Observational Study

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

Noriko Ihana-Sugiyama, Naoyoshi Nagata, Ritsuko Yamamoto-Honda, Eiko Izawa, Hiroshi Kajio, Takuro Shimbo, Masafumi Kakei, Naomi Uemura, Junichi Akiyama, Mitsuhiko Noda

Noriko Ihana-Sugiyama, Ritsuko Yamamoto-Honda, Hiroshi Kajio, Mitsuhiko Noda, Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

Noriko Ihana-Sugiyama, Masafumi Kakei, Division of General Medicine, Jichi Medical University Graduate School of Medicine, Tochigi 329-0498, Japan

Naoyoshi Nagata, Eiko Izawa, Junichi Akiyama, Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

Ritsuko Yamamoto-Honda, Department of Endocrinology and Metabolism, Toranomon Hospital, Tokyo 105-0001, Japan

Eiko Izawa, Mitsuhiko Noda, Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

Takuro Shimbo, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

Takuro Shimbo, Ohta Nishinouchi Hospital, Fukushima 963-8022, Japan

Masafumi Kakei, First Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University School of Medicine, Saitama 330-0834, Japan

Naomi Uemura, Department of Gastroenterology and Hepatology, Kohnozai Hospital, National Center for Global Health and Medicine, Chiba 272-8516, Japan

Mitsuhiko Noda, Department of Endocrinology and Diabetes, Saitama Medical University, Saitama 350-0495, Japan

Author contributions: Ihana-Sugiyama N and Nagata N wrote the manuscript; Nagata N is an equal first author; Nagata N and Noda M designed the study; Ihana-Sugiyama N, Yamamoto-Honda R, Izawa E and Nagata N collected clinical information; Shimbo T advised on statistical analysis; Nagata N and Akiyama J performed endoscopy; Kajio H, Kakei M, Noda M and Uemura N advised on the manuscript content; Nagata N, Akiyama J and Noda M edited the manuscript.

Supported by Health Sciences Research Grants (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus No. H25-016) from the Ministry of Health, Labour and Welfare of Japan, and supported in part by Grants-in-Aid for Research from the National Center for Global Health and Medicine No. 26A-201.

Institutional review board statement: Ethics approval was obtained from the institutional review board of the National Center for Global Health and Medicine in Tokyo, Japan.

Informed consent statement: Informed consent was obtained from all individual participants included in the study.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Naoyoshi Nagata, MD, Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. nnagata_ncgm@yahoo.co.jp

Received: November 9, 2015
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 ≥ 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

INTRODUCTION

Diabetes mellitus and its complications have become major worldwide public health concerns[1]. Gastrointestinal (GI) symptoms are common in diabetic autonomic neuropathy[2] and affect the quality of life of diabetic patients[3]. Several studies have shown that various GI symptoms are associated with diabetes, poor glycemic control, and duration of diabetes[4,5]. 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[6,7], which would improve assessment of the relationship between diabetes and the wide range of GI symptoms[6,7]. 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 (kg/m²). 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)⁹.

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 reported¹⁰.

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)¹¹. The reliability and validity of the GSRS for functional bowel disease are well-documented¹²,¹³. The 9 bowel symptoms were borborygmus, abdominal distension, increased flatus, constipation, diarrhea, loose stools, hard stools, fecal urgency, and feeling of incomplete evacuation¹⁴.

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 reported¹². 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 modeling¹³, and odds ratios (ORs) with 95%CI were estimated. Multivariate analysis was adjusted for age, sex¹², alcohol consumption¹⁴, and smoking status¹⁵,¹⁶, 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 a (%)  

| All  | Diabetes  | Non-diabetes  | P value  |
|------|-----------|--------------|----------|
| (n = 4738| (n = 603)| (n = 4135)|          |
| 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 | 165.3 ± 9.2 | 165.3 ± 8.7 | 162.9 ± 9.3 | < 0.001 |
| Weight | 61.1 ± 12.3 | 65.8 ± 12.7 | 60.3 ± 12.0 | < 0.001 |
| BMI, kg/m² | 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 |
| Dipyridamolone | 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 (71.1) | 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 a | 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 |

1Height was measured in 2834 patients (432 diabetics and 2402 non-diabetics); 2Weight was measured in 2833 patients (431 diabetics and 2402 non-diabetics); 3Other 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 (α) values were interpreted as follows: ≥ 0.90, excellent agreement; 0.9 > α ≥ 0.80, good agreement, 0.8 > α ≥ 0.7, acceptable; 0.7 > α ≥ 0.6, questionable; 0.6 > α ≥ 0.5, poor; and 0.5 < α, 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 ≤ 0.20 poor[10].

P < 0.05 was considered significant. All statistical analysis was performed using Stata 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 (0.95-1.33), AOR = 1.15 (1.00-1.33)]. 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 ± 3.4 mo. After excluding organic disease, the test-retest reliability of the bowel symptom scores in the GI symptom rating scale (GSRS) was good.
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 > 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 incomplete evacuation. 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 GRSR 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.\(^1\) 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.\(^2\) 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.\(^3\) conducted a population-based, case-controlled study and reported constipation and/or

---

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

| GI symptom                  | Crude OR (95%CI) | P value | Adjusted OR (95%CI) Model 1 | P value | Adjusted OR (95%CI) Model 2 | 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 (1.26-1.75) | < 0.001 | 1.57 (1.33-1.85)            | < 0.001 | 1.43 (1.20-1.70)            | < 0.001 |
| Diarrhea                    | 0.68 (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 (0.82-1.15) | 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    |

1Model 1: Adjusted for age, sex, current smoker, and alcohol consumption; 2Model 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 1st and 2nd questionnaire

| Bowel symptoms                  | All (n = 1197) | Kappa value | SE  | P value | Diabetes (n = 152) | Kappa value | SE  | P value | Non-Diabetes (n = 1045) | 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.
| Table 4  Associations between diabetes-related factors and the bowel symptoms in patients with diabetes ($n = 241$) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Constipation**                | **Number of patients** (%) | **Crude OR** | **P value** | **Adjusted OR (Model 1)** | **P value** | **Adjusted OR (Model 2)** | **P value** |
| HbA1c $\geq 8.0\%$ (64 mmol/mol) | 54/241 (22.4)   | 2.11 (1.23-3.64) | <0.01 | 2.10 (1.21-3.66) | <0.01 | 2.11 (1.19-3.73) | 0.01 |
| Duration of diabetes (yr)       | 13.0 ± 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 $\geq 25$ kg/m²              | 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-cardiovascular 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 ± 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 |
| **Diabetes medication**         | **Hard stool** | **BMI < 25 kg/m²** | **Duration of diabetes (yr)** | **BMI < 25 kg/m²** | **Cerebro-cardiovascular disease** | **Creatinine ($\mu$mol/L)** | **Urine protein positive** | **DPP-4 inhibitors** |
| Insulin                         | 69/241 (28.6)   | 1.83 (1.13-3.03) | 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 (0.41-1.36) | 0.25 |
| Glimeide                        | 21/241 (8.7)    | 1.52 (0.66-3.48) | 0.32 | 1.72 (0.75-3.95) | 0.20 | 2.00 (0.83-4.22) | 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 | 0.84 (0.40-1.97) | 0.49 |
| 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 |
| **Urinary symptoms**            | **Fecal urgency** | **BMI < 25 kg/m²** | **Duration of diabetes (yr)** | **BMI < 25 kg/m²** | **Cerebro-cardiovascular disease** | **Creatinine ($\mu$mol/L)** | **Urine protein positive** | **DPP-4 inhibitors** |
| 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 |
| Glimeide                        | 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 (0.69-1.95) | 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 (0.67-1.50) | 0.83 | 0.97 (0.59-1.62) | 0.92 |
| Thiazolidine                    | 28/241 (11.6)   | 0.84 (0.49-1.59) | 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 (0.33-1.52) | 0.27 | 0.70 (0.36-1.37) | 0.29 | 0.75 (0.38-1.47) | 0.40 |
| **Dyschezia**                   | **Incomplete evacuation** | **BMI < 25 kg/m²** | **Duration of diabetes (yr)** | **BMI < 25 kg/m²** | **Cerebro-cardiovascular disease** | **Creatinine ($\mu$mol/L)** | **Urine protein positive** | **DPP-4 inhibitors** |
| 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) | 0.06 | 0.61 (0.35-1.07) | 0.08 |
| Glimeide                        | 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)  | 1.57 (0.98-2.48) | 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 (0.52-1.22) | 0.09 | 1.06 (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 |

1Model 1: Adjusted for age, sex, smoking, and alcohol consumption; 2Model 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[20] 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[5,17-19] 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 polypeptide 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[4]. 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[21]. 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[22]. An epidemiological study also showed that poor glycemic control and long duration of diabetes worsened diabetic neuropathy[23]. Indeed our finding of a positive association between HbA1C ≥ 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[15] conducted a cross sectional study of 63344 Japanese workers and reported that irritable bowel syndrome is associated with lower BMI. Farzaneh et al[24] 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[25] 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[18] 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[26] 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[27].

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[28]. Quan et al[7] 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[29].

However, a prior study indicated that GSRS scores correlated with hospital anxiety and depression scale scores[6]. 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[30,31], 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[32]. In particular, chronic diarrhea is associated with lower amounts of Lactocacillus spp.[33]. 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.

ACKNOWLEDGMENTS

We thank clinical research coordinators Ms. Hisae Kawashiro, Sawako Iijima, Yoko Tanigawa, Aiko Gotannda, and Yaeko Sawada for help with data collection.

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, borborygms, 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.

REFERENCES

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103: 137-149 [PMID: 24630390 DOI: 10.1016/j.diabres.2013.11.002]

2. Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. Ann Intern Med 1983; 98: 378-384 [PMID: 640296 DOI: 10.7326/0003-4819-98-3-378]

3. Talley NJ, Young L, Bytzer P, Hammer J, Leemon M, Jones M, Horowitz M. Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. Am J Gastroenterol 2001; 96: 71-76 [PMID: 11197290]

4. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003; 26: 1553-1579 [PMID: 12716821 DOI: 10.2337/diacare.26.5.1553]

5. Ko GT, Chan WB, Chan JG, Tsang LW, Cockram CS. Gastrointestinal symptoms in Chinese patients with Type 2 diabetes mellitus. Diabet Med 1999; 16: 670-674 [PMID: 10416454 DOI: 10.1046/j.1464-5491.1999.00135.x]

6. Kulich KR, Madisch A, Pacini F, Piqué JM, Regula J, Van Rensburg CJ, Ujszászy L, Carlsson J, Halling K, Wiklund IK. Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. Health Qual Life Outcomes 2008; 6: 12 [PMID: 18237386 DOI: 10.1186/1477-7525-6-12]

7. Quan C, Talley NJ, Cross S, Jones M, Hammer J, Giles N, Horowitz M. Development and validation of the Diabetes Bowel Symptom Questionnaire. Aliment Pharmacol Ther 2003; 17: 1179-1187 [PMID: 12752555 DOI: 10.1046/j.1365-2036.2003.01553.x]

8. Svedlund J, Sjödin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988; 33: 129-134 [PMID: 3123181 DOI: 10.1007/BF01535722]

9. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014; 37 Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]

10. Yamamoto-Honda R, Takahashi Y, Yamashita S, Mori Y, Yanai H, Mishima S, Kajio H, Handa N, Shimokawa K, Yoshida A, Kitazato H, Shimbo T, Kawazu S, Noda M. Constructing the National Center Diabetes Database. Diabetologia International 2014; 5: 234-243 [DOI: 10.1007/s13340-014-0162-2]

11. Shiotani A, Miyaniishi T, Takahashi T. Sex differences in irritable bowel syndrome in Japanese university students. J Gastroenterol 2006; 41: 562-568 [PMID: 16868804 DOI: 10.1007/s00535-006-1805-2]

12. Nam SY, Kim BC, Ryu KH, Park BJ. Prevalence and risk factors of irritable bowel syndrome in healthy screenee undergoing colonoscopy and laboratory tests. J Neurogastroenterol Motil 2010; 16: 47-51 [PMID: 20535326 DOI: 10.5056/jnm.2010.16.1.47]

13. Long JS, Freese J. Regression Models for Categorical and Limited Dependent Variables Using Stata. Second Edition, 2014

14. Reding KW, Cain KC, Jarrett ME, Eugenio MD, Heitkemper MM. Relationship between patterns of alcohol consumption and gastrointestinal symptoms among patients with irritable bowel syndrome. Am J Gastroenterol 2013; 108: 270-276 [PMID: 23295280 DOI: 10.1038/ajg.2012.414]

15. Kubo M, Fujiiwara Y, Shibah M, Kohata Y, Yamagami H, Tanigawa T, Watanabe K, Watanabe T, Tominaoka K, Arakawa T. Differences between risk factors among irritable bowel syndrome subtypes in Japanese adults. J Neurogastroenterol Motil 2011; 23: 249-254 [PMID: 21120232 DOI: 10.1111/j.1365-2982.2010.01640.x]

16. Ham J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther 2005; 85: 257-268 [PMID: 15733050]

17. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Arch Intern Med 2001; 161: 1989-1996 [PMID: 11525701 DOI: 10.1001/archinte.161.16.1989]

18. Bytzer P, Talley NJ, Jones MP, Horowitz M. Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. Aliment Pharmacol Ther 2001; 15: 137-142 [PMID: 11136287 DOI: 10.1046/j.1365-2036.2001.00896.x]

19. MalekI D, Locke GR, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C, Melton LJ. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. Arch Intern Med 2000; 160: 2808-2816 [PMID: 11052791 DOI: 10.1001/ archinte.160.18.2808]

20. Tseng PH, Lee YC, Chiu HM, Chen CC, Liao WC, Tu CH, Yang WS, Wu MS. Association of diabetes and HbA1c levels with gastrointestinal manifestations. Diabetes Care 2012, 35: 1053-1060 [PMID: 22410812 DOI: 10.2337/dc11-1596]

21. Aring AM, Jones DE, Falko JM. Evaluation and prevention of diabetic neuropathy. Am Fam Physician 2005; 71: 2123-2128
Wald A, Tunuguntla AK. Anorectal sensorimotor dysfunction in fecal incontinence and diabetes mellitus. Modification with biofeedback therapy. *N Engl J Med* 1984; 310: 1282-1287 [PMID: 6717494 DOI: 10.1056/NEJM198405173102003]

Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333: 89-94 [PMID: 7777034 DOI: 10.1056/NEJM19950713333330203]

Farzaneh N, Gholabklou M, Moghimi-Dehkordi B, Naderi N, Fadai F. Effects of demographic factors, body mass index, alcohol drinking and smoking habits on irritable bowel syndrome: a case control study. *Ann Med Health Sci Res* 2013; 3: 391-396 [PMID: 24116320 DOI: 10.4103/2141-9248.117958]

Scarpello JH, Hodgson E, Howlett HC. Effect of metformin on bile salt circulation and intestinal motility in type 2 diabetes mellitus. *Diabet Med* 1998; 15: 651-656 [PMID: 9702467]

Bytzer P, Talley NJ, Hammer J, Young LJ, Jones MP, Horowitz M. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. *Am J Gastroenterol* 2002; 97: 604-611 [PMID: 11922554 DOI: 10.1111/j.1572-0241.2002.05537.x]

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364-1379 [PMID: 22517736 DOI: 10.2337/dc12-0413]

Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993; 46: 423-429 [PMID: 8501467 DOI: 10.1016/0895-4356(93)90018-V]

Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. *Gastroenterology* 1991; 100: 450-457 [PMID: 1985041]

Kawasaki E, Matsuura N, Eguchi K. Type 1 diabetes in Japan. *Diabetologia* 2006; 49: 828-836 [PMID: 16568259 DOI: 10.1007/s00125-006-0213-8]

DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabet Med* 2006; 23: 857-866 [PMID: 16911623 DOI: 10.1111/j.1464-5491.2006.01925.x]

Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; 5: e9085 [PMID: 20140211 DOI: 10.1371/journal.pone.0009085]

Malinen E, Rintilä T, Kajander K, Mätö J, Kassinen A, Krogus L, Saarelma M, Korpela R, Palva A. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. *Am J Gastroenterol* 2005; 100: 373-382 [PMID: 15667495 DOI: 10.1111/j.1572-0241.2005.04031.x]
