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Disability due to Inflammatory Bowel Disease Is Correlated with Drug Compliance, Disease Activity, and Quality of Life

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See editorial on page 319.

Background/Aims: The inflammatory bowel disease disability index (IBD-DI) was recently developed for IBD to assess the functional consequences and disease burden. We applied the IBD-DI to a Korean population and identified predictive factors influencing IBD-related disability. **Methods:** Between March and August 2015, 322 consecutive patients with IBD were prospectively recruited. Patients completed the IBD-DI questionnaire and Crohn's and Ulcerative Colitis Questionnaire (CUCQ-8) for assessing quality of life. We examined the relationships between IBD-DI and disease activity or quality of life and analyzed predictive factors in Korean IBD patients. **Results:** Enrolled patients completed both questionnaires. Total IBD-DI was correlated with CUCQ-8 scores in both ulcerative colitis (r=0.636, p<0.001) and Crohn's disease (r=0.711, p<0.001). Total IBD-DI was also correlated with disease activity in both ulcerative colitis (r= –0.224, p=0.003) and Crohn's disease (r= –0.307, p<0.001). Better drug compliance was associated with lower disability (p=0.001) and higher quality of life (p=0.003). **Conclusions:** Disability from IBD was correlated with disease activity and poor quality of life. Better drug compliance was associated with lower disability and higher quality of life. Our findings indicate that physicians should emphasize the importance of medication compliance for IBD patients. **(Gut Liver 2017;11:370-376)**

Key Words: Inflammatory bowel diseases; Colitis, ulcerative; Crohn disease; Disability; Quality of life

INTRODUCTION

Inflammatory bowel disease (IBD) consists of chronic disabling disorders of the gastrointestinal tract. In IBD, active disease has a progressive course with cumulative intestinal damage and frequently, development of complications that may result in disability.[1] Disability due to IBD affects mostly young people at ages when they are most active in their private and professional lives. The natural history of IBD may alter all dimensions of functioning, and therefore the development of a practical tool covering the entire spectrum of limitations in functioning in patients with IBD is desirable.[2,3] However, disability due to IBD has received little research attention because IBD is not considered to be as disabling as other chronic diseases and there is confusion regarding its definition.[4] Recently, the IBD disability index (IBD-DI) was developed to measure the functional consequences and disease burden of IBD through an extensive literature search and consensus pertaining to disability due to IBD.[5,6] IBD-DI has the potential to be valuable patient-reported outcome measures (PROMs), which provides the possibility to assess disability from the perspective of patients suffering from IBD.[7] IBD-DI will be used in both clinical trial and care of IBD patients as a target of PROM to better compare patients' experience with IBD. Currently, however, only two studies have validated the IBD-DI in Australia and the Netherlands.[8,9]

In recent decades, the incidence of IBD in the United States and Europe has been relatively stable,[10,11] but IBD has become more prevalent in Asia.[12-15] The crude annual overall incidence of IBD was 1.37 per 100,000 individuals in Asia for 2011 to 2012.[16] This increase is most likely related to environmental and lifestyle factors, as countries in Asia undergo socioeconomic

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Westernization and rapid industrialization.[12,14,15] Disability associated with IBD may differ in Asia and the West due to regional differences in the severity and natural course of IBD. Until now, no studies of IBD-related disability have been performed in East Asian populations. Therefore, a study of IBD-DI using an East Asian sample is warranted.

The main aim of this study was to apply the IBD-DI in a sample of Korean IBD patients, to assess its correlations with disease activity and quality of life (QOL), and to identify predictive factors including drug compliance and other disease characteristics.

MATERIALS AND METHODS

1. Patients

Consecutive ambulatory patients aged 16 to 81 years old with established IBD of at least 6 months were prospectively recruited from four IBD centers in Korea between March and August 2015. Patients were asked to participate in the study at outpatient clinic visits and to complete two questionnaires. Patients were excluded if they were unable to comprehend the questionnaire, had significant symptomatic comorbidities that might influence disability, or had active psychiatric disorders. Patients completed two questionnaires: the IBD-DI[5] and Crohn's and Ulcerative Colitis Questionnaire-8 (CUCQ-8).[17] We assessed the relationships between IBD-DI and disease activity or QOL scores, and analyzed predictive factors related to disease characteristics for disability and QOL of patients with IBD.

Clinical information was collected in three categories as follows: (1) physician perspective variables, including disease extent, behavior, and activity index, using the Crohn's Disease Activity Index (CDAI) for Crohn's disease (CD) and partial Mayo score (pMayo) for ulcerative colitis (UC);[18,19] (2) patient perspective variables, including, age, sex, disease duration, marriage, education, occupation, income, smoking, drinking, weight, and height; and (3) IBD treatment-related variables, including steroids, immunomodulators, biologics, hospitalization, surgery, adverse events, and drug compliance. Following prior studies using the Morisky scale in IBD patients, subjects were categorized into a poor compliance group if they reported "yes" to any of the four items (Morisky scale score $\geq$1).[20] This study was approved by the Institutional Review Board of each participating hospital (IRB KHNMC-2015-03-008), and any requirement for informed consent from IBD patients was waived for this survey-based study.

2. Questionnaires for disability and QOL in IBD

Both IBD-DI questionnaire and CUCQ-8 for assessing disability and QOL were translated into Korean. Two professional translators, who were native speakers of Korean and fluent in English, undertook two translations independently. Based on these translations, and on consultation with a specialist in Korean, a reconciled version of the questionnaire was developed. A report was then prepared and reviewed. A native speaker of English, also fluent in Korea, then translated the Korean version back into English. The original and back-translated (English) versions were compared to detect any misunderstandings, mistranslations, or inaccuracies in the Korean draft questionnaire. Reports in English were prepared on all issues, and these were discussed item by item. All decisions on the use of Korean expressions were carefully reviewed to ensure that the sense of questionnaire items was retained.

The IBD-DI consists of five categories and 19 items (Supplementary Appendix 1).[5] Five categories assess Overall Health, Body Functions (sleep/energy, affect, body image, pain, diarrhea, body mass index, weight loss), Body Structures (blood in stool, arthralgia/arthritis), Activity Participation (regulating defecation, looking after one's health, interpersonal activities, and work/education), and Environmental Factors (exacerbating effect or medication, food, family, and health care professional).[5,9] Patients were asked to complete the questionnaire based on disability over the past week. The responses to each item on the questionnaire were either dichotomous (yes/no) or ordinal on a 5-point Likert scale (1 being no difficulty and 5 being extreme difficulty). Scores for each question were combined into domain totals and a final composite score representative of the overall degree of disability ranging from –80 (maximum degree of disability) to 22 (no disability) with 0 as the anticipated point of neutrality.[5,8]

Patients also completed the CUCQ-8, which is a short questionnaire that has the potential to be an efficient tool for assessing the QOL of all IBD patients in clinical practice as a substitute for the lengthy and time consuming CUCQ-32. As the validity, internal reliability, reproducibility, and responsiveness of CUCQ-8 were previously confirmed in IBD patients, we measured disease-related QOL with CUCQ-8 in this study.[17] The response options included feeling tired, being disturbed in social life, feeling generally unwell, having pain in the abdomen, frequent use of the toilet, having a bloated abdomen, and feeling upset and rushing to the toilet, were transformed into a 4-level Likert scale ranging 0 to 3 (not at all, 1 to 2 days, 3 to 7 days, and 8 to 14 days) over the 2 weeks prior to completing the questionnaire (Supplementary Appendix 2). Scores for the CUCQ-8 ranged from 0 (greatest QOL) to 24 (poorest QOL).[17] In correlation analyses between IBD-DI and CUCQ-8, CUCQ-8 was converted temporally into negative numbers to facilitate understanding by positive correlation.

3. Statistics

Continuous values are given as the mean±standard deviation and were compared using two-sample t-tests and one-way ANOVA among more than three groups. Categorical values were presented as the number (percentt) and compared using chi-square tests or Fisher exact tests. Relationships between two continuous variables, including IBD-DI, CUCQ-8, disease activ-

ity, and other variables, were assessed using nonparametric tests of the Spearman rank correlation coefficient (r). The p-values less than 0.05 were considered significant. All statistical analyses were performed using the statistical software package SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

The clinical characteristics of 322 enrolled IBD patients are shown in Table 1. The mean age of IBD patients was 39.7 years, and the mean disease duration was 5.9 years. IBD patients included 218 men (67.7%) and 104 women (32.3%). Steroids were currently or previously administered in 203 patients (63.0%), immunomodulators in 191 (59.3%), and biologics in 113 (35.1%). Prior surgery for IBD was performed in 67 patients (20.8%) and hospitalization episodes occurred in 207 patients (64.3%). Disease severity at the time of study participation was mild in 295 patients (91.6%), moderate in 23 (7.1%), and severe in four (1.2%).

A total of 174 patients in UC and 148 in CD were recruited. The mean age was 45.2 years in UC and 33.2 years in CD, with male preponderance in both groups (57.5% in UC and 79.7% in CD). Comparing CD patients with UC patients, CD patients more frequently received current or prior immunomodulators (81.1% vs 59.2%) and biologics (50.0% vs 22.4%), surgery (39.9% vs 4.6%), and hospitalization (82.4% vs 48.9%). There were no significant differences in current or prior steroid administration or disease severity between UC and CD patients. In terms of disease activity, the mean of the pMayo score in UC was 0.8 and the mean of CDAI in CD was 63.3. The extent of UC was proctitis in 53 patients (30.5%), left-sided colitis in 71 (40.8%), and extensive colitis in 50 (28.7%). The disease location of CD was L1 (ileum) in 27 (18.2%), L2 (colon) in 15 (10.1%), L3 in 105 (70.9%), and L4 in 1 (0.7%).

2. Correlations between IBD-DI and QOL/disease activity

Table 2 shows correlations between IBD-DI and CUCQ-8 or activity indices. Total IBD-DI was correlated with CUCQ-8 in both UC (r=0.636, p<0.001) and CD patients (r=0.711, p<0.001).

Table 1. Demographic and Clinical Characteristics of Enrolled Patients

Characteristic	Total (n=322)	UC (n=174)	CD (n=148)
Age, yr	39.7±14.2	45.2±14.0	33.2±11.6
Male sex	218 (67.7)	100 (57.5)	118 (79.7)
Current or prior use of medications			
Steroids	203 (63.0)	105 (60.3)	98 (66.2)
Immunosuppressant	191 (59.3)	103 (59.2)	120 (81.1)
Biologics	113 (35.1)	39 (22.4)	74 (50.0)
Prior surgery for IBD	67 (20.8)	8 (4.6)	59 (39.9)
Hospitalization episodes	207 (64.3)	85 (48.9)	122 (82.4)
Disease activity (point)			
Crohn's Disease Activity Index	-	-	63.3±66.0
Partial Mayo score	-	0.8±1.3	-
Disease extent of UC			
Proctitis	-	53 (30.5)	-
Left-sided colitis	-	71 (40.8)	-
Extensive colitis	-	50 (28.7)	-
Disease location of CD			
L1 (ileum)	-	-	27 (18.2)
L2 (colon)	-	-	15 (10.1)
L3 (ileum+colon)	-	-	105 (70.9)
L4 (upper gastrointestinal tract)	-	-	1 (0.7)
Disease behavior of CD			
Inflammation	-	-	52 (35.1)
Stricture	-	-	57 (38.5)
Penetration	-	-	39 (26.4)

Data are presented as mean±SD or number (%).
UC, ulcerative colitis; IBD, inflammatory bowel disease; CD, Crohn's disease.

Table 2. Correlations between the Inflammatory Bowel Disease Disability Index and Crohn's and Ulcerative Colitis Questionnaire or Disease Activity

IBD-DI	UC (n=174)				CD (n=148)			
	CUCQ-8		Partial Mayo		CUCQ-8		CDAI	
	r	p-value	r	p-value	r	p-value	r	p-value
Total score	0.636	<0.001	–0.224	0.003	0.711	<0.001	–0.307	<0.001
Subcategories								
Overall Health	0.503	<0.001	–0.273	<0.001	0.475	<0.001	–0.352	<0.001
Body Functions	0.659	<0.001	–0.163	0.032	0.652	<0.001	–0.214	0.009
Body Structures	0.644	<0.001	–0.140	0.066	0.697	<0.001	–0.289	<0.001
Activity Participation	0.213	<0.001	–0.148	0.051	0.316	<0.001	–0.148	0.073
Environmental Factors	–0.034	0.657	–0.121	0.110	0.003	0.966	–0.103	0.214

IBD-DI, inflammatory bowel disease-disability index; UC, ulcerative colitis; CD, Crohn's disease; CUCQ-8, Crohn's and Ulcerative Colitis Questionnaire-8; CDAI, Crohn's Disease Activity Index; r, correlation coefficient.

Table 3. Clinical Factors Related to Inflammatory Bowel Disease Treatment for Inflammatory Bowel Disease Disability Index and Crohn's and Ulcerative Colitis Questionnaire

Factor	IBD-DI		CUCQ-8	
	r	p-value	r	p-value
Disease duration	0.036	0.525	–0.039	0.481
Total days in recent 1 year				
Outpatient clinic visit	–0.110	0.049	0.186	0.001
Hospitalization	–0.093	0.095	0.130	0.019

IBD-DI, inflammatory bowel disease-disability index; CUCQ-8, Crohn's and Ulcerative Colitis Questionnaire-8; r, correlation coefficient.

Categories of IBD-DI were also correlated with CUCQ-8, except for Environmental Factors. In UC patients, Body Functions had the highest correlations with CUCQ-8 scores (r=0.659), followed by Body Structures (r=0.644), Overall Health (r=0.503), and Activity Participation (r=0.213) in decreasing order. Patients with CD showed similar trends in correlations of the two disability indices. IBD-DI had weaker correlations with CDAI and pMayo scores than with CUCQ-8 scores. As expected, as disease activity increased, IBD-DI decreased. Although total IBD-DI was correlated with CDAI in CD patients (p<0.001), the correlation coefficient (r) was only –0.307. In UC patients, pMayo score was more weakly correlated with total IBD-DI (r= –0.224, p=0.003).

3. Predictive factors for IBD disability

We analyzed clinical factors related to IBD treatment that affected IBD-DI and CUCQ-8 (Table 3). IBD duration was not affected by either IBD-DI or CUCQ-8. While IBD-DI was not correlated with hospitalization days (p=0.095) and had only a marginal correlation with clinic visiting days (r= –0.110, p=0.049), CUCQ-8 was very weakly influenced by both hospitalization and clinic visiting days over the past year (r=0.130, p=0.019 and r=0.186, p=0.001, respectively). We also analyzed factors related to disease characteristics for IBD-DI and CUCQ-8 (Table 4). IBD-DI was significantly affected by current or prior use of biologics (p=0.034), but was not affected by administration of current or prior steroids, immunomodulators, or prior surgery for IBD. CUCQ-8 was significantly affected by current or prior use of immunomodulators (p=0.025), but not by the use of steroids, biologics, or prior surgery for IBD. Drug compliance was strongly related to both IBD-DI and CUCQ-8 (p=0.001 and p=0.003, respectively). Disease behavior of CD affected CUCQ-8 (p=0.043), but not IBD-DI. Furthermore, disease extent and location of IBD did not affect either IBD-ID or CUCQ-8.

DISCUSSION

To the best of our knowledge, this is the only prospective and multicenter study to date assessing the relationships between disability due to IBD, disease activity, and QOL, using IBD-DI, a potential target of PROM in East Asian IBD patients. In the current study, disability due to IBD was mainly correlated with disease activity and QOL scores. Improvements in medication compliance were associated with lower disability and higher QOL. This finding makes sense, as worse medication compliance may result in function deterioration. Previous studies have demonstrated poor treatment compliance rates ranging from 72% to 7% in IBD patients,[21,22] and therefore physicians should motivate their IBD patients to increase medication compliance. In our study, predictive factors of higher IBD disability included poor medication compliance, outpatient clinic visiting days, and current or prior use of biologics. These factors may lead to progressive deterioration of functional ability. The number of outpatient clinic visiting days was also associated with disability in a previous study.[23]

The self-reported IBD-DI has been shown to have good reliability and agreement with interview-based disability indexes.[9] In the current study, most data were collected by self-reporting, and trained researchers explained questionnaire items only

Table 4. Factors Related to Disease Characteristics for Inflammatory Bowel Disease Disability Index and Crohn's and Ulcerative Colitis Questionnaire

Variable	IBD-DI	p-value	CUCQ-8	p-value
Current or prior use of medications				
Steroids		0.237		0.066
No	−0.2±8.4		6.7±4.8	
Yes	−1.3±8.7		7.7±5.5	
Immunosuppressant		0.069		0.025
No	0.2±8.0		6.6±4.8	
Yes	−1.6±8.9		7.9±5.5	
Biologics		0.034		0.109
No	−0.1±8.1		7.0±5.1	
Yes	−2.3±9.3		8.0±5.6	
Prior surgery for IBD		0.285		0.160
No	−0.6±8.5		7.1±5.1	
Yes	−1.9±8.8		8.2±6.0	
Medication compliance		0.001		0.003
Good	−2.0±8.5		8.0±8.5	
Poor	1.3±8.4		6.2±4.8	
Disease extent of UC		0.469		0.615
Proctitis	−0.8±1.2		6.7±5.2	
Left-sided	0.5±8.3		7.0±4.6	
Extensive	−1.4±9.3		7.7±5.5	
Disease location of CD		0.663		0.904
L1 (ileum)	0.3±5.8		7.1±5.6	
L2 (colon)	−0.5±7.9		7.1±5.5	
L3 (ileum+colon)	−1.9±9.2		7.8±5.6	
L4 (upper GIT)	−1.0		8.0	
Disease behavior for CD		0.388		0.043
Inflammation	−0.1±6.7		6.1±5.1	
Stricture	−1.8±10.1		8.5±5.7	
Penetrate	−2.4±8.1		8.4±5.6	

Data are presented as mean±SD.
IBD-DI, inflammatory bowel disease-disability index; CUCQ-8, Crohn's and Ulcerative Colitis Questionnaire-8; UC, ulcerative colitis; CD, Crohn's disease; GIT, gastrointestinal tract.

when patients inquired about details of the IBD-DI. Therefore, our findings suggest that IBD-DI may be used as an efficient and convenient target of PROM for assessing IBD disability in East Asian clinical practice. Although other tools are also used to measure IBD disability, such as the World Health Organization Disability Assessment Schedule (WHODAS),[24] which is a generic scale to assess disability, and the Work and Social Adjustment Scale,[25] which was developed for psychiatric research,[26] most previous studies have used the recently-developed IBD-DI, as in the present study.[8,9] In a validation study from Australia, IBD-DI significantly correlated with CDAI, pMayo and IBD-Q, as demonstrated in our study.[8] Considering the fact that all prior studies were based in Western populations, our study is the first to identify similar predictive factors for IBD disability in East Asian populations.[8,9,26] Therefore, based on our findings, the IBD-DI could become an important target of PROM in East Asia as well as in the West.

In this study, age, gender, disease duration, hospitalization days, other medications except biologics, and prior surgery for IBD did not affect IBD disability, and these findings are consistent with those of previous studies.[26,27] Earlier studies suggested that the use of surgery to treat IBD is correlated with higher disability,[28,29] while two recent studies showed no associations between disability and surgery for IBD.[9,26] These opposing results may be explained by differences in postoperative duration. Studies of patients immediately after surgery showed positive associations between surgery and disability due to physical pain and temporary restrictions associated with convalescence, whereas studies assessing patients during longer follow-up after surgery may detect improvements in the complicated course of

disease and durable outcomes of surgery. Most studies showed no associations between disability and disease duration, regardless of tools used to measure IBD disability.[8,9,26,27] Hospitalization days did not affect IBD disability in our study, which was consistent with the results of previous studies.[9,26] East Asian patients with IBD did not experience greater disability than previous patients studied in Western countries, although East Asian IBD patients were more likely to experience hospitalization than Western IBD patients.[30]

CUCQ-8 was recently validated as a reliable and suitable tool for monitoring QOL in IBD patients similar to CUCQ-32, which is not convenient for use in routine clinical practice.[17] In our study, IBD-DI was more strongly correlated with CUCQ-8 comparing with disease activity (CDAI and pMayo scores), results consistent with those of prior studies showing correlations with higher disability and lower QOL.[29,31] As there is overlap between measurements of QOL and disability in IBD patients, these distinctions may not be clear. Disability refers to objective problems, whereas QOL refers to relatively subjective problems according to the WHO definition.[4] In our subanalyses of five categories of IBD-DI, only the Environmental Factors variable of IBD-DI was not associated with QOL. This may suggest that Environmental Factors, which refers to welfare from governmental policies and social health care systems, is important for assessing disability but not QOL due to the focus on personal experiences. Our findings indicate that modification of personal factors alone does not improve disability.

Our study has several limitations. First, our study included only IBD patients from large, tertiary referral centers, which limits the ability to generalize our findings. Our patients may have had more complicated disease courses than average patients, resulting in referrals to our centers. It is possible that in a general gastroenterology community practice, with patients with milder cases of IBD, patients may have different disability or QOL indexes. Second, we assessed IBD-DI at the time of study enrollment only, and did not assess patients longitudinally. Therefore, we were unable to assess fluctuations of disability during the natural course of IBD. Third, selection bias could not be avoided, as not all patients who were solicited were willing to participate. Fourth, this study in which only Korean patients with IBD were enrolled may be not able to represent whole East Asian population. Further multinational large study is recommended in East Asian population.

In conclusion, the IBD-DI, recently developed and validated in the West, could also be indicative of disability in East Asian IBD patients. Disability due to IBD was mainly correlated with disease activity and QOL scores in our patient sample. Improvements in drug compliance were associated with lower disability and higher QOL. Our findings provide evidence that IBD-DI will be a target of PROM in future trials for IBD patients of the West and the East.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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