Welfare of Japan has initiated a randomized controlled study to compare the efficacy of step biopsy and target biopsy. The present article gives an introduction to this ongoing randomized controlled trial in Japan.

Keywords Ulcerative colitis · Colorectal cancer · Dysplasia · Randomized controlled trial · Colonoscopy

Introduction

In longstanding ulcerative colitis (UC), colorectal cancer is one of the major complications that may determine the long-term outcome of the patient [1]. In Japan, the number of UC patients has been increasing in recent years. Also, the number of reports in the Japanese literature describing UC-associated colorectal cancer has been increasing since the 1980s [2]. It is well known that the risk of colorectal cancer increases as the duration of UC becomes longer. According to a meta-analysis by Eaden et al. [1] the cumulative rate of colorectal cancer is 2, 8, and 18% at 10, 20, and 30 years after the onset of UC, respectively. Similarly, in a Japanese study of longstanding UC, it has been reported that the frequency of cancer increases as the duration of the disease becomes longer [3].

Surveillance colonoscopy has been considered to be important for the early detection and early treatment of colorectal cancer, especially in longstanding UC. However, UC-associated colorectal cancer sometimes shows flat or diffuse infiltrative macroscopic types, and diagnosis is not always easy. Therefore, in surveillance colonoscopy, dysplasia is considered as a useful marker for detecting UC-associated colorectal cancer [4–6]. Dysplasia is considered to be a precancerous lesion, and it is known that when dysplasia is observed, the risk of complicating cancer nearby or in another region is high [4–6]. However, because it is not always easy to detect dysplasia endoscopically, guidelines for surveillance colonoscopy in the United States and Europe recommend the use of step biopsy, in which either 4 biopsy specimens for every 10 cm or a total of 33 or more biopsy specimens are obtained [7–10]. On the other hand, it has been pointed out that a step biopsy obtaining several tens of biopsy specimens may not be an ideal method in terms of invasiveness to the patient or medical cost. Instead, there have recently been reports on the usefulness of target biopsy using chromoendoscopy or pit-pattern diagnosis in order to improve the efficiency of surveillance [11, 12]. In target biopsy, biopsy tissues are obtained only from regions where endoscopic findings indicate the possibility of dysplasia. The usefulness of target biopsy in surveillance has been

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examined in multicenter studies of the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan. As a result, it is becoming clear that target biopsy may be used to detect dysplasia at a rate substantially similar to the rate achieved by step biopsy [13]. Therefore, the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan has initiated a randomized controlled study to compare the efficacy of step biopsy and target biopsy in Japan. The trial is registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000001608 (http://www.umin.ac.jp/ctr/index-j.htm). The present article gives an introduction to this ongoing randomized controlled trial.

Study protocol

Aim

The aim of this study is to compare the usefulness of target biopsy and step biopsy in surveillance for detecting cancer and dysplasia in UC patients (Fig. 1).

Study setting

This study is a multi-institutional (52 institutions) randomized controlled trial.

Resources

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and by Labour Sciences Research Grants for Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan.

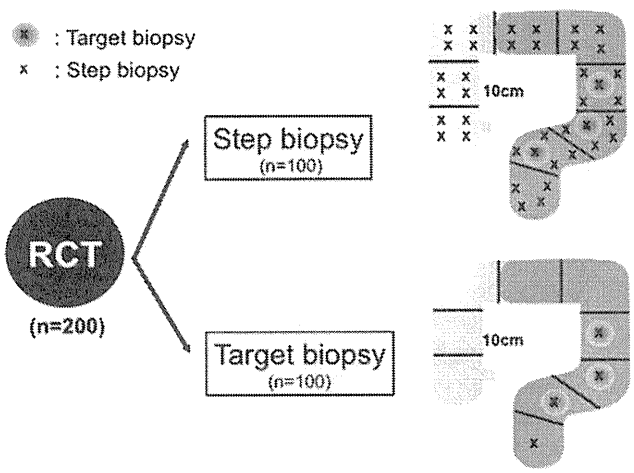

Fig. 1 Study design. After the confirmation of the inclusion and exclusion criteria, the patients are randomized to either the Step biopsy arm or the Target arm. *RCT* Randomized controlled trial

Endpoints

The primary endpoint is the number of neoplastic lesions detected in a single surveillance colonoscopic examination. The secondary endpoints are the proportion of surveillance colonoscopic examinations in which neoplastic lesions are detected out of all surveillance colonoscopic examinations, the examination time, the number of biopsies, economic efficiency, the incidence of examination complications requiring special treatments, and risk factors of neoplasia.

Eligibility criteria

The subjects comprise UC patients (including those with left-sided colitis and pancolitis) in whom 7 years or more have passed since the onset of the disease.

Inclusion criteria

Cases meeting all of the following selection criteria are selected as subjects:

1. Patients who are clinically and histologically diagnosed with UC
2. Cases in which the simple clinical colitis activity index is 8 or less [14]
3. Cases in which the activity index of Truelove and Witts is mild [15]
4. Patients who understand the main purpose of the study and provide consent for participation.

Exclusion criteria

Cases meeting any of the following conditions shall be excluded from the subjects:

1. Patients with a history of tumors or colorectal cancer associated with UC
2. Patients who are clinically suspected of having a hemorrhagic diathesis or who present with coagulopathy in examinations
3. Patients with renal dysfunction (serum creatinine level >1.2 mg/dl)
4. Patients who are pregnant or nursing
5. Other patients deemed ineligible for registration by a physician.

Randomization

After the confirmation of the inclusion and exclusion criteria by fax to the Data Center (Department of Preventive Medicine and Public Health, Keio University), the patients are randomized to either the step biopsy arm or the target

arm. Using stratified allocation, the Data Center takes into account the institutions and the severity of UC as factors to randomly assign the patients to the target biopsy group and the step biopsy group. The attending physician conducts surveillance according to the results of this assignment.

Surveillance methods

Target biopsy group (Target group)

The following procedures are used in the Target group:

1. Perform surveillance colonoscopy once a year.
2. Obtain biopsy specimens from regions where there are findings indicating the possibility of a neoplastic lesion (target biopsy) (Table 1). Photographs of the biopsied region are taken before and after the target biopsy.
3. For lesions suspected of neoplasia, perform normal endoscopy and chromoendoscopy. Also, if possible, perform magnifying endoscopy and determine pit-pattern diagnosis of the lesion.
4. Even if there are no findings indicating the possibility of a neoplastic lesion, obtain at least 1 biopsy tissue from the lower rectum.
5. The number of biopsy specimens obtained is not particularly limited, but the characteristics of the biopsied areas are noted (Table 1). In all cases, it is necessary to distinguish between protruded lesions, flat lesions, and depressed lesions. When describing protruded lesions, if possible, differentiate between plaque-like lesions, coarse granular lesions, papillary lesions, and polypoid lesions. Moreover, when describing flat lesions, if possible, differentiate between reddish mucosa, velvety or villous mucosa, and (fine) granular mucosa.

Table 1 Typical endoscopic findings to be biopsied

1. Protruded lesion
(1) Plaque-like lesion
(2) Coarse granular lesion
(3) Papillary lesion
(4) Polypoid lesion
(5) Others
2. Flat lesion
(1) Reddish mucosa
(2) Velvety or villous mucosa
(3) (fine) Granular mucosa
3. Depressed lesion
4. Others

Step biopsy group

The following procedures are used in the Step biopsy group:

1. Perform surveillance colonoscopy once a year.
2. Even if there are no findings indicating the possibility of a neoplastic lesion, obtain 4 biopsy specimens for every 10 cm between the cecum and the rectum. In addition, obtain biopsy specimens from areas with findings indicating the possibility of a neoplastic lesion (target biopsy) (Table 1). When performing target biopsy and step biopsy, take photographs of the biopsied region before and after the biopsy (for step biopsy, take photographs before the biopsy and after obtaining 4 biopsy specimens; if the 4 locations cannot be photographed at once, take multiple photographs).
3. For lesions suspected of neoplasia, perform normal endoscopy and chromoendoscopy. Also, if possible, perform magnifying endoscopy and determine pit-pattern diagnosis of the lesion.
4. The number of biopsy specimens obtained through target biopsy is not particularly limited, but the characteristics of the biopsied areas are noted (Table 1). In all cases, it is necessary to distinguish between protruded lesions, flat lesions, and depressed lesions. When describing protruded lesions, if possible, differentiate between plaque-like lesions, coarse granular lesions, papillary lesions, and polypoid lesions. Moreover, when describing flat lesions, if possible, differentiate between reddish mucosa, velvety or villous mucosa, and (fine) granular mucosa.

Data collection

Report the following patient data to the Data Center at the time of registration and after surveillance colonoscopy.

Patient data at the time of registration

1. Age
2. Sex
3. Duration of the disease (years)
4. Body mass index
5. Stool frequency (per day)
6. Number of hospitalizations for UC
7. History of steroid use in the past year
8. History of use of immunomodulatory drugs in the past year
9. Primary sclerosing cholangitis
10. Family history of cancer
11. History of maintenance therapy.

Data after surveillance colonoscopy

1. Number of years of experience with surveillance colonoscopy of the examining physician (if there are multiple examining physicians, report the highest number of years of experience)
2. Total examination time
3. Time required from the start of the examination to when the endoscope reached the ileocecal region
4. Time required from reaching the ileocecal region to the completion of the colonoscopy
5. Total number of biopsies
6. Number of target biopsies performed
7. Number of step biopsies performed
8. Characteristics of biopsied regions (Table 1)
9. Presence and details of complications believed to be due to the examination
10. Number of neoplastic lesions.

Pathological diagnosis

Each participating institution submits 4 unstained sections of biopsy specimens to the Data Center (1 each for H&E, P53, and Ki67 staining, and 1 spare). After all of the biopsy specimens are submitted to the Data Center, 3 pathologists make pathological diagnoses. The pathological diagnoses are sent to each institution by the Data Center.

Statistical method

Sample size calculation

To estimate the number of samples for this study, the type I error (one-sided) and the power are set at 0.025 and 0.8, respectively. From previous studies, the mean of the primary endpoint for the step biopsy group is 0.20, and that for the target biopsy group is 0.13 [11, 12, 15–18]. When the non-inferiority margin, Δ, is set at 0.05, the number of samples required for this study is 2009, and when Δ is set at 0.10, the number of samples is 1025. Because the step biopsy is rarely used in daily practice, a sample number of more than 1,000 is not realistic. Moreover, previous trials were conducted with 150–180 samples. For these reasons, we set the sample size for this study as 200. In this setting, the one side length of the 95% confidence interval for the primary endpoint in each group would be 0.078. As for the difference in the primary endpoint, that length would be 0.11.

Study period

The study period is from 1 October 2008 to 31 December 2010.

As of April 2010, 141 cases have been registered.

Participating institutions

The participating institutions are: Kurume University, Osaka City University, Teikyo University, Kyoto University, Hyogo College of Medicine, Yokohama City University Medical Center, Saga University, Showa University Northern Yokohama Hospital, Sapporo-Kosei General Hospital, Nara Medical University, Kaetsu Hospital, Niigata City General Hospital, Hirosaki University, Hiroshima University, Matsuyama Red Cross Hospital, Yokoyama Gastrointestinal Division Hospital, Keio University, Hamamatsu Minamai Hospital, Kitasato University, Research Hospital of the Institute of Medical Science of the University of Tokyo, Onomichi General Hospital, National Kyushu Medical Center, Tokyo Women's Medical University, Asahikawa Medical College, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Oita University, Social Insurance Tagawa Hospital, Tokyo Medical and Dental University, Ohfuna Chuo Hospital, Asahikawa City Hospital, Nagasaki University, Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Fukuoka Red Cross Hospital, Teine Keijinkai Hospital, Fukuoka University Chikushi Hospital, The Cancer Institute Hospital of JFCR, Niigata University, Niigata Cancer Center Hospital, Tohoku University, Fujita Health University, Kure Kyosai Hospital, Hiroshima Prefectural Hospital, Department of Gasteroenterology of Saiseikai Kumamoto Hospital, Imamura Hospital, Coloproctology Center of Takano Hospital, Chugoku Rosai Hospital, Shibata Hospital of Niigata Prefectural Hospital, Hiroshima Kinen Hospital, Hiroshima City Asa Hospital, Hiroshima General Hospital, Fukuoka University, University of the Ryukyus, Kyushu University, Sapporo Higashi Tokushukai Hospital, Jikei University, and Showa University.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Prevalence of metabolic syndrome is comparable between inflammatory bowel disease patients and the general population

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Abstract
Background Metabolic syndrome (MS) is associated with an increased risk of cardiovascular disease. However, its prevalence in inflammatory bowel disease (IBD) patients remains largely unknown. This study was planned to determine the prevalence of MS in Japanese IBD patients.
Methods The prevalence of MS among outpatients with IBD aged 18 or older was studied using the modified National Cholesterol Education Program Adult Treatment Panel III definition.
Results A total of 107 quiescent IBD patients, including 76 ulcerative colitis (UC) patients and 31 Crohn's disease (CD) patients, were studied. Sufficient data were collected from a total of 102 patients. Prevalence of MS was significantly higher in UC (23.0%) patients compared to CD patients (7.1%). MS prevalence was substantially higher among male IBD patients (21.1%) compared to female IBD patients (12.9%), particularly in patients over 30 years of age. No difference was observed in the prevalence of MS between our IBD cohort and the general population in both males and females aged 40 years and older ($P = 0.707$ in males, $P = 0.328$ in females). IBD patients with MS were also older than those without (50.2 ± 15.0 vs. 38.0 ± 11.9 years, $P = 0.013$). In a logistic regression analysis, age was the statistically significant predictor of MS among IBD patients. The odds ratio (95% confidence interval) was 1.064 (1.017–1.114).
Conclusions Prevalence of metabolic syndrome in our IBD patients was comparable to that of the general population. Because age was the independent risk factor for developing MS, evaluation for MS is needed for elderly IBD patients.

Keywords Metabolic syndrome · Inflammatory bowel disease

Abbreviations

MS	Metabolic syndrome
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CD	Crohn's disease
NCEP-ATP-III	National Cholesterol Education Program Adult Treatment Panel III
CVD	Cardiovascular disease
BMI	Body mass index
LDL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
TG	Triglyceride

Introduction

An overlap of the metabolic risk factors for type 2 diabetes and for atherosclerotic cardiovascular disease (CVD), including abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, have led to the currently well-recognized

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concept of the metabolic syndrome (MS) [1, 2]. Although many controversies still exist concerning its classification as a true "syndrome" [3], it is generally agreed that its cardinal pathophysiological feature is insulin resistance due to obesity [4–6]. For obese people with multiple risk factors, aggressive intervention is required to prevent fatal cardiovascular events [2, 7].

Weight loss and low body mass index (BMI) are early symptoms of patients with inflammatory bowel diseases (IBD). These symptoms are more common and severe in patients with Crohn's disease (CD) than in those with ulcerative colitis (UC) because of the anorexia, systemic inflammation, and malabsorption seen in Crohn's disease [8].

Because the Japanese lifestyle has been "Westernized," the proportion of obese people in Japan has rapidly increased over the past 20 years [9], raising the concern that Japanese patients with IBD may not be free from the obesity epidemic.

Although the increase of mortality in IBD patients has not been observed in several population-based studies [10–15], comorbidities such as diabetes mellitus and CVD may affect the prognosis of patients with IBD. Bernstein et al. [16] reported an increased risk of cardiac arterial thromboembolic diseases in an IBD population. In addition, obesity is known to increase the risk of colorectal cancer [17, 18], a serious concern for long-standing IBD patients, who already have an increased risk of developing colorectal cancer [19, 20]. Obesity may also have implications for the activity of IBD itself [21, 22]. Recent evidence suggests that in CD, hypertrophied mesenteric adipose tissue contributes to increased disease activity and development of complications [23–26]. Although some gastrointestinal disorders have been reported to be associated with MS [27], its association with IBD is as yet unknown. The aim of this study was to determine the current prevalence of MS among Japanese patients with IBD and to identify groups of IBD patients who are at risk of developing MS.

Methods

Patients

Patients with quiescent CD or UC who were seen at our outpatient clinic and were over 18 years of age were enrolled in this study between December 2008 and May 2009. Patients with indeterminate colitis or UC patients who had already undergone colectomy were excluded from the study. Informed consent was obtained from each patient, and the study was approved by the ethics committee of Tokyo Medical and Dental University and conducted in accordance with the Helsinki Declaration, adopted by the World Medical Association.

Data collection

The following data were collected from each patient at the time of study enrollment: (1) basic demographic characteristics (age, gender, body weight, height, and waist circumference, which was measured midway between the lower costal margin and iliac crest), (2) a thorough medical and surgical history (including diabetes, hypertension, dyslipidemia, and cardiovascular disease), (3) current medications, including lipid-lowering, anti-diabetic, and anti-hypertensive medications, and those for IBD, and (4) social habits, such as weekly drinking days, smoking, and exercise that could affect risk for MS. Blood pressure was measured with patients seated after 5 min of rest. Fasting blood samples were taken to determine plasma glucose, glycosylated hemoglobin (HbA1c), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglyceride (TG) concentrations.

Diagnosis of metabolic syndrome (MS)

In this study, the diagnosis of MS was made using the criteria set out by the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) definition. For waist circumference, Asian World Health Organization criteria were applied. Consequently, our modified criteria for MS require at least three of the following: (1) increased waist circumference (>80 cm for females and >90 cm for males), (2) high TG (150 mg/dl) or taking medication for high TG, (3) low HDL-C (<50 mg/dl in females and <40 mg/dl in males) or on medications for low HDL-C, (4) high blood pressure (130/85 mmHg) or currently on anti-hypertensive medication, and (5) high fasting glucose (100 mg/dl) or on anti-diabetic medication [3].

Statistical analysis

The chi-square test and Fisher's exact test were used for comparisons of categorical data. Differences in the means of continuous measurements were tested using Student's *t* test. The Wilcoxon rank sum test was used to compare ordinal variables between groups and ages between patients with and without MS.

The age distribution of subjects in our IBD cohorts was compared with results from a nationwide Japanese IBD cohort. The patient age of the two cohorts were categorized into −20, 20–29, 30–39, 40–49, 50–59, and ≥60 years. We used the chi-square test to analyze the difference between these cohorts. The nationwide Japanese IBD cohort was

Table 1 Patient characteristics

	Ulcerative colitis	Crohn's disease	*P* values
n	74	28	
Gender (male/female)	50/24	21/7	0.63
Age, mean ± SD (years)	43.6 ± 13.5	31.5 ± 8.1	<0.0001
Age at diagnosis, mean ± SD (years)	36.7 ± 13.0	22.8 ± 7.4	<0.0001
Disease duration, mean ± SD (years)	6.9 ± 7.1	8.7 ± 9.0	0.31
Body mass index, mean ± SD (kg/m^2)	23 ± 3.93	22.7 ± 5.14	0.32
Medication (*n*)			
5-Aminosalicylates	65	10	
Corticosteroids	6	0	
Immunomodulators	23	19	
Infliximab	0	8	
History of intestinal resection (*n*)	0	10	
Smoking status			
Nonsmoker	39	19	
Ex-smoker	26	3	0.030
Current smoker	9	6	

comprised of 48,347 UC and 13,766 CD patients whose data were submitted electronically to Japan's Ministry of Health, Labor, and Welfare in 2006. These data are submitted each year on application forms for financial support for treatment and research. We also used the chi-square test to analyze the difference of prevalence of metabolic syndrome (MS) in our cohort and that of the national population cohort. A multivariate logistic regression analysis was used to evaluate the impact of some risk factors of MS among IBD patients, in which age, sex, IBD type (UC or CD), and disease duration were included.

A P value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL).

Results

Patient characteristics

One hundred seven consecutive IBD patients (76 with UC and 31 with CD) in clinical remission were enrolled into the study during a routine follow-up visit at our outpatient clinic. Five patients were excluded from the analysis because of insufficient data. Subsequently, the data from 102 patients were subjected to further analysis (74 with UC and 28 with CD). Details of patient characteristics are shown in Table 1. Age was higher in patients with UC than in those with CD (43.6 ± 13.5 vs. 31.5 ± 8.1 years, $P < 0.0001$). The proportion of ex-smokers was significantly higher in UC than in CD patients. No difference was found in body mass index between UC and CD patients. No difference was observed in the age distribution of IBD patients between our cohort and the national cohort ($P = 0.142$ in UC, $P = 0.188$ in CD), as shown in Fig. 1.

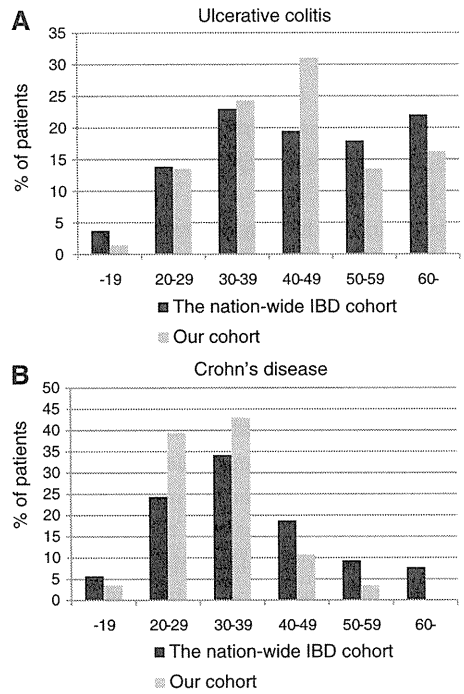

Fig. 1 Age distribution of our inflammatory bowel disease (IBD) cohort compared to the nationwide IBD cohort for both UC (**a**) and CD (**b**). No difference was observed in the age distribution between our cohort and the nationwide cohort ($P = 0.142$ in UC, $P = 0.188$ in CD)

Prevalence of MS in IBD patients

The overall prevalence of MS in the study cohort was 18.6%. The prevalence in patients with UC and CD was

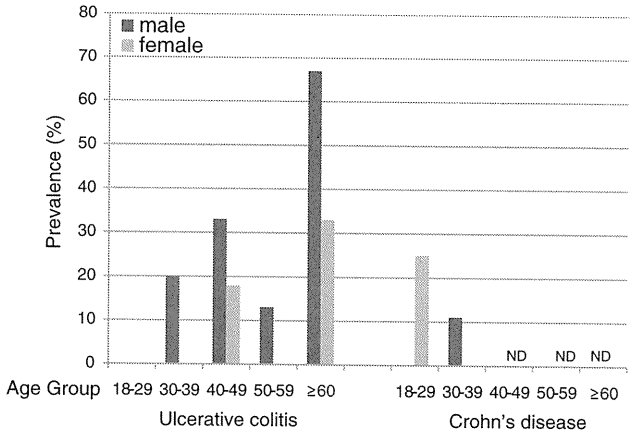

Fig. 2 Prevalence of metabolic syndrome in different age and sex groups with UC and CD. Data are shown as % of total patients observed in each group. ND represents "no data"

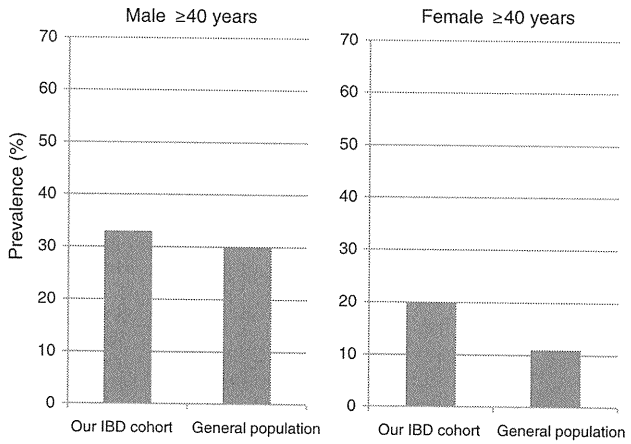

Fig. 3 Prevalence of MS in our IBD cohort and the Japanese general population in both males and females aged 40 years or older. No difference was observed in the prevalence of MS between these two cohorts in both males and females ($P = 0.707$ in males, $P = 0.328$ in females)

23.0% (17 of 74) and 7.1% (2 of 28), respectively [odds ratio = 3.88, 95% confidence interval (CI) = 0.83–18.02]. However, the difference was not significant ($P = 0.089$). The prevalence of MS in male and female patients was 21.1% (15 of 71) and 12.9% (4 of 31), respectively. Thus, MS appeared to be more prevalent in male IBD patients, but statistical analysis revealed no significant difference ($P = 0.414$).

The prevalence of MS in different age cohorts (18–29, 30–39, 40–49, 50–59, and ≥60 years of age) is shown in Fig. 2. MS was observed at a relatively higher prevalence in male UC patients over 30 years of age. No difference was observed in the prevalence of MS between our IBD cohort and the Japanese general population, which was comprised of 1,806 males and 2,600 females, in both males and females aged 40 years and older ($P = 0.707$ in males, $P = 0.328$ in females), as shown in Fig. 3 [9].

We then compared the possible risk factors of MS, such as patient demographics, IBD treatment, and social habits between IBD patients with and without MS. The results are shown in Table 2. No difference was found between the two cohorts in gender, IBD type (UC or CD), duration of disease, history of intestinal resection, medications, social history such as marital or work status, or health-related lifestyle characteristics such as exercise, sleeping, drinking, and smoking. IBD patients with MS were older than those without (50.2 ± 15.0 vs. 38.0 ± 11.9 years, $P = 0.013$). In addition, at the time of diagnosis of IBD, IBD patients with MS were older than those without (41.6 ± 16.7 vs. 30.9 ± 11.5, $P = 0.011$). Next, we performed a multivariate logistic regression analysis to determine the independent risks factors for MS. As shown in Table 3, age was the statistically significant predictor of MS among IBD patients. Odds ratios (95% confidence interval) were 1.064 (1.017–1.114).

Discussion

According to Japan's nationwide population-based survey, the prevalence of MS in a healthy population aged 40 years of age or older has been reported to be 30% and 11% in males and females, respectively [9]. The present study revealed that the prevalence of MS in our IBD patients in the same age group was comparable to that of the general population, suggesting that MS is not a rare complication among IBD patients.

Our study also revealed that in IBD patients, MS was observed at a relatively higher prevalence in male UC patients over 30 years of age. This difference in MS prevalence in UC versus CD patients might be explained solely by the difference in age distribution in these two cohorts in our study, as well as in the general IBD population [28], but not by differences in the underlying diseases. In fact, age, not IBD type, was the predictor of developing MS in a multivariate logistic regression analysis. An increasing prevalence of MS with increased age has also been observed in the general population [9], suggesting that the risk of developing MS is comparable between IBD patients and the general population. Because the present study was a cross-sectional study but not a prospective one, whether MS contributes to the development of IBD as well as its effects on disease activity and long-term prognosis remains unknown.

Because this study found that MS was common in IBD patients, the application of secondary prevention measures for diabetes and CVD in these patients may be required to improve their long-term prognosis. As Gutierrez commented in an editorial, we need to further increase awareness of secondary prevention of CVD in patients with IBD [29]. Lifestyle changes to prevent CVD are expected

Table 2 Comparison of IBD patients with and without metabolic syndrome

	MS	Non-MS	*P* values
n	19	83	
Gender (male/female)	15/4	56/24	0.41
Age, mean ± SD (years)	50.2 ± 15.0	38.0 ± 12.0	0.013
UC/CD	17/2	57/26	0.089
Age at diagnosis, mean ± SD (years)	41.6 ± 16.7	30.9 ± 11.5	0.011
Disease duration, mean ± SD (years)	8.6 ± 7.9	7.1 ± 7.7	0.26
History of intestinal resection (*n*)	3	10	0.70
Medication (*n*)			
5-Aminosalicylates	16	59	0.39
Immunomodulators	7	35	0.8
Corticosteroids	1	5	1
Infliximab	1	7	1
Married/unmarried	11/8	38/44	0.45
Employed (full and part time)/unemployed	14/6	66/17	0.36
Weekly exercise days (0–2/3–5/6≤)	15/3/1	65/15/3	0.93
Smoking (Ex-S/Non-S/S)	5/10/4	24/48/11	0.71
Sleeping hours, mean ± SD (h)	6.1 ± 1.0	6.3 ± 1.1	0.39
Weekly sleeping pill use (N/1–4/5≤)	16/1/2	70/6/6	0.86
Weekly drinking days (N/1–4/5≤)	14/5/0	55/25/3	0.64

Table 3 Result of logistic regression to predict the development of MS

	Age	Disease duration	IBD type (UC or CD)	Sex
Development of MS	1.064 (1.017–1.114)*	1.001 (0.931–1.077)	1.846 (0.151–10.671)	0.541 (0.319–10.671)

Odds ratio (confidence interval)

* $P < 0.05$

to reduce not only the risk of CVD, but also the risk of dysplasia and colorectal cancer development in IBD patients [17, 18, 30, 31]. Furthermore, a case report suggested that reducing body weight might also contribute to decreasing disease activity in UC [32]. Holtmann et al. [33] have also recently shown improved outcomes after azathioprine treatment in UC patients with BMI maintained under 25, suggesting the benefit of body weight control in IBD patients. The results from our study emphasize the importance of lifestyle modifications, such as regular exercise, body weight reduction, and smoking cessation, not only in the general population, but also in IBD patients. Because our study also suggests that MS is associated with age, secondary prevention in the elderly IBD cohort might be highly beneficial for improving the overall disease prognosis.

The prevalence of MS observed in our cohort might have been confounded by medical treatment for IBD. However, patients in this study were mainly treated with 5-aminosalicylates and/or immunomodulators. Although corticosteroid treatment has been reported to promote the development of MS [34], only 1 out of 19 IBD patients with MS was being treated with corticosteroids in the present study. Thus, the contribution of medical treatments to MS prevalence in our cohort is likely to be minimal.

Another limitation of our study is that the results might have been different in the nationwide IBD population because the cohort analyzed in our study consisted of a limited number of patients recruited from our institute, an urban, academic medical center specializing in IBD. Therefore, a prospective study using a larger cohort is required to confirm our results and to clarify the true contribution of MS to disease activity and prognosis, as measured by hospitalizations, surgical treatments, etc.

In conclusion, MS is an unexpectedly common complication in elderly IBD patients. Early identification and intervention for IBD patients complicated by MS that is directed at preventing the development of diabetes and cardiovascular complications might improve the long-term prognosis of these patients.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Ectopic expression of blood type antigens in inflamed mucosa with higher incidence of *FUT2* secretor status in colonic Crohn's disease

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Abstract
Background Host–intestinal microbial interaction plays an important role in the pathogenesis of inflammatory bowel diseases (IBDs). The surface molecules of the intestinal epithelium act as receptors for bacterial adhesion and regulate the intestinal bacteria. Some known receptors are the mucosal blood type antigens, which are regulated by the fucosyltransferase2 (*FUT2*) gene, and individuals who express these antigens in the gastrointestinal tract are called secretors. Recent research has revealed that the *FUT2* gene is associated with Crohn's disease (CD) in western populations.
Methods To clarify the contribution of mucosal blood type antigens in IBD, we determined the incidence of five previously reported single-nucleotide polymorphisms of the *FUT2* gene in Japanese patients. We also used immunohistochemistry to investigate the antigen expression in mucosal specimens from IBD patients and animal models.
Results Genetic analysis revealed that all of the patients with colonic CD were secretors, whereas the incidence of secretors was 80, 80, 67, and 80%, respectively, for the control, ileocolonic CD, ileal CD, and ulcerative colitis groups ($P = 0.036$). Abnormal expression of blood type antigens was observed only in colonic CD. Interleukin-$10^{-/-}$ mice, but not dextran sulfate sodium colitis mice, had enhanced colonic expression of blood type antigens, and the expression of these antigens preceded the development of colitis in the interleukin-$10^{-/-}$ mice.
Conclusions *FUT2* secretor status was associated with colonic-type CD. This finding, taken together with the immunohistochemistry data, suggests that the abnormal expression of blood type antigens in the colon may be a unique and essential factor for colonic CD.

Keywords Colonic Crohn's disease · *FUT2* · Blood type antigen

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Introduction

Inflammatory bowel diseases (IBDs) are chronic intestinal disorders that include Crohn's disease (CD) and ulcerative colitis (UC). The specific etiology of IBD remains unknown, but accumulating evidence has revealed that intestinal microorganisms play an important role. Thus far, no single specific bacterium has been identified as a cause of IBD, but many studies have shown that IBD patients have an imbalance in their intestinal flora [1–5]. Under normal conditions, the intestinal immune system does not overreact to commensal bacteria. Two principles are

thought to be involved in this delicate control: (1) bacteria are separated from mucosal immune cells by epithelial cells and their product, mucins [6, 7]; and (2) intestinal immune cells are by nature tolerant of commensal bacteria [8–10]. In the former context, many studies have shown that certain microorganisms can adhere to gastrointestinal mucosa by taking advantage of mucosal glycochains as their receptors. One well-known example is *Helicobacter pylori*, which is a cause of chronic atrophic gastritis and peptic ulcers and adheres to gastric mucosa through a surface molecule known as blood-group antigen-binding adhesin (BabA). The major receptors for BabA are fucosylated blood group antigens ABH(O) or Lewis b, which are expressed in the gastric mucins as well as epithelial cells [11–14]. It has also been reported that human blood group antigens in the gut mucosa might serve as receptors for Norwalk virus [15, 16] and *Campylobacter jejuni* [17].

The expression of blood group antigens ABH(O) in the gastrointestinal (GI) tract is regulated by the *FUT2* gene encoding the Se enzyme [18]. Individuals with wild-type homozygous or heterozygous *FUT2* express these blood group antigens in the GI tract and are called secretors. It has been reported that secretors express the antigens widely in the stomach and small intestine. However, the antigen expression decreases progressively from the proximal to the distal colon, and almost disappears in the rectum [19, 20]. On the other hand, individuals who are homozygous for the Se-enzyme-deficient alleles do not express blood type antigens in the colon. A nonsense mutation (G428A, se1) was found first in Caucasians [18], although it has not been detected in Japanese people. Instead, a missense mutation (A385T, se2), two nonsense mutations (C571T, se3 and C628T, se4), and a fusion gene (se5) have been reported in Japanese people. Approximately 25% of Japanese individuals are non-secretors who are homozygous for these Se enzyme-deficient alleles [21]. It has also been reported that the prevalence of non-secretors is ~20% in many ethnic populations [18, 22].

Recently, McGovern et al. [23] carried out linkage analysis of subjects of Northern European origin and reported that the *FUT2* non-secretor status was associated with CD, which highlights the role of glycochains in the pathogenesis of CD. In this study, we explored further the involvement of blood type antigens in IBD, using a genetic approach and immunohistochemistry of mucosal specimens. Our study showed that, in the Japanese population, the prevalence of secretors was significantly higher in individuals with colonic CD than in healthy controls and individuals with other types of IBD. Moreover, considering that abnormal expression was found only in colonic CD patients and a murine model for CD colitis, it appears that mucosal blood type antigens may play a unique and essential role in the pathogenesis of colonic-type CD.

Subjects, materials, and methods

Blood samples

Blood samples were obtained from 21 patients with colonic CD, 30 patients each with ileal CD, ileocolonic CD, and UC, and 30 controls at Keio University Hospital. The study was approved by the Keio University School of Medicine ethics board. The purpose and nature of this study were explained to each subject, and written informed consent was obtained. All subjects were Japanese. CD or UC was diagnosed based on clinical, radiographic, endoscopic, and histological criteria established by The Japanese Research Committee of Inflammatory Bowel Disease, supported by the Ministry of Health, Labour and Welfare.

Diagnostic misclassification reduces the ability to detect linkage in IBD genetic studies [24]; therefore, lesion distribution was carefully determined and other intestinal disorders were ruled out by the radiographic and endoscopic findings. The study was designed and performed in accordance with the principles of the Declaration of Helsinki V.

FUT2 genotyping

The open reading frame of *FUT2* is encoded by a single exon, exon 2. Samples of genomic DNA were obtained from peripheral blood leukocytes, and the specific region of the *FUT2* gene was amplified from genomic DNA by the polymerase chain reaction (PCR), followed by direct sequencing. To detect G428A (se1), A385T (se2), C571T (se3), and C628T (se4), and to rule out the fusion gene (se5), the primers targeted nucleotides 94–117 and 818–841 of *FUT2*; 5′-GTG CAG ATA CCA GTG CTA GCC TCA-3′ and 5′-CGA ACG TCC CAA TGG TCA TGA TGG-3′. The PCR materials using the iCycler thermal cycler 170-8720JA (Bio-Rad Laboratories, Tokyo, Japan) were as follows: 1.25 U PrimeStar HS DNA polymerase (Takara, Shiga, Japan), 200 μM dNTP mixture (Takara), 0.2 μM each primer, and 200 ng genomic DNA in 10 μM PrimeStar buffer (Takara). The PCR conditions were as follows: initial denaturation at 94°C for 2 min, followed by 35 cycles of denaturation at 98°C for 10 s, annealing at 56°C for 15 s, and extension at 72°C for 35 s.

The PCR products were purified by phenol/chloroform extraction and ethanol-precipitated. Sequences were analyzed using ABI Prism BigDye Terminator Cycle Sequencing Kits (Applied Biosystems, Foster City, CA, USA); the sequence primers were those used for PCR amplification. The cycle-sequencing products were analyzed by the Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems) according to the manufacturer's instructions.

Statistical analysis

Case–control analyses of *FUT2* phenotypes were performed with χ^2 statistics or Fisher's exact test by using IBM SPSS Statistics version 18 (SPSS, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Human tissue specimens

Colonic tissue specimens were studied immunohistochemically for expression of the blood group antigen. Rectal tissues were analyzed from five patients with colonic CD, three with ileocolonic CD, five with UC, and five controls. All these individuals had blood type A. All specimens were taken during colonoscopies performed at Keio University Hospital. The biopsied specimens obtained from CD/UC patients were inflammatory lesions, and the control group underwent examination for neoplastic lesions or health check-ups.

Human immunohistochemistry

First, we deparaffinized sections of 20% formalin-fixed paraffin-embedded rectal specimens from endoscopic biopsies, by performing the following washes at room temperature: (1) xylene: 2 × 3 min; (2) xylene 1:1 with 100% ethanol: 3 min; (3) 100% ethanol: 2 × 3 min; (4) 95% ethanol: 3 min; (5) 70% ethanol: 3 min; (6) 50% ethanol: 3 min; and (7) Dulbecco–PBS without Ca, Mg (PBS) (Immuno-Biological Laboratories, Gunma, Japan): 2 × 3 min. After deparaffinization, the sections were incubated with a mouse monoclonal antibody to blood group A antigen (ab3353) (Abcam, Cambridge, UK) at 4°C overnight in a moist chamber. After the primary reaction, the sections were washed twice with PBS, incubated with peroxidase-conjugated goat anti-mouse/rabbit IgG polyclonal antibodies (Nichirei, Tokyo, Japan) at room temperature for 30 min, developed with 3,3′-diaminobenzidine and H_2O_2 in PBS (Nichirei) for 3 min, and counterstained with hematoxylin. Positive staining was defined as the presence of stained goblet cells. If only the apical membrane of the epithelial cells was stained, this was considered non-specific staining.

Mouse immunohistochemistry

C57BL/6 (wild-type; WT), dextran sulfate sodium (DSS) model, and interleukin 10-deficient (IL-$10^{-/-}$) mice were raised under specific-pathogen-free (SPF) conditions. The DSS model and IL-$10^{-/-}$ mice were generated on a C57BL/6 background. DSS model mice were given 3% DSS from 8 weeks of age. The WT, DSS model, and IL-$10^{-/-}$ mice were killed between 8 and 10 weeks, and their colons were fixed in 10% formaldehyde. Tissues were embedded in paraffin and histological staining was performed. A mouse monoclonal antibody to blood group H1 antigen (GTX23355) (GeneTex, Irvine, CA, USA) was used for the primary reaction, and the immunohistochemistry protocol was the same as that described above.

Results

Analysis of *FUT2* single-nucleotide polymorphisms

We explored the single-nucleotide polymorphisms (SNPs) of *FUT2*, which determine the expression of blood group antigens in the GI tract, including the colon [18, 19, 21], in the CD, UC, and control groups. We analyzed 21 patients with colonic CD, 30 each with ileal CD, ileocolonic CD, and UC, and 30 control patients. The characteristics of the patients are shown in Table 1.

PCR products of *FUT2* were obtained from all patients, indicating that none was homozygous for the fusion gene (se5). We investigated four common *FUT2* SNPs (se1–4) by DNA sequencing (Fig. 1). A385T (se2) was the only mutation detected; we did not find G428A (se1), C571T (se3), or C628T (se4). The distributions of genotype, allele frequency, and phenotype of *FUT2* are listed in Table 2. In accordance with previous studies, 80% of the healthy controls in this study were secretors. Surprisingly, all colonic CD patients were secretors, which was significantly higher than the proportion in the control group (80%) ($P = 0.036$). The proportions of secretors in the ileocolonic CD, ileal CD, and UC patients were 80, 67, and 80%, respectively.

Human colonic expression of blood group antigen

To determine whether blood group antigen was actually expressed in the GI tract, we performed immunohistochemistry of colonic specimens from patients with blood type A. In accordance with previous studies, the expression

Table 1 Subjects recruited in this study

	Crohn's disease (CD)			Ulcerative colitis	Healthy controls
	Colonic	Ileal	Ileocolonic		
N	21	30	30	30	30
Sex (M/F)	15/6	26/4	20/10	12/18	18/12
Age, years (mean ± SD)	31.8 ± 10.0	39.7 ± 10.0	33.3 ± 12.1	34.5 ± 13.1	31.4 ± 6.9

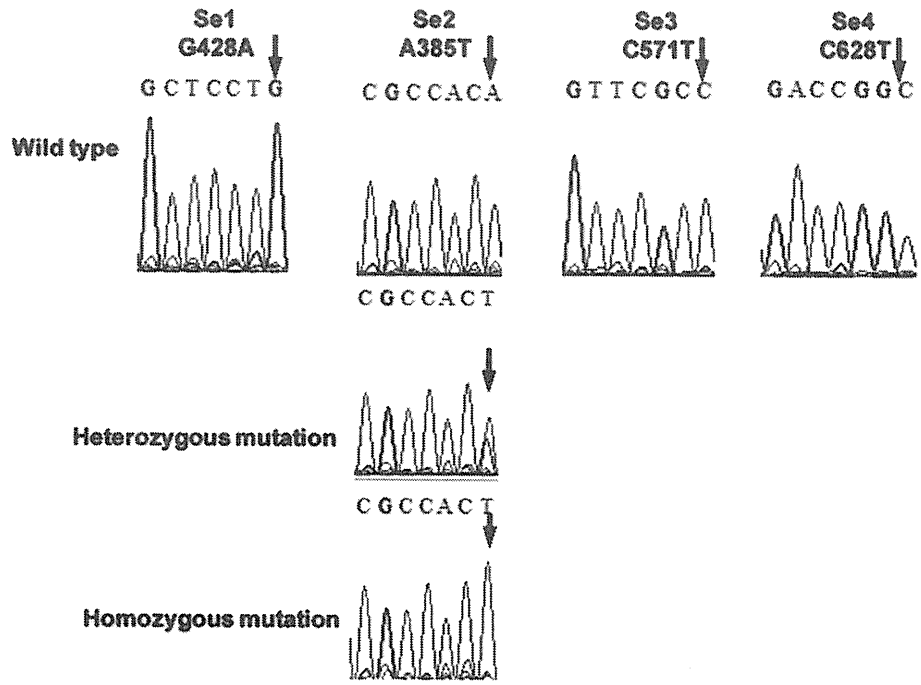

Fig. 1 DNA sequence electropherograms of four common *FUT2* single-nucleotide polymorphisms (SNPs) (se1–4)

Table 2 Distributions of genotype, allele, and phenotype of the *FUT2* polymorphisms

	CD			Ulcerative colitis ($n = 30$)	Healthy controls ($n = 30$)
	Colonic ($n = 21$)	Ileal ($n = 30$)	Ileocolonic ($n = 30$)		
A385T					
Genotype					
A/A	11	11	9	9	10
A/T	10	9	15	15	14
T/T	0	10	6	6	6
Allele					
A	32	31	33	33	34
T	10	29	27	27	26
Phenotype					
Secretor	21*	20	24	24	24
Non-secretor	0	10	6	6	6

* $P = 0.036$

of blood group antigen had a proximal–distal gradient in the normal colon, and it was virtually negative in the rectum (Fig. 2a, b). However, surprisingly, we detected blood group antigen A in two of five patients with colonic CD (Fig. 2c, d). This finding was exclusive to specimens from colonic CD patients, because we could not detect this expression in ileocolonic CD or UC specimens (Fig. 2e–h). Because all IBD rectal samples had chronic inflammation, it could be concluded that the blood type antigen A observed in colonic CD was not merely a reflection of concomitant inflammation. Combined with the SNP results, this result may highlight a unique and essential role for blood type antigens in mucosal inflammation in colonic CD.

Murine colonic expression of blood group antigen

To determine further the role of mucosal blood group antigen in the pathogenesis of IBD, we examined murine samples from two experimental IBD models. IL-$10^{-/-}$ mice develop spontaneous chronic colitis that resembles human CD colitis, whereas DSS colitis is considered to be an acute colitis model. In WT mice, the goblet cells in the colonic mucosa were weakly positive to antibody against blood group H1 antigen (Fig. 3a), as reported previously [25, 26]. In contrast, the colonic mucosa from 10-week-old IL-$10^{-/-}$ mice clearly showed strong staining (Fig. 3b) and all four mice examined had symptoms of colitis, such as rectal prolapse and diarrhea. The presence of inflammation

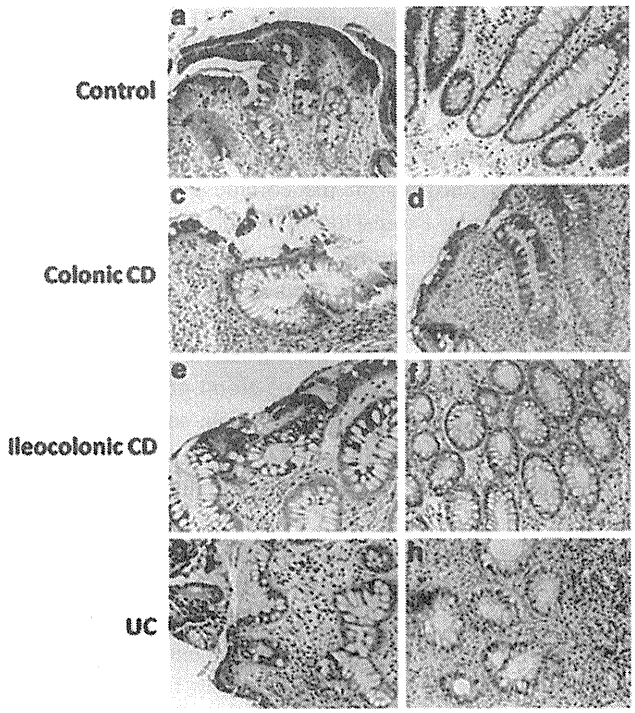

Fig. 2 Immunohistochemistry in colonic specimens from individuals with blood type A. The tissue sections were stained for the blood group A antigen using a monoclonal antibody. Representative sections from the ascending colon and rectum are shown at identical magnifications of ×200. Blood group A antigen was expressed in the ascending colon of the control (**a**), colonic Crohn's disease (*CD*) (**c**), ileocolonic CD (**e**), and ulcerative colitis (*UC*) (**g**) subjects. Blood group A antigen was positive in the rectum of colonic CD patients (**d**), but not in the control group (**b**), or in ileocolonic CD (**f**) or UC (**h**) patients

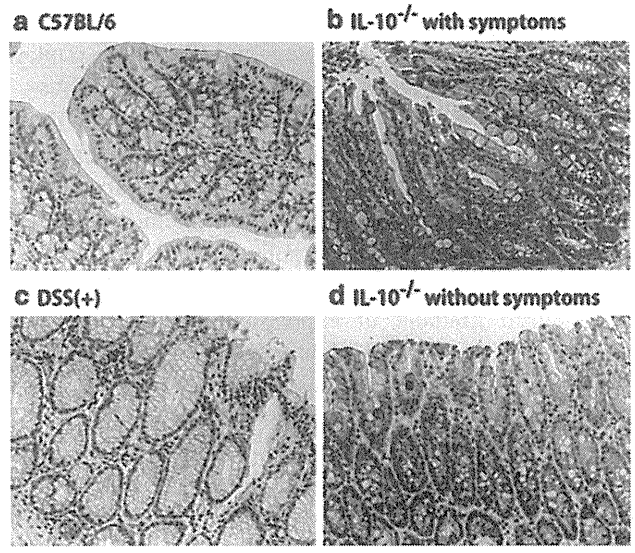

Fig. 3 Immunohistochemistry in specimens from inflammatory bowel disease (IBD) animal models. The tissue sections were stained for the blood group H1 antigen, using a monoclonal antibody. Specimens from wild-type (WT) mice showed weak staining in goblet cells (**a**). In contrast, goblet cells were strongly positive in interleukin (*IL*)-$10^{-/-}$ mice with colitis symptoms (**b**). The staining was weak in dextran sulfate sodium (*DSS*) mice (**c**). Younger IL-$10^{-/-}$ mice showed strong H1 staining in the absence of inflammation (**d**). Representative sections are shown at identical magnifications of ×200

was confirmed histologically. On the other hand, the intensity of H1 staining in four DSS mice was similar to that of WT mice, although they suffered from severe colitis, both clinically and histologically (Fig. 3c). These findings again suggested that the abnormal expression of blood type antigen was a unique feature in chronic colitis reminiscent of CD.

We examined four 8-week-old IL-$10^{-/-}$ mice without clinical symptoms. Surprisingly, we observed strong H1 staining in the colon, although there was no histological inflammation (Fig. 3d). This suggests that the abnormal expression of blood type antigens precedes the development of inflammation.

Discussion

Microorganisms are considered to play an essential role in the pathogenesis of IBD. Two hypotheses have arisen to explain how they cause chronic intestinal inflammation. One is that IBD patients inherently have an excessive immune response to normal gut flora. The other is that they have an imbalance in their flora, especially in terms of protective or harmful species. Swidsinski et al. [1] observed high concentrations of bacteria forming a biofilm on the surface of IBD mucosa. Moreover, several bacterial species have been reported to expand or be diminished in inflamed IBD mucosa. For instance, Sokol et al. [27] found a small population of *Faecalibacterium prausnitzii* in CD. Other investigators have reported that IBD patients have increased numbers of mucosa-associated *Escherichia coli* in the gut [28].

What causes this imbalance of intestinal flora in IBD patients? Although an abnormal composition can result from inflammation itself, possibly through the over-production of inflammatory cytokines, one regulatory factor could be the epithelial surface molecules that function as receptors for bacterial adhesion. Recently, Carvalho et al. [29] have shown that abnormally expressed carcinoembryonic antigen-related cell adhesion molecules in the ileum act as receptors for pathogenic *E. coli*. In the present study, we focused on the glycochain that might alter the composition of intestinal flora, taking a hint from the fact that epithelial ABO blood type antigens help *H. pylori* adhere to the gastric mucosa. In secretors, who have *FUT2 wild-type* or heterozygous mutation, blood type antigens are expressed on the intestinal epithelial surface, as well as

being present in the mucins that overlie the epithelium. During the time that we were preparing this manuscript, McGovern et al. [23] reported that *FUT2* was a CD susceptibility gene in Caucasians. We also found that the *FUT2* genetic status was associated with CD, but exclusively with colonic CD, in the Japanese population. In addition, we determined by immunohistochemistry whether blood type antigens were expressed in IBD inflamed mucosa. It has been shown that the normal colon has a proximal–distal gradient of expression of blood group antigen. Therefore, we focused on rectal specimens, which normally lack blood type antigens, and found that in some patients with colonic CD these antigens were expressed in inflamed rectal mucosa. Surprisingly, we could not detect their expression in specimens from either ileocolonic CD or UC. Together with the SNP data, this finding suggests that ABO blood type expression is not simply a result of colonic inflammation, but rather a specific feature of colonic CD.

Our result appears to contradict that of McGovern et al. [23], which indicated that *FUT2* non-secretor status was associated with CD. We suggest two possible explanations for this difference in results. First, there could have been a difference between the proportions of colonic CD patients in the two studies. We examined about 30 patients for each of the three phenotypes. Colonic CD is generally the least prevalent phenotype; therefore, the significance might have been obscured when a randomly recruited CD group was analyzed, as in the study of McGovern et al. [23]. Indeed, in our study, the proportion of patients with non-secretor status in the ileal CD group was higher than that in the healthy controls, although there was no statistically significant difference. Second, differences in the study populations could have been of importance. Although many CD susceptibility genes have been reported to date, the data are often inconsistent, varying according to the ethnic background. Even *NOD2/CARD15*, the most prominent CD-associated gene in the western population [30–32], has been reported not to be mutated in Asian individuals, including the Japanese [33].

Does the expression of blood group antigens in inflamed mucosa precede the development of inflammation? To answer this important question, we examined IL-$10^{-/-}$ mice, which are the most widely used animal model for IBD. These mice develop spontaneous colitis when raised under SPF conditions [34]. The fact that they do not suffer from colitis under germ-free conditions highlights the essential role of commensal bacteria in the pathogenesis of this CD-like murine colitis [35–37]. We performed immunohistochemistry investigations with antibodies against H antigen because previous studies have shown that mice express H antigens in colonic mucins, by the action of a fucosyltransferase that is encoded by the *FUT2* gene, as in humans [25, 26]. As shown in Fig. 3, H antigens were expressed weakly throughout the colon in WT mice. In accordance with the results from our human study, we found that 10-week-old IL-$10^{-/-}$ mice with colonic inflammation, compared with the WT mice, had stronger expression of H antigens on the colonic epithelium. We also observed strong expression of H antigens in younger mice without colonic inflammation. This finding shows that abnormal expression of blood type antigens precedes the development of inflammation, which implies that this abnormal expression is one of the causative factors of CD colitis. In addition, the expression of blood group antigens did not change in the presence of IL-10 in several human colon cell lines (data not shown), suggesting that expression in the epithelial cells may not be regulated directly by IL-10. On the other hand, in DSS mice, irrespective of severe inflammation, the expression of H antigens turned out to be weak, similar to that in normal mice. This finding also supports the idea that the altered expression of mucosal blood type antigens is a phenomenon unique to colonic CD.

Which specific bacteria cause chronic inflammation through upregulated blood type antigens in colonic CD? According to previous studies that have analyzed human intestinal bacteria, no specific species increased or decreased in numbers, but rather, the microfloral composition was altered in IBD patients [5, 38]. In IL-$10^{-/-}$ mice, Kim et al. [37] showed, by inoculating different bacterial species into mice raised under germ-free conditions, that *Enterococcus faecalis* and *E. coli*, but not *Pseudomonas fluorescens*, provoked inflammation. This monobacterial-associated system further clarifies the mutual interaction between commensal bacteria and blood type antigens on the colonic epithelium. Moreover, there could be numerous glycochains, in addition to ABO antigens, that can affect the adhesion of bacteria to the intestinal epithelium [39, 40]. Exhaustive investigations, such as those using a lectin-microarray approach, will be a promising modality for the comprehensive understanding of glycochains that are expressed on the epithelium in normal and pathological states. The glycochains involved in mucosal inflammation might differ among the types of IBD.

In conclusion, our study showed that *FUT2* secretor status was associated with colonic type CD, and that blood type antigens were expressed abnormally in patients with this type of CD, as well as in murine CD-like colitis. These data suggest that abnormal expression of glycochains, that is, blood type antigens, help bacteria adhere to the gut epithelium and could provoke inflammation. We believe that our study emphasizes the role of surface molecules on epithelial cells as receptors for intestinal bacteria, which are considered to be a key player in the pathogenesis of IBD.

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Conflict of interest The authors declare that they have no conflict of interest.

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GASTROENTEROLOGY

Diagnosis and treatment of functional gastrointestinal disorders in the Asia-Pacific region: A survey of current practices

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Abstract

Background and Aims: Functional gastrointestinal disorders (FGIDs), namely functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common disorders important to public health in the Asia-Pacific region. Our objectives were to determine the current practices in diagnosis and management of these disorders in the Asia-Pacific region.

Methods: Forty-three physicians and researchers in FGID who attended the first Asian Pacific Topic Conference at Tokyo in November 2010 were invited to answer a questionnaire. Twenty-three Japanese doctors and twenty doctors from other Asia-Pacific Societies answered the questionnaire, which consisted of 60 multiple-choice questions concerning physician's preferences in diagnosis and management of FGIDs.

Results: Overall, there were similarities in diagnostic approach, such as differential diagnosis, exclusion of organic diseases, psychophysiological assessment, medical advice or medication with psychological drugs, not only among different Asia-Pacific region but also between FD and IBS. Several notable differences were seen. For example, general practitioners did not commonly use the term FD or diagnose FD by themselves, while the term IBS was widely used and frequently diagnosed. Sub-categorization was more common in IBS than FD. There was also a difference between Japan and other Asia-Pacific region; upper GI endoscopy and blood examination were more common in Japan, while eradication of *Helicobacter pylori* was more frequently done in other countries. Anti-secretory drugs for FD and mild laxatives or anti-diarrheal drug for IBS were frequently used, and prokinetics were used for all patients with FD or IBS. Interestingly, drugs developed in Japan and Chinese herbal medicines were more frequently prescribed in Japan.

Conclusion: Information obtained in this survey is useful for understanding the most common clinical approaches for FGIDs in the Asia-Pacific region.