Gastrointestinal Symptoms in Diabetes Occur Long Before Diabetic Complications

Hwanseok Jung

Sungkyunkwan University School of Medicine

Eun-Jung Rhee

Sungkyunkwan University School of Medicine

Mi Yeon Lee

Sungkyunkwan University School of Medicine

Jung Ho Park

Sungkyunkwan University School of Medicine

Dong Il Park

Sungkyunkwan University School of Medicine

Woo Kyu Jeon

Sungkyunkwan University School of Medicine

Chong Il Sohn (✉ chongil.sohn@samsung.com)

Sungkyunkwan University School of Medicine

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Abstract

Background: Gastrointestinal (GI) manifestations are common in patients with diabetes complications such as autonomic neuropathy. However, the prevalence of GI symptoms before the development of diabetes complications remains unclear.

Method: We performed an interview survey of functional gastrointestinal disorders in diabetes patients who visited the endocrinology clinic of a general hospital using the ROME III criteria. The investigation consisted of various questions on functional dyspepsia, irritable bowel syndrome, and functional constipation including functional defecation disorder.

Results: A total of 509 patients were included in this analysis. The patients were analyzed in three groups, prediabetes patients (n = 115), diabetes patients without neuropathy (n = 275), and diabetes patients with neuropathy (n = 119). The prevalence of gastrointestinal symptoms in prediabetes patients, diabetes patients without neuropathy, and diabetes patients with neuropathy was estimated at 16.52%, 27.27%, and 23.53% for functional dyspepsia; 8.7%, 11.68%, and 16.81% for irritable bowel syndrome; and 8.85%, 11.85%, and 15.25% for functional constipation. In the subgroup analysis, postprandial distress syndrome symptoms such as postprandial fullness and early satiation were more prevalent than epigastric pain symptoms. In the constipation group, pelvic outlet obstruction symptoms such as the sensation of anorectal obstruction or blockage and manual maneuvers to facilitate defecation were more frequently observed than slow transit constipation symptoms.

Conclusions: The prevalence of functional gastrointestinal disorders increased with diabetes severity. Diabetes-related GI symptoms appeared long before the diabetes complications.

Introduction

The prevalence of diabetes mellitus has increased worldwide. Over the 400 million patients live with diabetes, and the number is expected to increase further in the future.[1] This epidemic metabolic disease is associated with many complications such as macrovascular, microvascular, and nervous system complications. Diabetic neuropathy, especially autonomic neuropathy, leads to gastrointestinal manifestations like gastroparesis, diarrhea, and bowel habit change.[2].

Adults with long standing type 1 and 2 diabetes report significantly more gastrointestinal symptoms than healthy controls without diabetes.[3] Upper gastroparesis and delayed gastric emptying represent a large proportion of the gastrointestinal tract disorders, and the largest proportion of those is diabetes-related.[4] In the lower gastrointestinal tract, constipation, diarrhea, and abdominal distension are known to be common disorders. A previous study reported that people with type 2 diabetes had a higher prevalence of constipation than those without diabetes.[5] The prevalence of functional gastrointestinal disorder symptoms was also higher in subjects with diabetes than in community-based subjects.[6, 7]

However, there are rare reports of gastrointestinal symptoms in hyperglycemic patients before diabetes mellitus developed, such as in the prediabetes state. Furthermore, whether abdominal symptoms in diabetes and/or hyperglycemic patients are associated with diabetic neuropathy has not been fully investigated. Therefore, we aimed to explore the prevalence of gastrointestinal symptoms in prediabetes patients, diabetes patients without neuropathy, and diabetes patients with neuropathy, and assess the association of gastrointestinal symptoms with the severity of diabetes using the Rome III criteria.

Methods

Subjects

We performed a questionnaire interview study among the patients who visited a diabetes clinic in a general hospital. The study was conducted over 18 months to survey the prevalence of GI symptoms in patients with diabetes. Outpatients with impaired fasting glucose diagnosed by an oral glucose tolerance test or diabetes mellitus were recruited and interviewed regarding their gastrointestinal symptoms. The exclusion criteria were patients 1) who refused to participate in the interview or produced an incomplete questionnaire, 2) with severe illness or mental illness, 3) who were pregnant, or 4) had a past abdominal surgery history except for appendectomy or hernia repair surgery. Written informed consent was obtained from all subjects before enrollment. This study was approved by the Institutional Review Board (IRB).

Functional gastrointestinal disorder criteria

There are many subgroups of functional gastrointestinal disorders (FGIDs) in the ROME III classification. We investigated the prevalence of functional dyspepsia, irritable bowel syndrome, and functional constipation using ROME III criteria in the study patients.[8] We also investigated the prevalence of functional gastrointestinal disorders in the presence of diabetes complications. The ROME III criteria classify functional dyspepsia into two subtypes, epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS), so we followed this classification. Irritable bowel syndrome (IBS) was stratified into three different subtypes according to bowel habits, IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and IBS with mixed bowel habit and unclassified IBS (IBS-M or U). Upper GI symptoms and bowel habit symptoms were also surveyed using a questionnaire. We asked about the upper GI symptoms of early satiation and postprandial fullness in reference to functional dyspepsia in the ROME III consensus. The questionnaires for bowel symptoms followed the ROME III consensus of functional constipation.

Questionnaire

The questionnaire on gastrointestinal symptoms manufactured by the Rome Foundation was translated into Korean by the Korean Society of Neurogastroenterology and Motility. A total of 45 questions categorized the symptoms into three diagnosis categories of functional dyspepsia, IBS, and constipation based on the Rome III criteria. Trained interviewers conducted the survey in the outpatient department.

The patients were given a specific questionnaire that evaluated the frequency and severity of functional dyspepsia. Early satiation, postprandial fullness, epigastric pain, epigastric burning sensation, epigastric bloating, and nausea symptoms were graded from 1 to 5 (1: absent, 2: mild, 3: moderate, 4: severe, and 5: very severe). The frequency of the symptoms was graded from 1 to 5 (1: never, 2: less than one day per month, 3: about two or three days per month, 4: at least one day per week, 5: at least several times per week, and 6: almost every day). In the functional dyspepsia diagnostic questionnaires of other studies including ROME III, severity was not specifically addressed, so we made our own cutoff value.[9, 10] However, we determined the PDS and EPS subgroups in agreement with the ROME III criteria. The functional dyspepsia patients were classified into the PDS subgroup if they responded that they experienced postprandial fullness and/or early satiation at least several times per week. The EPS subgroup included the patients who reported epigastric pain at least once per week.[8]

The questionnaire responses were used to divide the IBS group based upon the ROME III criteria. The IBS disorder group was categorized further into three subgroups according to the bowel patterns at a particular point in time.[11,

12] The frequency of recurrent abdominal pain or discomfort was scored. The Bristol stool form scale was used to divide the stool aspect to categorize the IBS subgroups.

Straining, lumpy or hard stools, the sensation of anorectal incomplete evacuation, the sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecation, and fewer than three defecations per week were investigated through the questionnaire. If two of these were satisfied, the patients were assigned to the functional constipation group according to the ROME III criteria.[12] The prevalence of each symptom was also investigated.

Diabetic factors

Among the patients with diabetes, tests for evaluating autonomic neuropathy were conducted in the endocrinology clinic by trained technicians. In addition, the HbA1c level in each patient was evaluated. Three tests were conducted, the Valsalva ratio test, the expiration/inspiration (E/I) ratio test, and the blood pressure (BP) response to standing test. And if any of the test results were abnormal, autonomic neuropathy was diagnosed. Prediabetes was diagnosed by a fasting glucose level of 100 – 125 mg/dl or an HbA1c level of 5.7 – 6.4%.

Statistical analysis

To analyze prevalence, crosstabs were used. Binodal logistic regression analysis was used to assess the association of each Rome III subgroup with diabetic neuropathy after adjusting for age and sex. All results were considered to be significant if the P-value was less than 0.05. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

Results

Baseline characteristics of the study population

Seven hundred and twenty patients who visited the endocrinology clinic due to impaired fasting glucose status or diabetes mellitus were recruited and surveyed. Two hundred and one patients who did not complete the questionnaire and 10 patients who did not meet the inclusion criteria were excluded [Fig. 1]. A total of 509 patients were enrolled. The enrolled patients were composed of prediabetes patients (n = 115, 22.6%), diabetes patients without neuropathy (n = 275, 54.0%), and diabetes patients with neuropathy (n = 119, 23.4%). Prediabetes patients and diabetes patients without neuropathy were included in the no complication group and diabetes patients with neuropathy were assigned to the complication group. Among the enrolled patients, 61.1% (n = 311) were males and the mean age was 53.9 ± 12.6 years [Table 1].

Prevalence of functional gastrointestinal disorders

The prevalence of functional dyspepsia in the prediabetes patients was 16.52% and that of EPS and PDS in the prediabetes patients was 11.3% and 6.09%, respectively. After adjusting for the confounding factors of age and sex, multinomial regression models were built and PDS (odds ratio (OR) = 3.915; 95% CI: 1.591 to 9.633) was associated with the complication group, but not in the EPS group (OR = 0.911; 95% CI: 0.388 to 2.142) [Table 2]. The prevalence of gastric symptoms was analyzed. The prevalence of postprandial fullness in the prediabetes patients was 6.09% and that of early satiety was 4.35% in the prediabetes patients. After adjusting for the confounding factors of age and sex, multinomial regression models were built and postprandial fullness (OR = 2.135; 95% CI: 0.827 to 5.509) and early satiety (OR = 3.419; 95% CI: 1.197 to 9.762) were related to complications. In subgroup analysis,

postprandial distress syndrome symptoms such as postprandial fullness and early satiation were more prevalent than epigastric pain symptoms.

The prevalence of IBS in the prediabetes patients was 8.7% (OR = 1.619; 95% CI: 0.742 to 3.532) and its diarrhea subtype (OR = 2.499; 95% CI: 0.412 to 15.165) and the mixed and unclassified subtype (OR = 2.428; 95% CI: 0.955 to 6.174) were also associated with neuropathy but none showed statistical significance ($p > 0.05$). Only one patient was assigned to the constipation subtype, so we could not analyze the prevalence of this subtype. The prevalence of functional constipation in prediabetes patients, diabetes without neuropathy, and diabetes with neuropathy patients was 8.85%, 11.85%, and 15.25%, respectively. Functional constipation was somewhat associated with the complication group (OR = 1.513; 95% CI: 0.642 to 3.563) but failed to show statistical significance [Table 4]. Like the upper gastrointestinal symptoms, the lower gastrointestinal symptoms were seen to start in the prediabetes state. However, in the upper gastrointestinal tract, symptoms, especially dyspepsia, tended to develop more in the hyperglycemic state.

The prevalence of bowel symptoms is shown in Table 5. In the constipation group, pelvic outlet obstruction symptoms such as the sensation of anorectal obstruction/blockage and manual maneuvers to facilitate defecation were more prevalent than slow transit constipation symptoms. The prevalence of the sensation of anorectal incomplete evacuation, the sensation of anorectal obstruction/blockage, and manual maneuvers to facilitate were generally higher than the rest. However, these symptoms also failed to show pathologic significance, suggesting that they may begin in the hyperglycemia state [Table 5].

Discussion

In this prevalence study, we found that the prevalence of functional gastrointestinal disorders and variable gastrointestinal symptoms tended to be elevated before complications occurred, contrary to the expectations. The ORs of functional gastrointestinal disorders in the upper and lower gastrointestinal were similar. However, higher ORs were noted for upper gastrointestinal symptoms such as postprandial fullness and early satiation.

Many factors can be associated with gastrointestinal disorders and symptoms in diabetes. In diabetes patients, gastrointestinal symptoms are known to be common in women, patients with poorly controlled blood sugar levels, and patients with psychosocial problems such as anxiety and depression.[5] Gastrointestinal symptoms are often associated with abnormalities in the diabetic autonomic neuropathy, which affects the entire gastrointestinal tract. [13] Various micro environmental changes, especially such as hyperglycemia, affect the nervous system of the entire gastrointestinal tract, leading to motor dysfunction and secretory dysfunction, and these changes result in various forms of symptoms, finally degrading the quality of life.[13] Furthermore, the expression of gastrointestinal symptoms affects the compliance with diabetes medications, which was reported to be reduced in patients taking metformin with gastrointestinal symptoms by up to 40%.[14]

Gastrointestinal symptoms are considered to be the result of abnormalities in the gut-brain axis in diabetes patients. [3] Structural and functional changes in the central nervous system can affect the recognition and occurrence of symptoms, such as gastrointestinal hypersensitivity and rectal sensitivity.[15] Hyperglycemia can affect the motor function and sensory recognition in the gastrointestinal tract, which is known to increase the proximal stomach compliance, delay gastric emptying, and increase symptoms such as satiety, fullness and nausea.[16] As shown by this prevalence studies,[Tables 2 and 3] the main symptoms in diabetes patients were nausea, vomiting, and bloating, consistent with a previous study.[17] Delayed gastric emptying is typical symptom of gastrointestinal

dysfunction, and highly related to the reduction and loss of interstitial cells of Cajal, and was reported to be associated with the infiltration of immune cells.[18]

Diabetes mellitus can affect the function of the colon promoting commonly encountered colonic symptoms such as constipation, diarrhea, abdominal distention, and abdominal pain.[19] IBS is a common condition and thus, also having diabetes is relatively common.[20] Both are linked to factors such as food, stress, and medication. Our study also showed the association with hyperglycemia, although the population in the IBS-C group was too small to analyze. [Table 4]

Although colonic motility has not been well studied in diabetes, transition time is usually delayed in diabetes.[21] The colon in diabetes mellitus patients has revealed myenteric neuronal loss and evidence of increased oxidants.[22] Anorectal dysfunction in diabetes includes impaired anal sphincter function and decreased rectal sensation to distension.[21] Just like in the upper GI tract, small intestine and colon motor function are worsen in the hyperglycemic state.[23]

In our study, neither the diabetes nor the neuropathy group showed statistically significant differences in prevalence compared to the prediabetes group. We hypothesized that the hyperglycemic state itself could serve as a worsening factor in the expression of gastrointestinal symptoms and that they could become chronic functional gastrointestinal disorders, even before they were expressed as diabetic autonomic neuropathy. Our study suggests that further research on the usefulness of dietary and psychosocial intervention are worthwhile, starting from the time of hyperglycemia, and on functional gastrointestinal disorders and gastrointestinal symptoms before diabetic autonomic neuropathy occurs.

Our study had some limitations. First, our prevalence study was not general-population-based, but included individuals who were seen in a hospital diabetes clinic. Second, gastrointestinal symptoms are also known to occur from taking diabetes medications such as metformin and α -glucosidase inhibitors like peptide-1 receptor agonist. [24, 25] Therefore, if diabetes patients complained of gastrointestinal symptoms, whether the symptoms were drug-related should be checked, and if they were drug-related, medication control could be necessary. Finally, data on dietary, occupational, and economic factors, and psychosocial status, which could be confounders, were not adjusted in this study.

Conclusion

We investigated the prevalence of functional gastrointestinal disorders in prediabetes patients, and diabetes patients with or without neuropathy using the Rome III criteria. The significantly increased prevalence of gastrointestinal symptoms suggested an association, not with autonomic neuropathy, but with the hyperglycemic state itself. We also demonstrated that this tendency was stronger in the upper gastrointestinal tract compared to the lower gastrointestinal tract, especially in dyspepsia-related symptoms. Symptoms related to obstruction or blockage were relatively prominent in the lower gastrointestinal tract.

Abbreviations

BP: Blood pressure;CI: Confidence interval; DM: Diabetes mellitus; E/I: expiration/inspiration; EPS: Epigastric pain syndrome; FGIDs: Functional gastrointestinal disorders; GI : Gastrointestinal; HbA1c: Glycated hemoglobin; IBS : Irritable bowel syndrome; ORs: Odds ratios; PDS : Postprandial distress syndrome.

Declarations

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Availability of data and materials

The questionnaire on gastrointestinal symptoms manufactured by the Rome Foundation was translated into Korean by The Korean Society of Neurogastroenterology and Motility. The questionnaire can be obtained at [<http://www.ksgm.org>]. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Hwanseok Jung carried out the data analysis and wrote the manuscript. Mi Yeon Lee contributed to advised statistical analyses. Eun-Jung Rhee contributed to analyzed and interpreted the patient data regarding the endocrine disease. Chong Il Sohn contributed to study design and critically reviewed the paper. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

Written informed consent was obtained from all subjects before enrollment. All the participants signed a written informed consent in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of the Kangbuk Samsung hospital, Sungkyunkwan university school of medicine. (IRB File No : 2020-07-047)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Tables

Table 1. Baseline characteristics of the patients enrolled in the study

	Total (N=509)	Prediabetes (N=115)	Diabetes without neuropathy (N=275)	Diabetes with neuropathy (N=119)	p- value
Male (%)	311 (61.1)	86 (74.8)	161 (58.5)	64 (53.8)	0.002
Age (mean±SD)	53.9±12.6	48.5±8.7	55.2±12.4	56.1±14.6	<0.001
HbA1c (%)	7.0±1.7	6.1±0.9	7.0±1.5	8.0±2.0	<0.001

Chi-squared test, ANOVA

Table 2. Prevalence of functional dyspepsia and subgroups based on Rome III criteria

	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs prediabetes		Diabetes with neuropathy vs prediabetes	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Functional dyspepsia	19 (16.52)	75 (27.27)	28 (23.53)	1.895 (1.083-3.314)	1.90 (1.068-3.379)	1.555 (0.812-2.976)	1.537 (0.788-3)
EPS	13 (11.3)	38 (13.82)	12 (10.08)	1.258 (0.643-2.46)	1.31 (0.654-2.622)	0.88 (0.384-2.018)	0.911 (0.388-2.142)
PDS	7 (6.09)	55 (20)	26 (21.85)	3.857 (1.7-8.754)	3.596 (1.557-8.305)	4.313 (1.79-10.393)	3.915 (1.591-9.633)

*p < 0.05, EPS, epigastric pain syndrome; PDS, postprandial distress syndrome; OR, odds ratio; CI, confidence interval

OR was adjusted for age and sex

Table 3. Prevalence of gastric symptoms

	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs prediabetes		Diabetes with neuropathy vs prediabetes	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Postprandial fullness	7 (6.09)	43 (15.64)	16 (13.45)	2.86 (1.246-6.563)	2.605 (1.116-6.077)	2.397 (0.947-6.064)	2.135 (0.827-5.509)
Early satiation	5 (4.35)	39 (14.18)	19 (15.97)	3.636 (1.395-9.479)	3.101 (1.162-8.275)	4.18 (1.505-11.613)	3.419 (1.197-9.762)

*p < 0.05, OR was adjusted for age and sex, OR, odds ratio; CI, confidence interval

Table 4. Prevalence of irritable bowel syndrome and functional constipation

	Prediabetes	Diabetes without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs prediabetes		Diabetes with neuropathy vs prediabetes	
				Crude OR	Adjusted OR	Crude OR	Adjusted OR
				(95% CI)	(95% CI)	(95% CI)	(95% CI)
IBS [†]	10 (8.7)	32 (11.68)	20 (16.81)	1.388 (0.658-2.928)	1.619 (0.742-3.532)	2.121 (0.946-4.755)	2.478 (1.062-5.783)
Constipation type	0 (0)	3 (1.09)	2 (1.68)	NA	NA	NA	NA
Diarrhea type	2 (1.74)	5 (1.82)	6 (5.04)	1.046 (0.2-5.473)	1.195 (0.219-6.514)	3.000 (0.593-15.182)	3.509 (0.655-18.805)
Mixed & Unclassified type	8 (6.96)	26 (9.49)	14 (11.76)	1.402 (0.615-3.197)	1.664 (0.701-3.949)	1.783 (0.718-4.428)	2.113 (0.812-5.498)
Functional constipation	10 (8.85)	32 (11.85)	18 (15.25)	1.385 (0.656-2.922)	1.173 (0.538-2.556)	1.854 (0.816-4.212)	1.513 (0.642-3.563)

*p < 0.05, IBS, Irritable bowel syndrome; OR, odds ratio; CI, confidence interval

OR was adjusted for age and sex

Table 5. Prevalence of bowel symptoms

	Prediabetes	Diabetes Without neuropathy	Diabetes with neuropathy	Diabetes without neuropathy vs prediabetes		Diabetes with neuropathy vs prediabetes	
				Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Straining	8 (6.96)	25 (9.23)	15 (12.61)	1.359 (0.594- 3.111)	1.045 (0.443- 2.464)	1.929 (0.785- 4.742)	1.432 (0.564- 3.636)
Lumpy or hard stools	26 (22.61)	50 (18.18)	16 (13.56)	0.761 (0.446- 1.297)	0.672 (0.385- 1.174)	0.537 (0.271- 1.065)	0.458 (0.225- 0.934)
Sensation of anorectal incomplete evacuation	4 (3.48)	24 (8.89)	11 (9.24)	2.708 (0.918- 7.989)	2.870 (0.947- 8.695)	2.827 (0.873- 9.151)	2.982 (0.894- 9.952)
Sensation of anorectal obstruction/blockage	3 (2.63)	12 (4.44)	16 (13.45)	1.721 (0.476- 6.218)	1.71 (0.45- 6.489)	5.748 (1.627- 20.302)	5.613 (1.502- 20.969)
Manual maneuver to facilitate defecation	1 (0.87)	3 (1.11)	9 (7.56)	1.276 (0.131- 12.4)	1.323 (0.125- 14.024)	9.327 (1.162- 74.854)	9.549 (1.068- 85.411)
Fewer than 3 defecations per week	7 (6.14)	26 (9.49)	16 (13.45)	1.603 (0.675- 3.805)	1.228 (0.499- 3.021)	2.374 (0.938- 6.009)	1.739 (0.66- 4.579)

*p < 0.05, OR was adjusted for age and sex, OR, odds ratio; CI, confidence interval

Figures

Figure 1

Summary of subject recruitment