

[ORIGINAL ARTICLE]

Constipation Is a Frequent Problem Associated with Vascular Complications in Patients with Type 2 Diabetes: A Cross-sectional Study

Hiroyuki Ito¹, Kiyoko Ito², Mahika Tanaka², Mayumi Hokamura², Mari Tanaka³, Eiji Kusano¹, Jiro Kondo¹, Takuma Izutsu¹, Suzuko Matsumoto¹, Hideyuki Inoue¹, Shinichi Antoku¹, Tomoko Yamasaki¹, Toshiko Mori¹ and Michiko Togane¹

Abstract:

Objective Diabetes is recognized as an underlying disease of constipation. However, the prevalence of constipation varies according to the diagnostic criteria applied. We investigated the prevalence of constipation based on the new guideline for constipation in Japanese patients with type 2 diabetes and examined the relationship with the clinical background, including diabetic vascular complications.

Methods Questionnaire surveys including items concerning the diagnosis and treatment status of constipation were administered to 410 patients with type 2 diabetes.

Results Although 29% of the patients considered that they had experienced constipation (self-judged), only 14% had consulted a physician about constipation. The prevalence of chronic constipation based on the guideline was 26%. After including laxative users, constipation was finally found in 36%. Despite the use of laxatives (n=81), 51% of the patients were still diagnosed with chronic constipation. Patients with constipation (chronic constipation or laxative use) were significantly older and had a longer duration of diabetes than those without constipation. The body mass index (BMI) of patients with constipation (24.9 ± 3.8 kg/m²) was significantly lower than that of those without constipation (26.3 ± 4.6 kg/m²). Diabetic neuropathy (49% vs. 32%) and coronary heart disease (CHD) (27% vs. 13%) were significantly more frequent in the patients with constipation than in those without constipation. A multivariate logistic regression analysis revealed that gender, BMI, diabetic neuropathy, insulin use, and CHD were significantly associated with constipation.

Conclusion An accurate diagnosis of constipation is desirable in patients with type 2 diabetes because constipation is independently associated with CHD.

Key words: constipation, type 2 diabetes, coronary heart disease, diabetic neuropathy, laxative

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Introduction

Constipation, one of the most common digestive disorders, is closely associated with lifestyle factors, such as dietary habits, exercise, and mental stress. According to the summary report of the Comprehensive Survey of Living Conditions 2016 by the Ministry of Health, Labour and

Welfare, in Japan, the number of subjects complaining of constipation increases with age, reaching 6.5% in men and 8.1% in women ≥ 65 years old (1). In addition to being associated with a reduced quality of life (QOL), both physically and mentally, it has been recently reported that constipation is associated with the development of cardiovascular events according to cohort studies conducted among subjects who had undergone medical examinations in Japan (2, 3), the

¹Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital, Japan, ²Department of Nursing, Edogawa Hospital, Japan and ³Medical Plaza Edogawa, Japan

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Correspondence to Dr. Hiroyuki Ito, ito@edogawa.or.jp

United States (4, 5), and China (6).

Diabetes is recognized as an underlying disease of constipation (2-7). However, the prevalence of constipation was found to range from 11-56% according to recent reviews (8, 9). Feldman et al. reported that 60% of 136 American outpatients with diabetes had constipation, although no definition of constipation was described (10). Approximately 11% (11, 12) and 56% (13) of diabetic patients had constipation in the United States according to a definition similar to the Rome IV criteria (14). Constipation defined as ≤ 2 defecations per week was found in 15% of 608 Korean patients with non-insulin-dependent diabetes mellitus (15). According to the gastrointestinal symptoms rating scale (16), which is widely utilized in Japan, symptoms of constipation were observed in 29% of 419 Japanese patients with diabetes (17) and were significantly more frequently observed than in patients without diabetes (18). Furthermore, constipation was found in 23% of 134 Japanese patients with type 2 diabetes and was associated with an impaired QOL (19) based on the Izumo scale, a self-administered questionnaire designed to assess the effects of abdominal symptoms on the QOL (20). The variations in the frequency of constipation may be caused by differences in the race and age range of the study subjects, as well as the diagnostic criteria. Although diabetic neuropathy (DN) and a long duration of diabetes are recognized as risk factors for constipation, very few reports have investigated the association between constipation and the detailed clinical characteristics of patients with diabetes (17).

There is no universally accepted definition of constipation, and constipation tends to be a subjective diagnosis in real-world clinical settings (8). In 2017, the *Evidence-based Clinical Practice Guideline for Chronic Constipation 2017* was published by the Research Society for the diagnosis and treatment of chronic constipation/Affiliated to The Japanese Society of Gastroenterology (21). In this guideline, the diagnostic criteria for constipation in Japanese adults are based on translational modifications of those for functional constipation according to the Rome IV criteria (14) and the Bristol Stool Form Scale (BSFS) (22).

We investigated the prevalence of constipation in Japanese patients with type 2 diabetes who were managed as outpatients at our department and examined the relationship between the prevalence and patients' clinical background, including diabetic vascular complications. We believe that the accumulation of further results based on unified diagnostic criteria will be useful for considering a treatment strategy for constipation in patients with type 2 diabetes.

Materials and Methods

Subjects

Patients who were undergoing chemotherapy or palliative therapy for malignant diseases, who were scheduled for surgery for abdominal tumors and who had been diagnosed

with inflammatory bowel disease were excluded from the study. After obtaining their written consent, questionnaire surveys were conducted among 479 patients with type 2 diabetes who visited our department and had no overt dementia between August and September 2019. After the exclusion of 69 patients with a history of abdominal surgery according to their medical records, 410 Japanese patients with type 2 diabetes were included in this cross-sectional study. Patients who underwent endoscopic removal of gastrointestinal tumors, such as endoscopic mucosal resection, or who were being followed up due to small gastrointestinal lesions were not excluded.

The diagnosis of constipation and classification of the stool form

The diagnosis of constipation was based on the *Evidence-based Clinical Practice Guideline for Chronic Constipation 2017* (21). Constipation was diagnosed when the patient's answers applied to two or more of the following six items:

1. Straining during more than 1/4 (25%) of defecations.
2. Lumpy or hard stools (BSFS 1-2) for more than 1/4 (25%) of defecations.
3. Sensation of incomplete evacuation for more than 1/4 (25%) of defecations.
4. Sensation of anorectal obstruction/blockage for more than 1/4 (25%) of defecations.
5. Manual maneuvers required to facilitate more than 1/4 (25%) of defecations (e.g. digital evacuation, support of the pelvic floor).
6. Fewer than three spontaneous bowel movements per week.

Furthermore, the patients who had symptoms for more than six months and fulfilled the above criteria for the last three months were diagnosed with chronic constipation. In the present study, the presence of constipation was defined as chronic constipation or the use of laxatives.

The stool form was classified using the BSFS (22). Stool types 1 and 2 were considered to be abnormally hard stools; types 3, 4, and 5 were considered to be normal stool form; and types 6 and 7 were considered to be abnormally liquid stool. This design was also supported by the *Evidence-based Clinical Practice Guideline for Chronic Constipation 2017* (21).

Questionnaire surveys

The questionnaire surveys including the above six items about the diagnosis of constipation, the duration of symptoms, and the BSFS (Fig. 1) were conducted at the time of the hospital visit with a picture of the BSFS attached. Other questionnaire surveys (Fig. 1) were also conducted to evaluate self-judged constipation (Q1), consultation with a physician about constipation (Q2), the use of laxatives (including over-the-counter drugs prescribed outside our hospital), (Q3) and symptoms associated with DN (Q7). In Q1 and Q2, we did not present any definition of constipation to the patients, only asking whether or not they were currently feeling con-

Q1. Do you think you have constipation?	(yes, no)
Q2. Have you consulted a physician about constipation?	(yes, no)
Q3. Do you use laxatives regularly, including OTC drugs, other than those prescribed outside our hospital?	(yes, no)
If you do, please write the name of the drug. ()	
Q4. Please answer "yes" or "no" concerning your defecation status.	
1. Straining during more than 1/4 (25%) of defecations.	(yes, no)
2. Lumpy or hard stools (BSFS 1-2) for more than 1/4 (25%) of defecations.	(yes, no)
3. Sensation of incomplete evacuation for more than 1/4 (25%) of defecations.	(yes, no)
4. Sensation of anorectal obstruction/blockage for more than 1/4 (25%) of defecations.	(yes, no)
5. Manual maneuvers required to facilitate more than 1/4 (25%) of defecations. (e.g., digital evacuation, support of the pelvic floor).	(yes, no)
6. Fewer than three spontaneous bowel movements per week.	(yes, no)
7. Have you had any of the above symptoms for more than 6 months and ≥ 2 of the above criteria for the last 3 months?	(yes, no)
Q5. Which is the closest to describing the form of your stool? ()	
1. Separate hard lumps, similar to nuts (difficult to pass).	
2. Sausage shaped but lumpy.	
3. Like a sausage but with cracks on the surface.	
4. Like a sausage or snake, smooth and soft.	
5. Soft blobs with clear cut edges (passed easily).	
6. Fluffy pieces with ragged edges, a mushy stool.	
7. Watery, no solid pieces, entirely liquid.	
Q6. Do you have following symptoms of the legs?	
1. Bilateral spontaneous pain.	(yes, no)
2. Bilateral hypoesthesia.	(yes, no)
3. Bilateral paraesthesia.	(yes, no)

Figure 1. Contents of the questionnaire. OTC: over-the-counter

stipated in their own sense, regardless of laxative use. This term thus does not always equate to medically defined constipation and is considered to simply represent dissatisfaction with one's bowel movements.

Confounding factors

A current drinker was defined as a person consuming >20 g ethanol equivalent/day. Obese individuals were defined as those with a body mass index (BMI) of ≥ 25.0 kg/m². Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg. Participants currently using antihypertensive medications were also classified as being positive for hypertension. Hyper-low-density lipoprotein (LDL) cholesterolemia was defined as a serum LDL-cholesterol concentration of ≥ 3.62 mmol/L (140 mg/dL) or the current use of statins or ezetimibe. Hypo-high-density lipoprotein (HDL) cholesterolemia was defined as a serum HDL-cholesterol concentration of <1.03 mmol/L (40 mg/dL). Hyper-non-HDL cholesterolemia was defined as a serum non-HDL cholesterol concentration of ≥ 4.40 mmol/L (170 mg/dL) or the current use of fibrates or ethyl icosapentate.

Diabetic retinopathy was graded as simple, preproliferative, or proliferative retinopathy based on the results of a funduscopy examination performed by an expert ophthalmologist. Diabetic nephropathy was defined as a urinary albumin-to-creatinine ratio of ≥ 30 mg/g creatinine in a random spot urine test. DN was diagnosed by the presence of two or more components among clinical symptoms (bilateral spontaneous pain, hypoesthesia, or paresthesia of the legs), the absence of ankle tendon reflexes, and decreased vibration sensations using a C128 tuning fork (23). Cerebrovascular disease was diagnosed by physicians as a history of ischemic stroke using brain computed tomography or mag-

netic resonance imaging. Only patients with symptoms were classified as having cerebrovascular disease, and cases of silent brain infarction, transient ischemic attack, and brain hemorrhaging were excluded from this study. Coronary heart disease (CHD) was diagnosed based on a history of myocardial infarction, angina pectoris, electrocardiogram abnormalities suggesting myocardial ischemia, or intervention after a coronary angiographic examination. Peripheral artery disease was diagnosed by the absence of a pulse in the legs, along with ischemic symptoms, obstructive findings on an ultrasonographic or angiographic examination of the lower extremities, or an ankle brachial pressure index <0.9 . The estimated glomerular filtration rate (eGFR) was calculated using the formula recommended by the Japanese Society of Nephrology (24).

Ethical conduct

This cross-sectional study was conducted in accordance with the principles expressed in the 2008 Declaration of Helsinki. The Ethics Committee of Edogawa Hospital approved the study protocol. The trial is registered on UMIN-CTR, identifier UMIN000043264.

Statistical analyses

All data are presented as the mean \pm standard deviation. The χ^2 test was used for between-group comparisons of categorical variables. After the Shapiro-Wilk test, Student's *t*-test and Wilcoxon's signed rank test were used to assess the significance of differences in continuous variables that showed a normal distribution (diastolic blood pressure and eGFR) and a non-normal distribution (age, duration of diabetes, BMI, systolic blood pressure, HbA1c, and serum lipid concentrations), respectively. Odds ratio (OR) and 95% confidence intervals (CIs) were determined to examine the

Table 1. Clinical Characteristics of the Study Subjects.

	n†	% or mean±SD
Female (%)	410	42
Age (years)	410	66±12
Duration of diabetes (years)	406	14±10
Current drinker (%)	406	21
Smoking history (%)	401	41
Body mass index (kg/m ²)	410	25.8±4.4
Obesity (%)	410	55
Systolic blood pressure (mmHg)	409	131±15
Diastolic blood pressure (mmHg)	409	76±12
Hypertension (%)	410	73
Hyper-LDL-cholesterolemia (%)	410	76
Hypo-HDL-cholesterolemia (%)	407	17
Hyper-non-HDL-cholesterolemia (%)	395	9
Diabetic retinopathy (%)	401	32
Diabetic nephropathy (%)	410	42
Diabetic neuropathy (%)	395	38
Cerebrovascular disease (%)	410	13
Coronary heart disease (%)	410	18
Peripheral arterial disease (%)	410	7
HbA1c (%)	408	7.3±1.0
LDL-cholesterol (mg/dL)	407	95±26
HDL-cholesterol (mg/dL)	407	52±14
Non-HDL-cholesterol (mg/dL)	392	120±28
eGFR (mL/min/1.73 m ²)	407	67±20
Bristol stool form scale (%)	304	
1 or 2		24
3, 4 or 5		73
6 or 7		2
Laxative use (%)	410	20
Osmotic laxatives		8
Stimulant laxatives		8
Lubiprostone or linaclotide		1
Probiotics		4
Others		1
Antidiabetic agent use (%)		
Sulfonylureas	410	8
Metformin	410	52
Thiazolidinediones	410	6
α -glucosidase inhibitors	410	9
Glinides	410	3
DPP-4 inhibitors	410	49
SGLT2 inhibitors	410	27
GLP-1 receptor agonists	410	10
Insulin	410	27
Number of anti-diabetic agents	410	1.9±1.1
Antihypertensive agent use (%)		
Diuretics	410	8
β blockers	410	12
Calcium channel blockers	410	42
ACE inhibitors	410	7
ARBs	410	42
Lipid lowering agent use (%)		
Statins	410	70
Ezetimibe	410	7
Fibrates	410	2
Ethyl eicosapentate	410	3

†: number estimated

LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate, DPP-4: dipeptidyl peptidase-4, SGLT2: sodium glucose cotransporter 2, GLP-1: glucagon-like peptide-1, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker

strength of the relationship between the clinical characteristics of patients and constipation by a logistic regression analysis. Independent variables in the logistic regression analysis were determined according to forward stepwise selection. Receiver operating characteristics (ROC) curve analyses were performed to derive the cut-off value for continuous variables between patients with and without constipation. P values of <0.05 were considered to indicate statistical significance.

Data analyses were performed using the JMP statistical software package (version 12.2.0; SAS Institute, Cary, USA), and the sample size required to determine the association between constipation and CHD was calculated using the EZR version 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study subjects

Table 1 shows the clinical characteristics of the study subjects. Osmotic and stimulant laxatives were most frequently used as drug therapies.

Constipation based on the questionnaire survey

Fig. 2A shows the frequency of constipation based on the questionnaire survey in the overall study population. Although self-judged constipation was found in 29% of patients, only 14% had consulted a physician about constipation. The prevalence of chronic constipation was 26% (n=105). After including laxative users (20%, n=81), the prevalence of constipation was 36% (n=146). The prevalence of patients who met the diagnostic criteria for chronic constipation was 8% in patients without self-judged constipation. The prevalence of patients who did not meet the diagnostic criteria for chronic constipation was 32% in patients with self-judged constipation.

Fig. 2B shows the frequency of constipation in the patients using laxatives (n=81). Despite the use of laxatives, 55% of the patients still complained of constipation, and chronic constipation based on the guideline (21) was found in 49%. According to the BSFS, 46% of laxative users showed abnormally hard stools.

Association between constipation and clinical characteristic

Table 2 shows the clinical characteristics of patients with and without constipation (chronic constipation or laxative use). The constipation group included a significantly higher percentage of women than the no constipation group. Patients with constipation were significantly older and had a longer duration of diabetes than those without constipation. Constipation was independent of the patients' drinking habits. The BMI and frequency of obesity were significantly

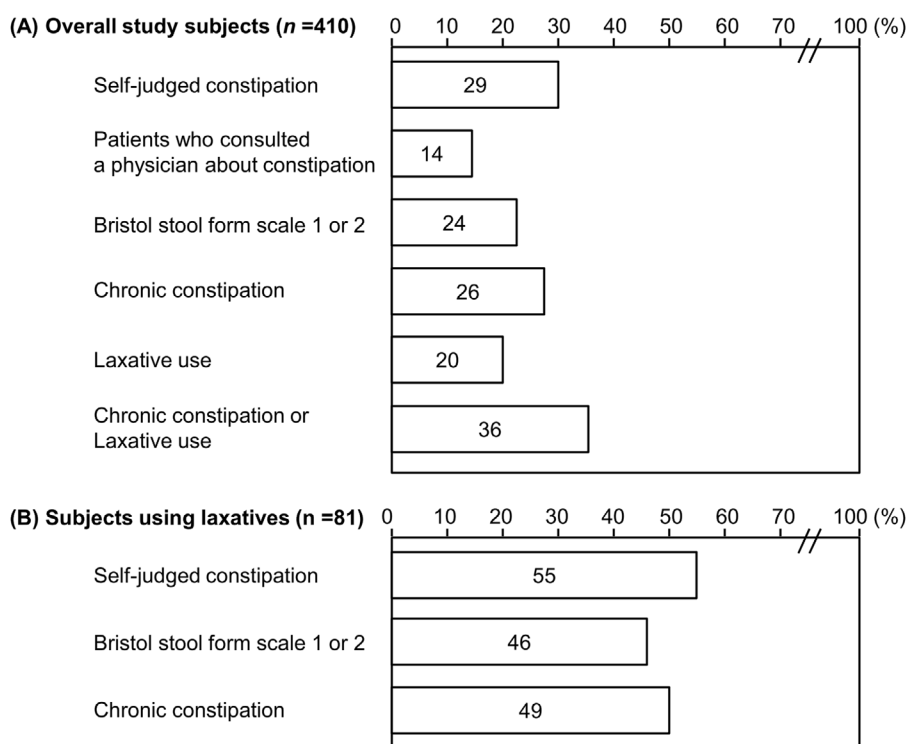


Figure 2. (A) The frequency of constipation based on the questionnaire survey and treatment status in the overall study population. (B) The frequency of constipation based on the questionnaire survey in the patients using laxatives.

lower in the patients with constipation than in those without constipation. Hyper-LDL-cholesterolemia, DN, CHD, insulin use, and statin use were significantly more frequent in the patients with constipation than in those without constipation. The HbA1c values of the two groups did not differ to a statistically significant extent. Antidiabetic agents, including α -glucosidase inhibitors and sodium glucose cotransporter 2 (SGLT2) inhibitors, as well as antihypertensive agents including diuretics and calcium channel blockers, were not associated with the prevalence of constipation. A multivariate logistic regression analysis revealed that gender, BMI, DN, CHD, and insulin use were significantly associated with constipation in patients with type 2 diabetes (Table 3).

When chronic constipation was set as the objective variable, metformin use (OR=0.54, 95% CI=0.33-0.87, $p=0.01$) and statin use (OR=1.85, 95% CI=1.07-3.30, $p=0.03$) were significantly associated with chronic constipation according to a multivariate logistic regression analysis. When laxative use was set as the objective variable, diastolic blood pressure (OR=0.97, 95% CI=0.94-0.99, $p=0.02$) and CHD (OR=1.96, 95% CI=1.01-3.74, $p=0.047$) were significantly associated with laxative use. When the presence of CHD was set as the objective variable, constipation (chronic constipation or laxative use), gender, age, duration of diabetes, smoking history, hypertension, hyper-LDL-cholesterolemia, hypo-HDL-cholesterolemia, diabetic retinopathy, DN, peripheral arterial disease, serum LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, eGFR and use of diuretics, β blockers, ACE inhibitors, statins and ezetimibe were significantly

associated with CHD according to a univariate logistic analysis. According to a multivariate logistic regression analysis, constipation (OR=2.82, 95% CI=1.39-5.85, $p<0.01$), hypo-HDL-cholesterolemia, peripheral arterial disease, serum LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol and use of β blockers, ACE inhibitors, and statins were significantly associated with CHD.

Fig. 3 shows the ROC curve for the BMI at the detection of constipation. The area under the curve (AUC) was 0.600 (sensitivity: 69%, specificity: 52%). The cut-off values were 26.0 kg/m².

Discussion

The present study is the first report investigating the frequency and treatment status of constipation in Japanese patients with type 2 diabetes based on the newly published guideline for constipation (21). In this study, constipation was significantly associated with gender, BMI, DN, CHD, and insulin use in patients with type 2 diabetes.

Constipation is commonly observed in patients with type 2 diabetes (2-13, 15, 17-19). Yamada et al. reported, based on a multicenter trial, that 120 of 419 (29%) patients with type 1 or type 2 diabetes complained of constipation symptoms (17). The authors also demonstrated that patient age, their mental health status, diabetic retinopathy, and DN were significantly associated with constipation. Because their investigation did not evaluate the prevalence of diabetic macroangiopathy, the relationship of constipation with CHD

Table 2. Comparisons of Clinical Characteristics between the Patients with and without Constipation (Chronic Constipation or Laxative Use).

	Constipation (n=146)	Non-constipation (n=264)	p
Female (%)	51	37	<0.01
Age (years)	68±12	66±12	0.046
Duration of diabetes (years)	15±9	14±10	0.02
Current drinker (%)	19	21	0.65
Smoking history (%)	39	43	0.50
Body mass index (kg/m ²)	24.9±3.8	26.3±4.6	<0.01
Obesity (%)	47	59	0.01
Systolic blood pressure (mmHg)	132±15	131±15	0.56
Diastolic blood pressure (mmHg)	73±11	77±12	<0.01
Hypertension (%)	69	75	0.18
Hyper-LDL-cholesterolemia (%)	83	72	0.02
Hypo-HDL-cholesterolemia (%)	18	17	0.85
Hyper-non-HDL-cholesterolemia (%)	6	11	0.12
Diabetic retinopathy (%)	37	29	0.09
Diabetic nephropathy (%)	37	45	0.10
Diabetic neuropathy (%)	49	32	<0.01
Cerebrovascular disease (%)	16	12	0.19
Coronary heart disease (%)	27	13	<0.01
Peripheral arterial disease (%)	8	6	0.56
HbA1c (%)	7.4±1.0	7.2±1.0	0.19
LDL-cholesterol (mg/dL)	92±26	96±26	0.10
HDL-cholesterol (mg/dL)	50±12	52±15	0.46
Non-HDL-cholesterol (mg/dL)	117±27	122±29	0.08
eGFR (mL/min/1.73 m ²)	66±20	68±20	0.33
Antidiabetic agent use (%)			
Sulfonylureas	8	8	0.99
Metformin	46	55	0.08
Thiazolidinediones	6	6	0.97
α -glucosidase inhibitors	8	9	0.86
Glinides	4	3	0.43
DPP-4 inhibitors	44	52	0.14
SGLT2 inhibitors	24	29	0.29
GLP-1 receptor agonists	14	8	0.09
Insulin	36	23	<0.01
Number of anti-diabetic agents	1.9±1.1	1.9±1.1	0.92
Antihypertensive agent use (%)			
Diuretics	8	8	0.97
β blockers	14	11	0.36
Calcium channel blockers	40	43	0.64
ACE inhibitors	5	8	0.27
ARBs	39	44	0.30
Lipid lowering agent use (%)			
Statins	79	64	<0.01
Ezetimibe	6	7	0.79
Fibrates	2	2	0.88
Ethyl eicosapentate	3	3	0.71

LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate, DPP-4: dipeptidyl peptidase-4, SGLT2: sodium glucose cotransporter 2, GLP-1: glucagon-like peptide-1, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker

in patients with diabetes was unclear. The present study was based on a cross-sectional design. Thus, it was not possible to discuss the causal relationships between the factors re-

lated to constipation. However, we emphasized the importance of the association between constipation and CHD in diabetic patients, even after adjusting for the patient age,

Table 3. ORs of Clinical Characteristics for Constipation (Chronic Constipation or Laxative Use).

	Univariate logistic		Multivariate logistic	
	OR [95%CI]	p	OR [95%CI]	p
Female	1.82 [1.21-2.74]	<0.01	1.73 [1.09-2.37]	0.02
Age (years)	1.02 [1.00-1.03]	0.07		
Duration of diabetes (years)	1.02 [1.00-1.04]	0.05		
Body mass index (kg/m ²)	0.93 [0.88-0.97]	<0.01	0.94 [0.89-1.00]	0.04
Obesity	0.59 [0.39-0.89]	0.01		
Diastolic blood pressure (mmHg)	0.97 [0.95-0.99]	<0.01	0.99 [0.97-1.01]	0.21
Hyper-LDL-cholesterolemia	1.85 [1.13-3.12]	0.02	0.83 [0.28-2.26]	0.72
Diabetic neuropathy	2.06 [1.36-3.15]	0.02	1.60 [1.01-2.52]	0.04
Coronary heart disease	2.38 [1.43-3.99]	<0.01	2.00 [1.14-3.52]	0.02
Insulin use	1.88 [1.20-2.94]	0.01	1.80 [1.11-2.94]	0.02
Statin use	2.05 [1.29-3.32]	<0.01	1.85 [0.74-5.10]	0.19

LDL: low-density lipoprotein, OR: odds ratio, CI: confidence interval

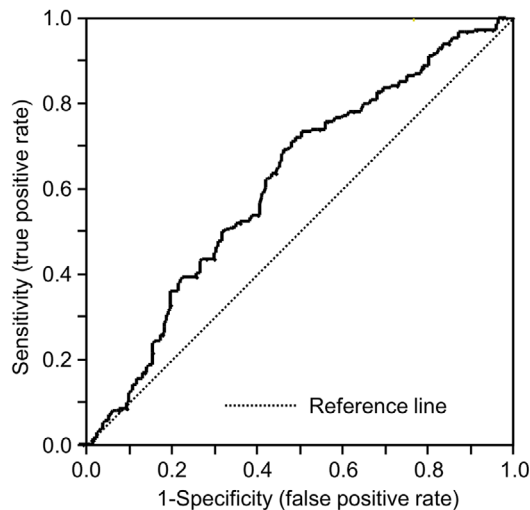


Figure 3. Receiver operating characteristics curve for the body mass index at the detection of constipation.

diabetic retinopathy, and DN. Why CHD is common in a general population with constipation is considered to be due to changes in blood pressure during defecation (25) and the gut flora (26-28). Patients with diabetes or constipation show many common points; they are frequently elderly, have lifestyle-related problems, and are at risk for cardiovascular disease (2-6), chronic kidney disease, and end-stage kidney disease (29, 30). Therefore, it is not surprising that constipation is a risk factor for CHD in patients with type 2 diabetes. In contrast, the possibility that CHD causes constipation cannot be denied. The mechanism underlying the onset of constipation in patients with CHD is considered to be somatic venous congestion due to an increased right atrial pressure and the effects of drugs (7) often used in the treatment of CHD such as diuretics, calcium channel blockers, and β blockers, although no significant relationship was found in this study.

The BMI was independently associated with constipation in this study. Although a BMI of ≥ 30 kg/m² was not related

to constipation in the study described above (17), the relationship between the BMI and constipation might be diminished when the definition of obesity is limited to moderate or severe, considering that the cut-off value of the BMI for constipation was 26.0 kg/m² in our study. Constipation is generally frequent in women (1-3), and a sex difference was also observed in the present study. Insulin use was extremely frequent, similar to findings in previous studies (17, 18). Because elderly patients with type 2 diabetes often require insulin treatment due to decreased endogenous insulin secretion or the presence of renal impairment (31), the relationship between age and constipation may have influenced the frequency of insulin use. The frequency at which antihypertensive were used did not differ markedly between patients with and without constipation. The large contribution of others significant factors to constipation might have eliminated drug use differences in the present study.

In this study, we also investigated the complaints and constipation treatment status using a questionnaire. Despite the high frequency of patients complaining of constipation, the percentage of patients who had consulted a physician seemed to be relatively low. Whether this fact was derived from the characteristics of diabetic patients or the cultural characteristics of Japanese individuals is unclear, as is the global nature of this trend, as to our knowledge, no such tendency has been reported. Because constipation has not been a target of treatment for non-gastroenterologists, patients may have been hesitant to complain about bowel movements. Therefore, it is possible that drug treatment was not performed properly and that the bowel movement remained inadequate even after using laxatives in the present study. Furthermore, there were patients who did not consider themselves to be constipated despite meeting the diagnostic criteria. If constipation can be treated after appropriate interviews, the patient's QOL may be improved. Because an impaired mental QOL was reported to be a risk factor for constipation (17), there may be a vicious cycle of association

between constipation and a reduced QOL. Therefore, the QOL should be simultaneously evaluated when determining the presence of constipation, although this was not performed in the present study. Efforts to manage the mental QOL as well as lifestyle modification may aid in relieving symptoms of constipation (17). Although the accuracy was not high, according to the ROC curve analysis in the current study, it would be desirable to interview diabetic patients with a low BMI about their bowel movements.

Several limitations associated with the present study warrant mention. First, our data were obtained from a single center, with a relatively small study population, and the study employed a cross-sectional design. No other studies have investigated constipation using diagnostic criteria based on the guideline. Therefore, the required sample size for the population was determined by the results of the present study. The prevalence of CHD was 27% and 13% in patients with and without constipation, respectively. To ensure a significance level (α) of 0.05 and power factor ($1-\beta$) of 80%, a sample size of at least 107 and 194 patients in the groups with and without constipation, respectively, was necessary. Although the sample size of the present study was considered sufficient to determine the association between constipation and CHD, these findings are inherently limited by our inability to eliminate causal relationships between constipation and CHD in patients with type 2 diabetes. A prospective study is necessary to investigate the incidence of CHD between the groups with and without constipation. Second, the indication and selection of laxatives may not be standard because the results were obtained in a specialized department (Department of Diabetes, Metabolism and Kidney Disease) in our hospital. It is necessary to pay attention to the possibility that the frequency of use and effects of laxatives may differ from those of other institutions. The definition of constipation in this study was not fully met the criteria of chronic constipation in accordance with the Rome IV criteria (14) and the Japanese guideline (21) because the patients with constipation included laxative users. However, it is worthwhile to show the real-world status of constipation in a field other than gastroenterology. Third, the DN prevalence in elderly patients may have been overestimated, as DN was diagnosed according to neurological examinations. Because sensory functions are generally attenuated with aging, the prevalence of DN was considered to be more frequent in the entire cohort of elderly diabetic patients than in patients diagnosed using nerve conduction velocity. Furthermore, DN should be diagnosed after the exclusion of other neurological disorders, such as lumbar spondylolisthesis and canal stenosis, which are frequently found in elderly patients. This may have influenced the high prevalence of DN among patients with constipation, as these diseases were not completely excluded among the patients in the present study. Fourth, the cause of constipation was not conclusively determined in the present study. Although whether or not constipation is a risk factor for colorectal cancer is controversial (32, 33), the relationship between colorectal cancer and

diabetes has been established (34). We excluded patients with an organic disease that might affect their bowel movement as much as possible in the present study. However, it should be noted that organic constipation that was not necessarily related to diabetes was not ruled out. Indeed, patients with drug-induced constipation were also included in this study. Type 2 diabetes mellitus is a disease complicated with various comorbidities, and drugs that can induce constipation, such as antidiabetics, antidepressants, anxiolytics, and hypnotics, are often used in real-world diabetes care.

Despite the abovementioned limitations, the present results will help deepen our understanding of the importance of constipation in patients with type 2 diabetes. The relationship between constipation and diabetic complications should be evaluated prospectively in a larger number of patients using common diagnostic criteria for constipation.

Conclusion

Constipation is independently associated with CHD in patients with type 2 diabetes. An accurate diagnosis of constipation is desirable in diabetic patients with a low BMI or DN, although constipation is unlikely to be noticed in daily diabetes treatment.

Author's disclosure of potential Conflicts of Interest (COI).

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