Risk Indicators of Delayed Gastric Emptying of Solids in Patients With Functional Dyspepsia

VINCENZO STANGHELLINI,* CESARE TOSETTI,* ANNA PATERNICÒ,* GIOVANNI BARBARA,*
ANTONIO MARIA MORSELLI–LABATE,* NINO MONETTI,† MARIO MARENGO,§
and ROBERTO CORINALDESI*

*Institute of Internal Medicine and Gastroenterology, University of Bologna, Bologna; and Departments of †Nuclear Medicine and §Medical Physics, Azienda Ospedaliera Policlinico Sant'Orsola-Malpighi, Bologna, Italy

Background & Aims: Although gastric dysmotility and dyspeptic symptoms are often associated, their relationship remains unclear. The aim of this study was to evaluate the relationship between gastric emptying abnormalities and clinical features in functional dyspepsia. Methods: In 343 patients with functional dyspepsia, the gastric emptying of solids was measured by a radioisotopic technique and four dyspeptic symptoms (epigastric pain and burning, postprandial fullness, nausea, and vomiting) were measured as absent, mild, relevant, and severe, according to their influence on patients' usual activities. Results: Delayed gastric emptying was detected in 33.5% of dyspeptics. Delayed gastric emptying was particularly frequent in patients characterized by female sex, low body weight, presence of relevant and severe postprandial fullness, nausea, vomiting, and absence of relevant and severe epigastric pain. Logistic regression showed that delayed gastric emptying was invariably associated with female sex and with postprandial fullness (odds ratio, 2.34; 95% confidence interval, 1.45–3.75) and vomiting (odds ratio, 4.04; 95% confidence interval, 1.30–12.54) when coded as severe and only postprandial fullness (odds ratio, 3.78; 95% confidence interval, 1.78–8.01) when coded as relevant and severe. Conclusions: Female sex, relevant and severe postprandial fullness, and severe vomiting are independently associated with delayed gastric emptying of solids in patients with functional dyspepsia seen in a referral center.

D yspepsia is a very common syndrome that accounts for about 30% of gastroenterologists' caseloads.[1,2] Patients complaining of long-term or recurrent symptoms that seem to arise from the stomach and proximal small bowel in the absence of organic, metabolic, or systemic diseases are usually classified as having been affected by functional (or idiopathic) dyspepsia.[2–6] This definition helps to differentiate dyspepsia from other gastrointestinal functional syndromes such as irritable bowel syndrome (IBS)[7] and gastroesophageal reflux disease (GERD).[8]

Epigastric pain and discomfort centered in the upper abdomen are the characteristic symptoms of dyspepsia. Discomfort is a term used to describe nonpainful but unpleasant symptoms such as postprandial fullness, bloating, nausea, and vomiting.[6] The existence of patients complaining mainly of epigastric pain and others citing nonpainful discomfort has led researchers to hypothesize about the existence of different subpopulations of dyspeptic patients who have been identified as having ulcer-like and dysmotility-like dyspepsia, respectively.[2,6] The definition of these subpopulations and whether they are characterized by distinctive underlying pathophysiological abnormalities remains to be elucidated.

Gastrointestinal motor abnormalities, Helicobacter pylori infection, nonfocal mucosal lesions, hypersensitivity of the afferent nerves of the gut, and psychological disturbances have been said to be involved in the pathogenesis of dyspepsia.[9] Studies of gastrointestinal motility performed by manometric techniques in patients with functional dyspepsia showed a decreased antral contractile response to meal ingestion in up to 50% of the cases,[10–12] whereas abnormalities of small bowel motility are less frequent and seem to characterize patients with autonomic neuropathies[13] or associated IBS.[11,12] Delayed gastric emptying has been found in 10%–64% of these cases.[14–26] Differences in techniques used and populations investigated may account for these impressive differences. Furthermore, the relationship between gastrointestinal motor abnormalities and dyspeptic symptoms has not been clarified. Finally, despite the intuitive feeling of both patients and physicians that the two phenomena may be associated, several studies have failed to identify

any correlation.[18,21,23,25,26] Inaccurate definitions of dyspepsia, a limited number of cases, inappropriate symptom questionnaires, or other methodological shortcomings might be responsible for these negative results.

The specific aims of this study were to evaluate whether (1) patients with functional dyspepsia have delayed gastric emptying of solids, (2) gastric emptying abnormalities and dyspeptic symptoms are related, and (3) this relationship is influenced by the symptom scoring technique and/or by other clinical features.

Materials and Methods

Between June 1986 and January 1993, 1057 consecutive dyspeptic patients were referred to our laboratory at the Institute of Internal Medicine and Gastroenterology at the University of Bologna. All the patients underwent careful history taking and physical examination, as well as upper gastrointestinal endoscopy, abdominal ultrasonography, and appropriate hematochemical tests. Only patients who were diagnosed as being affected by chronic functional dyspepsia were included in the study. Inclusion criteria were (1) presence of dyspeptic symptoms lasting for at least 3 months with a global symptom score of at least 3 or greater (see questionnaire below); (2) absence of esophagitis, gastric atrophy, or focal lesions of the gastroduodenal mucosa; (3) absence of organic, systemic, and metabolic diseases, as well as obvious psychiatric illness; and (4) negative history of peptic ulcer, major abdominal surgery, long-term use of steroids or nonsteroidal anti-inflammatory drugs, excess alcohol intake, and drug abuse.

The protocol was approved by the University of Bologna S. Orsola hospital ethics committee, and all the subjects gave their fully informed consent.

Symptom Questionnaire

Each patient completed a symptom questionnaire that assessed four symptoms of dyspepsia: epigastric pain and burning, postprandial fullness, nausea, and vomiting. Each symptom was graded 0–3 according to its influence on patients' usual activities: 0, absent; 1, mild (not influencing usual activities); 2, relevant (diverting from but not urging modifications of usual activities); and 3, severe (influencing usual activities markedly enough to urge modifications). The reproducibility of the symptom questionnaire in dyspeptic patients has been previously assessed.[24] Based on previously calculated normal values,[24] total symptom scores ≥3 with at least one of the four dyspeptic symptoms graded ≥2 were required for entry into the study.

Digestive symptoms other than those typical of dyspepsia were also investigated with appropriate questionnaires. The frequent occurrence of at least three of the classic Manning's criteria (pain relieved by defecation, looser stools at pain onset, more frequent stools at pain onset, visible abdominal distention, feeling of incomplete evacuation, mucus per rectum, and abdominal bloating)[7] was required to diagnose IBS, whereas

GERD was defined by the presence of at least one typical symptom (heartburn or acid regurgitation) severe enough to divert the patient from usual activities.[8]

Gastric Emptying

Gastric emptying of the solid components of a mixed meal was studied in each patient using a previously validated radioisotopic technique.[27] Briefly, all drugs potentially affecting gastrointestinal motility were discontinued at least 1 week before the study day. The test meal (638 kcal: 42% carbohydrates, 37% lipids, 21% proteins) was labeled (18.5 MBq of ^{99m}Tc-sulfur colloid) in the solid component (chicken liver) by a previously validated in vitro technique.[28]

Results expressed as the gastric emptying rate (%/min) were calculated as the slope of the rectilinear portion of the gastric emptying curve. Delayed emptying was defined by emptying rates below the lower limit of the sex-specific normal range calculated as mean values ± 2 SD of control subjects (males, 0.42–1.18; females, 0.35–0.93%/min). Lag time values were also calculated as the time between the end of meal ingestion (time 0) and the interception of the rectilinear portion of the curve with the tangent to the peak of the curve and compared with those of control subjects (normal values: males, ≤54 minutes; females, ≤37 minutes).

Gastric emptying results were compared with those obtained in 50 healthy controls who represented the reference group of our laboratory.

Statistical Analysis

Analysis of variance was used to compare age, weight, or changes vs. ideal body weight in dyspeptic patients and healthy controls. Ideal body weight was estimated according to the Metropolitan Relative Weight Tables.[29] χ^2 analysis was used to compare the distribution of sex in the two populations. Analysis of covariance adjusted for sex, age, and body weight was used to compare gastric emptying rates and lag times in dyspeptic patients and controls. Analysis of variance was also used to evaluate the influence exerted on emptying rates of dyspeptic patients by sex, age, body weight, changes vs. ideal body weight, overlapping IBS and GERD, and grading of symptoms. All these variables were analyzed as dichotomous factors. Linear regression analysis was applied to evaluate the relationship between gastric emptying rates and global symptom scores. Furthermore, individual dyspeptic symptoms were analyzed by considering the three possible cutoffs: (A, ≥1 vs. 0; B, ≥2 vs. ≤1; and C, 3 vs. ≤2). Stepwise multiple logistic regression analysis was used to identify the association between the risk of delayed gastric emptying and the above-mentioned possible independent risk indicators. All the possible interactions between these factors were also considered as independent variables. P values of 0.05 and 0.10 were chosen as cutoff points to enter and exit the stepwise procedure. Odds ratios with 95% confidence intervals were computed.

Two tailed P values of <0.05 were accepted as the level of statistical significance. Statistical evaluations were performed

Table 1. Final Diagnosis Formulated After Thorough Investigation in 1057 Patients Referred For Chronic Dyspepsia

Diseases	No.	%
Peptic ulcer	226	21.4
Esophagitis	99	9.4
Biliary tree surgeries	58	5.5
Biliary lithiasis	48	4.5
Atrophic gastritis	46	4.4
Major abdominal surgeries	34	3.2
Gastric malignancies	6	0.6
Other gastrointestinal diseases (chronic liver diseases, pancreatitis, malabsorption, food allergy, etc.)	56	5.3
Diabetes	22	2.1
Metabolic/endocrine diseases (Zollinger–Ellison syndrome, Addison's disease, thyroid diseases, obesity)	33	3.1
Organic/systemic diseases (neoplasms, connective diseases, severe heart or respiratory failure)	28	2.6
Gynecologic diseases	22	2.1
Psychiatric diseases (anorexia nervosa, psychosis, severe anxiety)	36	3.4
Functional (idiopathic) dyspepsia	343	32.5
Total	1057	100

using the statistical software package of SPSS/PC+ (SPSS Inc., Chicago, IL).[30]

Results

The final diagnoses made in the 1057 dyspeptic patients initially investigated are listed in Table 1. A putative cause of dyspepsia was detected in 714 of the patients (68%). The most frequent secondary form of dyspepsia was represented by the peptic ulcer that was found in approximately 20% of the cases. Approximately 10% of the patients had endoscopic evidence of esophagitis. A gastric cancer was disclosed in 6 patients (0.6%). Functional dyspepsia was diagnosed in 343 patients (32%) who were the object of further analysis. Of these, 96 (28%) had overlapping IBS and 108 (32%) overlapping GERD.

Patients and controls were significantly different in sex, age, and body weight. Females were more prevalent among dyspeptics (150 males and 193 females) compared with controls (30 males and 30 females; $P = 0.031$). Patients were also older (39.1 ± 12.4 years, mean ± SD) than controls (34.5 ± 12.4 years; F = 5.99; $P = 0.014$). Finally, patients had lower body weight (63.1 ± 12.1 kg) than controls (67.3 ± 11.2; F = 5.43; $P = 0.020$) but presented similar percentage changes vs. ideal body weight (respectively, −2.4 ± 12.5, 0.2 ± 9.7). Table 2 summarizes the prevalence and grading of dyspeptic symptoms. Among patients, postprandial fullness and

epigastric pain accounted for 94% and 84%, respectively, of frequently reported symptoms. Both symptoms were more often reported as relevant or severe. Nausea and vomiting were less frequent and severe, being reported as absent or mild by 72% and 90%, respectively, of the cases.

Dyspeptic patients had gastric emptying lag times (12.47 ± 17.04 minutes; mean ± SD) similar to those of controls (15.32 ± 15.43) but lower emptying rates (patients, 0.51 ± 0.24%/min; controls, 0.67 ± 0.18; F = 14.63; $P = 0.0001$). Gastric emptying was delayed in 24.7% of male patients and in 40.4% of female patients. On average, females had emptying rates (0.46 ± 0.22) lower than males (0.59 ± 0.23; F = 28.65; $P = 0.0001$). Similarly, patients with body weight lower than ideal body weight (n = 192) had lower emptying rates (0.47 ± 0.22) than those with body weight equal to or greater than ideal body weight (n = 151; 0.57 ± 0.25; F = 18.79; $P = 0.0001$). Gastric emptying was not influenced by age or by the presence of overlapping IBS and GERD.

A significant, although poor, negative relationship was found between total global scores and emptying rates ($r = -0.20$; $P = 0.0001$). However, when multiple logistic regression analysis was applied to test the influence of demographic features (i.e., age, sex, and body weight) and the global symptom score on the risk of gastric dysmotility, only the female sex turned out to be significantly associated with delayed gastric emptying (odds ratio, 2.07; 95% confidence interval, 1.30–3.31; $P = 0.0024$).

We also investigated the association between individual symptom grading and gastric dysmotility. Patients complaining of relevant and severe (score ≥2) postprandial fullness, nausea, and vomiting presented decreased emptying rates (respectively, 0.48 ± 0.22, 0.44 ± 0.21, and 0.41 ± 0.19) compared with patients with absent or mild (<2) forms of the corrispective symptoms (0.65 ± 0.25, F = 32.99, $P = 0.0001$; 0.54 ± 0.24, F = 11.46, $P = 0.0007$; 0.52 ± 0.24, F = 6.78, $P = 0.0092$).

Table 2. Frequency of Intensity Scoring For Each of Four Symptom Complaints in 343 Patients With Functional Dyspepsia

	0 (Absent)	1 (Mild)	2 (Relevant)	3 (Severe)
Epigastric pain	55 (16)	102 (30)	127 (37)	59 (17)
Postprandial fullness	22 (6)	47 (14)	145 (42)	129 (38)
Nausea	134 (39)	113 (33)	67 (20)	29 (8)
Vomiting	250 (73)	60 (17)	18 (5)	15 (4)

NOTE. Numbers in parentheses represent row percentages.

Table 3. Logistic Regression Model Testing For an Influence of Demographic Data and Symptom Scoring on Delayed Gastric Emptying of Solids in 343 Patients With Functional Dyspepsia

	Odds ratio	95% confidence intervals	P value
A			
Female sex	2.03	(1.27–3.25)	0.0033
Age <40 yr			
BW < IBW			
Epigastric pain ≥1	0.57	(0.32–1.04)	0.0646
Postprandial fullness ≥1			
Nausea ≥1			
Vomiting ≥1			
B			
Female sex	1.82	(1.13–2.96)	0.014
Age <40 yr			
BW < IBW			
Epigastric pain ≥2			
Postprandial fullness ≥2	3.78	(1.78–8.01)	0.001
Nausea ≥2			
Vomiting ≥2			
C			
Female sex	1.86	(1.15–3.02)	0.0119
Age <40 yr			
BW < IBW			
Epigastric pain = 3			
Postprandial fullness = 3	2.34	(1.45–3.75)	0.005
Nausea = 3			
Vomiting = 3	4.04	(1.30–12.54)	0.0157

NOTE. Symptom scoring is coded as: A, presence vs. absence of symptoms; B, presence of relevant and severe symptoms vs. the absence or presence of mild symptoms; and C, presence of severe symptoms vs. the absence or presence of mild and relevant symptoms.
BW, body weight; IBW, ideal body weight.

Patients with relevant and severe epigastric pain, conversely, showed accelerated emptying (0.55 ± 0.24) compared with patients with an absent or a mild (<2) grade of the symptom (0.47 ± 0.23; F = 5.18; P = 0.0036). When the influence of the presence or absence of dyspeptic symptoms on emptying rates was analyzed (score 0 vs. score ≥1), only postprandial fullness appeared to be associated with delayed emptying (score 0, 0.62 ± 0.28; score ≥1, 0.51 ± 0.23; F = 5.18; P = 0.0228).

Logistic regression analysis showed that female sex, relevant and severe postprandial fullness, and severe vomiting were the only factors independently associated with delayed gastric emptying (Table 3). Female sex was associated with delayed gastric emptying, regardless of symptom coding. When symptoms coded as severe (score, 3) were selected, both postprandial fullness and vomiting turned out to be significantly associated, whereas when selecting the symptom code as relevant and severe (score, ≥2), only postprandial fullness was significantly associated. Evaluation of all the interactions between the factors

potentially influencing gastric emptying did not show any significant further effect.

Discussion

This study confirms that gastric emptying of the solid components of caloric mixed meals is delayed in patients with chronic functional dyspepsia seen in a referral center. It also shows that, in this population, female sex, relevant and severe postprandial fullness, and severe vomiting are independently associated with delayed gastric emptying.

The number and type of associated diseases diagnosed in dyspeptic patients seen in our center are not substantially different from those of other groups previously described in Western countries.[31,32] Also, the extent of overlap between dyspepsia and other digestive functional syndromes of about 30% is similar to that reported by others with respect to overlapping IBS[32] but slightly lower with respect to overlapping GERD reported in up to 56% of the cases.[33] Different definitions of dyspepsia and GERD and inclusion of mild forms of the syndromes in these studies may account for these differences. Our patients mainly complained of postprandial fullness, a symptom suggestive of a digestive motor disorder. This confirms the majority of previous reports describing dysmotility-like symptoms as the most common complaint of dyspeptic patients seen by both gastroenterologists[34] and general practitioners.[35]

Gastric emptying of solids has been almost invariably found to be delayed in dyspeptic patients,[14–17,20,21,23,24,36] but the influence of demographic and clinical features on this parameter has not been thoroughly investigated. In the present study, female sex, low body weight, relevant and severe postprandial fullness, nausea, and vomiting as well as the absence of relevant and severe epigastric pain and burning were all found to be associated with delayed gastric emptying. However, the logistic regression analysis showed that only female sex, relevant and severe postprandial fullness, and severe vomiting are independent risk indicators of delayed emptying.

Some studies have already pointed out that gastric emptying abnormalities are more frequent in female than male dyspeptic patients.[18,21,26,36] Systematic studies on the influence of gender on gastric emptying have consistently shown that both premenopausal women and postmenopausal women on estrogen and progesterone replacement therapy have a delayed gastric emptying of solids compared with men,[37,38] but the mechanisms through which females have a higher risk of deranged gastric motility than males remain unclear.

Research in the field of functional dyspepsia is particu-

larly intriguing because, in the absence of specific pathophysiological markers, the diagnosis can be solely based on symptom questionnaires. International panels of clinical investigators agreed that dyspeptic patients may fall into distinct symptom subgroups that may indicate different underlying etiologies.[2,6] These subgroups included patients with typical ulcer symptoms (ulcer-like dyspepsia), patients with symptoms suggestive of gastrointestinal motor abnormalities (dysmotility-like dyspepsia), patients with symptoms suggestive of gastroesophageal reflux (reflux-like dyspepsia) who may also be classified as having GERD,[6] and patients with symptoms that do not fall into any of the above categories (unspecified dyspepsia).

Talley et al. tested a questionnaire designed to distinguish these different dyspepsia subgroups both in the general population[39] and in patients undergoing upper gstrointestinal endoscopy in a tertiary referral center.[32] They concluded that dyspepsia subgroups, as classified in these studies, had "little clinical utility" and were "an inappropriate way of classifying dyspepsia."[32] However, the results of these studies are difficult to interpret because the questionnaire adopted had two major shortcomings. First, it originated from a restrictive definition of dyspepsia focused on the presence of pain (i.e., 10 of the 15 symptoms on the questionnaire were variants of pain, and the presence of pain was requested for inclusion in all the different subgroups of dyspepsia). Second, it did not quantitate the severity of symptoms but only described their presence or absence. The simple perception of digestive symptoms is of limited clinical value because they are extremely frequent in the general population and among individuals who do not seek medical advice.[6] Similarly, in patients with GERD, the relevance of heartburn and regurgitation, but not their mere presence, has been shown to be of predictive value for pathological gastroesophageal reflux.[8] We adopted a multiple point adjectival scale that allows us to ascertain the frequency and the impact on usual activities of 4 dyspeptic symptoms that is easy to understand for the patient and also highly reproducible.[24,40]

The clinical utility of this questionnaire could probably be increased by asking more specific questions. For instance, epigastric burning pain localized in the upper portion of the epigastrium could be more specific for GERD than a nonburning painful sensation vaguely localized in the central part of the upper abdomen. Also, the postprandial duration of fullness could be at least as important as the severity of the symptom in predicting the presence of gastric stasis. Distinguishing early satiety from postprandial fullness could help to differentiate

those patients whose main pathophysiological abnormality is a defective gastric accomodation. However, these hypotheses require verification in well-designed studies with an appropriate number of throughly selected patients.

The relationship between dyspeptic symptoms and digestive motor functions is particularly controversial. A significant, although weak, negative correlation between gastric emptying rates and global symptom scores was detected in our study, suggesting that patients with more severe complaints also have lower emptying velocities. However, multivariate analysis showed that the global symptom score is not associated with gastric emptying rates as an independent variable and that its effect is overcome by gender. By analyzing individual symptom scoring, we observed that patients complaining of relevant and severe postprandial fullness or severe vomiting have an increased risk of delayed gastric emptying compared with patients with different symptom profiles. To the best of our knowledge, only one study adopted a similar (although more complex) scoring system.[18] Despite the small number of patients involved, a borderline significant correlation was found between belching and delayed gastric emptying when the symptom scores (but not the simple presence or absence of symptoms) were analyzed. By contrast, the majority of investigations that failed to identify a correlation between gastric emptying abnormalities and dyspeptic symptoms did not use any quantitative analysis of individual symptoms but simply analyzed the presence or absence of symptoms,[21,36] clusters of symptoms,[25,26] or global symptom scores.[20,36] In keeping with these studies, our findings showed that neither the symptoms or clusters of symptoms considered as a dichotomous variable and coded as present or absent nor the global symptom score had any predictive value for delayed gastric emptying. In addition to the different questionnaires adopted, other variances with previous reports include the use of a low caloric test meal,[23] the inclusion of secondary forms of dyspepsia[19,23,25] or of symptoms suggestive of digestive syndromes other than dyspepsia,[18,21,23,25,26] and the small number of cases investigated.[18,21,23,26]

Indeed, previous studies support the existence of a correlation between dyspeptic symptoms and gastric motor abnormalities. In a double-blind, crossover, placebo-controlled trial of the prokinetic cisapride in patients with symptomatic gastroparesis, we observed a significant positive relationship between the degree of improvement of gastric emptying and the degree of improvement of the symptoms limited to the active treatment arm.[41] In keeping with these findings, Jian et al. described a

greater gain induced by cisapride on symptoms suggestive of motor disorders in patients with delayed gastric emptying than in those with normal gastric motility.[20] A significant, although weak, correlation between severity of symptoms and gastric emptying times had also been found in diabetic patients.[42] More recently, it has been shown that the presence of *H. pylori* infection and delayed gastric emptying identify two subpopulations among dyspeptic patients[24,43] and that these subgroups present different symptom profiles characterized by the prevalence of epigastric pain and postprandial fullness, respectively.[24] Finally, stimulation of mechanoreceptors experimentally obtained by inflating rubber balloons either in the stomach or in the proximal small bowel has been shown to induce a rather monotonous and reproducible individual response with the perception of sensations suggestive of motor derangements such as fullness, pressure, and nausea.[44]

The correlation between dyspeptic symptoms and delayed gastric emptying is not a direct one, as indicated by the absence of any detectable abnormality of gastric emptying of solids in many of the dyspeptic patients we observed. Factors other than digestive motor disorders are probably involved in the complex mechanism leading to visceral perception, including sensitization of receptors other than mechanoreceptors, visceral hypersensitivity due to abnormal neural activity of afferent fibers, and abnormal perception of peripheral signals at the central level.[6]

In conclusion, the present study shows that gastric emptying of solids is delayed in patients with functional dyspepsia and that female sex, postprandial fullness severe enough to influence the usual activities, and vomiting severe enough to urge changes in the usual activities are independently associated with delayed gastric emptying. Analysis of the intensity of digestive symptoms, not only of their presence, is mandatory when investigating the relationship between visceral perception and potentially associated pathophysiological factors. The present study was performed in a highly selected group of patients seen in a referral center. Generalizability of these results regarding other dyspeptic patients commonly seen by general practitioners or gastroenterolgists remains to be established.

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