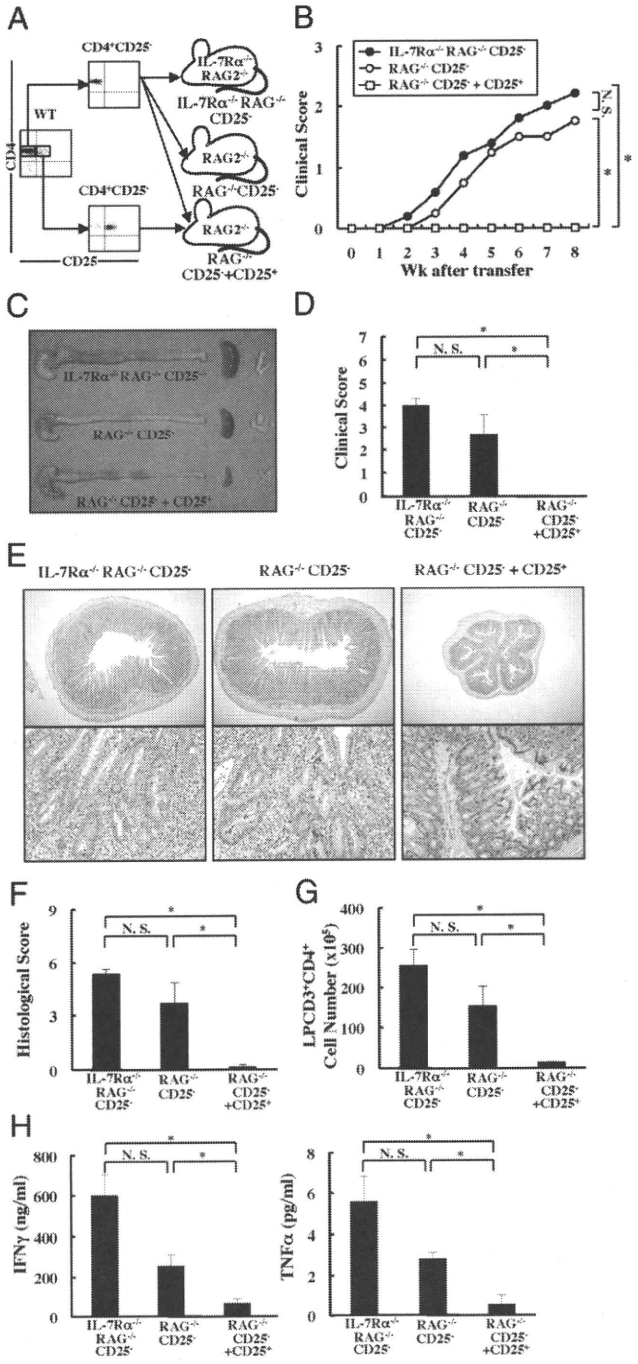

FIGURE 6. IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ transferred with WT CD4$^+$CD25$^-$ T cells developed chronic colitis. *A*, RAG-2$^{-/-}$ mice and IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ mice were transferred with splenic WT CD4$^+$CD25$^-$ T cells (3×10^5 cells per mouse). As a negative control, RAG-2$^{-/-}$ mice were transferred with splenic WT CD4$^+$CD25$^-$ T cells (3×10^5 cells per mouse) and CD4$^+$CD25$^+$ Tregs (1×10^5 cells per mouse). *B*, Disease activity index during 8 wk after transfer. *$p < 0.05$. *C*, Gross appearance of the colon, SP, and mesenteric lymph nodes from IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells (*top*), RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells (*middle*), and RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells and CD4$^+$CD25$^+$ Tregs. *D*, Clinical scores were determined at 8 wk after the transfer as described in *Materials and Methods*. Data are indicated as the mean ± SEM of seven mice in each group. *$p < 0.001$. *E*, Histologic examination of the colon from IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells (*left*), RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells (*middle*), and RAG-2$^{-/-}$ mice transferred with CD4$^+$CD25$^-$ T cells and CD4$^+$CD25$^+$ Tregs (*right*). Original magnification ×40 (*upper*) and ×100 (*lower*). *F*, Histologic scoring 8 wk after transfer. Data are indicated as the mean ± SEM of seven mice in each group. *$p < 0.05$. *G*, LP CD3$^+$CD4$^+$ T cells were isolated at 11 wk after transfer, and the number was determined by flow cytometry. Data are indicated as the mean ± SEM of seven mice in each group. *$p < 0.05$. *H*, Cytokine production by LP CD4$^+$ T cells. LP CD4$^+$ T cells were isolated at 11 wk after transfer and stimulated with anti-CD3 and anti-CD28 mAbs for 48 h. IFN-γ and TNF-α concentrations in culture supernatants were measured by ELISA. Data are indicated as the mean ± SD of seven mice in each group. *$p < 0.05$.

some LP populations, such as NK cells, granulocytes, macrophages, and CD11b$^+$CD11c$^+$ myeloid dendritic cells, in colitic mice was significantly downregulated compared with that in normal mice, the expression level of IL-7Rα on colitic CD4$^+$ T cells was conversely high, with the result that colitogenic memory CD4$^+$ T cells sustain the highest expression of IL-7Rα in inflammatory conditions.

IL-7Rα$^{-/-}$ mice are originally lymphopenic, because of the loss of IL-7/IL-7R signaling pathway in lymphocytes, which is a critical factor for their development in the thymus and their maintenance in the periphery. Comparison of the surface phenotypes of SP CD4$^+$ T cells in IL-7Rα$^{-/-}$ and WT mice by flow cytometric analysis revealed no significant differences in the expression of CD69, CD25, and Foxp3 (Fig. 2*A*). Manifestation of an antiapoptosis molecule Bcl-2 of CD4$^+$ T cells from IL-7Rα$^{-/-}$ mice was lower than that of CD4$^+$ T cells from WT mice, which corresponds to the previous reports that the IL-7/IL-7R signal maintains T cells, upregulating the antiapoptosis molecule. Nevertheless, we detected a substantial number of CD44^{low}CD62L$^+$ naive CD4$^+$ T cells resident in the SPs of IL-7Rα$^{-/-}$ mice, although their relative number in IL-7Rα$^{-/-}$ mice was significantly lower than that in WT mice. Because of the scarcity of naive CD4$^+$ T cells in IL-7Rα$^{-/-}$ mice, it was possible that the failure of some part of naive T cells to develop might occur in the thymus, which would lead to the loss of some TCR repertoires needed for the onset of colitis. Thus, we compared the TCR Vβ repertoires of SP CD4$^+$ T cells in IL-7Rα$^{-/-}$ mice to those in WT mice. However, except in the ratio of Vβ8.3, no evidence was found of skewed development in TCR Vβ repertoires between age-matched IL-7Rα$^{-/-}$ and WT mice.

As expected, RAG2$^{-/-}$ mice transferred with SP IL-7Rα$^{-/-}$ CD4$^+$CD25$^-$ T cells did not develop colitis, in sharp contrast to colitic RAG2$^{-/-}$ mice transferred with WT CD4$^+$CD25$^-$ T cells. Nevertheless, flow cytometric analysis revealed that SP and LP CD4$^+$ T cells from RAG2$^{-/-}$ mice transferred with IL-7Rα$^{-/-}$ CD4$^+$CD25$^-$ T cells differentiated to CD44^{high}CD62L$^-$ T_{EM} cells as well as those from colitic RAG2$^{-/-}$ mice transferred with WT CD4$^+$CD25$^-$ T cells. This result suggests that IL-7R deficiency in CD4$^+$ T cells causes the disorder of cell proliferation or maintenance rather than the impaired development of memory CD4$^+$ T cells, in accordance with the downmodulated Bcl-2 expression of IL-7Rα$^{-/-}$ CD4$^+$ T cells. As shown in Fig. 3*H*, production of Th1 cytokines from recovered LP CD4$^+$ T cells of the IL-7Rα$^{-/-}$ CD25$^-$ group was significantly lower than that of the WT CD25$^-$ group. However, IL-7Rα$^{-/-}$ CD4$^+$ T cells could express Th1 and Th17 cytokines to an extent similar to that in WT CD4$^+$ T cells in the colitic condition (Fig. 4). Therefore, we conclude that disorder of IL-7Rα$^{-/-}$ CD4$^+$ T cells to proliferate and survive is the main mechanism underlying their inability to induce colitis, whereas their reduced inflammatory cytokine production is a secondary effect. Furthermore, we also analyzed other common γ-receptor–associated receptor IL-15Rβ to determine whether it was upregulated to compensate for the lack of IL-7Rα. However, no dif-

ference was found in the expression of IL-15Rβ on SP or LP $CD4^+$ T cells from each group. These results suggest that IL-7Rα expression on colitogenic $CD4^+$ T cells is essential for the development and persistence of colitis.

Next, we used IL-7Rα$^{-/-}$ × RAG2$^{-/-}$ mice to access the importance of the IL-7/IL-7Rα signaling pathway in non-T cells. At the start of this project, we hypothesized that IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ mice transferred with $CD4^+CD25^-$ T cells would develop more severe colitis than the control transferred RAG-2$^{-/-}$ recipient mice by considering two points. First, we thought that the availability of IL-7 for colitogenic $CD4^+$ T cells might increase in IL-7Rα$^{-/-}$ × RAG2$^{-/-}$ mice as a result of the loss of IL-7 consumption by IL-7Rα–lacking non-T cells. Actually, IL-7 concentration in serum from IL-7Rα$^{-/-}$ mice is reported to be higher than that from WT mice (31). Thus, it was possible that the persistence of colitogenic memory $CD4^+$ T cells is affected by those cells in the form of IL-7 competition. Second, we had to consider the presence of newly identified RORγt$^+$ IL-22–producing NK cells (so called NK-22 cells) (27–29, 32, 33) for the development of chronic colitis, because it has been shown that these NK-22 cells constitutively express IL-7Rα. Importantly, it has been reported recently that IL-22 is protective in murine DSS-induced colitis model using IL-22$^{-/-}$ × RAG-2$^{-/-}$ mice (33), leading to speculation that these NK-22 cells reside in intestinal LP of RAG-2$^{-/-}$ mice and may be regulated by the IL-7/IL-7R signaling pathway. Unexpectedly, we could not detect any significant differences regarding the severity of colitis between RAG-2$^{-/-}$ and IL-7Rα$^{-/-}$ × RAG-2$^{-/-}$ recipient mice. This finding was also confirmed by the experiment using a smaller number of $CD4^+CD25^-$ T cells as donor cells. Instead, we found that the expression of IL-7Rα on colitic LP $CD4^+$ T cells was significantly higher than that on normal LP $CD4^+$ T cells (Fig. 1), suggesting a mechanism for exclusive use of IL-7 by highly IL-7Rα–expressing colitic $CD4^+$ T cells.

Previously, we showed that IL-7Rα expression on LP $CD4^+$ T cells in $CD4^+CD45RB^{high}$ T cell-transferred RAG-2$^{-/-}$ mice is downmodulated at the early effector phase of colitogenic $CD4^+$ T cell differentiation (1–2 wk after transfer) and is again upregulated at the memory phase when colitis is established (>4 wk after transfer) (22). Thus, it is possible that the competition for IL-7 between colitogenic $CD4^+$ T cells and other non-T cells occurs during such an early phase of colitis development. Otherwise, IL-7 competition between T cells versus non-T cells may occur at more acute immune responses, such as acute bacterial infections, which is mainly regulated by IL-7Rα–downmodulating effector T cells (10).

Finally, it is important to discuss the therapeutic strategies for the treatment of IBD. Because IL-7 is the most important cytokine for the maintenance of homeostasis of all the resting memory $CD4^+$ T cells, it seems to be unsafe to adopt the blockade of IL-7/IL7R signaling pathway for the treatment of IBD. As shown in this study, however, it should be emphasized that the highest expression of IL-7Rα is found in colitogenic memory LP $CD4^+$ T cells as compared with non-$CD4^+$ T cell compartments and normal $CD4^+$ T cells. In such a situation, it is possible that a neutralizing or depleting anti–IL-7Rα mAb would preferentially target colitogenic memory $CD4^+$ T cells with the highest expression of IL-7Rα. Consistent with this notion, a recent report has shown that targeted depletion of pathogenic Th1 and Th17 cells, which express high levels of lymphotoxin-α, inhibits autoimmune diseases (34). In addition, it may be necessary to develop a molecular targeting therapy against the IL-7Rα molecule that is more specific for the target organ, rather than a systemic therapy, using effective drug delivery to inflamed mucosa of IBD.

Collectively, we have shown that IL-7Rα expression on $CD4^+$ T cells is essential for the development of colitis in this model. This finding suggests that IL-7Rα on colitogenic memory LP $CD4^+$ T cells is one of the important targets in IL-7/IL-7R signal blocking therapy.

Disclosures

The authors have no financial conflicts of interest.

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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.

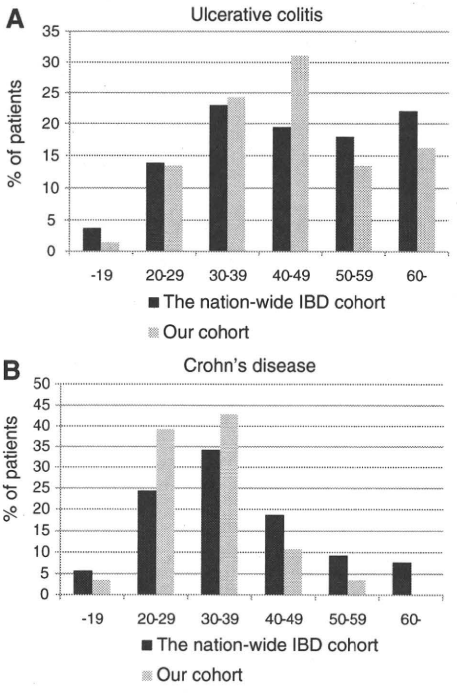

Fig. 1 Age distribution of our inflammatory bowel disease (IBD) cohort compared to the nationwide IBD cohort for both UC (**a**) and CD (**b**). No difference was observed in the age distribution between our cohort and the nationwide cohort ($P = 0.142$ in UC, $P = 0.188$ in CD)

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

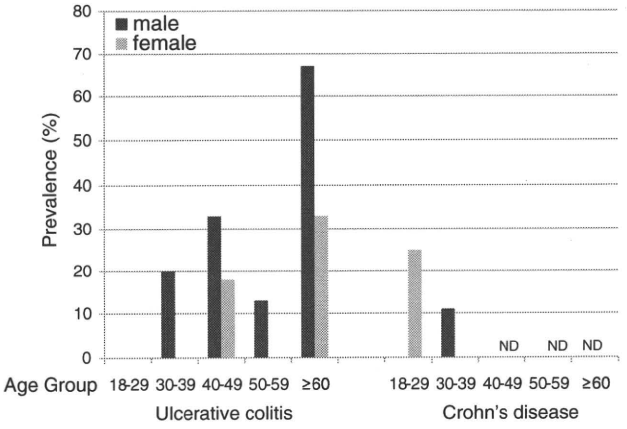

Fig. 2 Prevalence of metabolic syndrome in different age and sex groups with UC and CD. Data are shown as % of total patients observed in each group. ND represents "no data"

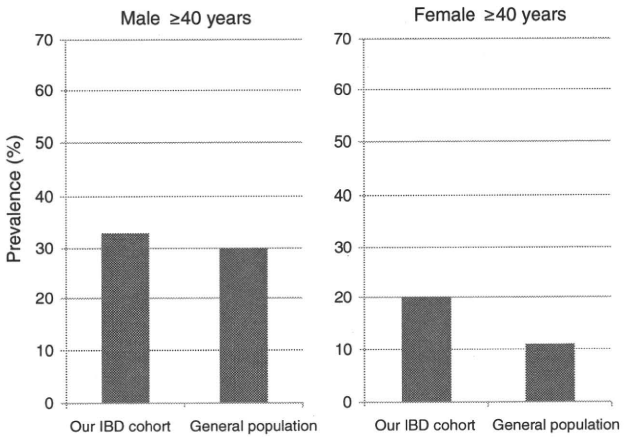

Fig. 3 Prevalence of MS in our IBD cohort and the Japanese general population in both males and females aged 40 years or older. No difference was observed in the prevalence of MS between these two cohorts in both males and females ($P = 0.707$ in males, $P = 0.328$ in females)

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

Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients

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Abstract
Aim Clinical symptoms are the most important factors used by physicians to evaluate the severity and extent of ulcerative colitis (UC). In this context, colonoscopy is also a useful diagnostic tool. We have recently developed an endoscopic activity index (EAI) to assess the severity of UC. Here, we assess the correlations among the EAI, other endoscopic indices, and clinical scores. The usefulness of the EAI for choosing treatment options, such as intravenous corticosteroid or cyclosporine A (CsA), in severe UC patients was also evaluated.
Methods Clinical symptoms and endoscopic finding were evaluated in 396 patients with UC (454 colonoscopies). The EAI was scored using the following six items: ulcer size, ulcer depth, redness, bleeding, edema, and mucus exudates. The patients were also scored using Matts' grade, Rachmilewitz's endoscopic index, and the Lichtiger index.
Results Our results showed that (1) the EAI scores were closely correlated with those of the Lichtiger index, Matts' grade, and Rachmilewitz's endoscopic index; (2) the EAI scores significantly decreased in patients who responded to treatment, while Matts' grade did not change in some responders treated with intravenous CsA and steroid; (3) patients with a higher EAI (14–16) tended to be refractory to corticosteroid therapy (responders 19%) compared to CsA (77%), while steroid treatment was effective in 58% of patients with EAI scores of 11–13.
Conclusions The EAI is equivalent to other endoscopic indices and relatively more useful in choosing a treatment for patients with severe UC.

Keywords Cyclosporine A · Endoscopic activity index · Ulcerative colitis

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown aetiology. It is characterized by severe inflammation of the colonic mucosa and by periods of remission and acute episodes of relapse. Corticosteroid treatment is considered to be the treatment of choice in patients with more severe symptoms who do not respond to initial therapy. Severe UC is a serious condition that is accompanied by diarrhea, abdominal pain, fever, dehydration, and tachycardia, and patients with this condition require hospitalization and intensive treatment. For many years, the standard therapy has been the administration of intravenous corticosteroids, which promotes remission in up to 60% of patients [1]. However, 20% of patients treated with intravenous steroid show no improvement of symptoms [1, 2] and require further therapy with intravenous cyclosporine A (CsA) or infliximab (IFX) or a total colectomy. Lichtiger et al. [3] demonstrated that intravenous CsA therapy is rapidly effective in more than 80% of steroid-refractory UC patients, and this result has been confirmed by a number of additional clinical trials [4–7]. The efficacy

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of IFX for steroid-refractory UC patients has also been demonstrated in a small controlled trial [8].

While total colonoscopy should not be performed at a time when it carries the risk of inducing toxic megacolon [9], sigmoidoscopy can be attempted by expert colonoscopists to assess the severity of the disease and rule out other causes of severe colitis. Sigmoidoscopy is a useful tool for evaluating the severity of UC because it allows the clinician to observed the inflamed mucosa directly and to take biopsies. The evaluation of disease activity based on endoscopy findings has been described in several articles. Truelove and Witts were the first to report the use of sigmoidoscopic assessment in an evaluation of the efficacy of steroid treatment in patients with active UC. Based on their results, they classified their patients into four categories: normal, improved, no change, and worse [1]. The Baron score, the Powell–Tuck sigmoidoscopic assessment, and the Mayo score for proctosigmoidoscopy have also been reported. These scores define patients into three or four categories based on specified findings. However, although these scores are easy for investigators to use, they do not show short-term changes because mucosal improvement and healing take a relatively long time compared to clinical responses. Rachmilewitz's endoscopic index uses four items, namely, granulation, vascular pattern, vulnerability of the mucosa, and mucosal damage [10], and the scores range from 0 to 12 points. Rachmilewitz's endoscopic index was used as an assessment tool in a controlled trial of mesalamine and sulfasalazine and the findings indicate that this index may be considered for use in patients with mild to moderate UC. When Rachmilewitz's endoscopic index is applied, most cases treated with IFX or CsA have the highest score (12 points).

We have recently developed an endoscopic activity index (EAI) to assess the severity of UC from remission to the most severe cases. Among patients with severe UC, this score may be able to distinguish more severe cases from moderate to severe cases. The aim of the study reported here was to analyze the correlations among EAI, other endoscopic indices, and clinical scores. The utility of the EAI in facilitating the treatment decision process in severe UC patients was also assessed.

Patients and methods

Scoring UC with the EAI

Clinical symptoms and endoscopic findings were evaluated in 396 UC patients who underwent 454 colonoscopies between 2006 and 2007. Total colonoscopies could not be performed in 28 (6.2%) patients due to the severity of the disease symptoms or reports of unbearable pain by the patient during the colonoscopy. These patients underwent a sigmoidoscopy. Inpatients and outpatients from the gastroenterology clinic between the ages of 13 and 71 years with active moderate to severe UC confirmed by colonoscopy were eligible for enrollment. At the time of diagnosis, infectious colitis, radiation colitis, ischemic colitis, Crohn's disease, and intestinal Behcet's disease were excluded. Table 1 shows the scoring system for the EAI. The EAI was scored using the following six items: (1) ulcer size, (2) ulcer depth, (3) redness, (4) bleeding, (5) edema, and (6) mucus exudates. Typical endoscopic findings for each sub-score are shown in Fig. 1. Scores using Matts' classification (1–4) [11] and Rachmilewitz's endoscopic index (0–12) [6] were also determined. The EAI was compared with the other endoscopic scores and the Lichtiger's clinical activity index (CAI) (0–21).

Table 1 Items included in the endoscopic activity index (EAI)

Items 1–3 of the EAI	
Size of ulcers	
0	None
1	Erosion/small ulcer
2	Intermediate
3	Wide-ranged mucosal defects
Depth of ulcers	
0	None
1	Shallow
2	Intermediate
3	Deep
Redness	
0	None
1	Mild
2	Marked
Items 4–6 of the EAI	
Bleeding	
0	None
1	Contact bleeding
2	Spontaneous bleeding
3	Massive bleeding
Mucosal edema	
0	None
1	Mild
2	Moderate
3	Severe
Mucous exudate	
0	None
1	Mild
2	Marked

For each of the six items, scores of zero to two/three can be given, depending on the severity of the item, with a higher score indicating the more severe condition

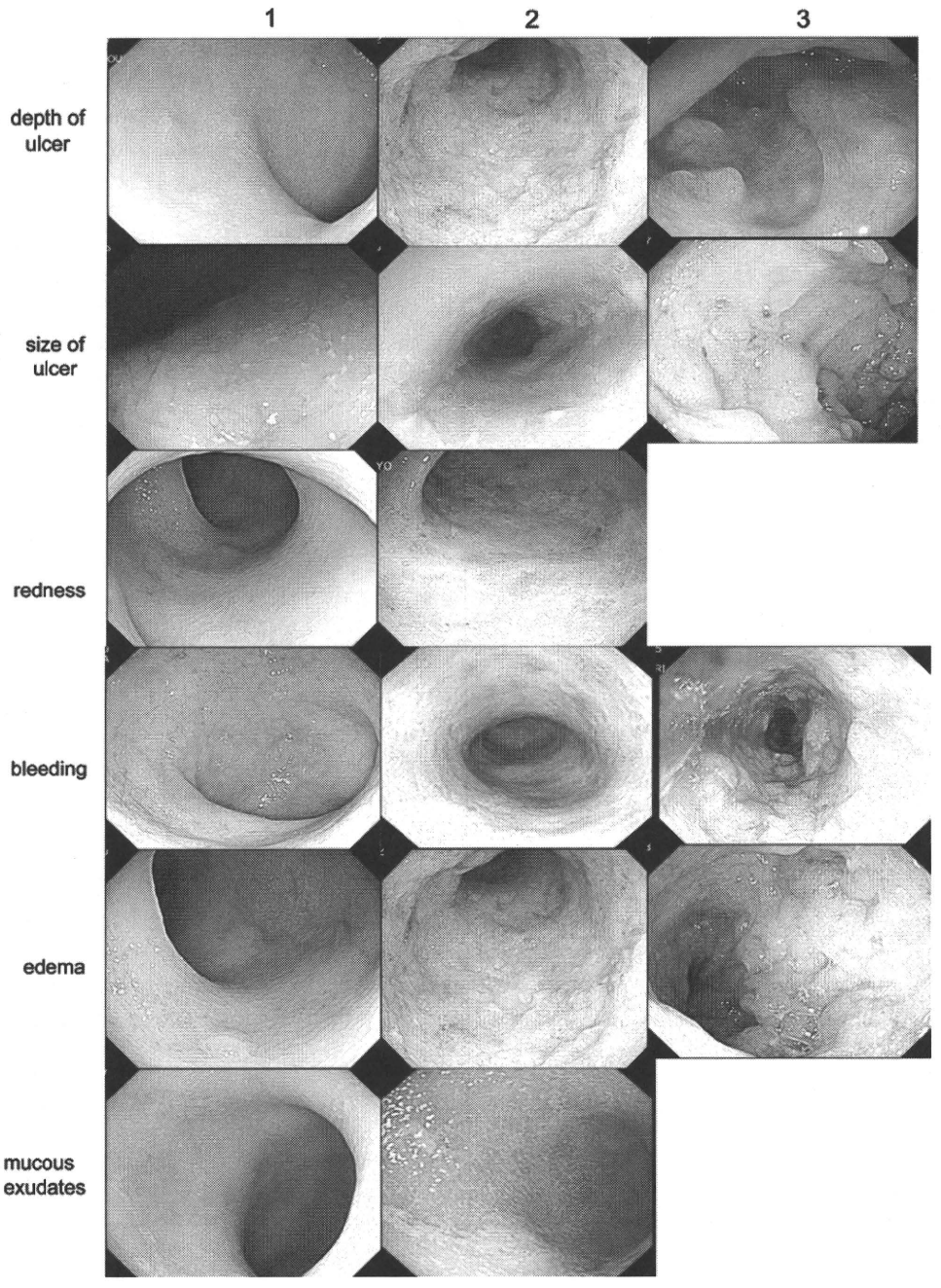

Fig. 1 The endoscopic activity index (EAI) was scored using the following six items: ulcer size (0 none, 1 erosion/small ulcers, 2 intermediate, 3 wide-ranging mucosal defect), ulcer depth (0 none, 1 shallow, 2 intermediate, 3 deep), redness (0 none, 1 mild, 2 severe), bleeding (0 none, 1 contact bleeding, 2 spontaneous, 3 massive), edema (0 none, 1 mild, 2 moderate, 3 severe), and mucus exudates (0 none, 1 mild, 2 marked)

Among our patient cohort, 25 colonoscopies were repeated within 30 (range 16–29) days to evaluate the efficacy of the chosen therapy. Seven patients were treated with CsA, 12 with steroid, three received apheresis therapy [12], and four were received other treatments, such as IFX and immunomodulators. The relationships between the changes in the CAI and the endoscopic severities (EAI and Matts' grade) were evaluated. The efficacy of the therapies for active UC was assessed as: remission (CAI <4 after treatment), clinical response (CAI <10 and decreased by at least 4 points with treatment, but remission was not induced), and non-response. The changes in the EAI and the Matts' scores in the remission, response, and non-response groups were compared. The CAI was scored at the start of treatment and on the day that the second colonoscopies were performed.

We reviewed and assessed the colonoscopic findings and the medical records. The EAI was scored by a single colonoscopist (M.N.). Inter-observer variations are often observed when sigmoidoscopy/colonoscopy activity

indices are used, and since the EAI has six different items, with scores ranging from 0 to 16 points, the EAI may also be sensitive to inter-observer variation. To assess this possibility, two colonoscopists (M.N. and H.O.) scored the 40 colonoscopic findings of UC patients with various disease activities. A difference of more than 2 points in the EAIs between the assessment of the two colonoscopists was defined as "variation". The variations in the change in the EAI (ΔEAI) following 25 treatments (described above) were also assessed. For example, if one colonoscopist gave a score of 12 points before treatment and 6 points after treatment (ΔEAI 6) and the other colonoscopist gave scores of 13 and 4, respectively (ΔEAI 9), variation was considered to be present.

Usefulness of the EAI for patients with severe active UC

The usefulness of the EAI for making treatment decisions for patients with severe active UC was also reviewed by analyzing the clinical and endoscopic efficacy of intravenous steroid therapy and CsA. Patients who were treated with CsA or intravenous steroid from 1998 to 2006 were analyzed, and the EAI was determined in each of the patients. Only patients who received sigmoidoscopy before and after treatments were selected for study. Of these, 48 patients treated with intravenous steroid and 43 treated with CsA had an EAI >10 (EAI 11–16). UC patients with relapses were hospitalized, sigmoidoscopy was performed to confirm the presence of active inflammation before CsA therapy or steroid therapy was initiated. Patients treated with intravenous CsA were given a continuous infusion for 14 days, with an initial dosage of 4 mg/kg daily [3], followed by dosage adjustments to maintain blood CsA levels in the range of 350–600 ng/ml. Blood samples for CsA measurement were taken every other day or more frequently, as necessary. Patients treated with steroid therapy received the same dose for 7 days. If they responded well and achieved remission, the steroid dose was tapered. If the patients did not achieve remission, the same dose was continued for 7 more days (total 14 days). Clinical efficacy was assessed 15 days from the initiation of CsA/steroid therapy and classified as remission, response, and non-response, respectively, as described above.

The rates of remission and response to intravenous steroid/CsA treatment were compared in the highest EAI group (EAI 14–15) and the moderate EAI group (EAI 11–13).

Statistics

Statistical analysis of the data was performed using Statcel (Tokyo, Japan). The data were analyzed using the Wilcoxon signed ranks test and the chi-square test at a statistical significance level of 5%.

Results

Development of EAI for UC patients

Table 2 shows the clinical features of the UC patients in this study. More than half of the patients maintained remission or did not complain of any abdominal symptoms. Endoscopic activity was assessed in UC patients using the EAI, Matts' classification, and Rachmilewitz's endoscopic index. The relationship between the EAI and clinical activity was also analyzed. The CAI ranged from 0 to 19, while the EAI ranged from 0 to 15. The EAI was closely correlated with clinical activity (CAI, $r = 0.77$, $p < 0.001$)

Table 2 Patients' clinical background

Clinical parameters	Values	Clinical parameters	Values
Gender, *n* (male:female)	264:190	Treatment at sigmoidoscopy	
Age (years)	42.8 (13–71)	SASP/5-ASA	389 (169/220)
Duration of disease (years)	8.4 (0–36)	5-ASA enema	52
Extension of disease, *n* (number of patients)		PSL enema	15 (5/10)
Total colitis	182	PSL	30
Left sided colitis	81	Apheresis	9
Procto-sigmoiditis	75	6-Mercaptopurine/azathioprine	54
Proctitis	79	Cyclosporine A	7
Others	37	Others	11
Purpose of colonoscopy, *n* (number of patients)		None	21
New patients	28		
Flare up	155		
Surveillance	169		
Evaluation of efficacy for treatment	84		

SASP/5-ASA sulphasalazine/5-aminosalicylic acid, *PSL* prednisolone

as Fig. 2 indicates. Discrepancies between the EAI and CAI were observed in 25 patients (5.5%). The CAI Hi group (CAI 6 or more points higher than the EAI) consisted of 18 patients, while the EAI Hi group (EAI 6 or more points higher than the CAI) consisted of eight patients. Rectal severity was mild in six of the eight patients in the EAI Hi group. In these patients, blood in the stool was not present or was not frequently observed, and endoscopic severity was relatively higher in the descending colon or right-sided colon. Thus, the EAI was relatively high with low clinical activity. In the CAI Hi group, eight patients had a CAI <12 (mild to moderate colitis), even though all patients received oral 5-aminosalicylic acid (5-ASA; CAI <11). Of these eight patients, five achieved spontaneous remission according to the colonoscopic findings, with no or mild endoscopic severity, without additional treatment; the remaining three patients were given only 5-ASA enemas or sulfasalazine. No patients needed steroid therapy.

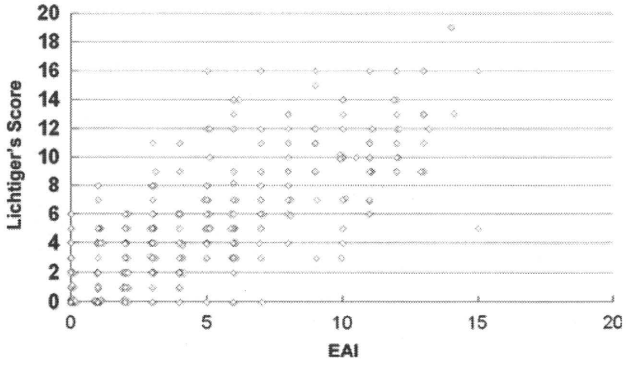

Fig. 2 Relationship between clinical activity and the EAI. The EAI was scored patients with active ulcerative colitis (UC) to assess endoscopic activity. A total of 454 colonoscopies were performed in 393 patients; 47 patients underwent repeat colonoscopy at 12 months (repeated two to five times). The EAI was closely correlated with Lichtiger's score ($r = 0.77$, $p < 0.001$)

The EAI is equivalent to other endoscopic indices and closely correlated to the CAI

We then assessed whether the EAI is equivalent to earlier endoscopic activity indices and found that the EAI score was closely correlated with Matts' grade ($r = 0.91$, $p < 0.001$) and the Rachmilewitz's endoscopic index score ($r = 0.87$, $p < 0.001$) (Fig. 3). However, there was a fairly wide range of EAI scores for patients with the highest Matts' grade or the highest Rachmilewitz endoscopic index score. Figure 4 shows examples of endoscopic findings with the same Matts' score (grade 4) with different EAI scores. It is apparent that more severe activity is present in the right panel of Fig. 4. In fact, patients on the left side of Fig. 4 responded to steroid treatment, while those on the right did not. These results suggest that EAI scores may be more useful for assessing patients with severe UC than Matts' score.

Whether the EAI score changed with improvement of the clinical symptoms was also assessed. The changes in the EAI score and Matts' grade before/after treatment were compared in the clinical remission, response, and non-response groups. With treatment, the EAI significantly decreased in the remission group (from 8.7 ± 1.0 to 2.7 ± 1.7, $p < 0.001$) and the response group (from 10.2 ± 2.1 to 6.5 ± 3.2, $p < 0.01$). As expected, it did not decrease in the non-response group (from 10.3 ± 1.7 to 10.0 ± 2.1) (Fig. 5). Interestingly, Matts' grade did not significantly decrease in the response group (from 3.7 ± 0.5 to 3.3 ± 0.8, $p = 0.27$), though the EAI scores did decrease significantly.

Since the EAI has more items (six items) and a wider range than the other indices/grades, it was expected that greater inter-observer variation would be present compared to these other scores. The EAI scores between the two colonoscopists were completely matched in only six (15%) of 40 patients. However, the difference in EAI scores between two observers was within 2 points in 35 cases (87.5%).

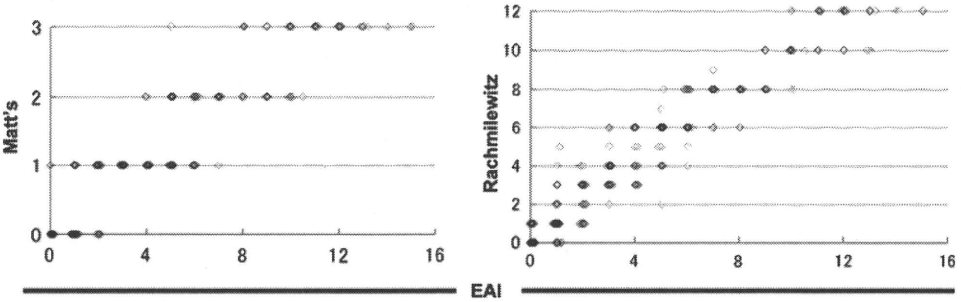

Fig. 3 The EAI is equivalent to other endoscopic indices. A total of 454 colonoscopies were performed in 393 patients. The EAI is closely correlated with Matts' grade ($r = 0.91$, $p < 0.001$) and the Rachmilewitz's endoscopic index score ($r = 0.87$, $p < 0.001$). Rachmilewitz's endoscopic index was scored using the following four items: granulation scattering reflected light (0 no, 2 yes); vascular pattern (0 normal, 1 faded/disturbed, 2 completely absent); vulnerability of mucosa (0 none, 2 contact bleeding, 4 spontaneous bleeding); mucosal damage (0 none, 2 slight, 4 pronounced)

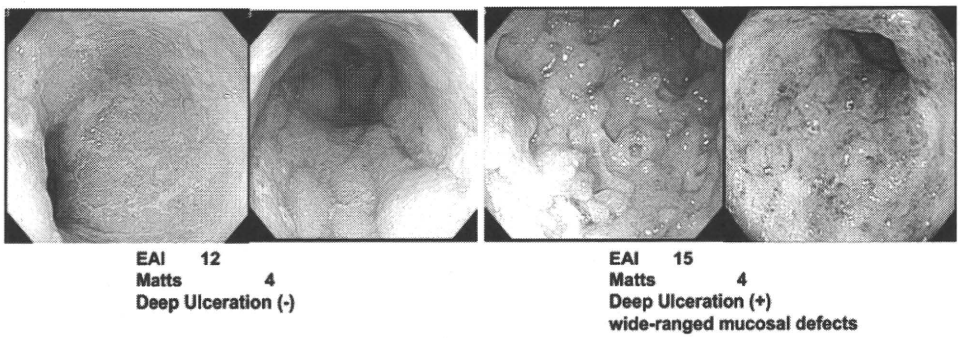

Fig. 4 Both *panels* show severe endoscopic findings; severe ulcerations are present in both (Matts' score = 4). The findings in the *left panel* were scored as 12 points according to the EAI, while those in the *right panel* were scored as 15 points

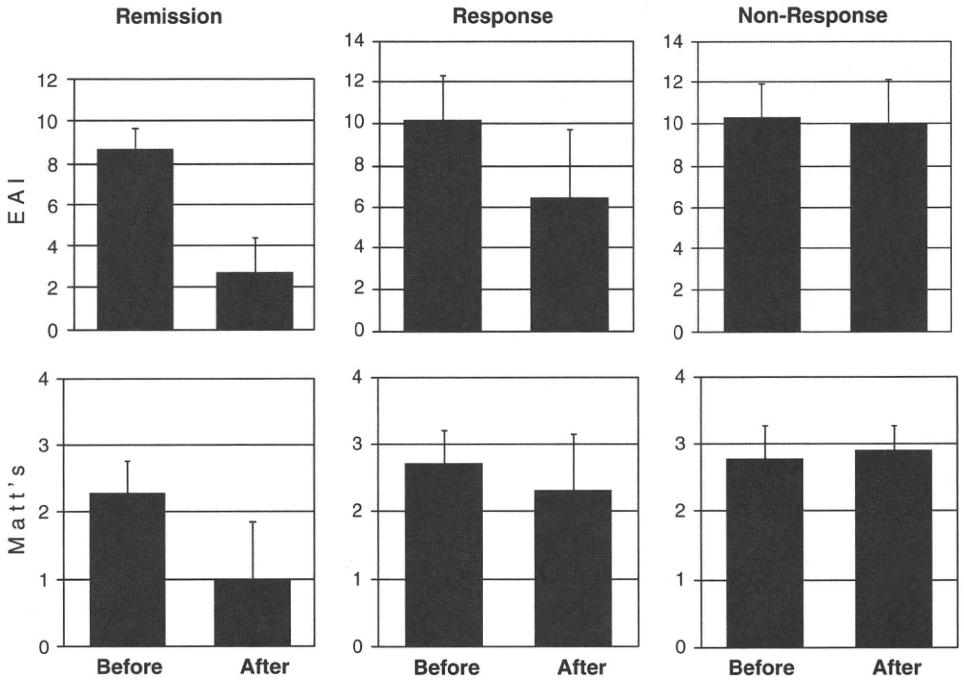

Fig. 5 The EAI is significantly decreased in the remission ($p = 0.03$) and response groups ($p = 0.01$). Matts' grade shows a tendency to decrease in the remission group, but the difference is not significant ($p = 0.07$). There were eight, ten, and seven patients in the remission, response, and non-response group, respectively

Variation for ΔEAI by treatment was also assessed. Interestingly, only two variations (8%) were observed in the 25 patients who had repeated colonoscopies after a short period.

The EAI is a useful tool for determining the initiation of intensive treatment in patients with severe UC

The EAI varied from 10 to 15 even in patients with the highest Rachmilewitz endoscopic index score (12 points). Whether the EAI can predict the efficacy of steroid/CsA was assessed by comparing the efficacy of steroid/CsA in the highest EAI (14–15) group with those in the moderate EAI (11–13) group. In patients with the highest EAI scores, 16 patients were treated with intravenous steroid therapy and 30 were given CsA, while in the moderate EAI group, 32 patients were given steroid therapy and 13 patients were received CsA. Patients with the highest EAI (14–15) tended to be refractory to corticosteroid therapy (responders 3/16; 18.8%), compared to CsA (responders:23/30; 76.7%). However, steroid therapy was effective in 59.3% (19/32) of patients in the moderate EAI group (Table 3). These results suggest that the EAI is useful for making treatment decisions in patients with severe UC.

Table 3 The efficacy of prednisolone/cyclosporine A in patients with EAI >10

Treatment	EAI >14		EAI 11–13	
	Responder	Non-responder	Responder	Non-responder
Prednisolone	3	13	19	13
Cyclosporine A	23	7	10	3

Discussion

The results of this study confirm that the newly developed EAI is comparable to other endoscopic activity scores and is closely correlated with clinical activity. Discrepancies

between the EAI and clinical activity were observed in <5% of the UC patients participating in this study. In some cases, psychological factors lead to frequent diarrhea with mild to moderate abdominal pain. If sigmoidoscopy/colonoscopy had not been performed, unnecessary treatment, such as steroid therapy, may have been given to these patients since their clinical activities were moderate and they did not respond to initial treatment. Therefore, sigmoidoscopy/colonoscopy is needed to avoid unnecessary steroid therapy when clinical activity flares and additional treatment, such as steroid therapy, is being considered.

There are several endoscopic indices for assessing the severity of colitis (for review, see D'Haens et al. [13]). The Mayo score for flexible proctosigmoidoscopy assessment is one of the most common endoscopic scores. It was originally used in a placebo-controlled trial of mesalamine by Schroeder et al. [14]. This score, as well as other clinical scores, such as blood in the stool, daily diarrhea, and physician's assessment, has been widely used in recent clinical trials. The Mayo score is easy to score and accurately reflects both the clinical and endoscopic activities of UC. The Sutherland mucosal appearance assessment index was used in a placebo-controlled trial of mesalamine enemas in patients with distal UC [15]; it also has a 4-point scale. Both of these scores consist of four categories. However, during short-term observation periods, endoscopic severities did not markedly change in some severe cases.

Prior to initiating this study, we noticed that mucosal edema and friability changed rapidly, consistent with decreasing C-reactive protein (CRP) levels and improving clinical symptoms, while deep ulceration remained, even though clinical remission was obtained. At that time, endoscopic scores, such as Matts' score, did not change in some cases. Consequently, we categorized six items based on endoscopic findings of UC patients and developed the EAI in 1996 to assess the severity of UC. By the beginning of this study, we had confirmed that the EAI score rapidly decreased in patients who achieved clinical response to intravenous steroid treatment even though Matts' score had not decreased. The data obtained in this study indicate that the EAI decreased in the remission group, while Matts' score was unchanged in some patients who actually did achieve clinical remission. Furthermore, the EAI was helpful in distinguishing between moderate to severe UC patients and those who would not respond to steroid and need rescue treatment, such as CsA, IFX, or surgery.

CsA is reported to be a lymphocyte-specific agent that inhibits interleukin-2 and, hence, the function of T-helper cells. During the past 10 years, CsA has been given to patients with severe steroid refractory UC with the intention of avoiding colectomy. Little information is currently available on factors predictive of response to intravenous CsA [16]. Cacheux et al. identified [17] higher body temperature, heart rate, and CRP at the initiation of CsA as predictive criteria for colectomy. Severe endoscopic findings were also an independent predictive factor of colectomy. Conversely, our data indicate that CsA was effective in patients with severe endoscopic findings (EAI 14–16), while patients with higher EAI scores did not respond to steroids. These discrepancies between our results and those of Cacheux et al. can be explained by the CsA concentration: we maintained CsA at 350–600 ng/ml, which was higher than that reported by Cacheux et al. Colectomy was defined as the clinical endpoint in Cacheux's study, while we focused on clinical response using Lichtiger's index. Our data indicate that 77% of our patients with severe inflammation and deep ulceration and edema responded to intravenous CsA. We also confirmed that colectomy within 12 months could be predicted by the endoscopic findings after 2–3 weeks of CsA treatment (data not shown).

It is difficult to state whether, in terms of EAI evaluation, a total colonoscopy is always needed or whether sigmoid colonoscopy is sufficient. Among most of our patients, severe lesions existed in the sigmoid colon, while the appearance of moderate to severe lesions in the right sided-colon without inflammation of the rectum and sigmoid colon was rare (6/454 cases). Furthermore, a total colonoscopy has the effect of negatively affecting disease deterioration in severe cases. Therefore, sigmoidoscopy may be both advisable and sufficient to evaluate EAI in most cases.

Since the EAI score has six items, inter-observer variation may occur. If there were a 1-point difference in each item, the difference in the total EAI would be 6 points. Our data indicate that variations in the EAI score do occur, we found that the variation was relatively minimal in patients with endoscopic findings of severe activity. Of note, the change in the EAI before/after treatment (ΔEAI) did not vary between observers. These results suggest inter-observer variations may be less when delta EAI is calculated to assess endoscopic improvement by intensive treatment (e.g., intravenous steroid or CsA).

In conclusion, the EAI score is closely correlated with scores obtained using other endoscopic and clinical indices. The EAI score decreases rapidly according to the clinical response, while other scores, such as the Matts' score, do not change in some cases. Since a higher EAI is a predictive factor for steroid-refractory UC, the EAI is a useful score for severe patients who require CsA or surgery to decrease the use of inappropriate intravenous steroid therapy.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan

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Abstract
Objective We analyzed the database of the Japanese nationwide inflammatory bowel disease (IBD) registry, which was started in 1975, to characterize basic epidemiological and clinical features of childhood IBD, comparing them to those in adults.
Study design We analyzed the age of disease onset, disease severity and anatomical distribution in patients that were newly registered between 2003 and 2006 ($n = 2{,}940$ for CD and 14,857 for UC). We also analyzed the current age, gender and family history of IBD of all patients filed in 2005, which included patients who were newly registered in 2005 and those who had been registered before 2005 and for whom an annual report had been received in 2005 (total number of subjects: 10,934 for CD and 37,846 for UC).
Results At the time of registration, 10.6% of CD and 5.9% of UC patients were ≤16 years old. In CD, the male to female ratio was 2.6 in adult- and 1.7 in childhood-onset patients ($P < 0.001$). In UC, the male to female ratio was close to 1 in both age groups. In comparison with adults, pediatric patients more commonly had a positive family history for CD and UC ($P < 0.001$), tended to have more severe disease at the time of registry ($P < 0.001$ for CD, $P < 0.05$ for UC) and more often had extensive colitis in UC ($P < 0.001$).
Conclusion The nationwide registry in Japan showed IBD in children has clinical features that are distinct from those in adults.

Keywords Crohn's disease · Incidence · Ulcerative colitis · Montreal classification · Child

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Introduction

Previous reports have suggested that childhood inflammatory bowel disease (IBD) has several clinical features that are distinct from those in adults [1–6]. The incidence of IBD in children is lower compared to that in adults. Pediatric ulcerative colitis (UC) patients are more likely to have total colitis than adults are [1, 6–8]. Growth failure is a serious clinical problem only in pediatric patients [5, 6, 9–11]. The above unique features of pediatric IBD have been described in relatively large prospective epidemiological studies and in recent registry data from the US [1, 12–14]. However, most of these studies did not include adult patients and therefore do not allow direct comparison between age groups. Epidemiological data for IBD vary widely with regard to time and place of collection [15]. For example, the prevalence of UC in Northern Europe is several times higher than that in Japan and other Eastern Asian countries [15]. The incidence of Crohn's disease (CD) has increased markedly in the last century [16–18] and may still be increasing in some countries [19].

Therefore, the proper way to characterize pediatric IBD without any significant bias is to obtain data from children and adults at the same place and time, and in the same manner.

Recognizing the social and economic impact of IBD and the need for epidemiological information, the Japanese government started a nationwide registry in 1975. Doctors are encouraged to file patient data at any one of the local offices of the Japanese Ministry of Health, Labor and Welfare (MHLW). Data are converted to electronic form and sent to the research committee of the MHLW. Data include clinical features, such as age, sex, family history and disease profile, and social factors, such as occupation and insurance status. If doctors send a report, patients receive all the medical cost for treatment of the disease from the government in return. Previous studies have shown that most patients agree to be registered, and 50–70% of new Japanese IBD patients are estimated to be registered every year [20]. Even though Japan's incidence of IBD is lower than that in Western countries, this nationwide database, which included more than 10,000 CD and 40,000 UC patients in 2005, provides valuable epidemiological information on IBD in Japan.

In this study, members of the working party of epidemiology in the IBD study group organized by the Japanese government analyzed the database to characterize basic clinical features of childhood IBD and compared them to those in adults.

Methods

In Japan, since 1975, when a definite diagnosis of UC or CD is made, the patient is asked if he or she wants to be registered in the national database. If the patient agrees, the doctors complete the questionnaire and file it with the local office of the MHLW. The questionnaire covers patient age, gender, address, time of onset, disease severity and distribution, complications, laboratory data, endoscopic and/or barium enema studies, histological findings, and family and social history, including place of birth, occupation and type of health insurance. Each patient must meet the diagnostic criteria for CD or UC published by the MHLW (http://www.nanbyou.or.jp: Japanese article). Members of local branches check the data in the questionnaire to confirm that it meets the diagnostic criteria. If it does, the data are then converted to electronic form and submitted to the MHLW.

Once the patient is registered, the doctor must send an annual report for the patient to the MHLW every year thereafter, until the disease is determined to be cured or the registration is cancelled by the patient, neither of which happens often. Therefore, the database contains two series of data; new registry data from patients newly registered each year and annual report data from all previously registered patients.

In this study, we analyzed the age of disease onset in patients that were newly registered between 2003 and 2006 ($n = 2{,}940$ for CD and 14,857 for UC). We also analyzed the current age, gender and family history of IBD of all patients filed in 2005, which included patients who were newly registered in 2005 and those who had been registered before 2005 and for whom an annual report was received in 2005 (total number of subjects: 10,934 for CD and 37,846 for UC).

Throughout this study, children were defined as individuals aged $\leq$16 years and adults as >16 years old, according to the Montreal classification. Family history was regarded as positive when a parent, brother or sister had IBD.

For disease severity and anatomical distribution, we used new registration data filed between 2003 and 2006. The International Organization of the Study of Inflammatory Bowel Disease (IOIBD) assessment score was used to assess severity of CD [21]. Severity of UC was on the report, which was determined according to Truelove's criteria [22].

Since this registry was started before the Montreal classification was published in 2006, it was not possible to analyze some data according to the Montreal classification [23]. To be more specific, disease behavior of CD was not analyzed.

Statistical analysis

Data were analyzed by chi-square test to compare categorical data between children and adults. Differences were considered statistically significant at $P < 0.01$. SPSS 15.0 (SPSS, Inc., Chicago, IL) was used for all analysis.

Ethical considerations

When the data were provided to us by the government, they were blinded (no names or initials) so that we could not identify the individuals. Data access was restricted to the authors T.I. and T. Tomomasa. This study was approved by the MHLW and the Ethical Committee in Gunma University, Department of Pediatrics.

Results

Age at diagnosis

Three hundred eleven (10.6%) of 2,940 CD patients newly registered between 2003 and 2006 were $\leq$16 years old. Among 10,934 CD patients in the whole registry in 2005,

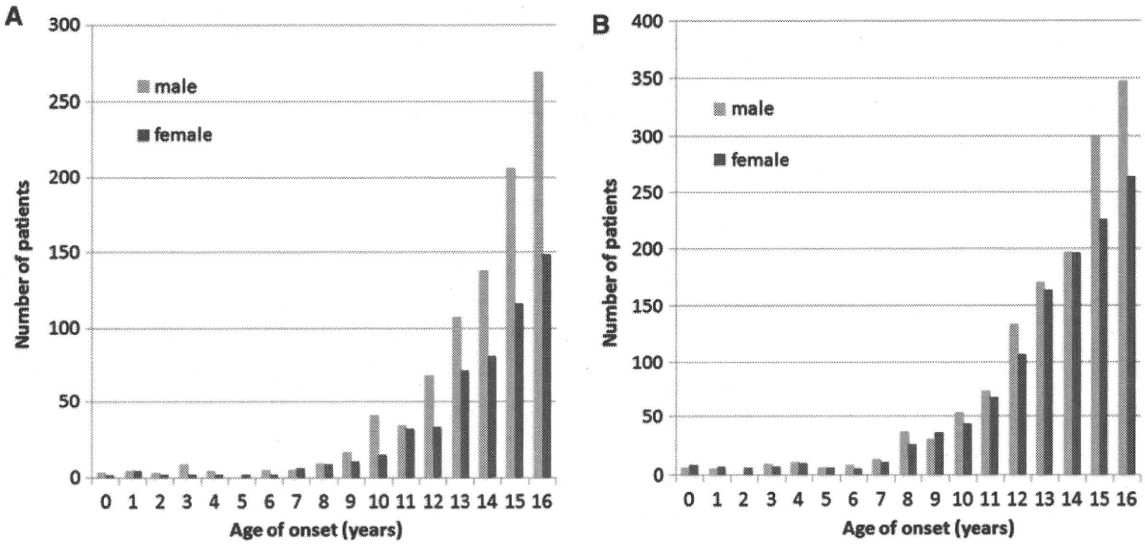

Fig. 1 **a** Age at onset of CD in Japanese patients registered in 2005 ($n = 1{,}450$); **b** age at onset of UC in Japanese patients registered in 2005 ($n = 2{,}355$)

1,450 (13.2%) were ≤16 years old (A1 in the Montreal classification) at the time of disease onset, and 219 (2.0%) were ≤16 years old at the time of the registration in 2005. The distribution of age at onset in these 1,450 patients is shown in Fig. 1a. There was an abrupt increase in the onset of CD after age 8–10 years old. Between 2003 and 2006, 14,857 UC patients were newly registered. Of these, 880 (5.9%) were ≤16 years old. Of 37,846 UC patients who were registered in 2005 (newly and previously registered), 2,355 (6.2%) had disease onset at ≤16 years old (A1), and 599 (1.6%) were ≤16 years old at the time of registration in 2005. The distribution of onset age in the 2,355 pediatric UC patients is shown in Fig. 1b. The age distribution of pediatric UC was similar to that of CD, having a trend to increase after 8–10 years of age.

Sex distribution (Table 1)

In CD, there was a significant difference in the sex distribution between adults and children. In adults, males were 2.6 times more likely to have CD than females, whereas in children, males were only 1.8 times more likely to have CD ($P < 0.001$, chi-square test). In UC patients, there were no significant differences in the male to female ratio compared between adults and children, as shown in Table 1. These trends did not alter after being adjusted by sex distribution for the whole Japanese population, which was 0.955 for adults and 1.049 for children [24].

Family history

For CD and UC, patients with a childhood onset had a positive family history more often than adults did. The percentage of those with childhood-onset CD with a family history for the same disease was 3.0%, while only 1.7% of adult-onset patients showed a positive family history of CD ($P < 0.001$, chi-square test). The percentage of CD patients with a positive family history of UC was 0.8% in childhood-onset and 0.6% in adult-onset patients (no significant difference). For UC, 4.1% of childhood-onset and 1.8% of adult-onset patients showed a positive family history for UC ($P < 0.001$, Fisher's exact test), while 0.2% of childhood and 0.2% of adult-onset patients showed a positive family history for CD (no significant difference).

Table 1 Sex distribution (male to female ratio) of IBD patients in Japanese children and adults

	Male	Female	Male-to-female ratio	P^b
CD ($n = 10{,}934$)				
Child (adjusted[a])	1,266	689	1.84	<0.001
			1.75	
Adult (adjusted[a])	6,391	2,588	2.58	
			2.58	
UC ($n = 37{,}846$)				
Child (adjusted[a])	1,791	1,512	1.05	0.183
			1.13	
Adult (adjusted[a])	18,307	16,236	1.18	
			1.18	

Analysis of patients who were newly registered in 2005 and those for whom the annual report was filed in 2005

[a] Adjusted by the male to female ratio in the Japanese population

[b] Chi-square test