

# Gastrointestinal hormone abnormalities and G and D cells in functional dyspepsia patients with gastric dysmotility

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## Abstract

**AIM:** To investigate the relationship between gastric dysmotility, gastrointestinal hormone abnormalities, and neuroendocrine cells in gastrointestinal mucosa in patients with functional dyspepsia (FD).

**METHODS:** Gastric emptying was assessed with solid radiopaque markers in 54 FD patients, and the patients were divided into two groups according to the results, one with delayed gastric emptying and the other with normal gastric emptying. Seventeen healthy volunteers acted as normal controls. Fasting and postprandial plasma levels and gastroduodenal mucosal levels of gastrointestinal hormones gastrin, somatostatin (SS) and neurotensin (NT) were measured by radioimmunoassay in all the subjects. G cells (gastrin-producing cells) and D cells (SS-producing cells) in gastric antral mucosa were immunostained with rabbit anti-gastrin polyclonal antibody and rabbit anti-SS polyclonal antibody, respectively, and analyzed quantitatively by computerized image analysis.

**RESULTS:** The postprandial plasma gastrin levels, the fasting and postprandial plasma levels and the gastric and duodenal mucosal levels of NT were significantly higher in the FD patients with delayed gastric emptying than in those with normal gastric emptying and normal controls. The number and gray value of G and D cells and the G cell/D cell number ratio did not differ significantly between normal controls and the FD patients with or without delayed gastric emptying.

**CONCLUSION:** Our findings suggest that the abnormalities of gastrin and NT may play a role in the pathophysiology of gastric dysmotility in FD patients, and the abnormality of postprandial plasma gastrin levels in FD patients with delayed gastric emptying is not related to the changes both in the number and gray value of G cells and in the G cell/D cell number ratio in gastric antral mucosa.

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**Key words:** Functional dyspepsia; Gastric emptying; Gastrointestinal hormone abnormalities; G cells; D cells

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## INTRODUCTION

Functional dyspepsia (FD) is a very common condition. The typical syndrome refers to various chronic symptoms, including upper abdominal bloating or pain, feeling of prolonged digestion, nausea, vomiting, and early satiety in the absence of organic disease<sup>[1]</sup>. The pathogenesis of FD is multifactorial<sup>[2-4]</sup>. There is evidence that gastric dysmotility plays a role in the pathogenesis of FD<sup>[5-7]</sup>. Gastrointestinal hormones are important factors affecting gastric motility<sup>[8,9]</sup>. Several gastrointestinal hormones, such as gastrin, somatostatin (SS) and neurotensin (NT) can inhibit gastric motility<sup>[10-12]</sup>, increased levels of these gastrointestinal hormones can result in gastric dysmotility. The most common type of gastric dysmotility in FD patients is delayed gastric emptying.

In the present study, we assessed gastric emptying using solid radiopaque markers, measured the fasting and postprandial plasma levels, gastric and duodenal mucosal levels of gastrin, SS and NT by radioimmunoassay, and immunostained gastrin-producing cells (G cells) and SS-producing cells (D cells) in gastric antral mucosa with rabbit anti-gastrin polyclonal antibody and rabbit anti-SS polyclonal antibody respectively, and then analyzed quantitatively the two kinds of cells by computerized image analysis. The aim of the study was to assess the relationship between the gastrin, SS, NT levels, the morphology of G and D cells, and delayed gastric emptying in FD patients, thus having a better understanding of the mechanism of delayed gastric emptying in FD.

## MATERIALS AND METHODS

### Materials

Seventeen healthy volunteers without any gastrointestinal symptoms [6 men and 11 women: aged 18-58 (mean, 34±10) years], and 54 FD patients who attended the Outpatient Department of Nanfang Hospital of the First Military Medical University [25 men and 29 women: aged 18-63 (mean, 40±16) years], were studied. The diagnosis of FD was based on the Rome II criteria<sup>[1]</sup>. Patients who had predominant symptoms of gastroesophageal reflux (defined as heartburn or acid regurgitation) or a history of peptic ulcer disease or gastrointestinal surgery were excluded. None of the 71 subjects had taken the medication within the last 7 d. Gastric emptying in the patients was assessed with solid radiopaque markers, and then the patients were divided into two groups according to the results, one (FDD group) with delayed gastric emptying [12 men and 17 women: aged 18-63 (mean, 42±17) years] and the other (FDN group) with normal gastric emptying [13 men and 12 women: aged 20-59 (mean, 38±14) years]. Written informed consent was obtained from all subjects.

### Methods

**Gastric emptying study** All experiments were performed at 8 AM after an overnight fast. All subjects received a test meal consisting of 90 g of instant noodles, 20 g of peanuts, 50 g of sausages, 400 mL of water (14 g of fat, 18 g of protein, 67 g of carbohydrate, 466 kcal). The test meal was ingested within 15 min,

and 20 solid radiopaque markers (1 cm in length and 1 mm in diameter) were administered in combination with the test meal (Medical Institute of Beijing Aerospace Aviation, Beijing). The subjects stayed without smoking or taking any food or water within 5 h after the test meal, and stood upright for counting the remaining solid radiopaque markers in the stomach using fluoroscopy 5 h after the test meal. All subjects were given 20 mL of 40% barium to show the stomach contour so as to make clear if the solid radiopaque markers were in the stomach. Gastric emptying rate 5 h after the test meal was calculated according to the following equation: gastric emptying rate = (20 - the number of the solid radiopaque markers in the stomach)/20 × 100%. Gastric emptying rate 5 h after the test meal <50% was considered to be abnormal.

**Extract and assay of gastrointestinal hormones from plasma and gastric and duodenal mucosa** Blood samples (4 mL) were drawn from the antecubital vein just before and 30 min after the test meal. The blood samples were collected into chilled tubes containing ethylene diamine tetraacetic acid (EDTA) (1.5 mg/mL) and aprotinin (Trasylol 125 KIU/mL, Libao Biochemical Medical Co., Zhuhai). The samples were centrifuged (3 000 r/min at 4 °C for 10 min), and the plasma was decanted and stored at -70 °C for subsequent radioimmunoassay. Three pieces of gastric antral mucosa and 3 pieces of mucosa of descending portion of duodenum were collected during upper gastrointestinal endoscopy. All the specimens were processed respectively as following. The specimens were weighed and boiled with distilled water, then homogenized with 0.5 mL of 1N acetic acid and centrifuged (3 000 r/min at 4 °C for 10 min). The mucosal homogenates were neutralized with 0.5 mL of 1N NaOH. The resultant supernatants were decanted and stored frozen at -70 °C for subsequent radioimmunoassay. The gastrin, SS, and NT levels in plasma and resultant supernatants of mucosal homogenates were measured by specific and sensitive radioimmunoassay previously described<sup>[13-15]</sup>. The levels of gastrointestinal hormones in the gastric and duodenal mucosa were expressed as picogram per gram wet weight (pg/g ww) for immunoreactive (ir)-SS and NT or nanogram per gram wet weight (ng/g ww) for ir-gastrin.

**Immunostaining and morphometric analysis of G and D cells in gastric mucosa** A piece of gastric antral mucosa was collected during upper gastrointestinal endoscopy, and made into a paraffin block. In each subject, two adjacent tissue sections were prepared. One was for immunostaining of G cells, the other for D cells. Rabbit anti-gastrin polyclonal antibody, rabbit anti-somatostatin polyclonal antibody, and streptavidin-biotin-enzyme complex (SABC) kit were used for immunostaining of G and D cells. Briefly, the sections were deparaffined, rehydrated through a graded series of ethanol, and heated in 0.01 mol/L sodium citrate for 15 min using a microwave oven. The two primary antibodies were used at a dilution of 1:50. The sections were incubated overnight at 4 °C, and then biotinylated anti-rabbit immunoglobulin and streptavidin conjugated to horseradish peroxidase were applied to them. 3,3'-diaminobenzidine was used for color development, and hematoxylin was employed for counterstaining. Under magnification of 400, 5 cyclograms selected randomly in each section was analysed by an image system. The number and gray value of G cells or D cells in the five cyclograms were counted and averaged, the G cell/D cell number ratio in two adjacent sections was calculated.

### Statistical analysis

Data were expressed as mean ± SD. Statistical significance between the groups was analyzed by one-way ANOVA test for the gastrin, SS, and NT levels, the number and gray value of G and D cells, and the G cell/D cell number ratio. Paired *t* test was

used in the comparison of fasting plasma data and postprandial plasma data. *P* < 0.05 was considered statistically significant.

## RESULTS

### Gastric emptying

Twenty-nine of 54 FD patients (53.70%) had delayed gastric emptying. The mean number of the solid radiopaque markers in the stomach 5 h after the test meal in the FDD group was 15.28 ± 6.76, and those in the FDN group and the normal control group were 6.56 ± 3.94 and 5.47 ± 4.26, respectively, which was significantly higher in the FDD group than in the normal control group (*P* < 0.01), and there was no significant difference between the two groups.

### Gastrointestinal hormones

The postprandial plasma gastrin level in the FDD group was significantly higher than those in the normal control group and FDN group. No differences were noted in the gastrin levels of fasting plasma and gastric and duodenal mucosae among the three groups. The gastrin levels in fasting and postprandial plasma and gastric and duodenal mucosa were not different in the FDN group and normal control group. The postprandial increments of the plasma gastrin levels were similar in the three groups. The mucosal gastrin levels in descending duodenum were significantly higher than those in gastric antrum in the three groups (Table 1).

**Table 1** Comparison of gastrin levels in fasting and postprandial plasma and mucosa of gastric antrum and duodenum in FD patients and normal controls (mean ± SD)

Group	n	Plasma (pg/mL)		Mucosa (ng/g ww)	
		Fasting	Postprandial	Gastric antrum	Duodenum
FDD	29	33.64 ± 6.71	50.24 ± 10.62 <sup>d</sup>	11.23 ± 2.34	5.31 ± 1.04 <sup>e</sup>
FDN	25	36.61 ± 7.84	42.76 ± 8.64 <sup>a,c</sup>	9.97 ± 3.12	4.97 ± 0.96 <sup>e</sup>
Normal controls	17	32.93 ± 8.01	39.17 ± 9.55 <sup>b,c</sup>	0.13 ± 2.86	4.89 ± 1.23 <sup>e</sup>

FDD: FD patients with delayed gastric emptying FDN: FD patients with normal gastric emptying <sup>a</sup>*P* < 0.05 vs FDD, <sup>b</sup>*P* < 0.01 vs FDD, <sup>c</sup>*P* < 0.05 vs fasting plasma, <sup>d</sup>*P* < 0.01 vs fasting plasma <sup>e</sup>*P* < 0.01 vs gastric antral mucosa.

The SS levels in fasting and postprandial plasma and gastrointestinal mucosa were not different in the three groups. The postprandial increments of plasma SS levels were similar in the three groups. The mucosal SS levels in descending duodenum were significantly lower than those in the gastric antrum in the three groups (Table 2).

**Table 2** Comparison of SS levels in fasting and postprandial plasma and mucosa of gastric antrum and duodenum in FD patients and normal controls (mean ± SD)

Group	n	Plasma (pg/mL)		Mucosa (pg/g ww)	
		Fasting	Postprandial	Gastric antrum	Duodenum
FDD	29	26.71 ± 8.47	37.21 ± 11.89 <sup>b</sup>	372.24 ± 88.27	158.66 ± 40.61 <sup>d</sup>
FDN	25	23.67 ± 7.41	35.45 ± 13.19 <sup>b</sup>	353.16 ± 106.14	143.94 ± 38.47 <sup>d</sup>
Normal controls	17	24.16 ± 9.75	39.92 ± 13.04 <sup>b</sup>	336.88 ± 116.24	150.76 ± 35.29 <sup>d</sup>

<sup>b</sup>*P* < 0.01 vs fasting plasma, <sup>d</sup>*P* < 0.01 vs gastric antral mucosa.

The NT levels in the fasting and postprandial plasma and

gastrointestinal mucosa were significantly higher in the FDD group than those in the other two groups, and there were no differences between the FDN group and the normal control group. The FDD group and FDN group had significantly greater postprandial increments of the plasma NT levels compared with the normal control group (Table 3).

**Table 3** Comparison of NT levels in fasting and postprandial plasma and mucosa of gastric antrum and duodenum in FD patients and normal controls (mean±SD)

Group	n	Plasma (pg/mL)		Mucosa (pg/g ww)	
		Fasting	Postprandial	Gastric antrum	Guodenum
FDD	29	58.41±23.49	70.82±27.3 <sup>c</sup>	196.94±66.67	217.93±61.28
FDN	25	43.52±16.21 <sup>b</sup>	56.68±19.72 <sup>a,c</sup>	150.77±53.34 <sup>a</sup>	139.21±46.65 <sup>b</sup>
Normal controls	17	45.47±14.65 <sup>a</sup>	54.29±20.37 <sup>a</sup>	141.81±47.53 <sup>b</sup>	162.39±54.52 <sup>b</sup>

<sup>a</sup>P<0.05 *vs* FDD, <sup>b</sup>P<0.01 *vs* FDD, <sup>c</sup>P<0.05 *vs* fasting plasma.

### G and D cells

G cells of the gastric antrum were mainly distributed in the lower 2/3 mucosa and rarely in the upper 1/3 mucosa. G cells appeared to be round, elliptical, triangular or irregular in shape. A few G cells had slender processes with small bulbous expanded endings stretching to the neighboring cells. Occasionally, the apex of G cells could even reach the glandular lumens. D cells of gastric antrum were mainly located in the lower 1/3 mucosa and rarely in the upper 2/3 mucosa. Appearance of D cells was similar to that of G cells. The number and gray value of G and D cells, and the G cell/D cell number ratio were not significantly different in the three groups (Table 4).

**Table 4** Comparison of the number of G and D cells, gray value, and the G cell/D cell number ratios in FD patients and normal controls (mean±SD)

Group	n	G cells		D cells		G cell/D cell number ratio
		Number	Gray value	Number	Gray value	
FDD	29	81.05±8.12	58.46±5.74	42.38±4.13	94.16±8.96	2.14±0.33
FDN	25	77.74±7.04	60.65±4.83	40.02±5.36	92.27±8.34	2.23±0.25
Normal controls	17	83.16±6.57	61.37±5.26	39.28±4.99	96.39±9.65	2.08±0.22

## DISCUSSION

The pathogenesis of FD is not clearly defined. Gastrointestinal motor abnormalities, altered visceral sensation, and psychosocial factors have all been identified as major pathogenic factors<sup>[2,16]</sup>. There is evidence that gastric dysmotility plays a role in the occurrence of FD. In early studies, about 40-60% of FD patients had delayed gastric emptying<sup>[17-19]</sup>. The present study showed that 29 of 54 FD patients (53.70%) had delayed gastric emptying. The finding further proves that gastric dysmotility is one of the pathogenic factors of FD. We observed 46.30% of FD patients had normal gastric emptying in the study, suggesting the pathogenesis of these patients is not related to delayed gastric emptying but to some other factors.

Our study showed that the postprandial plasma gastrin level and the NT levels in fasting and postprandial plasma and gastric and duodenal mucosa were significantly higher in FD patients with delayed gastric emptying than in the FD patients with normal gastric emptying and normal controls. The effects of gastrin on gastric motility are complicated, including slowing down gastric emptying, stimulating the contraction of gastric

antrum, and enhancing the grinding function of stomach<sup>[10,20,21]</sup>. NT can inhibit gastrointestinal motility and prolong gastric emptying<sup>[11,22,23]</sup>. N cells, NT-producing cells, mainly locate in ileal mucosa. In patients undergoing ileal resection, the plasma NT levels decrease due to the reduction of N cells, resulting in accelerated liquid gastric emptying. Our findings indicate that delayed gastric emptying in FD patients is related to the abnormal levels of gastrin and NT, and the elevated postprandial plasma gastrin and NT levels in fasting and postprandial plasma and gastric and duodenal mucosae might be part of the reasons for delayed gastric emptying in FD patients. It is impossible that the raised postprandial gastrin levels in the FD patients with delayed emptying are due to antral stimulation by the retained food, because antral stimulation was present in all the FD patients and normal controls 30 min after the test meal.

The present study showed that the gastrin and SS levels in gastric antral mucosa were higher than those in mucosa of descending portion of duodenum both in patients and in normal controls, suggesting that G and D cells are denser in the gastric antral mucosa than in mucosa of descending duodenum. In the study, the plasma gastrin, SS, and NT levels increased after ingestion of the test meal both in patients and in normal controls, indicating that food can stimulate the secretion of these gastrointestinal hormones. The gastrin, SS, and NT levels in plasma and gastric and duodenal mucosa did not differ significantly between FD patients with normal gastric emptying and normal controls, suggesting that the pathogenesis of FD is not related to the change in levels of these gastrointestinal hormones or gastric dysmotility, but to some other factors.

To find out the reasons why postprandial plasma gastrin level increased in FD patients with delayed gastric emptying, we observed the morphology of G and D cells in the gastric antral mucosa, and found that the number and gray value of G and D cells and the G cell/D cell number ratio were not significantly different between FD patients with delayed gastric emptying and those with normal gastric emptying and normal controls, suggesting that the abnormally elevated postprandial plasma gastrin level is not correlated with the change in the number of G cells, the pigmenting extent of secretory granules in G cells, or the G cell/D cell number ratio.

Gastrointestinal hormones are produced by neuroendocrine cells in gastrointestinal tract. The stimuli to the release of gastrointestinal hormones involve luminal, blood, and neurostimulations. Further studies are needed to determine the abnormalities of gastrin and NT levels in FD patients with delayed gastric emptying. FD patients have a disturbance of autonomic nerve function<sup>[24,25]</sup>, which may be related to the abnormal gastrin and NT release.

Abnormalities of gastrointestinal hormones are just one mechanism whereby gastric motility may be disturbed in some FD patients. Other mechanisms include disturbance of mental status and autonomic nerve function<sup>[24-26]</sup>. The significance of abnormalities of gastrointestinal hormones revealed in this study remains to be determined.

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