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BRIEF ARTICLE

Diabetic factors associated with gastrointestinal symptoms in patients with type 2 diabetes

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Abstract

AIM: To determine whether gastrointestinal (GI) symptoms are more frequent in type 2 diabetic patients and to examine which diabetic factors are associated with the symptoms.

METHODS: Consecutive subjects with diabetes and age-/gender-matched normal controls were recruited for this study. GI symptoms were assessed using a structured questionnaire divided into two GI symptom categories (upper and lower GI symptoms), and consisting of 11 individual symptoms. In the diabetic patient group, diabetic complications including peripheral neuropathy, nephropathy and retinopathy, glycosylated hemoglobin (HbA1c) level and diabetes duration were evaluated.

RESULTS: Among the total 190 diabetic patients and 190 controls enrolled, 137 (72%) of the diabetic patients and 116 (62%) of the controls had GI symptoms. In the diabetic patient group, 83 (43%) had upper GI symptoms and 110 (58%) lower GI symptoms; in the control group, 59 (31%) had upper GI symptoms and 104 (55%) lower GI symptoms. This difference between the two groups was significant for only the upper GI symptoms (P = 0.02). Among the diabetic factors, the HbA1c level was the only independent risk factor for upper GI symptoms in the multiple logistic regression analysis (odds ratio = 2.01, 95% confidence interval: 1.02-3.95).

CONCLUSION: Type 2 diabetes was associated with an increased prevalence of upper GI symptoms and these symptoms appeared to be independently linked to poor glycemic control, as measured by the HbA1c levels.

Key words: Diabetes; HbA1c; Upper gastrointestinal symptoms

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INTRODUCTION

Diabetes mellitus (DM) is becoming increasingly common because of the epidemic of obesity and sedentary lifestyles in South Korea and worldwide[1-3]. The prevalence of gastrointestinal (GI) symptoms in diabetic patients has been investigated previously in several studies; however, the results are inconsistent due to the different ethnic groups and populations studied[4-9]. Diabetes-related GI motor dysfunction is common and affects the esophagus, stomach and the lower GI tract[10]. Many patients with diabetes have upper and lower GI symptoms. The complications involving the GI tract are now recognized to be an important cause of morbidity in patients with diabetes[11]. Although several pathogenic mechanisms may be involved in these GI symptoms, such as autonomic neuropathy, diabetic peripheral neuropathy, glucose imbalance, diabetic duration, and psychiatric disorders, there is substantial controversy about their etiology.

Therefore, the aim of this study was to determine the frequency of GI symptoms in type 2 diabetic patients and whether GI symptoms are more common in diabetic patients than normal controls. In addition, the diabetic factors associated with the GI symptoms were studied.

MATERIALS AND METHODS

Subjects

We performed a prospective study of a consecutive series of outpatients with type 2 diabetes who visited Konkuk University Medical Center from October 2005 to September 2007 for the first time. All patients were referred by an endocrinologist after a comprehensive evaluation at the endocrine center. These patients underwent screening with esophago-gastro-duodenoscopy (EGD) and colonoscopy (or sigmoidoscopy with fecal occult blood test) to rule out upper and lower GI organic disorders, such as a malignancy, peptic ulcer, or erosive esophagitis. The control subjects were carefully matched for age and gender, and were randomly selected from subjects who underwent a screening EGD and colonoscopy at the Health Promotion Center of Konkuk University Medical Center. The exclusion criteria were the presence of upper and lower GI organic disorders on the EGD; a history of upper and lower GI malignancy, peptic ulcer, major abdominal surgery, or underlying psychiatric illness; a medical history of taking a proton pump inhibitor within the last month; severe liver, lung, renal, or hematological disorders. Patients were also excluded if they were unwilling or unable to provide informed consent, or if they could not complete all phases of the study. Subjects provided written informed consent before enrollment, and the study protocol was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice, and was approved by the human ethics review board of Konkuk University Medical Center. After enrollment, each subject completed a structured questionnaire to precisely assess the GI symptoms, in the absence of organic, systemic or metabolic diseases; data on smoking and alcohol consumption (> 40 g/d) was included. In addition, for the diabetic patients, diabetic complications including peripheral neuropathy, nephropathy and retinopathy, glycosylated hemoglobin (HbA1c) level, the treatment of diabetes and the duration of diabetes were recorded.

Symptom assessment

The questionnaire contained questions regarding GI symptoms and consisted of two subgroups: an upper GI symptom group and a lower GI symptom group. The upper GI symptom group included six items (globus, heartburn, acid regurgitation, non-cardiac chest pain (NCCP), ulcer-like dyspepsia and dysmotility-like dyspepsia) and the lower GI symptom group included five items (irritable bowel syndrome, abdominal bloating, constipation, diarrhea and anal discomfort). A 'predominant upper GI symptoms' classification was defined as: more frequent and/or more severe upper GI symptoms than lower GI symptoms reported on the questionnaire, and assessed separately. A 'predominant lower GI symptoms' classification was defined in the same way. The questions were analyzed inclusive of all symptoms regardless of the severity or frequency of each item. An interview, using the structured questionnaire, was conducted by two investigators, who provided the patients with standard explanations of the questions and definitions of the symptoms. All symptoms that were not completely self-explanatory were explained by a standard description. The 11 items used for the GI symptoms were constructed to comply as closely as possible with the Rome Ⅱ criteria for functional GI disease[12].

Diabetic factors

In the diabetic patient group, diabetic complications were evaluated including peripheral neuropathy, nephropathy and retinopathy. In addition, the HbA1c level and duration of diabetes in each patient were evaluated. The diabetic complications were classified according to the following definitions: (1) Nephropathy was defined as prominent proteinuria on the urine analysis or a serum creatinine that exceeded 133 μmol/L; (2) Peripheral neuropathy was assessed by the recommended protocol of nerve conduction study (NCS), including six sensory nerves and six motor nerves[13]; and (3) Retinopathy was diagnosed based on fundoscopic examination by a skilled ophthalmologist. In addition, HbA1c level was measured using the high performance liquid chromatography method within 1 mo of the questionnaire study. Furthermore, treatment of diabetes included oral hypoglycemic agents and insulin.

Table 1 Baseline characteristics *n* (%)

	DM group (*n* = 190)	Control group (*n* = 190)	*P*-value
Age (mean ± SD, yr)	57.1 ± 12.5	57.0 ± 10.6	NS
M/F	86 (45)/104 (55)	86 (45)/104 (55)	NS
Smoking	52 (27)	61 (32)	NS
Alcohol use	51 (27)	78 (41)	NS

DM: Diabetes mellitus; NS: Not significant.

Statistical analysis

Statistical analysis was performed using the χ^2 test for comparison of discrete variables and the *t*-test was used for comparison of continuous variables. The continuous variables measured in this study are expressed as the mean ± SD. Multivariate analysis was performed using logistic regression. To examine the association between GI symptoms and type 2 diabetes, multivariate models included adjustment for smoking and alcohol as categorical factors. In the models used to examine the diabetic factors associated with upper GI symptoms, adjustments for smoking, alcohol, the treatment of diabetes, and other diabetic factors were included. For each variable, the odds ratio (OR) and 95% confidence interval (CI) were determined. A two tailed *P* value of < 0.05 was considered statistically significant.

RESULTS

Ten out of a total of 200 subjects with type 2 diabetes who were recruited for the study were excluded because they were unwilling or unable to provide informed consent, or could not complete all phases of the study. Finally, 190 subjects with type 2 diabetes and 190 controls were included in this study. The diabetic and normal subjects were well matched in terms of age and gender (86 men and 104 women with a mean age of 57 years). The clinical factors, including a history of current smoking and alcohol use are shown in Table 1.

The frequency of GI symptoms (any or several) was 72% in the diabetic subjects and 62% in the controls (*P* = NS). Among the upper GI symptoms and the lower GI symptoms, the multiple logistic regression analyses showed that the diabetic patients presented with a significantly higher frequency of upper GI symptoms than the controls (43% *vs* 31%, *P* < 0.05, OR = 1.68, 95% CI: 1.07-2.63); however, no differences were observed for the lower GI symptoms (Table 2). When the individual items of the upper GI symptoms were analyzed separately, globus, heartburn and dysmotility-like dyspepsia were more common in the diabetic patients than in the controls (Figure 1).

The demographic and diabetic characteristics according to the presence or absence of upper GI symptoms in the diabetic patient group are shown in Table 3. Subjects with upper GI symptoms tended to have more complications (66% *vs* 46%), a higher HbA1c level (8.06% *vs* 7.39%) and a longer duration of symptoms (10.4 years *vs* 6.5 years) than the upper GI symptom-negative group. On multiple logistic regression analyses, only the higher HbA1c level was significantly associated with smoking, alcohol, the treatment of diabetes, and other covariate factors by the adjusted OR for upper GI symptoms (OR = 2.01, 95% CI: 1.02-3.95) (Table 4).

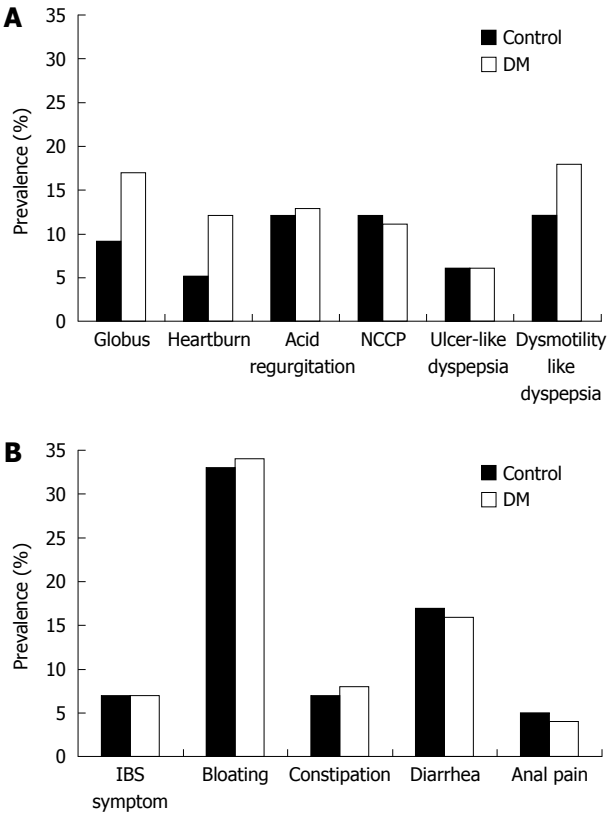

Figure 1 Differences in individual upper (A) and lower (B) gastrointestinal (GI) symptoms between diabetic patients and control groups. A: The diabetic patients had a higher frequency of globus, heartburn and dysmotility-like dyspepsia than the controls; B: There was no difference for any item of the lower GI symptoms between the two groups. DM: Diabetes mellitus; NCCP: Non-cardiac chest pain.

The relationship of the HbA1c level with upper GI symptoms was studied using the normal HbA1c group (HbA1c < 6%) as the reference standard. There was a significant increase in the prevalence of upper GI symptoms in subjects with an 8% ≤ HbA1c < 9% (OR = 3.38%, 95% CI: 1.06%-10.71%), in subjects with a HbA1c ≥ 9% (OR = 3.23%, 95% CI: 1.13%-9.24%) (Figure 2), and in subjects with HbA1c ≥ 8%. All individual upper GI symptoms including globus, heartburn, acid regurgitation, NCCP, ulcer-like dyspepsia and dysmotility-like dyspepsia were more common than in subjects with a HbA1c < 8% (Figure 3).

DISCUSSION

The prevalence of DM worldwide is estimated to be around 200 million people, more than 5% of the adult population, globally. The current high prevalence of type 2 diabetes is likely to eventually result in a heavy burden of diabetes complications; this will pose a significant

Table 2 Symptomatic characteristics *n* (%)

	DM group (*n* = 190)	Control group (*n* = 190)	Unadjusted		Adjusted[1]	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
GI symptom	136 (72)	118 (62)	1.54 (1.03-2.31)	0.020	1.45 (0.92-2.29)	0.110
UGI symptom	83 (43)	59 (31)	1.7 (1.15-2.50)	0.005	1.68 (1.07-2.63)	0.020
LGI symptom	110 (58)	105 (55)	1.11 (0.76-1.61)	0.340	1.1 (0.71-1.70)	0.680

[1]Adjusted for smoking and alcohol use. OR: Odds ratio; CI: Confidence interval; GI: Gastrointestinal; UGI: Upper GI; LGI: Lower GI.

Table 3 Characteristics according to the presence or absence of upper GI symptoms in the diabetic patient group *n* (%)

	UGI symptoms (+) (*n* = 83)	UGI symptoms (-) (*n* = 107)	Total (*n* = 190)
Age (mean ± SD, yr)	57.3 ± 13.1	57.1 ± 12.1	57.2 ± 12.5
M/F	34 (40)/52 (60)	52 (50)/52 (50)	86 (45)/104 (55)
Smoking	24 (29)	28 (26)	52 (27)
Alcohol use	19 (23)	32 (30)	51 (27)
Diabetic treatment	76 (92)	97 (91)	175 (91)
Complication	55 (66)	49 (46)	104 (55)
Peripheral neuropathy	49 (59)	44 (41)	93 (49)
Nephropathy	33 (40)	23 (22)	56 (30)
Retinopathy	32 (39)	16 (15)	48 (25)
HbA1c			
mean ± SD	8.06 ± 1.90	7.39 ± 1.94	7.68 ± 1.95
⩾ 8	38 (46)	26 (24)	64 (34)
Duration (yr)			
mean ± SD	10.4 ± 7.3	6.5 ± 5.9	8.2 ± 6.8
⩾ 10	44 (53)	35 (33)	79 (42)

Table 4 Diabetic factors associated with upper GI symptoms

	Unadjusted		Adjusted[1]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Complication	2.35 (1.27-4.33)	0.005	1.64 (0.81-3.32)	0.170
HbA1c level	2.63 (1.39-4.96)	0.003	2.01 (1.02-3.95)	0.040
Diabetes duration	1.67 (0.84-3.29)	0.006	1.67 (0.84-3.29)	0.140

[1]Adjusted for age, gender, smoking, alcohol use and other covariate factors.

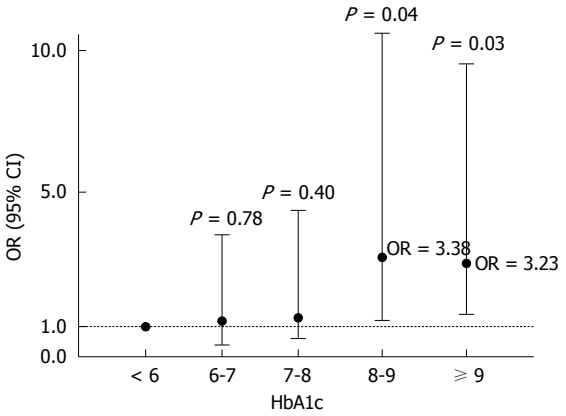

Figure 2 Differences in upper GI symptoms according to the HbA1c level. There was a significant increase in the prevalence of upper GI symptoms in subjects with 8% ⩽ HbA1c < 9% and in subjects with HbA1c ⩾ 9%; subjects with normal HbA1c (HbA1c < 6%) were used as the reference group. OR: Odds ratio.

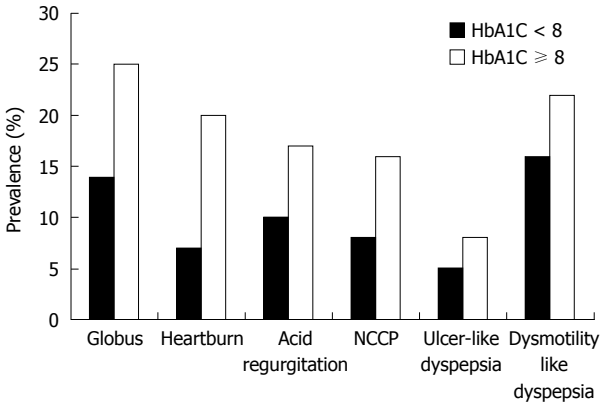

Figure 3 Differences in individual upper GI symptoms according to the HbA1c Level. In subjects with an HbA1c ⩾ 8%, all upper GI symptoms were more common than in subjects with an HbA1c < 8%.

challenge to individuals, communities and healthcare systems during the coming decades, worldwide[14].

Chronic GI symptoms may represent a clinically important problem in a substantial number of patients with diabetes[15]. There are several papers which report the association of GI symptoms with diabetes. Epidemiological data regarding the association of GI symptoms with diabetes are, however, inconsistent[6], and the reported frequency of upper and lower GI symptoms varies among different ethnic groups/populations, although population-based studies, in general, have demonstrated an increase in upper and lower GI symptoms[16]. Our present study is the first study in Korea to examine the GI symptoms in type 2 diabetic patients and to analyze the diabetic factors associated with these symptoms. We found that the frequency of overall GI symptoms, upper GI symptoms and lower GI symptoms in the 190 patients with diabetes studied was 72%, 43% and 58%, respectively. Comparison of the frequency of the overall GI symptoms, upper GI symptoms and lower GI symptoms between the diabetic patient group and the age- and gender-matched control group showed 1.45 times as many overall GI symptoms, 1.68 times as many upper GI symptoms and 1.10 times as many lower GI symptoms in individuals with diabetes. The risk of only upper GI symptoms in this group showed a statistically significant increase, with adjustments for age, gender, smoking and alcohol consumption.

The natural history and pathogenesis of GI symp-

toms in patients with diabetes remains poorly defined. Several pathogenic mechanisms such as autonomic neuropathy, diabetic peripheral neuropathy, glucose imbalance, diabetic treatment, diabetes duration, and psychiatric disorders may be involved in GI symptoms. Traditionally, GI symptoms in diabetic patients have been attributed to disordered motor function as a result of the irreversible autonomic neuropathy that frequently accompanies diabetes[17]. Also, the hypothesis that poor glycemic control by itself is a major cause of chronic GI symptoms has been raised recently, based primarily on data from large population studies[16,18,19] as well as small physiological studies[17,20-22]. Other factors that may be important in the etiology of GI symptoms in patients with diabetes include the duration of diabetes[23] and psychiatric comorbidity[24,25].

Systematically, we attempted to evaluate the relationship between upper GI symptoms and the various features of diabetes such as diabetic complications (including peripheral neuropathy, nephropathy and retinopathy), HbA1c level, the treatment of diabetes and the duration of diabetes. Among several diabetic factors, only the HbA1c level reflecting glycemic control was found to be significantly associated with the upper GI symptoms in the diabetic patients when the individual factors of diabetes were analyzed separately by multiple logistic regression analyses. Hyperglycemia has been shown to affect the perception of GI sensations[17,20-22,26] such as nausea and fullness, produced by distension of the proximal stomach or duodenum; such sensations are more intense during hyperglycemia than during euglycemia. Acute changes in the blood glucose concentration have also been shown to impair autonomic nerve function[27] and lower pain thresholds in patients with diabetes[28]; although there appear to be regional variations in the effects of the blood glucose concentration on both GI motility and the perception of sensations from the GI tract[21,29]. In addition, these effects have been reported to have less of an impact on lower GI symptoms, similar to the results of this study.

In our study, we focused on the association between upper GI symptoms and HbA1c levels. As a result, we found 3.38 times as many upper GI symptoms in the cases with HbA1c $\geq$ 8% compared to those with HbA1c < 6%; all individual upper GI symptoms were common in the cases with HbA1c $\geq$ 8%. This result is in agreement with the recommendation for a maintenance of HbA1c < 8% to prevent serious diabetic complications[30].

The limitations of this study include the following: only the presence or absence of individual GI symptoms, not the severity and/or frequency, was examined in the symptom assessment, regardless of the major symptoms. There were no data collected on coexisting psychiatric disorders associated with GI symptoms in patients with diabetes; this might be an important factor according to the recent reports by Quan *et al*[24,25]. Nevertheless, our present study is a case-control study with age- and sex-matched controls and is the first of its kind performed in Korea. In addition, this study has a large methodological advantage with regard to the well established subjective analysis for diabetic complications such as peripheral neuropathy, and not objective answers such as the 'yes' or 'no' of self-reports.

In conclusion, upper GI symptoms were more common in patients with type 2 diabetes than in well-matched control subjects. The results of this study provide evidence that upper GI symptoms appear to be independently linked to poor glycemic control as measured by HbA1c level. Therefore, we cautiously suggest that chronic upper GI symptoms may be reversible with tight control of blood glucose level.

COMMENTS

Background

Diabetes is known to be associated with gastrointestinal (GI) symptoms and several mechanisms have been implicated in the pathogenesis of GI symptoms. However, there is little information from Korea as well as few reports from Asia.

Research frontiers

Researchers have previously assessed the increase of the prevalence of GI symptoms in diabetic patients and the diabetic factors associated with the GI symptoms. However, results of the prevalence of GI symptoms in diabetic patients and the diabetic factors associated with these GI symptoms are inconsistent due to the different ethnic groups and populations assessed.

Innovations and breakthroughs

This study is a case-control study with age- and sex-matched controls and is the first study of its kind performed in Korea. In addition, this study has a methodological advantage with regard to the well established subjective analysis for diabetic complications such as peripheral neuropathy.

Applications

Upper GI symptoms were more common in patients with type 2 diabetes than in well-matched control subjects and appeared to be independently linked to poor glycemic control as measured by the HbA1c levels in Korean individuals. Therefore, chronic upper GI symptoms may be reversible with tight control of blood glucose level.

Peer review

This is a purely observational, prospectively planned study. Prevalence of GI symptoms in diabetic patients and non-diabetic healthy subjects has been widely studied and well documented. The fact that poor glycemic control is associated with increased frequency of upper and lower GI tract symptoms also has been well established. On the other hand, this topic still may be interesting to readers since the study focused on different ethnic groups.

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