

Disturbed gastric motility in patients with long-standing diabetes mellitus

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Abstract

Purpose: Gastric dysmotility has been reported in patients with long-standing diabetes mellitus (DM). Some patients with DM are diagnosed as diabetes gastroparesis and have several upper gastrointestinal (GI) symptoms such as appetite loss and abdominal pain. This study aimed to identify the relationship between gastric motility and upper GI symptoms in patients with long-standing DM. **Method:** This study was conducted among 23 patients with DM and 15 healthy controls. All the patients with DM were receiving insulin treatment and had at least one history of incidence of diabetic nephropathy, retinopathy or neuropathy. Gastric motility was evaluated using electrogastrography (EGG) and gastric emptying using the ¹³C-acetic acid breath test. The most severe upper gastrointestinal symptoms were assessed in all patients. **Results:** Compared to healthy controls, patients with long-standing DM showed a significantly lower percentage of normogastria at the postprandial state with a lower power ratio in EGG. Gastric emptying was significantly delayed in patients with DM in the overall analysis. Sixteen patients with DM (69.6%) demonstrated abnormalities in either gastric myoelectrical activity or gastric emptying. Among patients with abnormal EGG or delayed gastric emptying, 12 had some GI symptoms, compared with 3 patients with normal gastric motility. No significant correlation was observed between the gastric emptying parameters and HbA1c values. **Conclusion:** Patients with long-standing DM showed gastric dysmotility, including impaired gastric myoelectrical activity and delayed gastric emptying. Gastric dysmotility appears to be closely correlated with upper GI symptoms in patients with long-standing DM.

Key words: gastric myoelectrical activity, gastric emptying, electrogastrography, diabetes mellitus, gastrointestinal symptoms

Introduction

Many upper gastrointestinal (GI) symptoms, such as appetite loss, nausea, vomiting, epigastric pain, and postprandial fullness, are common in patients with diabetes mellitus (DM). It is likely that various factors may contribute to these symptoms, however, the underlying mechanisms have not yet been elucidated. Impaired gastric motor function including delayed gastric emptying has been reported in patients with DM (1–7). Gastric dysmotility is thought to be an important pathogenesis of symptom generation and probably influences glycemic control in patients with DM. In Western countries, some DM patients with delayed gastric emptying are diagnosed with diabetic gastroparesis (GP). However, the concept of GP is not well understood in Japan.

In this study, to investigate gastric motility in patients with long-standing DM, we simultaneously measured gastric myoelectrical activity using cutaneously recorded electrogastrography (EGG) and gastric emptying with the ^{13}C -acetic acid breath test. We then examined the relationship between these gastric motility parameters and upper GI symptoms.

Subjects and Methods

Subjects

This study was conducted between 2007 and 2010. The subjects of this study were 23 patients with long-standing type 2 DM. Patients data were compared to those of a control group, which comprised 15 asymptomatic, age and sex matched healthy volunteers with no history of DM and GI disease. Data of 12 control subjects were used in a previous study (8). The duration of DM were all more than 10 years and ranged from 13 to 39 years. All patients with DM were receiving insulin treatment and had at least one history of the incidence of diabetic nephropathy, neuropathy, or retinopathy (Table 1). The patients who were undergoing maintenance hemodialysis were excluded from this study. Informed consent was obtained from all subjects prior to the study, in accordance with the Declaration of Helsinki (1991), and the experimental procedure was approved by the ethics review committee of the Faculty of Medicine, Nagoya City University.

Experimental procedure

Gastric motility was evaluated from cutaneously recorded EGGs and by measurement of gastric emptying using ^{13}C -acetic acid breath tests. After fasting for at least 6 h, the EGG was recorded for 60 min in the supine position. The subjects then ingested 100 mg of ^{13}C -acetic acid in the sitting position, mixed with a semi-solid test meal (Jerry Ace; 200 ml of jerry, containing 4.4 g of protein, 0.4 g of fat, 42.0 g of carbohydrate, and an energy content of 190 kcal; House Foods, Osaka, Japan). Immediately after consuming the test meal, the subjects returned to the supine position and EGG recording was continued for another 60 min.

Table 1. Clinical characteristics of the control subjects and patients with diabetes mellitus

	Controls (n=15)	DM Patients (n=23)
Age (years)	57.4 ± 18.6	63.8 ± 15.5
Sex (M/F)	9/6	13/10
Treatment length		13–34 years (average 16.7 years)

Data values are presented as mean ± SD. DM: diabetes mellitus.

Recording and analysis of EGG

This methodology has been previously published elsewhere (8–10). In brief, the EGG was measured using a portable EGG recorder (Digitrapper EGG; Synectics Medical, Stockholm, Sweden). Bipolar Ag-AgCl electrodes were placed on the right and left midclavicular lines along the long axis of the stomach over the surface of the upper abdomen. The EGG data obtained were digitalized using an analog-to-digital converter installed on the recorder.

The following parameters were calculated using fast Fourier transform and evaluated for each subject.

1. Percentage of normogastria: defined as the percentage of time during which normal 2–4 cycles per minute (cpm) slow waves were present over the entire observation period. This parameter reflects the regularity of gastric myoelectrical activity.

2. The power ratio is defined as the ratio of the EGG dominant power values both after and before meal intake (i.e., postprandial power/fasting power), where the dominant power refers to the power at the EGG dominant frequency.

Based on control values, an abnormal EGG was defined greater than 2SD from the mean for at least one of the parameters, either before or after the test meal.

Measurement of gastric emptying

Breath samples were collected in polyethylene storage bags before the test meal as a baseline, then at 15-min intervals during the first hour following the test meal, followed by samples taken every 30 min during the remaining 3 h. The amount of ^{13}C in the breath storage bags was measured using infrared isotope spectrometry (UBiT-IR300; Otsuka Electronics, Osaka, Japan). Half-emptying time ($T_{1/2}$) and maximum excretion time (T_{max}) were calculated as described by Ghoo et al. (11). $T_{1/2}$ is defined as the area under the fitted curve until half of the cumulative ^{13}C excretion is excreted where time is infinite, and T_{max} is the time corresponding to the maximum ^{13}C excretion of the fitted curve. These two parameters were used to assess the degree of gastric emptying. The criterion for abnormal gastric emptying was defined to be greater or lesser than 2SD from the mean of $T_{1/2}$ or T_{max} in 15 control subjects. Furthermore, the correlation between gastric emptying parameters and the subjects HbA1c value was determined on the day that the gastric emptying measurement was performed.

Assessment of GI symptoms

All patients were asked whether they had upper abdominal symptoms on the day that gastric motility measurements were made. If they answered yes, they were required to choose the most bothersome symptoms from five symptoms of nausea, vomiting, appetite loss, epigastric pain, and postprandial fullness to assess subjective upper GI symptoms.

Statistical analysis

Values of EGG and ^{13}C -acetic acid breath test parameters are expressed as the mean \pm SD. The Student's *t*-test (unpaired) was used as appropriate. The relationship between upper GI symptoms and gastric motility parameters was analyzed using Fisher's exact test. Statistical significance was set at a $P < 0.05$.

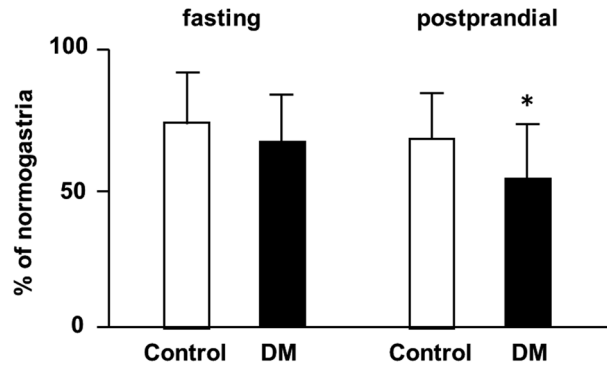


Fig. 1. Percentage of normogastric activity in the electrogastragram for control subjects (open bars) and patients with diabetes mellitus (DM; solid bars) in both fasting and postprandial states. Data values are presented as mean \pm SD. DM: diabetes mellitus; * $P < 0.05$ vs. control. Control: $n = 15$, DM: $n = 23$.

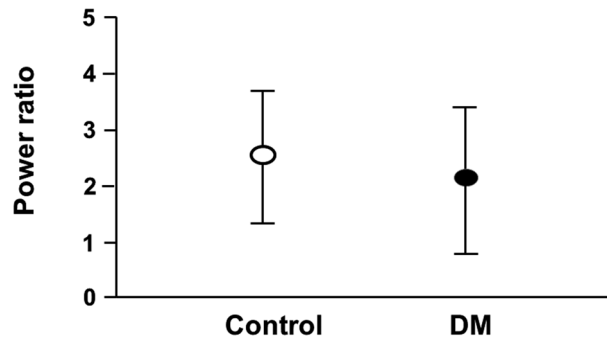


Fig. 2. Power ratio in the electrogastragram for control subjects (open circle) and patients with diabetes mellitus (DM; solid circle). Data values are presented as mean \pm SD. DM: diabetes mellitus. Control: $n = 15$, DM: $n = 23$.

Results

Electrogastrography and gastric emptying

The percentage of normal 2- to 4-cpm slow waves in the postprandial state was significantly lower in patients with DM than that in the controls (Fig. 1). There was no significant difference in EGG power ratio between controls and patients with DM (Fig. 2). Both $T_{1/2}$ and T_{max} in patients with DM were longer than those in controls, indicating that gastric emptying in the former was delayed compared with that in the controls in the overall analysis (Fig. 3). However, some patients with DM showed accelerated gastric emptying based on the results of individual data (Fig. 4). Sixteen patients (69.6%) showed abnormalities in either gastric myoelectrical activity or in gastric emptying.

We separated the patients into the following two subgroups according to the gastric motility results:

Group A, with normal EGG and normal gastric emptying (7 patients).

Group B, with abnormal EGG and/or delayed gastric emptying (16 patients).

GI symptoms

Fifteen patients (65.2%) had GI symptoms such as appetite loss, nausea and epigastric pain, while eight patients (34.8%) had no symptoms. Of the most bothersome GI symptoms among these 15 patients, the two most common were appetite loss and postprandial fullness reported by 4 patients in each case (Table 2). Five

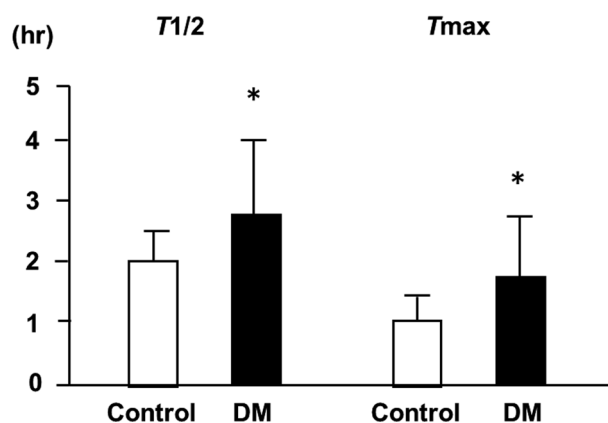


Fig. 3. Gastric emptying, expressed as half-emptying time ($T_{1/2}$) and lag time (T_{max}), in ^{13}C -acetic acid breath test for control subjects (open bars) and patients with diabetes mellitus (DM; solid bars). Data values are presented as mean \pm SD. * $P < 0.05$ vs. control; DM: diabetes mellitus. Control: $n=15$, DM: $n=23$.

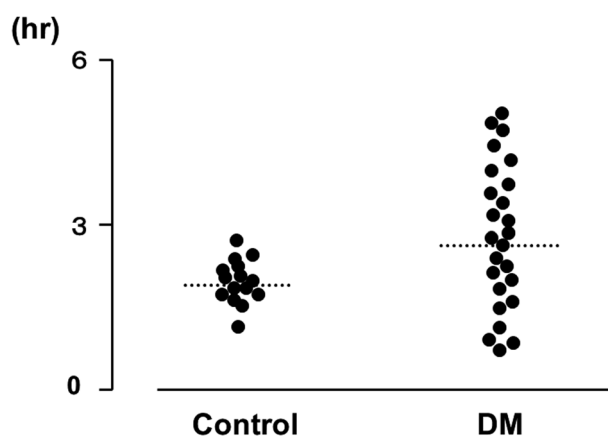


Fig. 4. Individual values of half-emptying time from ^{13}C -acetic acid breath tests in both control subjects and patients with diabetes mellitus. DM: diabetes mellitus. Control: $n=15$, DM: $n=23$.

Table 2. Number of the most bothersome upper gastrointestinal symptoms of patients with DM

Appetite loss	4
Postprandial fullness	4
Nausea	3
Upper abdominal pain	3
Vomiting	1

DM: diabetes mellitus.

patients with normal gastric motility showed no GI symptoms, whereas 12 patients with GI symptoms demonstrated impaired gastric motility demonstrated as either abnormal EGG or delayed gastric emptying ($P=0.066$) (Table 3).

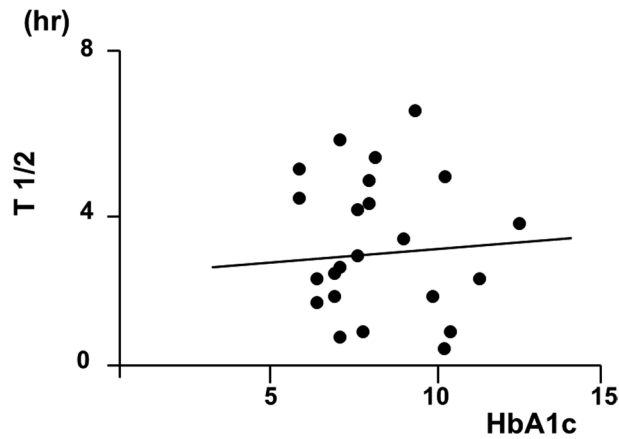
HbA1c

No significant correlation was observed between the gastric-emptying parameters and HbA1c values (Fig. 5).

Table 3. Relationship between gastric motility and upper gastrointestinal symptoms in patients with DM

	Group A: Normal gastric motility (n=7)	Group B: Abnormal EGG or delayed GE (n=16)	<i>P</i> value
Upper GI symptoms (+)	2	12	0.066
Upper GI symptoms (-)	5	4	

GI: gastrointestinal; EGG: electrogastrogram; GE: gastric emptying; DM: diabetes mellitus.

**Fig. 5.** Correlation between the value of HbA1c and the half-emptying time from ^{13}C -acetic acid breath tests in patients with DM. DM: diabetes mellitus.

Discussion

The findings of this study were as follows: 1) Patients with long-standing DM showed a significantly lower percentage of normogastria in the postprandial state with a lower power ratio in EGG, 2) Gastric emptying was significantly delayed in patients with DM in the overall analysis, 3) Sixteen patients with DM (69.6%) demonstrated abnormalities of either gastric myoelectrical activity or gastric emptying, 4) The number of patients who had some GI symptoms was 13 in those with abnormal EGG or delayed gastric emptying versus 2 in those with normal gastric motility, and 5) No significant correlation was observed between gastric-emptying parameters and HbA1c values.

We simultaneously measured EGGs and gastric emptying to assess gastric motility. Gastric myoelectrical activity is an essential trigger for gastric movement, and measurements using the EGG provides a noninvasive method for recording gastric myoelectrical activity (12). Changes in dominant power appear to reflect gastric contraction (13–16).

Our previous study demonstrated a significant correlation between certain EGG parameters and the results of the ^{13}C -acetic acid gastric emptying test (8). Chen et al. showed that postprandial gastric dysrhythmia and abnormality in the postprandial EGG power predict delayed gastric emptying with an accuracy of more than 70% (15). Other studies have shown that reduced slow-wave activity appears to be associated with antral hypomotility and delayed gastric emptying (16, 17). Furthermore, EGG provides information on both fasting and postprandial gastric motility. Therefore, simultaneous recording of both EGG and gastric emptying is a very useful method for evaluating gastric motor function.

Several studies measuring gastric myoelectrical activity in patients with DM have shown that gastric dysrhythmias, including tachygastria and bradygastria, occur in a high proportion of patients with DM and

that the percentage with a dominant frequency in the normal range was significantly lower than that in healthy controls (6, 18–22). In addition, many studies have evaluated gastric emptying in patients with DM. In most of these studies, gastric emptying was delayed. These reports support our results. Only a few studies measured EGG and gastric emptying simultaneously. El-Salhy et al. reported that patients with DM showed delayed gastric emptying, whereas gastric dysrhythmias in patients with DM did not differ from those in controls (23). There is a minor difference in the finding of EGG between their report and our results. This discrepancy may be due to differences in the patients' conditions (i.e., type 1 DM or type 2 DM, duration of disease, etc.).

The mechanism by which DM induces gastric hypomotility is probably multifactorial. Gastric motor function, including gastric emptying, requires interactions between the interstitial cells of Cajal (ICC), which are specialized pacemaker cells, enteric and extrinsic autonomic nerves, and smooth muscle cells (24–26). Possible factors causing disturbed gastric motility in diabetes are autonomic neuropathy, abnormality of the ICC, enteric neuropathy, and incretin-based medication used to normalize blood glucose levels (25, 27). Although we did not assess the severity of neuropathy in patients with DM of this study, all patients in this study had a long duration of DM, and most of them may have either an autonomic or enteric neuropathy. Neuropathy of both autonomic and enteric nerves may play an important role in impaired gastric motility in these patients with DM.

In this study, gastric emptying was significantly delayed in patients with DM in the overall analysis. In general, it is thought that delayed gastric emptying is associated with poor blood glucose control in patients with DM, especially in those with diabetic gastroparesis. However, gastric emptying was faster in some patients with DM than in controls. Recently, it has become clear that rapid gastric emptying is a frequent and important diabetic complication. Watson et al. reported that gastric emptying was faster in patients with type 2 diabetes than in age- and BMI-matched subjects without diabetes (28, 29). Additionally, rapid gastric emptying of liquids has been associated with type 2 DM, particularly in the early stages of the disease, which may persist even in the late stage. In rats with mild diabetes, gastric emptying was faster after treatment with streptozotocin when compared with control animals (30). Acute hyperglycemia might be thought to cause rapid gastric emptying by stimulating the gastric excitatory vagal motor circuit (26). However, all patients in our study were in the late stages of DM. The relationship between rapid gastric emptying, normal gastric emptying, and blood glucose control is not clear. Further studies are needed to clarify the role of both rapid and normal gastric emptying in the pathophysiology, including blood glucose control, of DM.

The important finding of this study is that patients with long-standing DM have shown impaired gastric motility compared with healthy controls, displaying upper abdominal symptoms such as appetite loss, nausea and epigastric pain. We found that abnormal gastric myoelectrical activity or delayed gastric emptying in patients with DM tended to be associated with GI symptoms, although these did not reach statistical significance. Previous studies have shown that combining EGG and gastric-emptying data is useful when correlating symptoms with gastric motility in patients with functional dyspepsia (8, 15, 31, 32). These data suggest that impaired gastric motility is an important factor in upper GI symptom generation.

Some patients with delayed gastric emptying are considered to have GP. GP is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach (33–36). The main etiology of GP is DM, accounting for almost one-third of GP cases, and another one-third is idiopathic (37, 38). The main clinical symptoms of GP include nausea, vomiting, epigastric pain and postprandial fullness. The prevalence of diabetic GP was estimated to be 5% in type 1 DM and 1% in type 2 DM in a US community (39). GP is a relatively common disease in Western countries, whereas in Japan, GP has received little attention, and there is little data on gastric emptying in DM. The reason why GP can be challenging to diagnose in Japan

might be due to the lack of necessary instrumentation. It is difficult to perform both EGG and ^{13}C breath test in Japanese clinical settings. At least, gastric emptying tests, including the ^{13}C breath test, are desirable in Japan.

There was no significant correlation between gastric-emptying parameters and HbA1c values. HbA1c reflects the mean blood glucose levels within the previous three months, whereas all patients in this study had DM for more than 10 years. Therefore, it is not surprising that gastric motility in patients with long-standing DM is not always related to glucose levels 1–2 months before the test.

In conclusion, patients with long-standing DM showed gastric dysmotility, including impaired gastric myoelectrical activity and delayed gastric emptying. Gastric dysmotility appears to be closely correlated with upper GI symptoms in patients with long-standing DM.

Conflict of Interest

There is no conflict of interest to declare on this manuscript.

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