloon dilatation was performed in 20 patients. The scope reached the proximal ileum in 98 patients (98.0%), the jejunum in 40 patients (40.0%), and the entire intestine in 11 patients (11.0%) (Supplementary Table 2). The median reach for the scope was 200 cm from the valve. The endoscopic findings also are shown in Supplementary Table 2. AMLs were observed by enteroscopy in 123 (51.7%) of 238 small intestinal segments and in 104 (29.5%) of 353 large intestinal segments; among these, ULs were observed in 85 (35.7%) small intestinal segments and in 45 (12.7%) large intestinal segments. ULs were observed in 41 (41.0%) of 100 terminal ileal segments, in 39 (39.8%) of 98 proximal ileal segments, and in 5 (12.5 %) of 40 jejunal segments. AMLs were observed in 57 (57.0 %) of 100 terminal ileal segments, in 59 (60.2%) of 98 proximal ileal segments, and in 7 (17.5%) of 40 jejunal segments. Assessment of small intestinal damage by enteroscopy showed major stenotic lesions (score D = 3) in 17 segments (7.1%), all stenotic lesions (score D $\geq$ 1) in 49 segments (20.6%), major scarred lesions (score E = 3) in 53 segments (22.3%), and all scarred lesions (score E $\geq$ 1) in 89 segments (37.4%). In contrast, active lesions were detected by MREC in 89 small intestinal segments and in 57 large intestinal segments. Twelve patients had MR findings for active lesions beyond the reach of the scope. Because all of them had endoscopic ulcerative lesions in the same segment reached by the scope, we evaluated these patients as UL positive and MREC positive. Stenoses (32 segments) and scars (45 segments) in the small intestine were detected by MREC. Internal fistulae were detected by MREC in 8 patients. Fistulae also were detected by enteroscopy in 7 patients. In another patient, the fistula was considered to have closed. An example of the comparison between enteroscopy and MREC is shown in Figure 1.

We also evaluated the relationship between endoscopic findings and CDAI or CRP level exclusively in the

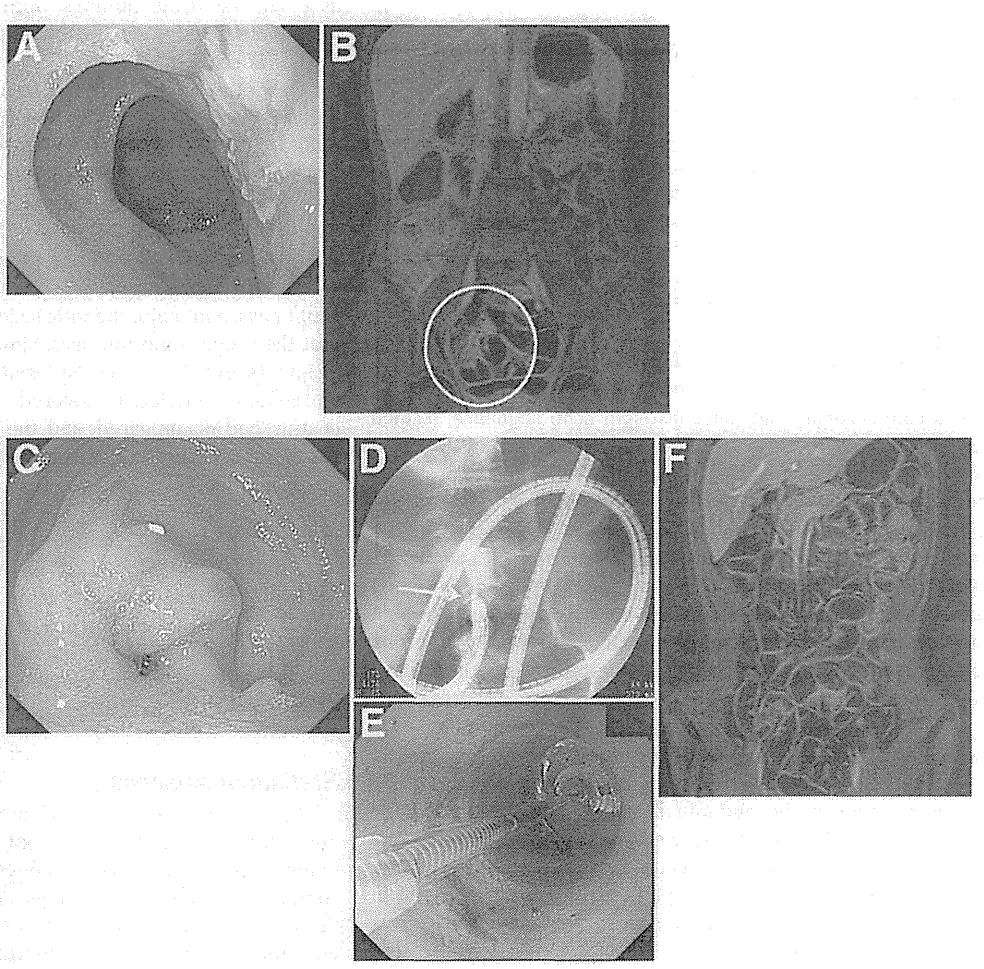

Figure 1. An example of comparison between enteroscopy and MREC for ULs and major stenoses. (*A*) Enteroscopy detected ULs in the proximal ileum. (*B*) MREC with 3-dimensional T1-weighted contrast-enhanced GRE sequence also detected it in the same segment as wall thickening and increased contrast enhancement (*yellow circle*). (*C*) In contrast, enteroscopy detected major stenosis that the scope could not pass in the proximal ileum. (*D*) The length of stenosis (*yellow arrow*) was 1 cm, and (*E*) balloon dilatation was performed. (*F*) However, MREC with any sequence could not detect this stenosis.

small intestine (Supplementary Figure 1). The endoscopic score was determined according to modified SES-CD (0–45; add A + B + C + D + E for each small intestinal segment), whereas the endoscopic active score also was determined (0–27; add A + B + C for each small intestinal segment). The Spearman rank correlation coefficient between the endoscopic score and CDAI was 0.199 (P = .052), whereas that between the endoscopic active score and CDAI was 0.249 (P = .014). Similarly, the Spearman rank correlation coefficient between the endoscopic score and the CRP level was 0.336 (P = .001), whereas that between the endoscopic active score and the CRP level was 0.460 (P < .001).

With regard to the assessment of active lesions, the MREC and enteroscopy findings are shown in Figure 2. MREC sensitivities for ULs and AMLs in the small intestine were 82.4% (95% CI, 75.4%–87.7%) and 67.5% (95% CI, 63.1%–70.0%), respectively, whereas the specificities were 87.6% (95% CI, 83.7%–90.6%) and 94.8% (95% CI, 90.1%–97.5%), respectively (Figure 3). The sensitivities for ULs were 87.8% in the terminal ileum and 77.3% in the proximal ileum and jejunum where scope insertion was feasible only by enteroscopy (Figure 4). There were no significant differences between these 2 segments (P = .203). Similarly, the sensitivities for AMLs were 71.9% in the terminal ileum segment and 63.6% in the proximal ileum and jejunum. There were no significant differences between these 2 segments (P = .328). On the other hand, MREC sensitivities for ULs and AMLs in the colonic segments (defined as the left colon, transverse colon, and right colon segment) were 82.8% (95% CI, 68.1%–91.9%) and 46.3% (95% CI, 38.4%–52.0%), respectively, whereas the specificities were 93.2% (95% CI, 91.5%–94.4%) and 95.5% (95% CI, 92.8%–97.4%), respectively (Figure 3). The sensitivity (31.3%) and specificity (83.1%) for ULs in the rectum were lower than those for ULs in the colonic segments (P = .001 and .009, respectively), whereas those for AMLs in the rectum (21.6% and 82.0%, respectively) were lower than those for AMLs in the colonic segments (P = .013 and .001, respectively).

Assessment of intestinal damage in the small intestine showed that MREC sensitivity and specificity for major stenoses were 58.8% (95% CI, 37.6%–77.2%) and 90.0% (95% CI, 88.4%–91.5%), respectively, whereas those for all stenoses were 40.8% (95% CI, 30.8%–49.4%) and 93.7% (95% CI, 91.1%–95.9%), respectively (Table 3). Similarly, MREC sensitivity and specificity for major scarring were 37.7% (95% CI, 27.6%–47.9%) and 86.5% (95% CI, 83.6%–89.4%), respectively, whereas those for all scars were 32.6% (95% CI, 26.0%–38.3%) and 89.3% (95% CI, 85.3%–92.7%), respectively. Major stenoses could be detected in 11 patients by MREC, whereas they were not detected in 8 patients. There was no association between intestinal stenoses on MREC and patient characteristics (Supplementary Table 3). Lesions with oral dilation of stenosis and symptoms of narrowing generally are considered to require surgical or endoscopic treatment, and these lesions were detected by MREC in all the patients (n = 4). The accuracy of MREC in locating intestinal damage in the large intestine was not studied because major intestinal damage existed in few cases. Assessment of large intestinal damage by enteroscopy showed major stenotic lesions in 2 segments (0.5%) and major scarred lesions in 45 segments (12.7%).

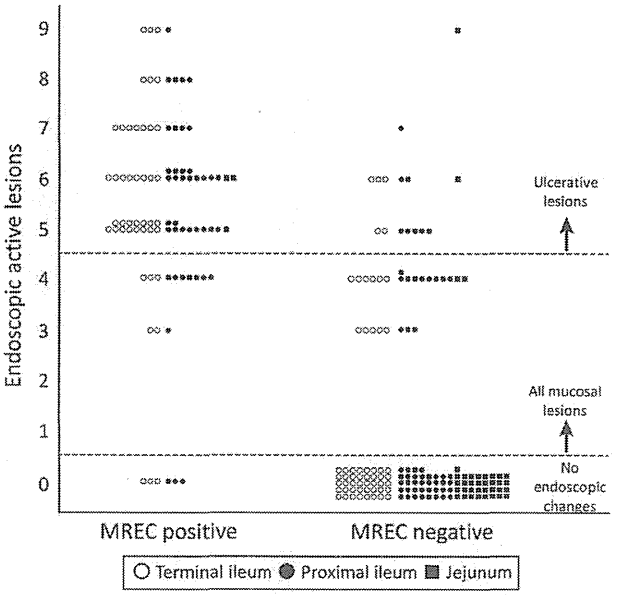

Figure 2. The findings of MREC and enteroscopy. Each finding in each segment is shown as a *circle* and a *square*. Endoscopic active lesions were determined by the summed scores A, B, and C. The active lesions were defined in the following manner: no endoscopic changes (A + B + C = 0), AMLs (A + B + C ≥ 1), and ULs (A + B + C ≥ 5). *Open circles* show the findings in the terminal ileum, *closed circles* show findings in the proximal ileum, and *closed squares* show findings in the jejunum that could be accessed only by enteroscopy.

Discussion

Evaluation of the small and large intestine in CD patients is important. In the past, Rimola et al[34] showed that MRE was useful for detecting active disease and assessing the severity of CD lesions in the terminal ileum and colon. However, they did not evaluate CD lesions in the jejunum and proximal ileum. A prospective randomized study showed similar diagnostic sensitivities for MRE and MR enteroclysis (88% for both).[35] Therefore, we developed MREC with oral contrast to evaluate jejunal, ileal, and colonic CD lesions simultaneously.[31] We also confirmed that MREC showed a high sensitivity and specificity for CD lesions such as ULs. Furthermore, the severity detected by MREC was correlated closely with that detected by endoscopy. These results suggest that MREC can be a useful tool for detecting CD lesions without excessive pain or radiologic exposure. However, in the previous study, we only performed 10 DBE procedures for endoscopic assessment. The present study evaluated small intestinal CD lesions by comparing MREC and enteroscopic findings.

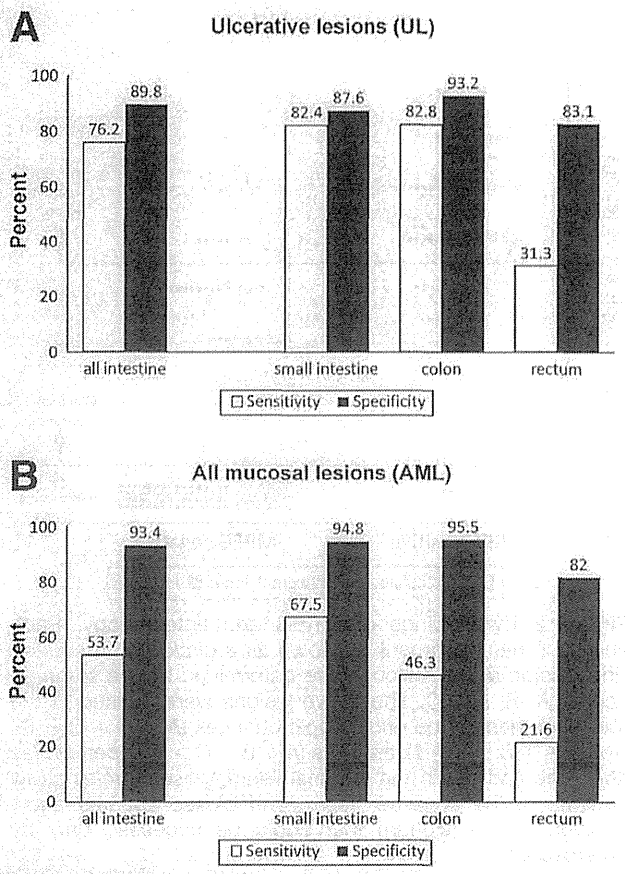

Figure 3. MREC sensitivities and specificities for (*A*) ULs and (*B*) AMLs in each bowel. The small intestine was divided into the terminal ileum, proximal ileum, and jejunum. The colon was divided into the left colon, transverse colon, and right colon. MREC sensitivity and specificity were significantly lower for ULs and AMLs in the rectum than for those in the colon.

In addition, we only enrolled patients with mild and moderate disease because it was important to evaluate MR and endoscopic findings for determining treatment for these patients.

Recent studies have suggested that mucosal healing is critical for the prognosis of CD.[1,2] ICS generally is used for the assessment of endoscopic lesions in CD patients; however, it can be used to assess only the colon and terminal ileum. We performed enteroscopy in a relatively large number of CD patients and identified characteristic endoscopic findings in the proximal ileum and jejunum in the present study. Enteroscopy enables tissue sampling and pathologic examination in the small intestine. Subsequent histologic examination can provide beneficial information to aid in assessing the severity of inflammatory changes; therefore, enteroscopy can be used to identify suitable CD treatment strategies in otherwise inconclusive cases.[36] We showed that endoscopic active lesions were detected not only in the terminal ileal segment but also in the proximal ileal segment at a similar rate. In addition, we showed a mild correlation between endoscopic lesions (R = 0.199) or endoscopic active lesions (R = 0.249) and CDAI. These results suggest that the assessment of CD lesions in deep small intestine is necessary.

MREC can function as a surrogate for enteroscopy. Adhesions and fistulae frequently are observed in CD patients and can result in technical difficulties during observation of the entire small intestine by enteroscopy, which is reported to be accompanied by severe complications in a few patients. MREC facilitated the observation of the entire small intestine and colon, with less invasion compared with enteroscopy. In the present study, the sensitivity and specificity of MREC for active lesions in the small intestine were high (Figure 3). There was no significant difference in the sensitivity and specificity for active lesions in the terminal ileal segment and the sensitivity and specificity for active lesions in other small intestinal segments (Figure 4). In addition, the sensitivity for CD lesions in the terminal ileal segment, which was the most frequent site of occurrence, was high (87.8% for ULs, 71.9% for AMLs). These results support the European Crohn's and Colitis Organisation guideline recommendation that MR or CT enterography or enteroclysis is an imaging technique for the detection of intestinal involvement in CD, including extramural complications.[23]

The sensitivity and specificity for ULs in the colonic segments were as high as those for ULs in the small intestine. These results show the efficacy of MREC in detecting colonic severe lesions. In addition, MREC has the potential to evaluate jejunal, ileal, and colonic severe lesions.

However, there were some limitations in the present study. First, the sensitivity and specificity for active lesions in the rectal segment were significantly lower than those for active lesions in other colonic segments. We obtained a similar result in our past study,[31] which suggests the limitation of MREC for detecting rectal mucosal lesions. To

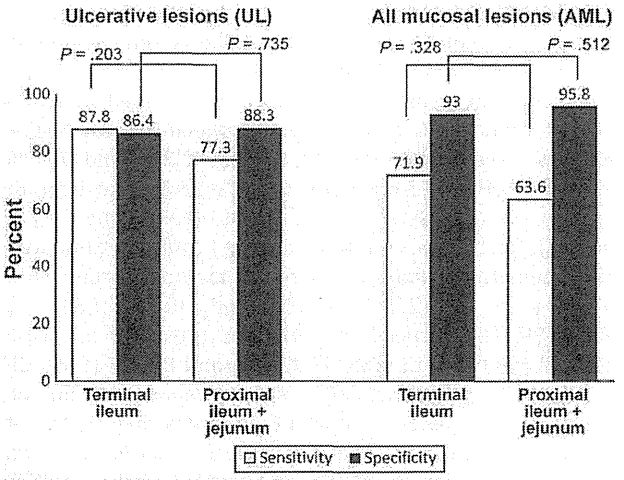

Figure 4. MREC sensitivities and specificities for ULs and AMLs in the small intestine. The proximal ileum and jejunum segments could be accessed only by enteroscopy. MREC sensitivities and specificities for ULs and AMLs were not significantly different between the terminal ileum and other small intestinal segments.

Table 3. Diagnostic Accuracy of MREC for Intestinal Damage in the Small Intestine

	Sensitivity	Specificity	PPV	NPV	Accuracy
Major stenoses	58.8%	90.0%	31.3%	96.6%	87.8%
All stenoses	40.8%	93.7%	62.5%	85.9%	82.8%
Major scar	37.7%	86.5%	44.4%	82.9%	75.6%
All scars	32.6%	89.3%	64.4%	68.9%	68.1%

NPV, negative predictive value; PPV, positive predictive value.

resolve this problem, however, sigmoidoscopy along with a glycerin enema can be combined with MREC for observing the rectum. In addition, the sensitivity for detecting AMLs in colonic segments was not high (46.3%), and this may be another limitation. Colonic distension with rectal contrast is effective to obtain high sensitivity for detecting all colorectal lesions.[37]

Second, the present study showed that MREC sensitivities for ULs and AMLs in the small intestine were 82.4% and 67.5%, respectively. In other words, approximately 20% of ulcerative lesions could not be detected using MR imaging. Although the limitations of MR imaging for the detection of superficial mucosal lesions have been shown previously in several studies,[15,16,38] we showed that MR imaging could not detect ULs in some patients. The same limitation was shown in recent studies assessing the accuracy of MR for the diagnosis of small intestinal lesions in CD that used WCE as a reference standard. Böcker et al[39] showed that WCE was superior to MR for the detection of lesions related to CD. Jensen et al[40] showed that the sensitivity and specificity (100% and 91%, respectively) for the diagnosis of CD of the terminal ileum by WCE were higher than those by MRE (81% and 86%, respectively). In contrast, few lesions were positive by MREC and negative by enteroscopy (MREC specificity for AMLs in the small intestine was 94.8%). We considered that these lesions could be intramural diseases because CD affected the entire thickness of the bowel wall. The endoscopists were blinded to MR findings in this study; therefore, they could not collect specimens from that site and histologic assessment was difficult.

Finally, the present study also showed low MREC sensitivity for intestinal damage in the small intestine (Table 3). Assessment of intestinal damage is considered to be increasingly important, and new scoring systems such as the Lemann score have been developed.[41] Detection of stenoses in the small intestine also is considered to be important. However, MR imaging could not detect stenoses that could not be passed by the scope in some patients. MREC procedures required the adequate distention of both the small and large intestines; therefore, we considered this to be a limitation of MR imaging. Our study showed that MR imaging was insufficient for the detection of intestinal damage such as stenoses. Endoscopy should be the gold standard for identifying stenoses. However, patients with severe disease were excluded from the present study. These patients particularly may benefit from cross-sectional imaging and avoidance of enteroscopy. Furthermore, they are more prone to develop penetrating disease that would be diagnosed by MR.

In conclusion, the present study showed high MREC sensitivity for active lesions and low MREC sensitivity for intestinal damage. MREC specificities for both active lesions and intestinal damage were high. Our MREC protocol is useful for detecting active CD lesions in both the small intestine and colon and has the potential to confirm mucosal healing. However, the detection of intestinal damage using MR imaging is difficult. Enteroscopy is useful for the assessment of both active lesions and intestinal damage such as stenosis exclusively in the small intestine. The detection of active lesions is important for determining the appropriate pharmacologic treatment for CD, and the detection of intestinal damage is important for determining surgical or endoscopic treatment. Various detection methods are required to ensure the detection of CD lesions in deep small intestine and to choose an appropriate treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.04.008.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Table 1. Subscore of the CDAI

Number of liquid or soft stools each day for seven days, mean	17.3
Abdominal pain (graded from 0 to 3 on severity) each day for 7 days, mean	4.9
General well being (assessed from 0 to 4) each day for seven days, mean	3.9
Presence of complications, n (%)	27 (27)
Taking Lomotil or opiates for diarrhea, n (%)	3 (3)
Presence of an abdominal mass, n (%)	2 (2)
Hematocrit (%), mean	39.5
Percentage deviation (%) from standard weight, median	6.5

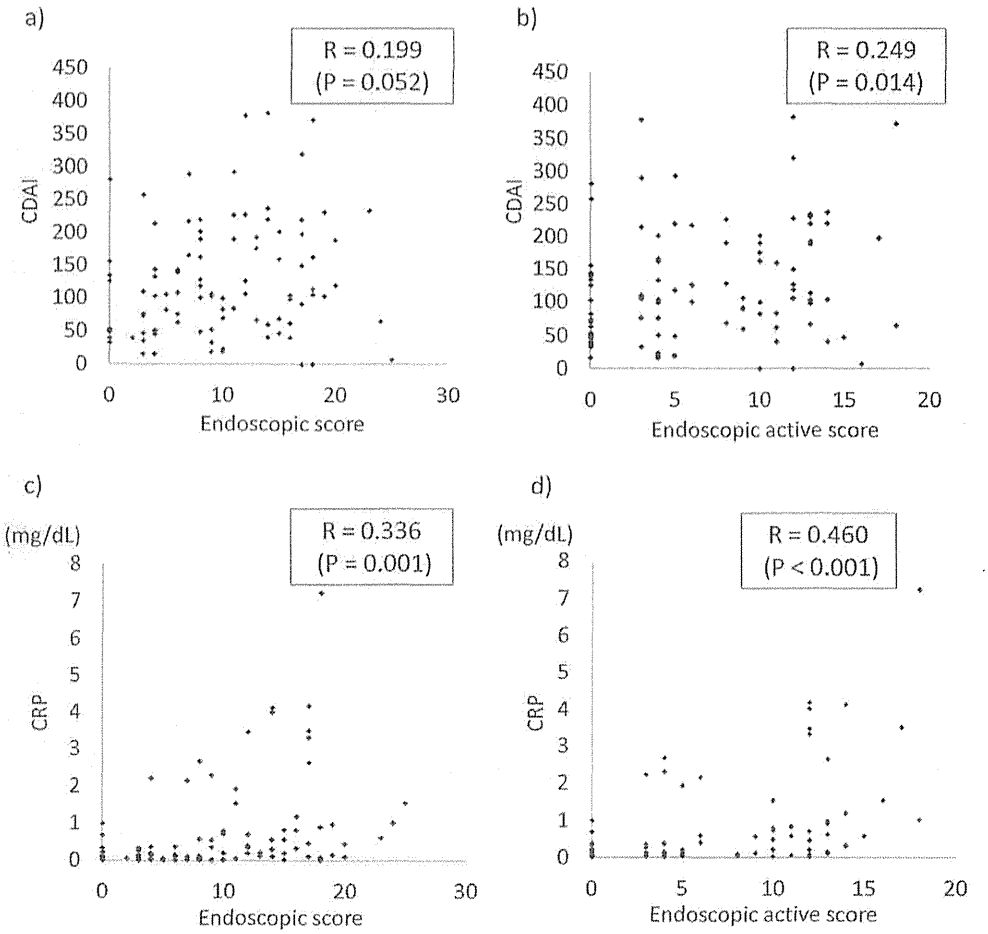
Supplementary Table 2. Results of endoscopic findings

	terminal ileum	proximal ileum	jejunum
Patients in whom the scope could be inserted sufficiently to access each lesion, n (%)	100 (100)	98 (98.0)	40 (40.0)
Active lesions			
Ulcerative lesions, n (% in each segment)	41 (41.0)	39 (39.8)	5 (12.5)
All mucosal lesions, n (% in each segment)	57 (57.0)	59 (60.2)	7 (17.5)
Intestinal damage			
Major stenotic lesions, n (% in each segment)	4 (4.0)	12 (12.2)	1 (2.5)
All stenotic lesions, n (% in each segment)	16 (16.0)	31 (31.6)	2 (5.0)
Major sacr lesions, n (% in each segment)	21 (21.0)	27 (27.6)	5 (12.5)
All Scar lesions, n (% in each segment)	33 (33.0)	48 (49.0)	8 (20.0)

Supplementary Table 3. Characteristics of patients who had major stenosis and its forms

Clinical characteristics of patients								the forms of stenosis					
sex	Age (years)	duration of CD (years)	disease type	previous surgery	CDAI	CRP (mg/dL)	symptom	segment of stenosis	diameter of stenosis (mm)	length of stenosis (mm)	ulcer on stenosis	oral dilation	detection in MREC
F	37	4	ileocolonic	-	190	0.05	+	ileocecal valve	3	10	-	+	+
F	27	4	ileocolonic	-	41	0.58	+	proximal ileum	3	50	+	+	+
M	50	0	ileal	-	0	0.08	+	proximal ileum	4	10	-	-	+
M	38	11	ileocolonic	+	290	0.04	+	anastomosis site	4	30	+	-	+
M	48	9	ileal	+	7	1.54	-	proximal ileum	5	5	+	-	+
M	52	13	ileocolonic	-	19	0.21	+	proximal ileum	5	5	+	-	+
F	41	15	ileocolonic	-	189	0.1	+	proximal ileum	5	10	-	+	+
M	51	0	ileocolonic	-	99	0.02	-	proximal ileum	5	20	+	+	+
F	44	32	ileal	-	156	0.17	-	proximal ileum	7	5	-	+	+
M	46	2	ileal	-	130	0.2	-	proximal ileum	7	10	+	+	+
M	50	19	ileocolonic	+	126	0.41	+	proximal ileum	7	20	+	+	+
M	31	14	ileal	+	220	0.06	-	anastomosis site	2	5	-	-	-
M	20	0	ileal	-	119	0.45	-	ileocecal valve	2	10	-	+	-
F	45	4	ileocolonic	-	293	1.92	+	proximal ileum	2	20	+	-	-
F	20	1	ileocolonic	+	258	0.03	+	jejunum	3	5	-	-	-
M	41	11	ileocolonic	+	234	0.61	-	proximal ileum	5	10	+	+	-
M	31	1	ileal	+	53	0.02	+	proximal ileum	5	10	-	-	-
M	30	10	ileocolonic	+	60	0.12	-	terminal ileum	6	10	+	-	-
M	39	14	ileocolonic	-	378	0.36	-	terminal ileum	7	15	+	+	-
P value†		0.600		0.144	0.091	0.778	0.255		0.272	0.657	0.449	0.255	

†Mann–Whitney test or Fisher exact test probability test was used as appropriate.



Supplementary Figure 1. Correlation in the small intestine between (*A*) endoscopic score and CDAI, (*B*) endoscopic active score and CDAI, (*C*) endoscopic score and CRP level, and (*D*) endoscopic active score and CRP level. The endoscopic score was determined according to modified SES-CD (0–45; add A + B + C + D + E for each small intestinal segment), whereas the endoscopic active score also was determined (0–27; add A + B + C for each small intestinal segment).

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Diagnosis and Treatment of Ulcerative Colitis with Cytomegalovirus Infection: Importance of Controlling Mucosal Inflammation to Prevent Cytomegalovirus Reactivation

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Human cytomegalovirus (HCMV) is a member of the herpesvirus family. HCMV infection persists throughout the host lifespan in a latent state following primary infection. The ability of HCMV to escape control by the host immune system and its resulting reactivation suggests the importance of ongoing immune surveillance in the prevention of HCMV reactivation. HCMV is a common cause of opportunistic infection that causes severe and fatal disease in immune-compromised individuals. In inflammatory bowel disease patients, particularly those with ulcerative colitis (UC), HCMV is often reactivated because these patients are frequently treated with immunosuppressive agents. This reactivation exacerbates colitis. Additionally, HCMV infection can induce severe colitis, even in patients with UC who have never been treated with immunosuppressive agents. However, the role of HCMV in colonic inflammation in patients with UC remains unclear. Here, we present previous and current clinical data on the diagnosis and treatment of HCMV infection in UC. Additionally, our experimental data from a newly established mouse model mimicking UC with concomitant CMV infection clearly demonstrate that inflammation could result in the exacerbation of UC disease activity with induction of HCMV reactivation. In summary, optimal control of colonic inflammation should be achieved in UC patients who are refractory to conventional immunosuppressive therapies and are positive for HCMV. **(Intest Res 2014;12:5-11)**

Key Words: Cytomegalovirus; Ulcerative colitis; Tumor necrosis factor alpha

INTRODUCTION

Corticosteroids and immunosuppressive agents have been used to treat patients with refractory UC. Much attention has been paid to the involvement of human cytomegalovirus (HCMV) infection in resistance to medical treatment for UC.[1-3] Many studies have reported the prevalence of HCMV infection in patients with IBD. The prevalence of CMV infection in UC patients with severe colitis and steroid-refractory colitis has been reported as 21-38%[4-8] and 32-36%,[7,9,10] respectively. The HCMV infection rates in patients with severe UC and patients with steroid-dependent UC are higher than those in patients with active Crohn's disease.[11,12] HCMV infection causes significant clinical morbidity in patients with UC. In this regard, the establishment of an appropriate diagnosis and treatment for HCMV infection in UC is a critical issue for gastroenterologists. This article highlights diagnostic and therapeutic strategies for HCMV infection in UC, and provides new insights into the mechanism of HCMV reactivation.

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