

# Early Satiety Is the Only Patient-Reported Symptom Associated With Delayed Gastric Emptying, as Assessed by Breath-Test

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## Background/Aims

To evaluate associations between delayed gastric emptying (GE) assessed by the octanoic acid breath test and upper gastrointestinal (GI) symptoms.

## Methods

A historical, prospective study included 111 consecutive symptomatic adults referred for a GE breath test because of upper abdominal symptoms suggestive of delayed GE. Exclusion criteria included underlying organic disease associated with delayed GE. Patients completed a symptom questionnaire and underwent a GE octanoic breath test. Patients with delayed GE were compared with those with normal results, for upper GI symptoms.

## Results

Early satiety was the only symptom significantly associated with delayed GE. It was observed in 52% of subjects with delayed GE compared to 33% patients with no evidence of delayed GE ( $P = 0.005$ ). This association was seen for all degrees of severity of delayed GE. Patients with early satiety had a  $t_{1/2}$  of  $153.9 \pm 84.6$  minutes compared to  $110.9 \pm 47.6$  minutes in subjects without it ( $P = 0.002$ ). In a logistic regression model, early satiety was significantly associated with delayed GE (OR, 2.29; 95% CI, 1.01-5.18;  $P = 0.048$ ).

## Conclusions

Early satiety is the only patient-reported GI symptom associated with delayed GE. The utility of GE tests as a clinical diagnostic tool in the work-up of dyspeptic symptoms may be overrated.

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## Key Words

Breath tests; Dyspepsia; Gastric emptying

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## Introduction

Delayed gastric emptying (GE) is associated with a wide spectrum of gastrointestinal (GI) symptoms, in particular post prandial fullness/early satiety, nausea and vomiting.<sup>1</sup> Although several studies have reported an association between delayed gastric emptying and clinical symptoms,<sup>2,3</sup> others have not found support for this association.<sup>4,5</sup> A recent study in patients with delayed GE did not find an association between GE and GI symptoms, except for symptoms that were associated with proximal stomach dysfunction.<sup>6</sup> It is noteworthy that rapid GE may also result in nausea, bloating and epigastric fullness, making the clinical diagnosis of delayed gastric emptying problematic.<sup>7</sup>

Thus, symptoms of delayed GE are nonspecific and may overlap with other GI disorders including functional dyspepsia, peptic ulcer disease or gastric malignancy.<sup>8</sup> Moreover, in some prokinetic drug trials, there has been a poor correlation between medical facilitation of GE and symptom improvement, suggesting that delayed GE was not the cause of the symptoms. In addition, no dose dependent effect was seen, ie, between increasing severity of GE delay and symptom severity.<sup>9,10</sup>

Several mechanisms have been proposed to explain the clinical manifestation of delayed GE, including antral hypomotility, impaired gastric accommodation,<sup>11</sup> visceral hypersensitivity, absence of the interstitial cells of Cajal<sup>12</sup> and gastric dysrhythmias. These putative mechanisms are controversial, because a moderate delay of GE in healthy individuals is not associated with an increase in meal-related symptoms.<sup>13</sup>

Ghoos et al<sup>14</sup> were the first to show the benefit of measuring the GE rate of solids by a non-invasive octanoic acid breath test. Although GE scintigraphy of a solid-phase meal is considered the gold standard for the diagnosis of delayed GE,<sup>15</sup> the octanoic acid breath test provides reproducible results that correlate with GE scintigraphy.<sup>14,16,17</sup> The primary aim of the present study was to further characterize associations between upper GI symptoms and delayed GE as assessed by patient reports of symptoms and results of the octanoic acid breath test. An additional objective was to look at possible associations between the severity of GE delay (classified as mild, moderate and severe) and upper GI symptoms.

## Materials and Methods

The E. Wolfson Medical center serves as a secondary and

tertiary referral center. This study was approved by the hospital's institutional review board. Each patient gave written informed consent.

This was a historical, prospective study of 111 consecutive adults, aged 18 to 79 years, who were referred for a GE breath test because of upper abdominal symptoms suggestive of delayed GE. Only patients fulfilling the Rome II criteria for functional dyspepsia and failed empirical medical therapy were included. Patients were excluded at entry if they had a peptic ulcer, an organic disease associated with delayed GE such as diabetes mellitus, Parkinson's disease, cerebrovascular accident, neuromuscular disease, eating disorder, gastrostomy tube, gastric outlet obstruction, history of gastric surgery, fundoplication or treatment with anticholinergic or antidepressants drugs.

Endoscopic criteria for exclusion were esophagitis of over grade 2 by Savary-Miller classification or all types of Los Angeles classification. Patients with diaphragmatic hernia of larger than 3 cm or erosive gastritis were excluded. Medical treatment was prescribed for all patients with pathologic findings and the GE tests were conducted between 2 weeks to 3 months after cessation of treatment only in those patients who did not respond to medical therapy.

As detailed below, the study participants completed a socio-demographic and symptom questionnaire and underwent a GE breath test. *Helicobacter pylori* (*H. pylori*) status was determined by endoscopic biopsy (CUTest, Temmler Pharma, Marburg, Germany) or urea breath test.

The questionnaire included socio-demographic data, a review of medical history, and the section of the official Rome II questionnaire on upper GI symptoms, with particular emphasis on relation to nausea and vomiting, post-prandial fullness, early satiety and bloating. Only patients with frequent symptoms of at least 25% of time were included in the study.

## Gastric Emptying Breath Tests

GE was evaluated using the previously validated <sup>13</sup>C-labelled octanoic acid 4 hour breath test (BreathID, Exalenz, Jerusalem, Israel).<sup>17</sup> All breath tests were performed in the morning, over a 4-hour period in a sitting position after an overnight fast. Proton pump inhibitors were discontinued at least 1 week prior to evaluation of GE.

The BreathID collected breath samples continuously from patients who were connected to the instrument through a nasal canula based circuit. The instrument analyzed breath samples before and after <sup>13</sup>C enriched octanoic acid administration. The

BreathID system utilized 100 mg  $^{13}\text{C}$ -labelled octanoic acid dissolved in a standard sized scrambled egg with 2 slices of bread, which provide 250 kcal, as the test meal. Based on Molecular Correlation Spectrometry, the BreathID continuously measured  $^{13}\text{CO}_2$  and  $^{12}\text{CO}_2$  concentrations from the patient's breath and established the  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratio, which was displayed vs time on the screen. The  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratio was normalized for patient's weight, height and  $^{13}\text{C}$  substrate and dose. This provided percentage dose recovery and cumulative percentage dose recovery and calculated the  $t_{1/2}$ , tlag and the gastric emptying coefficient (GEC, data not presented in this article). These calculations were based on analyses using a non-linear model, as described by Ghoo et al.<sup>14</sup> The results have been printed on a thermal printer and saved to a hard disk.

Based on Ghoo et al,<sup>14</sup> the normal ranges for the GE parameters were defined as  $t_{1/2}$  50-94 minutes, tlag 12-52 minutes and GEC 2.95-3.55 (delayed emptying < 2.95). Based on the  $t_{1/2}$  values and as we could not find any severity index in assessment of delayed GE time in the literature, we divided our patients into 4 groups: normal emptying, 50-94 minutes; mild delay, 95-199 minutes (up to 2 times of upper normal limit); moderate delay, 200-299 minutes (up to 3 times of upper normal limit); and severe delay,  $\geq 300$  minutes (over 3 times of upper normal limit).

In order to evaluate the association between GI symptoms and delayed GE, patients with delayed GE were compared to a group without delayed GE and a dose effect was sought for individual symptoms.

## Statistical Methods

Data were analyzed using the SPSS 9.0 statistical analysis software (SPSS Inc, Chicago, IL, USA). For continuous variables descriptive statistics were calculated and were reported as mean  $\pm$  SD. Normality of distribution was assessed using the Kolmogorov-Smirnov test (cut-off at  $P = 0.01$ ). All continuous variables had approximately normal distributions permitting the use of parametric methods. The  $t$  test for independent samples was used to compare continuous variables between subjects with and without delayed GE. One way analysis of variance was used to compare continuous variables across breath test categories. Pearson's correlation coefficient was calculated to describe associations between continuous variables.

Categorical variables are presented as frequency (%). The  $\chi^2$  test (exact test when indicated) was used to assess associations between delayed GE and symptoms, gender and breath test categories. All tests were 2-sided and statistical significance was set at

$P < 0.05$ .

## Results

The study population was comprised of 111 consecutive patients referred for a GE breath test because of upper abdominal dyspeptic symptoms suggestive of delayed GE. There were 76 females (mean age  $42 \pm 16$  years) and 35 males (mean age  $43 \pm 16$  years). According to the Rome II criteria for functional dyspepsia, there were 36 patients with ulcer like dyspepsia, 63 with dysmotility like dyspepsia and 13 with unspecified dyspepsia.

### Gastric Emptying Tests

The results of the GE breath tests showed that 48 patients had no evidence of delayed GE (Group 1), while 63 (Group 2) had evidence for it. There was no difference between the groups in terms of age or body mass index (Table 1). Looking at the data from all patients (Groups 1 and 2), epigastric bloating was reported by 67 patients (60.4%), post-prandial nausea or vomiting by 60 (54.1%) and early satiety by 49 (44.1%). A significant, positive correlation was observed between the number of symptoms and the  $t_{1/2}$  result ( $r = 0.217$ ,  $P = 0.026$ ) in Group 2 with the delayed GE. However, there was no significant association between GE and symptoms of abdominal pain, nausea, vomiting, bloating, heartburn and hiccups. There was also no significant association between these symptoms and the severity of delayed GE. The only symptom that was significantly associated with delayed GE was early satiety, which was reported by 33% in Group 1 and 52% in Group 2 ( $P = 0.005$ ) (Table 1). The mean  $t_{1/2}$  was  $153.9 \pm 84.6$  minutes in subjects with early satiety vs  $110.9 \pm 47.6$  minutes in subjects without it ( $P = 0.002$ ). In a logistic regression model, early satiety was significantly associated with delayed GE (OR, 2.29; 95% CI, 1.01-5.18;  $P = 0.048$ ). Early satiety increases the odds of mild degree of delayed GE by a factor of 2.5 (OR, 2.5; 95% CI, 1.1-5.6;  $P = 0.024$ ) and of moderate to severe degree of delayed GE by a factor of more than 6 (OR, 6.2; 95% CI, 1.6-23.7;  $P = 0.003$ ). All subjects with severe degree of delayed GE had early satiety (OR, 1.2; 95% CI, 1.04-1.33;  $P = 0.003$ ). There was no significant correlation between early satiety and tlag and GEC.

### *Helicobacter pylori* and Delayed Gastric Emptying

There was no significant association between delayed GE and *H. pylori* status. Of 80 patients who were tested for *H. pylori*

**Table 1.** Comparison of the Age, Gender, Body Mass Index, Clinical Symptoms and *Helicobacter pylori* Status Between Group 1 and 2

	Group 1 (n = 48)	Group 2				P-value
		Mild (n = 46)	Moderate (n = 9)	Severe (n = 8)	All (n = 63)	
Age (mean ± SD)	43.6 ± 15.8	41.4 ± 17.8	42.2 ± 17.7	44.4 ± 18.6	42 ± 17.5	NS
Gender (male/female)	13/35	16/30	5/4	1/7	22/41	NS
BMI (mean ± SD [kg/m <sup>2</sup> ])	24.7 ± 4.8	23.3 ± 4.5	27.0 ± 6.5	24.6 ± 4.8	24 ± 5	NS
Abdominal pain	33 (68.8)	24 (52.2)	7 (77.8)	6 (75.0)	37 (58.8)	NS
Bloating	27 (56.3)	27 (58.6)	5 (55.6)	8 (100.0)	40 (63.5)	NS
Nausea	21 (43.8)	20 (43.5)	5 (55.6)	6 (75.0)	31 (49.2)	NS
Vomiting	9 (18.8)	16 (34.8)	4 (44.5)	1 (12.5)	21 (33.3)	NS
Heartburn	21 (43.8)	18 (39.1)	2 (22.3)	3 (37.5)	23 (36.5)	NS
Hiccups	8 (16.7)	6 (13.0)	3 (33.3)	3 (37.5)	12 (19.0)	NS
Early satiety	16 (33.4)	20 (43.5)	5 (55.6)	8 (100.0)	33 (52.4)	0.002
<i>H. pylori</i>	10 (20.1)	5 (10.8)	0	0	5 (7.9)	NS

*H. pylori*, *Helicobacter pylori*.

Data are presented as n (%) unless otherwise stated.

**Table 2.** Comparison of the Endoscopic Findings Between the Control and Delayed Gastric Emptying Group

	Group 1 (n = 37)	Group 2				P-value
		Mild (n = 35)	Moderate (n = 7)	Severe (n = 5)	All (n = 47)	
Normal	26 (70.3)	21 (60.0)	6 (85.7)	3 (60.0)	30 (63.8)	NS
Esophagitis	6 (16.2)	3 (8.6)	0	1 (20.0)	4 (8.5)	NS
Hiatal hernia	3 (8.1)	6 (17.1)	0	0	6 (12.7)	NS
Duodenitis	1 (2.7)	4 (11.4)	0	0	4 (8.5)	NS
Food remnants	3 (8.1)	3 (8.6)	1(14.3)	1 (20.0)	5 (10.6)	NS

Group 1, control group; Group 2, delayed gastric emptying group.

Some patients had more than 1 finding. None of the differences was statistically significant. Data are presented as n (%).

by urea breath test or by CUTest, 15 were positive, 10 (21%) in Group 1 and 5 (11%) in Group 2 (Table 1).

## Endoscopic Findings and $t_{1/2}$ , tlag or Gastric Emptying Coefficient

Eighty-four patients underwent esophagogastroduodenoscopy prior the GE test. The distribution of endoscopic findings are presented in Table 2. None of the endoscopic findings was associated with  $t_{1/2}$ , tlag or GEC.

## Discussion

Delayed GE has been associated with various GI symptoms. An evaluation of GE is often performed when no other rational explanation is found for persistent symptoms. Identifying the presence of delayed GE may enable physicians to establish a final diagnosis in patients with vexing symptoms and no other clear

explanation.<sup>18</sup>

The results of this study indicate that the majority of GI symptoms leading to the performance of a GE test are not associated with delayed GE. Early satiety was the only symptom that was found to have a significant association with delayed GE. The association with early satiety was demonstrated in mild, moderate and severe degree of GE delay. Early satiety increases the odds of mild degree of delayed GE by a factor of 2.5 and of moderate to severe degree of delayed GE by a factor of more than 6. All subjects with severe degree of delayed GE had early satiety (OR, 1.2). There was no association between early satiety and the other 2 measured parameters of GE, tlag or GEC. Our results confirmed the previous findings of Stanghellini and Sarnelli.<sup>2,3,19</sup> However, they also found an association between delayed GE and nausea and vomiting, which was not seen in the present study. Sarnelli et al<sup>2</sup> reported a significant association between delayed solid or liquid GE and postprandial fullness and vomiting.

Vomiting is a non-specific symptom that may be induced by other etiologies such as regurgitation associated with gastroesophageal reflux disease or rumination.<sup>20,21</sup> The prevalence of delayed GE among gastroesophageal reflux disease patients ranges from 10%-41%.<sup>21,22</sup> Delayed GE may be a proxy for other disorders that lead to vomiting and early satiety. Karamanolis et al<sup>6</sup> recently demonstrated that many of the symptoms previously associated with delayed GE are actually due to fundic dysmotility.

Another factor that may have impact on delayed GE is *H. pylori*. This hypothesis is based on theoretical grounds as well as epidemiologic and clinical studies.<sup>23</sup> *H. pylori* has been found to be inversely correlated with the prevalence of delayed GE and certain studies have shown improvement of GE with eradication.<sup>24</sup> We failed to demonstrate an association between *H. pylori* status and delayed GE and confirmed the previous reports of no association between delayed GE and *H. pylori*.<sup>25,26</sup> Moreover, since the prevalence of *H. pylori* in our country is high, we would expect to see an aggravation of delayed GE symptoms if there actually is an association between them.

The major drawback of this study is the arbitrary setting of severity of GE delay to 3 groups of mild (up to twice normal GE time), moderate (up to 3 times normal GE time) and severe (over 3 times normal GE time). This setting is due to the fact that there is no valid data from the literature we could rely on. Future research is essential in grading the severity of delayed GE and comparison with symptom frequency and severity.

In conclusion, we found that among all the patient with reported symptoms, early satiety was the only symptom that was associated with delayed GE regardless of its severity. These findings suggest that the utility of GE tests as a clinical diagnostic tool in the work-up of upper GI symptoms suggestive of delayed GE may be overrated.

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