



Observational Study

## Constipation, hard stools, fecal urgency, and incomplete evacuation, but not diarrhea is associated with diabetes and its related factors

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## Abstract

**AIM:** To determine the bowel symptoms associated with diabetes and diabetes-related factors after excluding gastrointestinal (GI) organic diseases.

**METHODS:** Participants were 4738 (603 diabetic and 4135 non-diabetic) patients who underwent colonoscopy and completed a questionnaire. On the day of pre-colonoscopy, 9 symptoms (borborygmus, abdominal distension, increased flatus, constipation, diarrhea, loose stools, hard stools, fecal urgency, and incomplete evacuation) were prospectively evaluated on a 7-point Likert scale. The test-retest reliability of the bowel symptom scores from the baseline and second questionnaires was analyzed using kappa statistics. Associations between bowel symptom scores and diabetes or diabetes-related factors were analyzed by a rank-ordered logistic model adjusted for related confounders, and odds ratios (ORs) were estimated.

**RESULTS:** In multivariate analysis, constipation [adjusted odds ratio (AOR) = 1.57, CI: 1.33-1.85,  $P < 0.01$ ] and hard stools (AOR = 1.56, CI: 1.33-1.84,  $P < 0.01$ ) were associated with diabetes, and fecal urgency (AOR = 1.16, CI: 0.99-1.37,  $P = 0.07$ ) and incomplete evacuation (AOR = 1.16, CI: 1.00-1.36,  $P = 0.06$ ) were marginally associated with diabetes. These symptoms remained associated even after excluding organic GI diseases on colonoscopy. Test-retest reliability of symptom score with a mean duration of 3.2 mo was good (mean kappa, 0.69). Associations of symptoms with diabetes-related factors were found; constipation with HbA1c  $\geq 8.0\%$  (AOR = 2.11, CI: 1.19-3.73), body mass index (BMI)  $< 25$  (AOR = 2.11, CI: 1.22-3.66), and insulin use (AOR = 1.90, CI: 1.08-3.36); hard stools with diabetes duration (AOR = 1.03, CI: 1.00-1.07); fecal urgency with BMI  $< 25$  (AOR = 1.73, CI: 1.00-2.98); and incomplete evacuation with BMI  $< 25$  (AOR = 2.60, CI: 1.52-4.43), serum creatinine level (AOR = 1.27, CI: 1.10-1.47), and insulin use (AOR = 1.92, CI: 1.09-3.38).

**CONCLUSION:** Diabetes is associated with constipation, hard stools, fecal urgency, and incomplete evacuation, and poor glycemic control, duration, leanness, and nephropathy affect the risk of these symptoms.

**Key words:** Functional bowel disease; Gastrointestinal symptom rating scale; Decreased passage of stools; Diabetic complications

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**Core tip:** This study determined the bowel symptoms associated with diabetes. Patients underwent colonoscopy and completed a questionnaire on 9 bowel symptoms. Symptoms evaluated on a 7-point Likert scale were compared between baseline and the second questionnaire for test-retest reliability. Constipation and hard stools were associated with diabetes, and fecal urgency and incomplete evacuation were marginally associated with diabetes. These relations remained after excluding organic gastrointestinal diseases. Long-term reliability of symptom score suggested that these symptoms remain consistent over a given period. In diabetes, poor glycemic control, diabetes duration, low BMI, and high creatinine level were associated with these symptoms.

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## INTRODUCTION

Diabetes mellitus and its complications have become major worldwide public health concerns<sup>[1]</sup>. Gastrointestinal (GI) symptoms are common in diabetic autonomic neuropathy<sup>[2]</sup> and affect the quality of life of diabetic patients<sup>[3]</sup>. Several studies have shown that various GI symptoms are associated with diabetes, poor glycemic control, and duration of diabetes<sup>[4,5]</sup>. However, neither the GI symptoms typically associated with diabetes nor the diabetes-related factors have been clarified. In addition, prior studies have experienced the following methodological issues. First, GI symptoms were not substantially evaluated quantitatively or with a reliable and validated scoring system<sup>[6,7]</sup>, which would improve assessment of the relationship between diabetes and the wide range of GI symptoms<sup>[6,8]</sup>. Second, although GI symptoms can be induced by various GI diseases, most prior studies did not exclude organic GI diseases evaluated by colonoscopy. Third, studies on this association with a large sample population are rather scarce.

In the light of these issues, we conducted a large colonoscopy-based study and evaluated 9 specific bowel symptoms on a 7-point Likert scale. The objective of the study was to determine the bowel symptoms associated with diabetes and diabetes-related factors in clinical practice, even after excluding organic GI diseases.

## MATERIALS AND METHODS

### **Study design, participants, data sources and measurement**

We conducted this hospital-based cross-sectional study at the National Center for Global Health and Medicine (NCGM), Japan. Participants who were scheduled to undergo elective colonoscopy and completed questionnaires at the endoscopy unit of the NCGM between September 2009 and April 2014 were enrolled. Inclusion criteria were as follows: (1) > 18 years old; (2) Japanese nationality; (3) patients for colorectal adenoma/cancer screening or surveillance for polyps after resection of colorectal adenoma; (4) patients who required examination for specific diseases because of abnormal abdominal findings on ultrasonography, computed tomography, positron emission tomography-computed tomography, or magnetic resonance imaging; and (5) patients with intermittent or continuous GI symptoms. Exclusion criteria were as follows: (1) no informed consent obtained; (2) unknown use of medications; (3) not independent in activities of daily living; (4) inability to understand written documents; or (5) previous urgent or early colonoscopy for acute onset of GI symptoms. All inclusion criteria were fulfilled before the patients were enrolled. This study was approved by the ethics committee of the National Center for Global Health and Medicine Center, and included protocol number 1712. The study was conducted in accordance with the provisions of the Declaration of Helsinki.

A detailed questionnaire was completed at the endoscopy unit on the day prior to colonoscopy. Well-trained medical researchers asked patients about alcohol consumption, smoking status, medical history, and co-morbidities. Researchers also checked prescriptions and medical records in addition to the information provided by the patients to avoid omissions. Medical history included hypertension and dyslipidemia, which were considered present in patients taking specific drugs. History of cerebro-cardiovascular disease was also asked. BMI was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). The diagnosis of diabetes was based on the updated criteria of the American Diabetes Association, including a past history of diabetes, a fasting plasma glucose level (126 mg/dL), or a glycated hemoglobin (HbA1c) level of 6.5% (48 mmol/mol)<sup>[9]</sup>.

Precise analysis was performed with the diabetic patients followed-up at the Department of Diabetes, Endocrinology and Metabolism of the NCGM. Laboratory data (HbA1c, serum creatinine, and qualitative urine protein levels) were measured within 3 mo and BMI was measured within 6 mo of undergoing colonoscopy. Other clinical data (duration of diabetes, use of hypoglycemic agents: insulin, sulfonylurea, glinide, alpha-glucosidase inhibitors, biguanide, thiazolidine, and dipeptidyl peptidase-4 [DPP-4] inhibitors) were collected from clinical records

and the National Center Diabetes Database, as previously reported<sup>[10]</sup>.

### **Evaluation of bowel symptoms and diagnosis of colorectal diseases**

The questionnaire contained detailed information about bowel symptoms occurring within the last 3 mo of colonoscopy. Before the colonoscopy, 9 bowel symptoms were evaluated using the GI symptom rating scale (GSRS) and a 7-point Likert scale (1, none; 2, minor; 3, mild; 4, moderate; 5, moderately severe; 6, severe; and 7, very severe)<sup>[8]</sup>. The reliability and validity of the GSRS for functional bowel disease are well-documented<sup>[8,11]</sup>. The 9 bowel symptoms were borborygmus, abdominal distension, increased flatus, constipation, diarrhea, loose stools, hard stools, fecal urgency, and feeling of incomplete evacuation<sup>[8]</sup>.

To assess the reliability of bowel symptoms scores, we conducted a test-retest analysis for first and secondary questionnaires using the same GSRS among participants who visited our department from 1 week to 1 year after the first interview.

A high-resolution electronic video colonoscope (CFH260; Olympus Optical, Tokyo, Japan) with full preparation was used for the diagnosis of colorectal diseases. Well-trained staff who were blinded to the questionnaire results performed colonoscopy. When abnormal findings were detected on colonoscopy, biopsy, polypectomy, or endoscopic mucosal resection was performed. All removed specimens were evaluated by expert pathologists, and final diagnoses of colorectal diseases were made.

Organic GI disease was defined as colorectal cancer, post-colectomy for colorectal cancer, other colorectal tumor, inflammatory bowel disease, ischemic colitis, and other colitis (infectious colitis, non-specific colitis, and drug-induced colitis) as previously reported<sup>[12]</sup>. The above information on endoscopic or pathological diagnoses was systematically stored in an electronic endoscopic database (Solemio; Olympus Optical, Tokyo, Japan).

### **Statistical analysis**

Pearson's Chi-squared test or Fisher's exact test for categorical data was used to assess the differences in clinical factors between participants with and without diabetes. Continuous values were compared using the Mann-Whitney *U* test. Associations between bowel symptom scores and diabetes or diabetes-related factors were analyzed by univariate and multivariate rank ordered logistic modeling<sup>[13]</sup>, and odds ratios (ORs) with 95%CI were estimated. Multivariate analysis was adjusted for age, sex<sup>[12]</sup>, alcohol consumption<sup>[14]</sup>, and smoking status<sup>[12,15]</sup>, all of which are known or probable factors associated with bowel symptoms. These associations were evaluated after excluding organic GI diseases. Associations between positive bowel symptoms and diabetes mellitus were also analyzed by univariate and multivariate logistic

**Table 1 Characteristics of 4738 participants *n* (%)**

	All ( <i>n</i> = 4738)	Diabetes ( <i>n</i> = 603)	Non-diabetes ( <i>n</i> = 4135)	<i>P</i> value
Age (yr)	60.0 ± 14.3	65.0 ± 11.9	59.3 ± 14.5	< 0.001
Age ≥ 65 (yr)	2102 (44.4)	345 (57.2)	1757 (42.5)	< 0.001
Male sex	2988 (63.1)	472 (78.3)	2516 (60.9)	< 0.001
Height <sup>1</sup>	163.3 ± 9.2	165.3 ± 8.7	162.9 ± 9.3	< 0.001
Weight <sup>2</sup>	61.1 ± 12.3	65.8 ± 12.7	60.3 ± 12.0	< 0.001
<sup>2</sup> BMI, kg/m <sup>2</sup>	22.8 ± 3.5	24.0 ± 3.9	22.6 ± 3.4	< 0.001
Lifestyle factors				
Current smoker	2297 (48.5)	337 (55.9)	1960 (47.4)	< 0.001
Current alcohol consumption	2735 (57.7)	322 (53.4)	2413 (58.4)	0.021
Chronic disease				
Hypertension	1520 (31.9)	338 (56.1)	1172 (28.3)	< 0.001
Dyslipidemia	802 (16.9)	169 (28.0)	633 (15.3)	< 0.001
Cerebro-cardiovascular disease	435 (9.2)	106 (17.6)	329 (8.0)	< 0.001
Chronic kidney disease	160 (3.4)	56 (9.3)	104 (2.5)	< 0.001
Liver cirrhosis	318 (6.7)	42 (7.0)	276 (6.7)	0.790
Familial history of colorectal cancer	351 (7.4)	43 (7.1)	308 (7.5)	0.781
Medication				
NSAIDs	407 (8.6)	53 (8.8)	354 (8.6)	0.852
Low-dose aspirin	445 (9.4)	111 (18.4)	334 (8.1)	< 0.001
Thienopyridine	130 (2.7)	40 (6.6)	90 (2.2)	< 0.001
Dipyridamole	40 (0.84)	4 (0.7)	36 (0.9)	0.603
Cilostazol	55 (1.2)	19 (3.2)	36 (0.9)	< 0.001
Anticoagulants	231 (4.9)	40 (6.6)	191 (4.6)	0.032
Cecum intubation rate	3484 (97.1)	592 (98.2)	4042 (97.8)	0.506
Colorectal disease on colonoscopy with pathology				
Colorectal cancer	80 (1.7)	16 (2.7)	64 (1.6)	0.049
Post-colectomy for colorectal cancer	227 (4.8)	40 (6.6)	187 (4.5)	0.023
Other colorectal tumor <sup>3</sup>	62 (1.3)	8 (1.3)	54 (1.3)	0.967
Inflammatory bowel disease	246 (5.2)	19 (3.2)	227 (5.5)	0.016
Ischemic colitis	50 (1.1)	3 (0.5)	47 (1.1)	0.151
Other colitis	50 (1.1)	3 (0.5)	47 (1.1)	0.151

<sup>1</sup>Height was measured in 2834 patients (432 diabetics and 2402 non-diabetics); <sup>2</sup>Weight was measured in 2833 patients (431 diabetics and 2402 non-diabetics); <sup>3</sup>Other colorectal malignancies included lymphoma, sarcoma, and lipoma. Data presented as number (%). Values presented with plus/minus signs indicate means ± SD. *P* value is for the comparison between diabetics and non-diabetics. BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs.

regression analysis.

To evaluate the reliability of the GSRS, we analyzed internal consistency and long-term test-retest. Cronbach's alpha was used for measurement of internal consistency of 9 items of the GSRS. Cronbach's alpha ( $\alpha$ ) values were interpreted as follows:  $\geq 0.90$ , excellent agreement;  $0.9 > \alpha \geq 0.80$ , good agreement,  $0.8 > \alpha \geq 0.7$ , acceptable;  $0.7 > \alpha \geq 0.6$ , questionable;  $0.6 > \alpha \geq 0.5$ , poor; and  $0.5 < \alpha$ ,

unacceptable. The test-retest reliability of the bowel symptom scores in the GSRS from the first and second questionnaires was analyzed using kappa statistics. Kappa values  $> 0.80$  denoted excellent agreement,  $> 0.60$  to  $0.80$  good,  $> 0.40$  to  $0.60$  moderate,  $> 0.20$  to  $0.40$  fair, and  $\leq 0.20$  poor<sup>[16]</sup>.

*P* < 0.05 was considered significant. All statistical analysis was performed using Stata version 13 software (StataCorp, College Station, TX).

## RESULTS

### Baseline characteristics

During the study period, 4738 Japanese patients who completed the questionnaire were enrolled in the study. Among the 4738 participants, there were 603 diabetic (12.7%) and 4135 non-diabetic (87.3%) patients. Patient characteristics are shown in Table 1. The factors associated with diabetes were advanced age, male sex, high BMI, current smoker, hypertension, dyslipidemia, cerebro-cardiovascular disease, chronic kidney disease, and the use of low-dose aspirin, thienopyridine, cilostazol, and anticoagulants. Colonoscopy revealed organic GI disease in 13.7% (651/4738) of the patients. Organic GI diseases included colorectal cancer (*n* = 80), post-colectomy for colorectal cancer (*n* = 227), other colorectal tumor (*n* = 62), inflammatory bowel disease (*n* = 246), ischemic colitis (*n* = 50), and other colitis (*n* = 50).

### Associations between diabetes mellitus and bowel symptoms

Associations between diabetes and bowel symptom scores are shown in Table 2. Ordered logistic model analysis revealed that diabetes was independently associated with constipation [crude OR (COR) = 1.47 (1.26-1.73), adjusted OR (AOR) = 1.57 (1.33-1.85)] and hard stools [COR = 1.57 (1.34-1.84), AOR = 1.56 (1.33-1.84)] and marginally associated with fecal urgency [COR = 1.13 (0.97-1.33), AOR = 1.16 (0.99-1.37)] and incomplete evacuation [COR = 1.11 (0.96-1.30), AOR = 1.16 (1.00-1.36)]. After excluding organic GI diseases, ordered logistic regression analysis revealed that diabetes remained independently associated with constipation [AOR = 1.43 (1.20-1.70)], hard stools [AOR = 1.50 (1.26-1.78)], and fecal urgency [AOR = 1.20 (1.01-1.43)] and marginally associated with incomplete evacuation [OR = 1.16 (0.98-1.37)] (Table 2).

The tests of internal consistency using Cronbach's alpha revealed that measurement of bowel symptom scores with 9 items were good (Cronbach's alpha of 0.84). Among the 4678 participants, 1197 completed a secondary questionnaire using the GSRS within a mean duration of  $3.2 \pm 3.4$  mo. After excluding organic disease, the test-retest reliability of the bowel



**Table 2** Associations between diabetes and bowel symptoms (*n* = 4738)

GI symptom	Crude OR	P value	Adjusted OR Model 1 <sup>1</sup>	P value	Adjusted OR Model 2 <sup>2</sup>	P value
Borborygmus	0.81 (0.68-0.96)	0.02	0.93 (0.78-1.11)	0.43	0.94 (0.78-1.14)	0.53
Abdominal distension	1.00 (0.84-1.19)	0.98	1.10 (0.91-1.30)	0.34	1.04 (0.86-1.26)	0.71
Increased flatus	1.14 (0.97-1.33)	0.11	1.12 (0.96-1.32)	0.15	1.15 (0.97-1.37)	0.10
Constipation	1.47 (1.26-1.73)	< 0.001	1.57 (1.33-1.85)	< 0.001	1.43 (1.20-1.70)	< 0.001
Diarrhea	0.88 (0.75-1.04)	0.13	0.98 (0.83-1.15)	0.77	0.97 (0.81-1.17)	0.77
Loose stools	0.96 (0.82-1.13)	0.66	1.06 (0.90-1.25)	0.50	1.02 (0.86-1.23)	0.79
Hard stools	1.57 (1.34-1.84)	< 0.001	1.56 (1.33-1.84)	< 0.001	1.50 (1.26-1.78)	< 0.001
Fecal urgency	1.13 (0.97-1.33)	0.12	1.16 (0.99-1.37)	0.07	1.20 (1.01-1.43)	0.04
Incomplete evacuation	1.11 (0.96-1.30)	0.17	1.16 (1.00-1.36)	0.06	1.16 (0.98-1.37)	0.08

<sup>1</sup>Model 1: Adjusted for age, sex, current smoker, and alcohol consumption; <sup>2</sup>Model 2: Adjusted for age, sex, smoking, and alcohol consumption after exclusion of organic disease (*n* = 4087). The numbers in parentheses represent the 95% CI. GI: Gastrointestinal; OR: Odds ratio.

**Table 3** Test-retest reliability of bowel symptom score between 1<sup>st</sup> and 2<sup>nd</sup> questionnaire

Bowel symptoms	All ( <i>n</i> = 1197)			Diabetes ( <i>n</i> = 152)			Non-Diabetes ( <i>n</i> = 1045)		
	Kappa value	SE	P value	Kappa value	SE	P value	Kappa value	SE	P value
Borborygmus	0.67	0.02	< 0.001	0.69	0.05	< 0.001	0.67	0.02	< 0.001
Abdominal distension	0.68	0.02	< 0.001	0.71	0.05	< 0.001	0.68	0.02	< 0.001
Increased flatus	0.67	0.02	< 0.001	0.67	0.04	< 0.001	0.67	0.02	< 0.001
Constipation	0.70	0.02	< 0.001	0.71	0.04	< 0.001	0.70	0.02	< 0.001
Diarrhea	0.70	0.02	< 0.001	0.73	0.05	< 0.001	0.69	0.02	< 0.001
Loose stools	0.70	0.02	< 0.001	0.77	0.05	< 0.001	0.70	0.02	< 0.001
Hard stools	0.68	0.02	< 0.001	0.75	0.04	< 0.001	0.67	0.02	< 0.001
Fecal urgency	0.69	0.02	< 0.001	0.69	0.04	< 0.001	0.69	0.02	< 0.001
Incomplete evacuation	0.68	0.02	< 0.001	0.73	0.04	< 0.001	0.67	0.02	< 0.001

GI: Gastrointestinal.

symptom score between baseline and the second questionnaire was good (mean Kappa values was 0.69). The Kappa value of diabetic patients was higher than non-diabetic patients (Table 3).

#### **Effect of diabetes mellitus-related factors on the risk of bowel symptoms**

Of the 603 diabetic patients treated at our hospital or neighboring hospitals, 241 were regularly followed-up at our hospital and their clinical information were collected more precisely. The association between diabetes-related factors and bowel symptoms is shown in Table 4. After excluding organic disease, HbA1c  $\geq$  8.0% (64 mmol/mol) [AOR = 2.11 (1.19-3.73)], BMI < 25 [AOR = 2.11 (1.22-3.66)], and insulin use [AOR = 1.90 (1.08-3.36)] were significantly associated with constipation. Long duration of diabetes [AOR = 1.03 (1.00-1.07)] was significantly associated with hard stools. BMI < 25 [AOR = 1.73 (1.00-2.98)] was associated with fecal urgency, and biguanide use was marginally associated with fecal urgency. BMI < 25 [AOR = 2.60 (1.52-4.43)], serum creatinine level [AOR = 1.27 (1.10-1.47)], and insulin use [AOR = 1.92 (1.09-3.38)] were significantly associated with incomplete evacuation.

## **DISCUSSION**

In this study, we found that constipation, hard stools, and fecal urgency were associated with diabetes, and incomplete evacuation was marginally associated with diabetes. These symptoms remained associated even after excluding organic GI diseases. The long-term reliability of bowel symptom scores in the GSRS was found to be good. Finally, we found that high HbA1c levels, long duration of diabetes, low BMI, high serum creatinine levels, and insulin use affect the risk of these symptoms in patients with diabetes.

Several studies have reported an association between bowel symptoms and diabetes. Bytzer *et al.*<sup>[17,18]</sup> conducted a mail-based survey of 15000 people in Australia and reported that diabetes had an OR of 1.8 for any bowel symptom, 2.1 for diarrhea, and 1.5 for constipation, and also showed the associations between symptoms and poor glycemic control. In Hong Kong, Ko *et al.*<sup>[5]</sup> conducted an interview-based study which revealed abdominal pain/cramps, diarrhea, steatorrhea, and constipation to be significantly associated with type 2 diabetes mellitus. In the United States, Maleki *et al.*<sup>[19]</sup> conducted a population-based, case-controlled study and reported constipation and/or

Table 4 Associations between diabetes-related factors and the bowel symptoms in patients with diabetes (*n* = 241)

	Number of patients (%) or mean $\pm$ SD	Crude OR	<i>P</i> value	Adjusted OR (Model 1) <sup>1</sup>	<i>P</i> value	Adjusted OR (Model 2) <sup>2</sup>	<i>P</i> value
<b>Constipation</b>							
HbA1c $\geq$ 8.0% (64 mmol/mol)	54/241 (22.4)	2.11 (1.22-3.64)	< 0.01	2.10 (1.21-3.66)	< 0.01	2.11 (1.19-3.73)	0.01
Duration of diabetes (yr)	13.0 $\pm$ 8.9	1.02 (0.99-1.04)	0.22	1.02 (1.00-1.05)	0.10	1.02 (0.99-1.05)	0.22
BMI < 25 kg/m <sup>2</sup>	137/230 (59.6)	1.62 (0.99-2.64)	0.06	1.76 (1.06-2.93)	0.03	2.11 (1.22-3.66)	< 0.01
Cerebro-cardio vascular disease	37/241 (15.3)	1.51 (0.82-2.80)	0.19	1.38 (0.73-2.62)	0.33	1.13 (0.56-2.27)	0.73
Creatinine ( $\mu$ mol/L)	109.6 $\pm$ 149.4	0.97 (0.81-1.21)	0.71	0.97 (0.81-1.16)	0.74	1.02 (0.84-1.23)	0.87
Urine protein positive	51/224 (22.8)	0.95 (0.53-1.70)	0.85	0.89 (0.49-1.61)	0.70	0.83 (0.44-1.58)	0.57
Hypoglycemic agents							
Insulin	69/241 (28.6)	1.83 (1.11-3.03)	0.02	1.82 (1.07-3.09)	0.03	1.90 (1.08-3.36)	0.03
Sulfonylurea	75/241 (31.1)	0.77 (0.46-1.29)	0.32	0.79 (0.46-1.34)	0.38	0.72 (0.41-1.26)	0.25
Glinide	21/241 (8.7)	1.52 (0.66-3.48)	0.32	1.72 (0.75-3.95)	0.20	2.00 (0.83-4.82)	0.12
Alpha-glucosidase inhibitors	68/241 (28.2)	1.01 (0.60-1.68)	0.98	1.04 (0.62-1.76)	0.88	0.99 (0.58-1.71)	0.98
Biguanide	104/241 (43.1)	1.24 (0.78-1.99)	0.36	1.32 (0.81-2.13)	0.26	1.38 (0.82-2.30)	0.22
Thiazolidine	28/241 (11.6)	0.88 (0.41-1.86)	0.73	0.86 (0.40-1.84)	0.69	0.87 (0.40-1.92)	0.74
DPP-4 inhibitors	36/241 (14.9)	0.73 (0.38-1.39)	0.33	0.77 (0.40-1.49)	0.44	0.83 (0.42-1.62)	0.58
<b>Hard stool</b>							
HbA1c $\geq$ 8.0% (64 mmol/mol)	54/241 (22.4)	1.72 (0.99-2.98)	0.05	1.75 (1.00-3.03)	< 0.05	1.71 (0.97-3.02)	0.06
Duration of diabetes (yr)	13.0 ( $\pm$ 8.9)	1.02 (1.00-1.05)	0.08	1.03 (1.00-1.06)	0.07	1.03 (1.00-1.07)	0.04
BMI < 25 kg/m <sup>2</sup>	137/230 (59.6)	1.24 (0.76-2.01)	0.39	1.28 (0.78-2.11)	0.33	1.44 (0.85-2.45)	0.17
Cerebro-cardio vascular disease	37/241 (15.3)	1.28 (0.68-2.40)	0.44	1.15 (0.60-2.21)	0.67	1.31 (0.65-2.65)	0.45
Creatinine ( $\mu$ mol/L)	109.6 $\pm$ 149.4	1.08 (0.94-1.23)	0.28	1.09 (0.95-1.25)	0.22	1.12 (0.97-1.30)	0.12
Urine protein positive	51/224 (22.8)	1.08 (0.60-1.93)	0.80	1.04 (0.57-1.87)	0.91	1.07 (0.57-2.03)	0.83
Hypoglycemic agents							
Insulin	69/241 (28.6)	1.08 (0.65-1.81)	0.76	1.10 (0.65-1.88)	0.72	1.08 (0.61-1.90)	0.79
Sulfonylurea	75/241 (31.1)	0.65 (0.39-1.08)	0.10	0.63 (0.37-1.06)	0.08	0.65 (0.38-1.13)	0.13
Glinide	21/241 (8.7)	1.94 (0.83-4.51)	0.13	2.07 (0.88-4.89)	0.10	2.20 (0.90-5.39)	0.08
Alpha-glucosidase inhibitors	68/241 (28.2)	1.16 (0.69-1.93)	0.57	1.19 (0.70-2.01)	0.52	1.08 (0.63-1.86)	0.78
Biguanide	104/241 (43.1)	1.01 (0.63-1.61)	0.98	1.05 (0.65-1.70)	0.83	0.97 (0.59-1.62)	0.92
Thiazolidine	28/241 (11.6)	0.84 (0.39-1.80)	0.65	0.81 (0.38-1.75)	0.59	0.76 (0.35-1.66)	0.49
DPP-4 inhibitors	36/241 (14.9)	0.69 (0.35-1.33)	0.27	0.70 (0.36-1.37)	0.29	0.75 (0.38-1.47)	0.40
<b>Fecal urgency</b>							
HbA1c $\geq$ 8.0% (64 mmol/mol)	54/241 (22.4)	0.99 (0.56-1.74)	0.97	0.94 (0.53-1.67)	0.83	0.96 (0.53-1.72)	0.88
Duration of diabetes (yr)	13.0 $\pm$ 8.9	1.01 (0.98-1.03)	0.65	1.00 (0.98-1.03)	0.76	1.01 (0.98-1.04)	0.56
BMI < 25 kg/m <sup>2</sup>	137/230 (59.6)	1.62 (0.98-2.67)	0.06	1.81 (1.08-3.03)	0.03	1.73 (1.00-2.98)	< 0.05
Cerebro-cardio vascular disease	37/241 (15.3)	1.41 (0.73-2.71)	0.31	1.41 (0.72-2.78)	0.32	1.74 (0.84-3.59)	0.14
Creatinine ( $\mu$ mol/L)	109.6 ( $\pm$ 149.4)	1.16 (0.98-1.39)	0.09	1.15 (0.97-1.36)	0.12	1.14 (0.94-1.39)	0.18
Urine protein positive	51/224 (22.8)	0.72 (0.39-1.33)	0.29	0.70 (0.38-1.29)	0.25	0.78 (0.40-1.51)	0.45
Hypoglycemic agents							
Insulin	69/241 (28.6)	1.59 (0.95-2.66)	0.08	1.65 (0.96-2.83)	0.07	1.67 (0.94-2.95)	0.08
Sulfonylurea	75/241 (31.1)	0.56 (0.33-0.93)	0.03	0.57 (0.33-0.96)	0.03	0.61 (0.35-1.07)	0.08
Glinide	21/241 (8.7)	1.29 (0.57-2.91)	0.55	1.38 (0.60-3.16)	0.45	1.43 (0.59-3.44)	0.42
Alpha-glucosidase inhibitors	68/241 (28.2)	1.17 (0.70-1.96)	0.54	1.18 (0.70-1.98)	0.53	1.22 (0.71-2.08)	0.47
Biguanide	104/241 (43.1)	1.55 (0.97-2.48)	0.07	1.63 (1.01-2.63)	< 0.05	1.65 (0.99-2.73)	0.05
Thiazolidine	28/241 (11.6)	0.77 (0.52-2.12)	0.90	1.08 (0.53-2.21)	0.83	1.23 (0.60-2.54)	0.58
DPP-4 inhibitors	36/241 (14.9)	0.64 (0.33-1.26)	0.20	0.64 (0.32-1.30)	0.20	0.67 (0.34-1.34)	0.26
<b>Incomplete evacuation</b>							
HbA1c $\geq$ 8.0% (64 mmol/mol)	54/241 (22.4)	1.49 (0.85-2.60)	0.16	1.50 (0.86-2.64)	0.15	1.49 (0.84-2.64)	0.18
Duration of diabetes (yr)	13.0 $\pm$ 8.9	1.02 (1.00-1.05)	0.08	1.02 (1.00-1.06)	0.07	1.03 (1.00-1.06)	0.08
BMI < 25 kg/m <sup>2</sup>	137/230 (59.6)	2.09 (1.29-3.40)	< 0.01	2.21 (1.34-3.65)	< 0.01	2.60 (1.52-4.43)	< 0.01
Cerebro-cardio vascular disease	37/241 (15.3)	1.67 (0.89-3.12)	0.11	1.61 (0.84-3.07)	0.15	1.81 (0.90-3.61)	0.09
Creatinine ( $\mu$ mol/L)	109.6 $\pm$ 149.4	1.24 (1.08-1.42)	< 0.01	1.25 (1.09-1.43)	< 0.01	1.27 (1.10-1.47)	< 0.01
Urine protein positive	51/224 (22.8)	1.41 (0.80-2.48)	0.24	1.38 (0.78-2.45)	0.27	1.45 (0.79-2.69)	0.23
Hypoglycemic agents							
Insulin	69/241 (28.6)	1.65 (0.99-2.76)	0.05	1.77 (1.03-3.02)	0.04	1.92 (1.09-3.38)	0.02
Sulfonylurea	75/241 (31.1)	0.85 (0.52-1.40)	0.53	0.83 (0.50-1.38)	0.47	0.89 (0.52-1.52)	0.68
Glinide	21/241 (8.7)	2.27 (1.00-5.18)	0.05	2.39 (1.03-5.52)	0.04	2.33 (0.95-5.73)	0.06
Alpha-glucosidase inhibitors	68/241 (28.2)	0.92 (0.55-1.52)	0.74	0.92 (0.55-1.54)	0.76	0.85 (0.50-1.44)	0.55
Biguanide	104/241 (43.1)	1.19 (0.76-1.89)	0.44	1.22 (0.77-1.94)	0.40	1.15 (0.70-1.87)	0.58
Thiazolidine	28/241 (11.6)	1.07 (0.52-2.25)	0.84	1.07 (0.51-2.24)	0.86	1.14 (0.53-2.42)	0.74
DPP-4 inhibitors	36/241 (14.9)	0.49 (0.26-0.94)	0.03	0.49 (0.25-0.94)	0.03	0.52 (0.27-1.01)	0.05

<sup>1</sup>Model 1: Adjusted for age, sex, smoking, and alcohol consumption; <sup>2</sup>Model 2: Adjusted for age, sex, smoking, and alcohol consumption after exclusion of organic disease (*n* = 201). The numbers in parentheses represent the 95% confidence interval. BMI: Body mass index; DPP-4: Dipeptidyl peptidase-4; HbA1c: Glycated hemoglobin; OR: Odds ratio.

laxative use was more common in men with type 1 diabetes, but not type 2 diabetes. On the other hand, Tseng *et al.*<sup>[20]</sup> conducted a cross-sectional study of a large sample population in Taiwan and reported no significant differences between diabetes and bowel symptoms, including constipation and diarrhea. These results were in conflict with our results, which could be attributed to selection bias, variations in study design and the lack of quantification of bowel symptom scores, the narrow range of bowel symptoms, or the inclusion of organic GI disease. However, both the results of some prior studies<sup>[5,17-19]</sup> and our findings suggested positive associations between diabetes and constipation symptoms.

Although the exact mechanism of diabetic bowel dysfunction is obscure, it is suggested that neuropathy caused by hyperglycemia influences colon motility. Activation of multiple causes of diabetic neuropathy, such as the polyol pathway and protein kinase C, increasing oxidative stress, excess nitric oxide production, and immune mechanisms are caused by hyperglycemia, and all of these induce autonomic neuronal damage, nerve flow reduction, and vascular endothelium damage<sup>[4]</sup>. Autonomic neurons and smooth muscle are considered to regulate GI motility. Thus, diabetes increases the risk of constipation or hard stool because of decreasing motility, bowel transit time, and atony of the colon<sup>[21]</sup>. In addition, diabetic neuropathy leads to reduced rectal sensation and/or impaired external sphincter function which result in symptoms of rectal dysfunction such as fecal urgency and feeling of incomplete evacuation<sup>[22]</sup>. An epidemiological study also showed that poor glycemic control and long duration of diabetes worsened diabetic neuropathy<sup>[23]</sup>. Indeed our finding of a positive association between HbA1c  $\geq$  8% (64 mmol/mol) and long duration of diabetes and bowel or rectal dysfunction supports this notion.

In this study, we found that low BMI was associated with constipation, fecal urgency, and incomplete evacuation in diabetes patients. Some studies have revealed a relationship between a lower BMI and bowel symptoms. Kubo *et al.*<sup>[15]</sup> conducted a cross sectional study of 63344 Japanese workers and reported that irritable bowel syndrome is associated with lower BMI. Farzaneh *et al.*<sup>[24]</sup> identified low BMI (OR = 0.94) as an independent risk factor associated with irritable bowel syndrome in Iran. These two Asian studies support our findings.

We evaluated the relationship between bowel symptoms and 6 oral hypoglycemic agents and insulin. Only biguanide was found to be positively associated with fecal urgency. Scarpello *et al.*<sup>[25]</sup> conducted a randomized, double-blind, crossover study with either metformin or placebo and reported that a significant association emerged for stool bile salt content and watery stool formation from the increased osmotic burden in patients on biguanide. Bytzer *et al.*<sup>[18]</sup> reported that biguanide use was

independently associated with chronic diarrhea and fecal incontinence. These two studies support our finding. We found that insulin use was associated with constipation and incomplete evacuation. Although there are few reports that indicate a relationship between insulin use and GI symptoms, Bytzer *et al.*<sup>[26]</sup> reported that more GI symptoms occurred with type 2 diabetes mellitus treated with insulin. Indeed, insulin use is related to long duration of diabetes and poor glycemic control<sup>[27]</sup>.

In our study, we assessed the reliability of GSRS using kappa statistics, finding a good long-term test-retest reliability (mean kappa, 0.69), in which the kappa value of  $>$  0.60 is usually considered to be good<sup>[28]</sup>. Quan *et al.*<sup>[7]</sup> reported that test-retest reliability for GI symptoms using a 5-point Likert scale was good (median kappa, 0.63) with a 1 wk interval. Our results imply that the number of patients with or without specific GI symptoms and the severity of these symptoms remain consistent over a given period. Furthermore, for diabetics, the mean kappa value was higher than that of non-diabetics, which suggested that diabetic patients tend to have more chronic GI symptoms than non-diabetic patients.

This study had several strengths. First, we conducted colonoscopy and administered a questionnaire to all subjects, which enabled us to evaluate the bowel symptoms exclusive of organic GI diseases. Second, we were able to confirm the internal consistency and long-term reliability of the GSRS. Third, the sample population was large, facilitating adjustment for many confounding factors. However, this study also has some limitations. First, it was a hospital-based study and may have included a few healthy subjects, which might have led to selection bias. Second, we did not assess their psychological status, which is known to affect bowel symptoms<sup>[29]</sup>. However, a prior study indicated that GSRS scores correlated with hospital anxiety and depression scale scores<sup>[6]</sup>. Third, we did not classify diabetes as type 1 or type 2. However, as the prevalence of type 1 diabetes is notably lower than type 2 diabetes in Asia<sup>[30,31]</sup>, this omission is likely to have little impact on our results. Fourth, we did not examine intestinal microbiome which might associate with GI symptoms. In recent studies, the intestinal microbiome is known to interfere with GI symptoms and there are several studies suggesting that it is also involved in the pathogenesis of diabetes<sup>[32]</sup>. In particular, chronic diarrhea is associated with lower amounts of *Lactococcus* spp.<sup>[33]</sup>. In this study, we did not examine such an important biomarker. Further investigation of these points is needed.

In conclusion, diabetes mellitus is associated with an increased risk of constipation, hard stools, fecal urgency, and incomplete evacuation, and poor glycemic control, diabetes duration, low BMI, and nephropathy affect the risk of these symptoms. Long-term reliability of symptom score suggested that these

symptoms remain consistent over a given period.

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## COMMENTS

### Background

Although gastrointestinal (GI) symptoms are common in diabetic autonomic neuropathy, the lower GI symptoms that are typically associated with diabetes mellitus or diabetes-related clinical factors have not been clarified.

### Research frontiers

Some studies have partly addressed this issue, but GI symptoms were not evaluated quantitatively by a reliable and validated means, organic GI diseases were not assessed on colonoscopy, and sample populations were small. The present study aimed to determine the bowel symptoms associated with diabetes and diabetes-related factors in 4783 (603 diabetic and 4135 non-diabetic) patients who underwent colonoscopy and completed a questionnaire on 9 bowel symptoms. Symptoms evaluated on a 7-point Likert scale were compared between baseline and the second questionnaire for test-retest reliability.

### Innovations and breakthroughs

The authors found that constipation, hard stools, fecal urgency, and incomplete evacuation were associated with diabetes and remained associated after excluding organic GI diseases. However, borborygmus, abdominal distension, diarrhea, loose stools, and increased flatus were not associated with diabetes. Long-term reliability of symptom score suggested that these symptoms remain consistent over a given period. In diabetes, poor glycemic control, diabetes duration, low BMI, and nephropathy were associated with these symptoms.

### Applications

In clinical practice, physicians need to know that people with diabetes are at a high risk of bowel dysfunction symptoms, and these symptoms were one of the chronic complications of diabetes.

### Terminology

All authors findings provide new information on the association between bowel symptoms and diabetes mellitus.

### Peer-review

This manuscript gives us informative knowledges about diabetes and related factors and can be published in this magazine.

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