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직장의 감각 및 운동 기능의 관점에서 과민성 장 증후군의 증상에 의한 아형 분류의 임상적 타당성에 대한 검토

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The Clinical Validity of Symptom-based Subgrouping of Irritable Bowel Syndrome According to the Rectal Sensory and Motor Function

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Background/Aims: It is uncertain what difference exists in the rectal motor and sensory characteristics between the diarrhea-predominant (D-IBS) and constipation-predominant (C-IBS) IBS subgroups. Our aim was to investigate the differences in the compliance, sensitivity and postprandial response of the rectum between the D-IBS and C-IBS patients. **Methods:** Twenty-one D-IBS patients, sixteen C-IBS patients and fourteen healthy controls participated in this study. Using a barostat, sequential isobaric rectal distensions were performed, and then the postprandial change of the rectal tone was evaluated. Subsequently, the isobaric rectal distensions were repeated. **Results:** While no differences in rectal compliance and the prevalence of hypocompliant rectum between two subgroups were observed during the fasting period, the D-IBS patients exhibited lower rectal compliance and a higher prevalence of hypocompliant rectum in the postprandial period compared to the C-IBS patients. A significant postprandial decrease of rectal compliance was observed in the D-IBS patients, but not in the C-IBS patients. No differences were observed between the subgroups in the threshold pressures for discomfort or pain, the prevalence of hypersensitive rectum and the response of rectal sensitivity to a meal. The postprandial increase of the rectal tone was significantly lower in the C-IBS patients, as compared with D-IBS patients. **Conclusions:** The symptom-based subgrouping of IBS is related to the responsiveness of rectal compliance and tone to a meal. **(Kor J Neurogastroenterol Motil 2005;11:135-141)**

Key words: Constipation-predominant irritable bowel syndrome, Diarrhea-predominant irritable bowel syndrome, Rectal compliance, Rectal sensitivity

서 론

Irritable bowel syndrome (IBS) comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation. Patients with IBS present with diverse symptoms including abdominal pain, abnormal stool frequency, abnormal stool form, abnormal stool passage, passage of mucus, and bloating. Based on these symptoms, IBS patients can be subdivided into patients with predominant diarrhea (D-IBS) and with predominant constipation (C-IBS).[1] This subclassification has been used for entry into clinical trials or selection of pharmacologic agents. However, it is uncertain whether these subgroups are related to a common pathophysiology or what difference exists in rectal motor and sensory characteristics between two subgroups.

Altered rectal physiology has been demonstrated in patients

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with IBS, which is detectable by a barostat study. Patients with IBS perceive sensations or discomfort at lower distending pressures than healthy controls.[2-4] Although this abnormal sensitivity is a frequent finding in IBS patients, all patients with IBS are not hypersensitive to distension.[5,6] Differences in rectal sensitivity to distension between two subgroups of IBS have not been consistently reported. Some studies have shown that D-IBS patients are more hypersensitive to rectal distension than C-IBS patients, whereas other studies failed to find this difference.[2,7] Alterations in rectal motor function are more controversial. Rectal compliance was reported to be lower in IBS patients in some studies,[8-11] but not in others.[2,3,12-14] Moreover, differences in rectal motor function between D-IBS and C-IBS patients remain unclear. We investigated differences in the compliance, sensitivity and postprandial response of the rectum between D-IBS and C-IBS patients in order to evaluate clinical validity of this subclassification.

MATERIALS AND METHODS

Subjects

Thirty-seven patients with IBS in accordance with Rome II criteria1 were enrolled in this study. All patients were recruited from outpatient clinic of the Department of Gastroenterology of Ajou University Hospital, which is a tertiary referral center. Patients who had previously undergone major abdominal surgical procedures were excluded. The presence of organic disease was also excluded by standard clinical investigations. Based on the predominant presenting symptoms, the group of patients was subdivided into diarrhea-predominant and constipation-predominant subgroups. Twenty-one of thirty-seven IBS patients were diagnosed as being diarrhea-predominant, and sixteen were diagnosed as being constipation-predominant. There were no statistically significant differences in gender and age between two subgroups. Patients who met criteria for functional, slow-transit or outlet-obstruction constipation were excluded. All patients were instructed to stop any medication affecting gastrointestinal function at least 3 days prior to the study. Fourteen healthy volunteers were participated in the study as controls. None of the control subjects had a history of gastrointestinal disease, nor were they taking any medication. None of them had a history of chronic abdominal symptoms including diarrhea and constipation. No statistically significant differences in gender and age between IBS patients and healthy controls were observed.

Study protocol

Figure 1 depicted the study protocol including the barostat study. After including in the study, patients received a barostat study with assessments of symptoms. All patients were requested to fast from midnight and to evacuate their bowel on the morning of the experiment day. Barostat device consisted of an infinitely compliant polyethylene bag catheter (10 cm long and 700 mL capacity; Mui Scientific, Mississauga, ON, Canada) connected to a computer-controlled barostat (Distender Series II, G & J Electronics, Toronto, ON, Canada). A single 500 mL tap water enema was performed to ensure cleansing the rectum. Before each experiment, the barostat bag was checked for air leaks by maintaining a constant pressure of 20 mmHg. With the subject in the left lateral position, the lubricated and tightly folded bag was introduced through the anus and positioned in the rectal ampulla. To unfold the bag, 200 mL air was manually inflated under controlled pressure (< 20 mmHg) and the catheter was pulled back carefully until its passage was restricted by the anal sphincter. The catheter was then introduced a further 2 cm and fixed. Subsequently, the bag deflated and the catheter connected to the barostat. During the experiment, subjects were in a prone 10^{o} Trendelenburg position to reduce the gravitational effects of the abdominal organs.

The bag was inflated by means of isobaric distension procedure from 5 mmHg with steps of 1 mmHg per min in order to

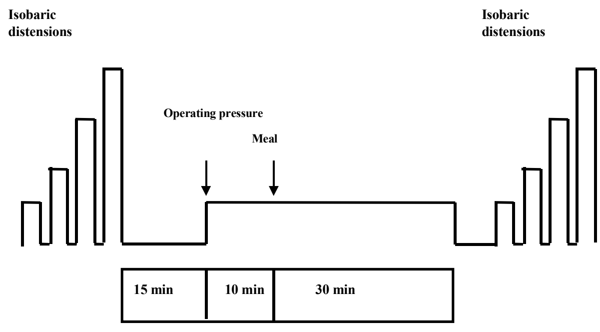

Fig. 1. Study design showing sequence of procedures that were applied in each subject. Sequential isobaric rectal distensions were performed in the fasting period, and then postprandial tonic change of the rectum was evaluated. Subsequently, isobaric rectal distensions were repeated.

determine the operating pressure. The operating pressure was defined as the first pressure level that provided an intrabag volume continuously above 80 mL.[11] After determination of the operating pressure, the balloon was immediately deflated and subjects were allowed a 5 min rest period while the bag remained deflated. Isobaric phasic distensions were then performed at 2 mmHg intervals. Each step lasted 1 min followed by a 30 sec rest period at 0 mmHg. At 30 sec during each step distension, subjects were instructed to score their perception of abdominal sensation, using both a graphic rating scale that combined verbal descriptors on a scale graded 0-6 ('none', 'weak', 'definite', 'strong', 'discomfort', 'pain'). and 100 mm visual analogue scales (VAS) for abdominal discomfort and pain. The word anchors for VAS scales were set as weak (1-2), mild (3-4), moderate (5-6), strong (7-8), and intense (9-10). These scales were used to determine thresholds for discomfort or pain, defined as the first distension to evoke discomfort of at least moderate intensity or pain. Sequential phasic distensions continued until an intrabag pressure of 40 mmHg reached or the subjects reported discomfort of at least moderate intensity or pain. At each pressure increment, intrabag volume was monitored in order to build up pressure-volume curves. Rectal compliance was defined as the slope of the linear part of the pressure-volume curve.[8,11] Afterwards, the bag remained completely deflated during 15 min, and then a baseline volume recording was obtained over a period of 10 min during maintaining an operating pressure. Thereafter, subjects were asked to drink a 500 mL nutrient liquid meal (Ensure, Abott Korea, Seoul, Korea; 1 kcal/mL, carbohydrate 64%, protein 14%, fat 22%) over a 5 min period with a straw. Volume of the barostat bag was then continuously recorded during 30 min after the ingestion of meal. Subsequently, isobaric phasic distensions were repeated with the same methodology as the previous ones.

Data analysis

The mean intrabag volume was measured during each isobaric distension step. Rectal compliance was approximated by calculating the difference in intrabag volume divided by the difference in intrabag pressure. Rectal wall tension was calculated during each pressure distension step by Laplace's law and is expressed in cm × mmHg.[11] Rectal volumes measured during the set pressure procedure are represented as average volumes over 5 min periods. The maximum postprandial increase of rectal tone was defined as the maximum decrease in intrabag volume during the 30 min postprandial period compared with the volume recorded during the last 5 min preprandial period.

Statistical analysis

All values are presented as mean±standard deviation (SD). A student's t-test and chi-square test was used for demographic comparison between treatment groups. The slopes of pressure-volume curves were compared within the group with a paired student's t-test and between the groups with a student's t-test. For comparison of sensory thresholds, statistical analysis was performed within the group by Wilcoxon signed rank test and between the groups by Mann-Whitney U test. The prevalence of hypersensitive rectum or hypocompliant rectum was compared within the group using Wilcoxon signed rank test and between the groups using chi-square test. SPSS version 10.0 (SPSS Inc., Chicago, IL, U.S.A.) was used for all statistical calculations. The p value below 0.05 was considered to be statistically significant.

RESULTS

Rectal compliance

Rectal compliance of IBS patients was significantly lower than that of healthy controls both in the preprandial period (8.0±1.6 vs. 10.5±1.2 mL/mmHg; $p<0.001$) and in the postprandial period (6.8±1.6 vs. 9.4±0.9 mL/mmHg; $p<0.001$) (Fig. 2A). Both D-IBS and C-IBS patients had significantly lower compliance of the rectum in the preprandial (8.0±1.7 and 8.1±1.6, respectively vs. 10.5±1.2 mL/mmHg; $p<0.001$) and postprandial period (6.3±1.6 and 7.4±1.5, respectively vs. 9.4±0.9 mL/mmHg; $p<0.001$), compared with healthy controls. There was no difference in the fasting rectal compliance between D-IBS and C-IBS patients. In contrast, the postprandial compliance of the rectum in D-IBS patients was significantly lower than that in C-IBS patients (Fig. 2B). Significant postprandial decrease of rectal compliance was observed in the control group (9.4±0.9 vs. 10.5±0.9 mL/mmHg; $p<0.005$) and in the D-IBS subgroup (6.2±1.6 vs. 8.0±1.7 mL/mmHg; $p<0.001$), whereas it was not statistically significant in the C-IBS subgroup (7.4±1.5 vs. 8.1±1.6 mL/mmHg; $p=0.06$).

The prevalence of hypocompliant rectum was defined as the

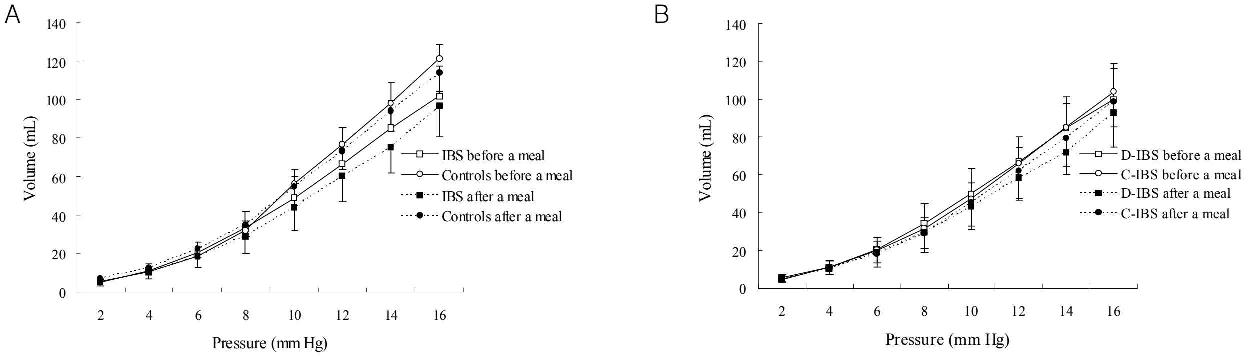

Fig. 2. Pressure-volume curves during sequential isobaric distensions of the rectum before and after a meal. Values are mean ± SD. Rectal compliance of IBS patients was significantly lower compared to that of healthy controls, both in the fasting period and in the postprandial period (A). No difference in the fasting rectal compliance between D-IBS and C-IBS patients was observed, whereas the postprandial rectal compliance in D-IBS patients was significantly lower than that in C-IBS patients (B).

rectal compliance below the control mean-2SD (8.7 mL/mmHg before a meal and 7.6 mL/mmHg after a meal). It did not differ between D-IBS and C-IBS patients in the fasting period (57% vs. 44%, respectively; NS). Whereas, in the postprandial period, it was significantly higher in D-IBS patients than in C-IBS patients (76% vs. 38%, respectively; p<0.05). Significant postprandial increase in the prevalence of hypocompliant rectum was observed in D-IBS patients (p<0.05), but not in C-IBS patients.

Sensory thresholds

Compared with healthy controls, threshold pressures and corresponding wall tensions, inducing discomfort or pain, were significantly lower in IBS patients both in the fasting period (17.5 ±2.6 vs. 23.0±2.3 mmHg; p<0.001 and 68.0±15.1 vs. 96.7± 14.0 cm × mmHg; p<0.001, respectively) and in the postprandial period (15.6±2.5 vs. 19.7±1.7 mmHg; p<0.001 and 56.2±14.1 vs. 84.1±12.7 cm × mmHg; p<0.001, respectively). Significantly lower threshold pressures and corresponding wall tensions for discomfort or pain were observed in both D-IBS and C-IBS patients. Significant postprandial decrease in those pressures and tensions was observed in the control group, in the D-IBS subgroup and in the C-IBS subgroup. Threshold pressures and corresponding wall tensions for discomfort or pain did not significantly differ between D-IBS and C-IBS patients both in the fasting period and in the postprandial period (Table 1).

The prevalence of hypersensitive rectum was defined as the threshold pressure for discomfort or pain below the control mean-2SD (18.4 mmHg before a meal and 16.3 mmHg after a meal). It did not differ between D-IBS and C-IBS patients both in the fasting period (57% vs. 50%, respectively; NS) and in the postprandial period (67% vs. 56%, respectively; NS). Ingestion of the meal did not significantly affect the prevalence of hypersensitive rectum in D-IBS patients and in C-IBS patients.

Postprandial tonic response

The average operating pressure did not differ between IBS patients and healthy controls (13.6±1.6 vs. 12.9±1.3 mmHg, respectively; NS) and between D-IBS and C-IBS patients (13.7± 1.8 vs. 13.5±1.4 mmHg, respectively; NS). After 10 min of basal volume recording with the distending pressure set at the operating

Table 1. Comparison of pressure thresholds and corresponding wall tensions for discomfort or pain between D-IBS and C-IBS patients

	D-IBS		C-IBS	
	Preprandial	Postprandial	Preprandial	Postprandial
Pressure (mmHg)	17.3±2.7	15.2±2.5*	17.6±2.6	16.1±2.5†
Tension (cm × mmHg)	67.3±15.2	54.0±13.5*	68.9±15.5	59.1±14.8†

Data are given as means±SEM.
* P<0.001 vs. preprandial values using Wilcoxon signed rank test.
†P<0.01 vs. preprandial values using Wilcoxon signed rank test.

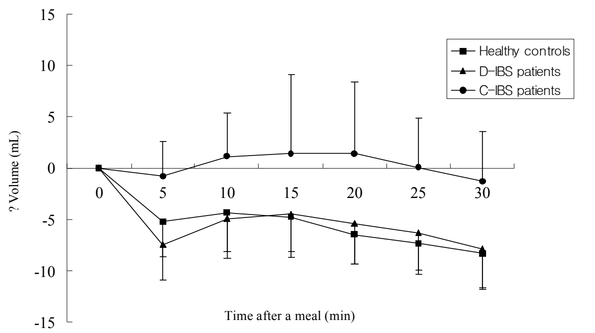

Fig. 3. Postprandial change in intrabag volume relative to the volume during the last 5 min of the preprandial period. Values are mean±SD. No significant difference in the amount of maximum decrease in intrabag volume during the 30 min postprandial period was observed between D-IBS patients and healthy controls. However, it was significantly lower in C-IBS patients, compared with D-IBS patients and healthy controls.

pressure, the liquid nutrient meal was consumed, followed by 30 min postprandial recording. Postprandial change in intrabag volume relative to the volume during the last 5 min of the preprandial period is shown in Fig. 3. No significant difference in the amount of maximum decrease in intrabag volume during the 30 min postprandial period between IBS patients and healthy controls (7.2 ±4.4 vs. 9.1±3.0 mL; NS) was observed. It was significantly lower in C-IBS patients, compared with D-IBS patients (3.6±2.8 vs. 10.0±3.2 mL; $p<0.001$) and healthy controls (3.6±2.8 vs. 9.1 ±3.0 mL; $p<0.001$).

DISCUSSION

The present study demonstrated that 54% of IBS patients had rectal hypersensitivity to distension in the fasting period. The prevalence of hypersensitive rectum did not differ between two subgroups of IBS patients, indicating that this subclassification is not based on the rectal sensitivity to distension. Fifty seven percent of D-IBS patients and 50% of C-IBS patients showed rectal hypersensitivity to distension, which suggests that both D-IBS and C-IBS are heterogeneous groups from the aspect of rectal sensory characteristics. Visceral hypersensitivity has been more consistently reported in D-IBS patients than in C-IBS patients.[2-5,15] Studies in C-IBS patients have produced conflicting results. Although C-IBS patients were thought to be predominantly hyposensitive, rectal hypersensitivity has been observed in a considerable number of C-IBS patients.[9,10] In keeping with those studies, we failed to find a difference in the prevalence of hypersensitive rectum between D-IBS and C-IBS patients since rectal hypersensitivity to distension was observed in a similar percentage of C-IBS patients to that of D-IBS patients. Given that the threshold pressures and corresponding wall tensions inducing discomfort or pain decreased after a meal, ingestion of a meal appears to enhance rectal sensitivity. This finding was observed in C-IBS patients as well as in healthy controls and D-IBS patients. However, in spite of the enhancing effect of a meal on rectal sensitivity, the prevalence of hypersensitive rectum was not significantly changed after a meal in both subgroups of IBS patients.

The sequential phasic distension protocol was used for measuring sensory thresholds in this study. Abnormal sensory responses in IBS patients were reported through the ascending methods of limits.[5,8,16] Although randomly sequenced distensions or multiple distensions at each pressure step seem to enable more reliable estimation of sensory thresholds, some studies have revealed that practical aspects limit the number of trials and the simple ascending method of limits are equivalent to the more complicated random staircase method to determine sensory thresholds.[5,17] Data to recommend one of these protocols over another are insufficient yet. We prefer the ascending method of limits to the random method since progressive distension seems better accepted by the patients, especially for repeated measurements. Furthermore, a simple ascending method of limits may be used provided there is a control group tested in the same way.[18]

The rectum plays a role as a dynamic reservoir for the temporary storage of faeces with rectal pressures being maintained at a low level until defecation is initiated. Rectal compliance is a measure of the resistance of the rectal wall to distension reflecting the tone of the rectal wall. Apart from disturbances in rectal sensitivity, significant alterations in rectal tone or compliance may be observed in IBS patients. Although previous studies have shown controversial results on compliance or wall tone of the rectum in IBS patients, decreased rectal compliance appears to be more frequently observed than increased rectal compliance.[10,15,19] This study showed a significant decrease in rectal compliance in both subgroups of IBS patients compared to healthy controls. Unlike our observation, some studies have shown no difference in rectal compliance in IBS patients, even in D-IBS patients.[5,13,20]

However, they used a different technique for measuring rectal compliance.

Although abnormal rectal compliance is considered to be related to abnormal defecation sensations, we failed to find a difference in rectal compliance and the prevalence of hypocompliant rectum between D-IBS and C-IBS patients in the fasting period. In keeping with our finding, decreased compliance of the rectum has been identified in D-IBS patients15 and in C-IBS patients.[10] In contrast to the fasting rectal compliance, the postprandial compliance of the rectum in D-IBS patients was significantly lower than that in C-IBS patients. The present study showed that the ingestion of a meal significantly decreased rectal compliance in the D-IBS subgroup, but this effect attenuated in the C-IBS subgroup. Similarly, significant postprandial increase in the prevalence of hypocompliant rectum was observed only in D-IBS patients. Moreover, differences were also observed in the responsiveness of rectal tone to a meal. Although the amount of maximum postprandial decrease in intrabag volume did not significantly differ between D-IBS patients and healthy controls, it was significantly lower in C-IBS patients than in healthy controls. Thus, it may be suggested that differences between two subgroups of IBS patients exist in the responsiveness of rectal compliance and tone to a meal. Based on our results, it is conceivable that enhanced responsiveness to meal stimulation results in a reduced rectal capacity and increased defecation sensations in D-IBS patients, whereas decreased responsiveness to a meal leads to an increased rectal capacity and decreased defecation sensations in C-IBS patients. This difference may at least partly explain the clinical pattern of complaints in both subgroups of IBS patients. Thus, subclassification into D-IBS and C-IBS subgroups based on the predominant symptoms seems to reflect the postprandial change of rectal compliance and tone.

Our findings of the present study provide possible therapeutic targets according to the subgroups of IBS. Rectal hypersensitivity to distension and reduced rectal compliance may be a target at which therapeutic endeavour is directed. Since those alterations may be accompanied by both diarrhea and constipation-predominant symptoms, they seem to be common abnormalities underlying IBS. Given that there are differences in the responsiveness of the rectal compliance and tone to a meal between two subgroups of IBS patients, drugs increasing rectal compliance are more likely to provide a therapeutic benefit for D-IBS patients than for C-IBS patients. However, drugs decreasing visceral sensitivity seem to present a possible therapeutic option both for D-IBS and C-IBS patients.

In conclusion, our results indicate that decreased rectal compliance and increased rectal sensitivity to distension are observed in both D-IBS and C-IBS patients. Differences between D-IBS and C-IBS subgroups do not exist in the fasting rectal compliance, the fasting rectal sensitivity and the responsiveness of rectal sensitivity to a meal, but in the responsiveness of rectal compliance and tone to a meal. Compared with C-IBS patients, D-IBS patients are characterized by more decrease of rectal compliance and more increase of rectal tone after a meal. Further study is required to confirm differences in the response to drugs targeting rectal compliance or rectal sensitivity between two subgroups of IBS patients.

요 약

목적: 로마기준에 의해 과민성 장 증후군은 설사 우세형과 변비 우세형으로 아형을 나누어 볼 수 있다. 그렇지만 증상에 의한 분류가 병태생리의 측면에서 타당한 것인지는 확실하지 않다. 이에 저자들은 설사 우세형과 변비 우세형 과민성 장 증후군 간에 식전 및 식후의 직장의 감각 및 운동기능에 차이가 있는 지를 알아보고자 하였다. **대상 및 방법:** 바로스타트를 사용해서 공복시에 순차적인 직장의 확장 자극을 통해서 직장의 감각에 대한 예민도와 순응도를 측정하였고, 이어서 표준 유동식을 투여한 후에 직장의 긴장도의 변화를 보았으며 식후 30분에 다시 순차적인 확장 자극을 통해서 직장의 감각에 대한 예민도와 순응도를 측정하였다. **결과:** 공복시에는 두 아형 간에 직장의 순응도 및 저순응도를 보이는 빈도에 유의한 차이가 없었으나 식후에는 설사 우세형 환자의 직장 순응도가 변비 우세형에 비해 유의하게 낮았고, 저순응도를 보이는 빈도도 유의하게 높았다. 직장 감각에서 불편감이나 통증의 역치와 과민성을 보이는 빈도에 두 아형간에 유의한 차이가 없었다. 식후의 직장 긴장도의 증가가 변비 우세형에서 설사 우세형에 비해 유의하게 낮았다. **결론:** 과민성 장 증후군에서 증상에 의한 아형 분류는 음식에 대한 직장의 운동 반응, 즉 직장 순응도와 긴장도의 식후 변화와 관련이 있다.

색인단어: 설사 우세형 과민성 장 증후군, 변비 우세형 과민성 장 증후군, 직장 예민도, 직장 순응도

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