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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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I-IX Editorial Board

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
September 28, 2017

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Retrospective Study

Gastrointestinal symptom prevalence depends on disease duration and gastrointestinal region in type 2 diabetes mellitus

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Institutional review board statement: The study was reviewed and approved by the University of Tokyo Hospital Institutional Review Board.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: December 14, 2016

Peer-review started: December 15, 2016

First decision: February 23, 2017

Revised: March 12, 2017

Accepted: June 1, 2017

Article in press: June 1, 2017

Published online: September 28, 2017

Abstract**AIM**

To unravel relationships between gastrointestinal (GI) symptoms impairing quality of life (QOL) and clinical profiles of diabetes mellitus (DM) patients.

METHODS

We enrolled 134 outpatients with type 2 DM. Mean

age was 64.7 years, mean body mass index was 24.7 kg/m², mean glycosylated hemoglobin was 7.1%, and mean DM duration was 13.7 years. GI symptom-related QOL was determined using the Izumo scale, based on five factors, *i.e.*, heartburn, gastralgia, postprandial fullness, constipation and diarrhea. The sum of scores obtained for the three questions in each domain was calculated, and subjects with a score of 5 or higher were considered to be symptomatic with impaired QOL. JMP Clinical version 5.0 was used for all statistical analyses.

RESULTS

Lower abdominal symptoms were found to be more frequent than those affecting the upper abdomen. Diabetic duration and medications showed associations with GI symptoms. We identified differences in peak prevalences of the five symptoms. Gastralgia ($P = 0.02$ vs 10-14 years) and total GI symptoms ($P = 0.01$ and $P = 0.02$ vs 5-9 years and 10-14 years, respectively) peaked at a diabetes duration of 15-19 years. Heartburn ($P = 0.004$) and postprandial fullness ($P = 0.03$) tended to increase with disease duration. Constipation and diarrhea showed bimodal peaks, with the first early and the second late (*e.g.*, $P = 0.03$ at 15-19 years vs 10-14 years for diarrhea) in the disease course. Finally, GI symptoms showed clustering that reflected the region of the GI tract affected, *i.e.*, constipation and diarrhea had similar frequencies ($P < 0.0001$).

CONCLUSION

Our study highlights the importance of questioning patients about QOL impairment due to abdominal symptoms, especially in the early and the late periods of diabetes.

Key words: Gastrointestinal symptoms; Questionnaire survey; Disease duration; Type 2 diabetes; Quality of life; Gastrointestinal tract regions

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Core tip: We describe the results of a questionnaire survey of 134 type 2 diabetes mellitus outpatients experiencing gastrointestinal symptoms. The novel finding is that symptom frequencies differed among disease durations and according to affected gastrointestinal regions. Lower abdominal symptoms not only manifested during the late but also in the early stage of diabetes when there were no organ complications related to this disease. Our study highlights the importance of not underestimating gastrointestinal symptoms and of questioning patients about quality of life impairment due to abdominal symptoms, especially in both the early period and after a diabetes duration of 10 or even 15 years.

Fujishiro M, Kushiyaama A, Yamazaki H, Kaneko S, Koketsu Y, Yamamotoya T, Kikuchi T, Sakoda H, Suzuki R, Kadowaki T.

Gastrointestinal symptom prevalence depends on disease duration and gastrointestinal region in type 2 diabetes mellitus. *World J Gastroenterol* 2017; 23(36): 6694-6704 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i36/6694.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i36.6694>

INTRODUCTION

The dramatic increase in the incidence of type (T)2 diabetes mellitus (DM) over the last century has become a major public health concern worldwide^[1]. Both micro- and macrovascular complications of diabetes damage a variety of organs, leading to various symptoms, and impair quality of life (QOL) in patients with T2DM.

Among these symptoms, those affecting the gastrointestinal (GI) tract occur frequently in patients with diabetes^[2]. Various GI symptoms are associated with this disease^[3-5], especially diabetic neuropathy which develops with longstanding diabetes^[6,7]. GI hyper- and hypofunction lead to delayed gastric or esophageal emptying, diabetic gastroparesis, constipation and diarrhea^[6,8,9]. Other GI-related disorders and symptoms are also known to accompany diabetes, such as obesity with gastroesophageal reflux disease^[10,11], and aging with gastric mucosal injury^[12].

GI disorders in diabetes have thus far been poorly characterized, despite their high frequencies in both T1DM and T2DM patients^[13]. Hyperglycemia-associated neuropathy was long considered to be a major mechanism underlying the pathogenesis of GI symptoms, probably *via* oxidative stress and inflammation, as with other microangiopathies. Levels of enteric hormones, such as incretin-related peptides [*e.g.*, glucagon-like peptide-1 (GLP-1), GLP-2, pancreatic polypeptide (PPY)]^[14] and serotonin^[15], and enteric neurotransmitters, such as vasoactive intestinal peptide (VIP)^[16], are altered in patients with DM, and affect GI motility and neural fiber growth. Furthermore, smooth muscle cells, interstitial cells of Cajal^[17], gut microbiota^[18] and intestinal stem cells^[19], may be altered in DM and these changes are potentially related to GI symptoms. The relevance of these mechanisms in the development of human GI symptoms in T2DM remains uncertain.

As for the pathophysiological mechanisms underlying the development of complications, hyperglycemia and the resultant glycation products^[20], oxidative stress^[21] and inflammation^[22], are the main candidates. GI symptoms in DM are associated with both poor glycemic control and diabetic complications, as shown in a large number of subjects^[23], although we found no relationships between GI symptoms and glycemic control, probably due to the long and varied disease durations of our subjects.

There has been little systematic and comprehensive research focusing on GI conditions in patients with

T2DM. The Izumo Scale, a validated and useful tool for QOL assessment, is a scale for assessing GI symptoms^[13,14]. Applying this scale, we investigated actual GI symptoms employing a questionnaire and determined whether the symptoms identified are related to the clinical profiles of patients with T2DM.

MATERIALS AND METHODS

Patients

Patients who visited the department of diabetes and metabolic diseases in our hospital, including those with T1DM and T2DM, from December 2011 to March 2014, were enrolled in this study. We asked 200 consecutive patients to answer the questionnaire. Of the 170 patients who gave informed consent and responded to the questionnaire, data from 134 were analyzed after exclusion of 31 non-T2DM patients and 5 with a past history of GI tract surgery. This protocol was approved by our institutional ethics review committees (approval number 3643). Patient QOL was assessed by asking the subjects if they suffered from GI symptoms and then scoring the symptoms according to the Izumo scale, as described below.

Patient profiles, including diabetic microangiopathy, were collected from medical records. We considered subjects to have "diabetic autonomic neuropathy (DAN)" if they had any autonomic signs or symptoms. Distal symmetric polyneuropathy (DSP) includes symmetric neurosensory signs and symptoms, such as tingling, numbness or cramps in the legs, based on the attending physician's assessment. Diabetic retinopathy (DR) includes non-proliferative DR diagnosed by the presence of microaneurysms and retinal hemorrhages^[24], and all DR cases were confirmed by an ophthalmologist. Diabetic nephropathy was clinically diagnosed by attending physicians based on microalbuminuria or overt proteinuria with no evidence of other kidney or urological disease^[25].

Izumo Scale

The Izumo Scale was developed and validated by Furuta *et al.*^[26]. The Izumo Scale is a self-administered questionnaire designed to assess the effects of abdominal symptoms on QOL and includes 15 items in five domains with three items in each domain: heartburn (questions 1-3), gastralgia (questions 4-6), postprandial fullness (questions 7-9), constipation (questions 10-12), and diarrhea (questions 13-15)^[27]. Each question is rated on a 6-point Likert scale from 0 to 5, with higher values indicating more severe symptoms. This scale has been shown to have good internal consistency, reproducibility, as well as good correlations with the visual analogue scale of abdominal symptoms and the Gastrointestinal Symptoms Rating Scale (GSRS), and is thus widely utilized in Japan^[28-31]. The sum of scores obtained for the three questions in each domain was calculated, and subjects with a score of 5 or higher were considered to be symptomatic

with impaired QOL^[30]. When the five symptoms were classified by GI region, heartburn was considered to involve the esophagus, gastralgia and postprandial fullness the upper GI tract, and constipation and diarrhea the lower GI tract.

Statistical analysis

JMP Clinical version 5.0 (SAS Institute, Cary, NC, United States) was used for all statistical analyses. ANOVA was used to compare scores among different groups. Frequencies were compared using Fisher's exact test. Trend comparisons for frequencies among disease duration, age, body mass index (BMI), and glycated hemoglobin (HbA1c) were performed using a Cochran-Armitage test. Hierarchical cluster analysis was performed to assess the relationships among GI symptoms. All *P* values are two-sided, and *P* < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Characteristics of the enrolled patients

The characteristics of enrolled patients are listed in Table 1. We enrolled 134 patients with T2DM (87 males and 47 females, mean age: 64.7 years, range: 29-88 years). Mean diabetes duration was 13.7 (0.3-33.0) years, BMI was 24.7 (16.5-42.5) kg/m² and HbA1c was 7.1 (5.2-11.6)%. As to incidences of diabetic microangiopathy, 32 patients (24%) had DAN, 20 (15%) had DSP, 31 (23%) had DR and 64 (48%) had nephropathy. As to antidiabetic drugs, 8 patients (6%) received no medications, 34 (25%) used various forms of insulin including 22 (16%) also taking oral antidiabetic drugs (OADs), the details of which are presented in Table 1.

Eighty-six (64%) patients received OAD only, including 63 (47%) with one OAD, 30 (22%) with 2 OADs, 22 (16%) with three OADs, and 11 (8%) with four or more OADs. In detail, 38 patients (28%) used α -glucosidase inhibitors, 67 (50%) used biguanides, 26 (19%) used thiazolidinediones, 54 (40%) used sulfonylureas, 3 (2%) used glinides and 53 (40%) used dipeptidyl peptidase-4 (DPP4) inhibitors, at various daily doses, as indicated in Table 1. Six patients (4%) used GLP-1 agonists, 3 of whom were also taking an OAD. Sixty-two patients (46%) were receiving diet therapy with daily intakes ranging from 1200-1800 kcal (21-29 kcal/IBW) and, in 51 patients (38%), salt was restricted to less than 6 g/d.

As to antithrombotic or anti-inflammatory agents, 29 patients (22%) used antiplatelet agents, 7 (5%) used anticoagulants, 8 (6%) used steroids or non-steroidal anti-inflammatory drugs and 7 (5%) used other antithrombotic agents such as prostaglandin E1 derivatives, prostaglandin I2 derivatives, or ethyl esters of eicosapentaenoic acid. As to GI agents, 29 patients (22%) used antacids, 13 (10%) used mucosal protectives, 11 (8%) used antimicrobials, and 18

Table 1 Characteristics of the study population

Variable	n (%)	mean (95%CI)
Sex, male/female	87/47 (65/35)	
Age of 65 yr or older	72 (54)	64.7 (62.8-66.6)
BMI of 25 kg/m ² or more	56 (42)	24.7 (24.0-25.4)
HbA1c of 7% or more	69 (51)	7.1 (6.9-7.3)
Duration of diabetes, yr		13.7 (12.4-14.9)
≤ 4	12 (9)	
5-9	27 (20)	
10-14	35 (26)	
15-19	31 (23)	
≥ 20	29 (22)	
Incidence of diabetic microangiopathy		
Autonomic neuropathy	32 (24)	
Distal symmetric polyneuropathy	20 (15)	
Retinopathy	31 (23)	
Nephropathy	64 (48)	
Use of antidiabetic drugs		
None	8 (6)	
Insulins	34 (25)	
Insulins with OAD	22 (16)	
OAD only	86 (64)	
1 OAD	63 (47)	
2 OAD	30 (22)	
3 OAD	22 (16)	
≥ 4 OAD	11 (8)	
GLP-1	6 (4)	
GLP-1 with OAD	3 (2)	
Insulins	34 (25)	
Range of injections per day	1-5	
Range of total daily insulin doses, IU	2-114	
Insulin glargine	12	
Insulin detemir	7	
Human NPH insulin	14	
Insulin aspart	2	
Insulin glulisine	4	
Insulin lispro	2	
Premixed human insulin 30/70	9	
Biphasic insulin aspart 30/70	1	
α-Glucosidase inhibitors	38 (28)	
Acarbose (150/200/300 mg)	3 (1/1/1)	
Miglitol (50/75/100/150 mg)	22 (1/12/18)	
Voglibose (0.6/0.9 mg)	13 (5/8)	
Biguanides	67 (50)	
Buformin 150 mg	1	
Metformin (500/750/1000/1500/2250 mg)	66 (12/20/14/19/1)	
Thiazolidinediones	26 (19)	
Pioglitazone (15/30 mg)	26 (18/8)	
Sulfonylureas	54 (40)	
Glimepiride (0.5/1/2/3/4 mg)	26 (10/10/2/1/3/)	
Gliclazide (20/40/120 mg)	21 (15/5/1)	
Glibenclamide (1.25/2.5/5 mg)	7 (1/4/2)	
Glinides	3 (2)	
Repaglinide 0.75 mg	1	
Mitiglinide (10/30 mg)	2 (1/1)	
Dipeptidyl peptidase-4 inhibitors	53 (40)	
Alogliptin 25 mg	12	
Sitagliptin (50/100 mg)	17 (15/2)	
Vildagliptin (50/100 mg)	24 (5/19)	
Glucagon-like peptide-1 agonists	6 (4)	
Liraglutide (0.6/0.9 mg)	4 (1/3)	
Exenatide 20 mg	2	
Dietary information		
Receiving dietary therapy	62 (46)	
With salt restriction to < 6 g per day	51 (38)	
Range of total energy intake, kcal	1200-1800	
Range of total energy intake per IBW, kcal/IBW	21-29	
Use of antithrombotic or anti-inflammatory agents		
Antiplatelet agents	29 (22)	
Anticoagulants	7 (5)	

Steroids/NSAIDs	8 (6)
Others ¹	7 (5)
Use of GI agents	
Antacids	29 (22)
Mucosal protectives	13 (10)
Antimicrobials	11 (8)
GI stimulants	18 (13)
Anti-diarrheals	0 (0)
Baseline blood parameters, mean ± SD	
WBC, × 1000/μL	6.1 ± 1.9
RBC, × 10000/μL	439 ± 78.1
Hb, g/dL	13.4 ± 2.4
Hct, %	40.8 ± 6.9
Plt, × 10000/μL	21.9 ± 6.6
TP, g/dL	7.1 ± 0.5
Alb, g/dL	3.8 ± 0.3
AST(GOT), U/L	24.4 ± 13.4
ALT(GPT), U/L	24.5 ± 17.7
γ-GTP, U/L	34.1 ± 24.3
CK, U/L	113 ± 63.6
T-Cho, mg/dL	180 ± 39.2
HDL-C, mg/dL	60.3 ± 18.3
TG, mg/dL	128 ± 67.2
cLDL, mg/dL	95.4 ± 26.2
BUN, mg/dL	17.6 ± 11.9
Cre, mg/dL	0.9 ± 0.8
eGFR, mL/min per 1.73 m ²	66.6 ± 22.8
UA, mg/dL	5.5 ± 1.4

¹Others' includes other antithrombotic agents such as prostaglandin E1 derivatives, prostaglandin I2 derivatives, or ethyl esters of eicosapentaenoic acid. Data are expressed as means with the 95%CI in parentheses, with numbers for each sex or numbers with the percentage of the total in parentheses. BMI: Body mass index; GI: Gastrointestinal; HbA1c: Hemoglobin A1c; IBW: Ideal body weight; NPH: Neutral protamine Hagedorn; NSAIDs: Nonsteroidal anti-inflammatory drugs; OAD: Oral antidiabetic drug.

(13%) used GI stimulants, but none were taking anti-diarrheal agents. Baseline blood parameter findings were unremarkable.

GI symptoms and diabetes duration

In the QOL assessment employing the Izumo Scale, the scores of total GI symptoms peaked during the 15- to 19-year diabetes duration period (Figure 1). When GI symptoms were analyzed separately, lower GI symptoms were found to be most frequent. Prevalence patterns differed between the esophagus/upper GI tract and lower GI tract regions. Scores for heartburn ($P = 0.004$) and postprandial fullness ($P = 0.03$) consistently and significantly rose as disease duration increased (Figure 2A).

Scores for gastralgia, like total GI symptoms, peaked during the 15- to 19-year diabetes duration period. Interestingly, only the scores for constipation and diarrhea showed bimodal peaks, the first in the early period of diabetes and the second late in the disease course. Age showed a similar but weaker relationship to diabetes duration. There were no apparent relationships of GI symptoms with age or BMI, but postprandial fullness, alone among the five symptoms, was slightly associated with high HbA1c levels (Figure 2B-D).

Relationships of GI symptoms with diabetic complications and medications

Next, we examined whether there were any relation-

ships between GI symptoms and patient characteristics such as diabetic microangiopathy and the drugs administered (Figure 3A-D). None of the GI symptoms showed significant relationships with any of the forms of diabetic microangiopathy (Figure 3A), though symptoms tended to be more frequent in patients with than in those without DAN and/or DSP. As shown in Figure 3B, the rate of DPP4 inhibitor use was lower in patients suffering from constipation ($P = 0.04$). Insulin therapy and oral hypoglycemic agents other than DPP4 inhibitors were not related to GI symptoms. The numbers of patients using glinides or GLP-1 agonists were too small to allow statistically meaningful evaluation. As shown in Figure 3C, of the 29 patients taking antiplatelet agents, 38% ($n = 11$) had constipation ($P = 0.046$) and 62% ($n = 18$) had diarrhea ($P = 0.03$). Of the 18 patients using GI stimulants, 44% ($n = 8$) had constipation ($P = 0.03$) (Figure 3D).

We next investigated the effect of diabetic duration on constipation, excluding users of DPP4 inhibitors, antiplatelet agents or GI stimulants. We focused on the association of diabetes duration with constipation (Figure 4A), and on that with diarrhea, except in antiplatelet agent users (Figure 4B). When users of these medications were excluded, the early and late peaks in constipation and diarrhea remained.

Clustering and overlap of GI symptoms

A cluster analysis tree is presented in Figure 5. Gastralgia and postprandial fullness are more similar to

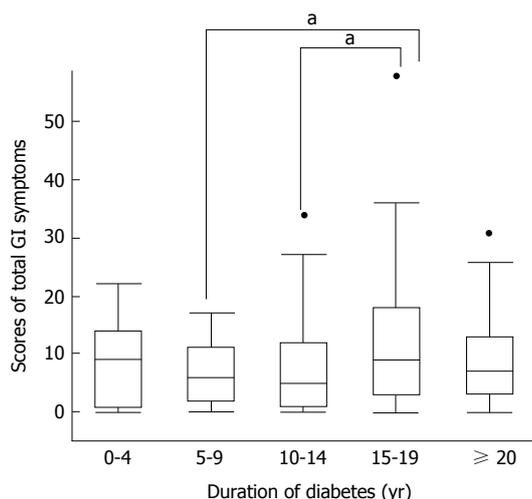


Figure 1 Distribution of the sum of scores of symptoms related to all GI areas by duration of diabetes. ^a $P < 0.05$, significantly different. Sums of symptom scores peaked during the 15- to 19-yr diabetes duration period, compared by Student's *t*-tests for paired periods ($P = 0.01$ and $P = 0.02$ when compared with 5-9 yr and 10-14 yr disease durations, respectively).

each other than to constipation and diarrhea. Heartburn is closer to upper than to lower GI symptoms. The relationship between constipation and diarrhea was found to be closer than the other associations identified in this study. The overlaps between two different symptoms on the Izumo Scale are shown in Table 2. Significant differences, determined by Fisher's exact test, between the presence and absence of two distinct symptoms, were demonstrated.

As in the cluster analysis, heartburn was associated with gastralgia ($P = 0.03$) or postprandial fullness ($P = 0.002$). Gastralgia and postprandial fullness ($P < 0.0001$) were strongly related to each other, as were constipation and diarrhea ($P < 0.0001$). Postprandial fullness was found to be related to all GI tract regions, showing modest interactions with both constipation ($P = 0.004$) and diarrhea ($P = 0.001$). Furthermore, all 31 patients with constipation also had episodes of diarrhea, while only 52.5% of those complaining mainly of diarrhea also had constipation (Table 2).

DISCUSSION

We investigated whether outpatients with T2DM actually have GI symptoms and, if present, the clinical severity of such symptoms. However, patients do not usually complain of GI symptoms. Overall, 10%-20% of adults have functional GI disorders^[32-35]. In patients with diabetes, symptoms involving all portions of the GI tract are reportedly more common than in the general population^[36]. However, we found that total symptom scores did not increase linearly with disease duration. In fact, rates peaked during different periods, according to GI regions. Lower abdominal symptoms were prominent early in the disease course, while diabetic complications were still mild, as well as in the late stage.

Significant confounding factors include aging, glycemic control and BMI reduction^[5,8-10,37]. Japanese patients have become increasingly obese over the past 20 years and those in the younger generation have poor glycemic control at the diagnosis of T2DM, independent of hyperglycemic symptoms^[38]. Therefore, symptom prevalence may change in the future.

We found no significant relationships between GI symptoms and either DAN or DSP. There might, however, be a detection bias or low sensitivity for DAN and DSP, since a previous report noted that symptoms tend to be related to lifestyle factors, rather than to either glycemic control or peripheral neuropathy^[36]. Another study found no association of GI symptoms with either diabetic neuropathy or psychiatric illnesses^[39]. Early symptoms might well be related to psychiatric illnesses and/or lifestyle factors but we did not obtain data pertaining to such factors in the present study.

Among anti-hyperglycemic medications, only the relationship between DPP4 inhibitors and constipation was significant. Constipation is a well-known side effect of these drugs^[40], and physicians often discontinue or do not start DPP4 inhibitors due to this adverse effect^[41]. Oral medications are generally prescribed to patients with poor glycemic control^[42] and are frequently used to manage longstanding diabetes^[43]. Administration of anti-platelet agents was associated with a variety of symptoms, as expected. These agents were still preferentially used despite apparently being harmful to the upper, middle and lower GI tracts^[44,45], since the treatment of cardiovascular diseases has the highest priority. However, the bimodal peaks for constipation and diarrhea late and early in the course of diabetes were maintained and were independent of medication use.

The mechanisms underlying rapid development of lower GI complications, such as diarrhea and constipation, are unknown. In our cluster analysis, the affected GI tract region was found to be an important factor. Furthermore, the mechanisms underlying the bimodal early and late disturbances are suggested to not be the same. Early diabetic neuropathy is reportedly multifactorial, being triggered by impairment of insulin signaling, abnormal blood flow, and oxidative stress including N-acetylglucosamine, activation of protein kinase C, activation of the polyol sugar pathway and glucose autooxidation, as well as non-enzymatic protein glycation^[46]. Insulin growth factors (IGFs) possess multiple neurotrophic functions, including neuronal survival, neurite outgrowth and regeneration. C-peptide also exerts IGF-like activity, such that endogenous proinsulin production might be related to the pathogenesis of GI symptoms^[47]. One possible explanation of mechanistic differences between early lower GI symptoms and upper GI symptoms might involve cellular composition. The lower GI tract contains colonic stem cells and their functions are disrupted in states of diabetic enteropathy^[19].

Table 2 Overlapping of gastrointestinal symptoms

Overlapping symptom	Heartburn, <i>n</i> = 9	Gastralgia, <i>n</i> = 11	Postprandial fullness, <i>n</i> = 17	Constipation, <i>n</i> = 31	Diarrhea, <i>n</i> = 59
Heartburn	-	3/11 ^a	5/17 ^b	5/31	6/59
Gastralgia	3/9 ^a	-	8/17 ^b	4/31	7/59
Postprandial fullness	5/9 ^b	8/11 ^a	-	9/31 ^b	14/59 ^b
Constipation	5/9	4/11	9/17 ^b	-	31/59 ^b
Diarrhea	6/9	7/11	13/17 ^b	31/31 ^b	-

^a*P* < 0.05 or ^b*P* < 0.01, significantly different.

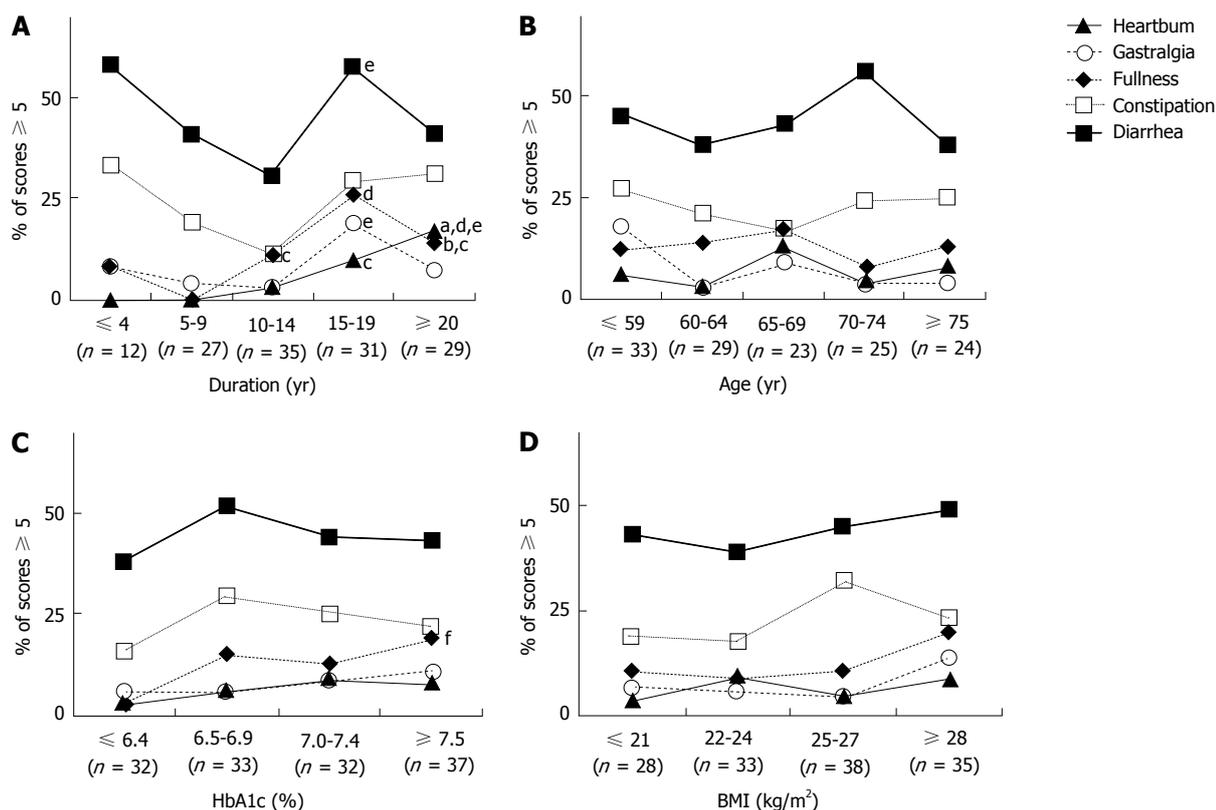


Figure 2 Relationships of abdominal symptoms with duration of diabetes, age, body mass index and hemoglobin A1c. The lines show the percentages of subjects with a score of 5 or higher, for each GI region, among those considered to be sufficiently symptomatic to impair quality of life. Comparisons among groups with five disease duration periods (A), five age ranges (B), four HbA1c levels (C) and four BMI levels (D) were performed using a Cochran-Armitage-trend-test. ^a*P* < 0.05 or ^b*P* < 0.01, significantly different. As shown in the figure (A), scores for heartburn (*P* = 0.004) and postprandial fullness (*P* = 0.029) consistently and significantly increased with disease duration. Student's *t*-tests for paired samples were performed to compare percentages of subjects with a score of 5 or higher, for each GI region, among five durations of diabetes (A), five age ranges (B), four HbA1c levels (C) and four BMI levels (D). ^c*P* < 0.05 vs 5-9 years, ^d*P* < 0.01 vs 5-9 years, or ^e*P* < 0.05 vs 10-14 years when compared with other disease duration periods and ^f*P* < 0.05 vs 6.4% or less which indicate significant differences. As shown in the figure (A), percentages of subjects with a score of 5 or higher for all symptoms except constipation in the disease duration period of 15-19 years were significantly higher than those in the 5-9 years and 10-14 years periods; *P* = 0.048 for heartburn, *P* = 0.024 for gastralgia, *P* = 0.008 for fullness and *P* = 0.03 for diarrhea. Likewise, percentages of subjects with a score of 5 or higher for heartburn and fullness in the disease duration period of 20 years or more were significantly higher than those in the 5-9 years and 10-14 years periods; *P* = 0.01 and *P* = 0.04 for heartburn and *P* = 0.02 for fullness. Furthermore, the percentage of subjects with a score of 5 or higher for fullness in the disease duration period of 10-14 yr was significantly higher than that in the 5-9 years period (*P* = 0.029). As shown in the figure (C), the percentage of subjects with a score of 5 or higher for fullness in those with HbA1c levels of 7.5% or above was significantly higher than that in those whose HbA1c was 6.4% or less (*P* = 0.030). BMI: Body mass index; HbA1c: Hemoglobin A1c.

Lower GI tract symptoms were found to be most frequent and cluster analysis demonstrated these symptoms to be related more to the affected region of the GI tract than to its functions, such as acid secretion and motility. In fact, a high concordance between constipation and diarrhea is unusual in general populations^[48]. Upper and lower GI symptoms reportedly overlap and early satiety more frequently

overlaps with constipation than diarrhea in general populations^[49,50].

This study has several limitations. First, it is difficult to determine the causes of symptoms with a cross-sectional study design. There is diagnostic uncertainty regarding the GI disorders studied, because the reporting of symptoms was mainly subjective. Endoscopy can be used to exclude organic diseases with

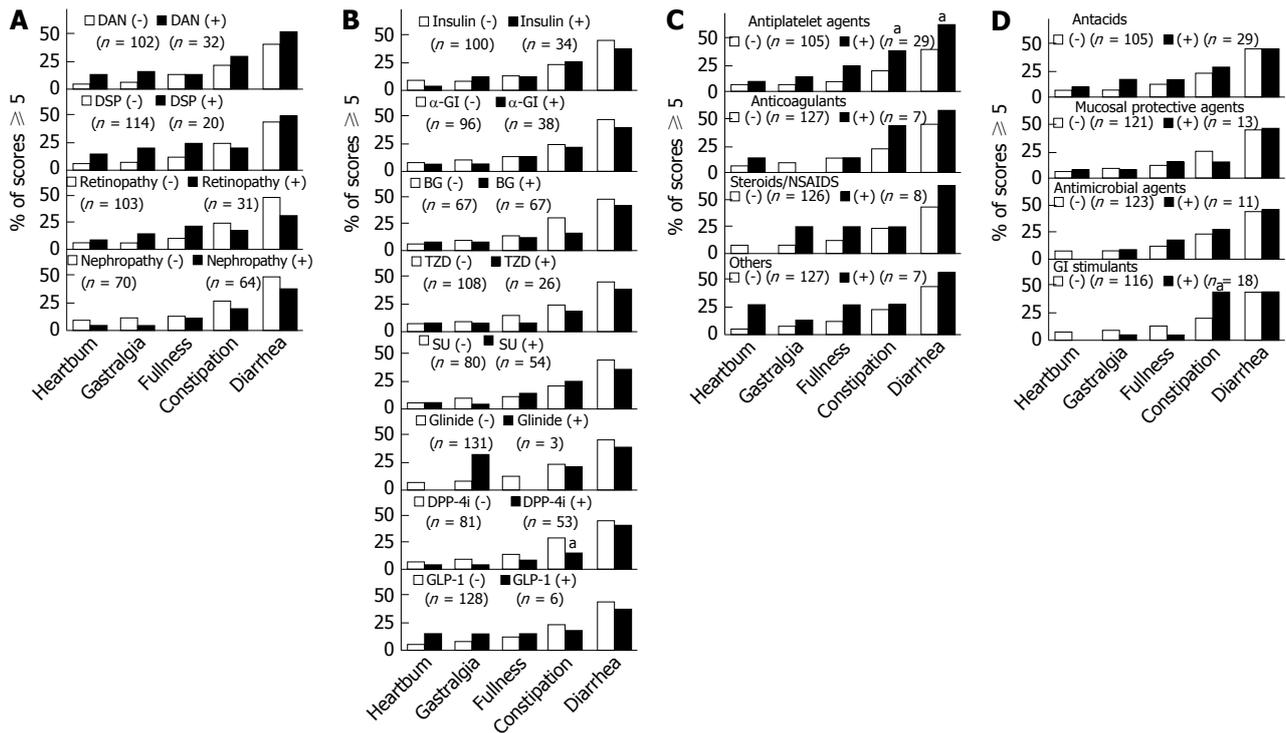


Figure 3 Relationships between various parameters and gastrointestinal symptoms involving each gastrointestinal region (“Heartburn” for esophagus, “Gastralgia” and “Postprandial Fullness” for upper abdomen, and “Constipation” and “Diarrhea” for lower abdomen). Bars: White indicates the absence and black the presence of each parameter. The percentages of subjects with a score of 5 or higher, for each GI region, considered to be sufficiently symptomatic to cause impaired quality of life, are shown. ^a*P* < 0.05, significant difference between presence and absence of each parameter, as analyzed by Fisher’s exact test. A: Comparison between subjects with and without diabetic microangiopathy. The indicated percentages were obtained by dividing the number of subjects with a score of 5 or higher by the total number of patients in the same group (with or without diabetic microangiopathy); B: Comparisons between groups of patients with and without antidiabetic agent administration; C: Comparisons between groups of patients with and without antithrombotic or anti-inflammatory agents. ‘Others’ includes other antithrombotic agents such as prostaglandin E1 derivatives, prostaglandin I2 derivatives, or ethyl esters of eicosapentaenoic acid; D: Comparisons between groups of patients with and without GI agents. αGI: Alpha-glucosidase inhibitors; DAN: Diabetic autonomic neuropathy; DPP-4i: Dipeptidyl-peptidase 4 inhibitor; DSP: Distal symmetric polyneuropathy; GI: Gastrointestinal; GLP-1: Glucagon-like peptide-1; NSAIDs: Nonsteroidal anti-inflammatory drugs; SU: Sulphonyl urea; TZD: Thiazolidinedione.

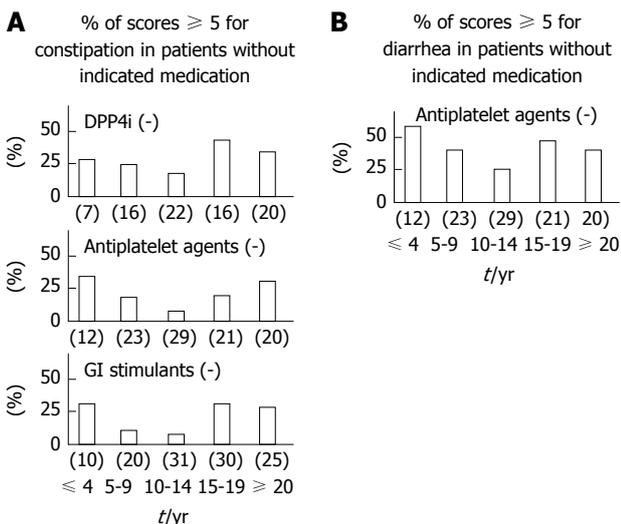


Figure 4 Relationships between various medications, which demonstrated significance as shown in Figure 3, and diabetes duration in terms of the presence of related gastrointestinal symptoms. White bars show the percentages of subjects with a score of 5 or higher for the indicated GI symptoms (A: Constipation, B: Diarrhea) without use of the indicated medications. Numbers under each bar within brackets are the number of patients not using the indicated medications. DPP-4i: Dipeptidyl-peptidase 4 inhibitor; GI: Gastrointestinal.

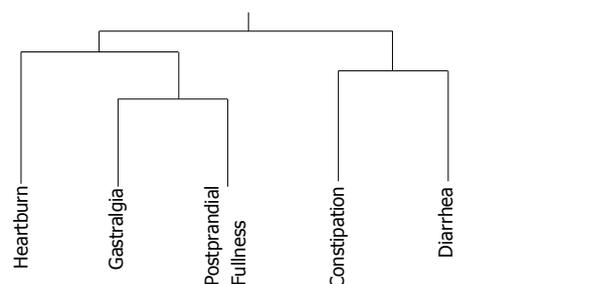


Figure 5 Cluster analysis was conducted for various gastrointestinal symptoms. The treeplot shows relationships among the five symptoms. Lengths of branches between symptoms indicate symptom similarity.

symptoms similar to those of diabetic GI disorders (e.g., inflammatory bowel disease, colonic polyposis, and celiac disease)^[51]. Few therapeutic or diagnostic approaches are available to assess the GI disorders possibly associated with diabetes. Organic diseases not requiring surgery and functional disorders could not be precisely distinguished because we did not perform upper and lower GI endoscopy or gastric emptying scintigraphy at the time of this study, since it was retrospective. Our results might have low sensitivity due to the small sample sizes in some groups.

In conclusion, our study highlights the importance of questioning patients about QOL impairment due to abdominal symptoms, especially lower GI symptoms in the early period and both lower and upper GI symptoms in the late period of diabetes. The heterogeneous nature of the underlying pathophysiological mechanisms underlying GI symptoms, including medication usage, should be taken into consideration when managing patients with T2DM.

COMMENTS

Background

Type 2 diabetes mellitus (T2DM) incidence is dramatically increasing, and both micro- and macrovascular complications of diabetes lead to various symptoms and impair quality of life (QOL) in T2DM patients. Among these symptoms, those affecting the gastrointestinal (GI) tract are frequent in T2DM patients. GI disorders in diabetes have been poorly characterized. Hyperglycemia-associated neuropathy was considered to be related to GI symptoms, probably via oxidative stress and inflammation. Levels of enteral hormones are altered in patients with DM, affecting both GI motility and neural fiber growth. Furthermore, smooth muscle cells, interstitial cells of Cajal, gut microbiota and intestinal stem cells may also be altered in DM and these changes might be related to GI symptoms. The relevance of these mechanisms in human GI symptoms affecting T2DM patients have yet to be clarified. The Izumo Scale, a validated and useful tool for QOL assessment, is a scale for assessing GI symptoms. Applying this scale, we investigated actual GI symptoms employing a questionnaire and determined whether the symptoms identified are related to the clinical profiles of patients with T2DM.

Research frontiers

This study highlights the importance of not underestimating gastrointestinal symptoms and of questioning patients about QOL impairment due to abdominal symptoms, especially in both the early period and after a diabetes duration of 10 or even 15 years.

Innovations and breakthroughs

The novel finding of this study is that symptom frequencies differed among disease durations and according to affected gastrointestinal regions. Lower abdominal symptoms not only manifested during the late but also in the early stage of diabetes when there were no organ complications related to this disease. This results are apparently inconsistent with the previously suggested mechanisms of GI symptoms related to DM, especially diabetic neuropathy which develops with longstanding diabetes.

Applications

This study highlights the importance of questioning patients about QOL impairment due to abdominal symptoms, especially lower GI symptoms in the early period and both lower and upper GI symptoms in the late period of diabetes, while underscoring the need for systematic and comprehensive research focusing on GI conditions in patients with T2DM.

Terminology

Izumo Scale: This self-administered questionnaire designed to assess the effects of abdominal symptoms on QOL includes 15 items in five domains with three items in each domain: heartburn, gastralgia, postprandial fullness, constipation, and diarrhea. This scale was developed and validated by Furuta *et al.* Each question is rated on a 6-point Likert scale from 0 to 5, with higher values indicating more severe symptoms.

Peer-review

Considering the paucity of data available in the literature on this topic, this study may reinforce the clinical relevance of assessing intestinal disorders in diabetes and increase the interest of the scientific community in this topic. Overall, this report describes relevant novel findings that may be further addressed and

confirmed with detailed experimental studies.

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P- Reviewer: Bulc M, Fiorina P **S- Editor:** Gong ZM
L- Editor: Filipodia **E- Editor:** Li D





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ISSN 1007-9327

