Altered gastric emptying in patients with irritable bowel syndrome

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Abstract. Irritable bowel syndrome is the most frequent functional disorder of the digestive system. Patients with irritable bowel syndrome have motor disorders not only in the colon, but also in other parts of the digestive tract such as the oesophagus and small intestine; however, it is not known whether the stomach is also involved. We used a radiolabelled mixed solid-liquid meal (technetium-99m for the solid component, indium-111 for the liquid component) to study gastric emptying of solids (GES), liquids (GEL) and indigestible solids (GER) in 50 patients diagnosed as having irritable bowel syndrome (30 with predominant constipation and 20 with predominant diarrhoea). GER was measured by counting the number of indigestible solids remaining in the stomach 4 h after they were swallowed. In patients with irritable bowel syndrome, GES and GEL were slower than in control subjects ($P<0.05$). GER was normal in all patients except for two women. Thirty-two patients (64%) showed delayed GES, 29 (58%) delayed GEL, and 2 (4%) delayed GER. Among patients with irritable bowel syndrome, GES was slower in those with predominant constipation than in those with predominant diarrhoea ($P<0.05$); GEL and GER were similar in both groups. Gastroparesis was found in a large proportion of patients with irritable bowel syndrome, suggesting the presence of a more generalised motor disorder of the gut.

Key words: Gastric emptying – Gastroparesis – Irritable bowel syndrome

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Introduction

Irritable bowel syndrome (IBS) has a high prevalence in the general population [1]. The aetiology and pathogenesis of IBS remain unknown, although several causal factors have been suggested, including motor alterations [2], visceral perception disorder [3] and psychological factors [4]. Patients with IBS often have diffuse anomalies in gastrointestinal motility, such as decreased pressure in the lower oesophageal sphincter [5], reduced interdigestive migrating motor complexes in the jejunum [6] and, in the colon, alterations in the basic electrical rhythm and increased smooth muscle reactivity to parasympathomimetic drugs, hormones, food intake and stress [7]. In addition, patients with IBS often have functional dyspepsia [8], and one study found that one-third of the patients with functional dyspepsia also report symptoms of IBS [9]. Gastroparesis also occurs frequently in patients with functional dyspepsia [10]. These findings have led some authors to suggest that functional dyspepsia and IBS are part of a single syndrome with manifestations predominantly in the upper or lower gastrointestinal tract [8, 11, 12].

The few studies that have examined gastric motility in patients with IBS have yielded contradictory findings. Some authors have found no motor disorder [13–16], whereas others have reported gastroparesis [17, 18]. However, the methods used by different authors have varied widely, making the results difficult to compare. The present study was designed to analyse gastric emptying of digestible solids (GES), liquids (GEL) and indigestible solids (GER) in patients with IBS, and to compare these patients with a group of age- and sex-matched control subjects. None of the patients or control subjects was overweight.

Materials and methods

Patients

We studied 50 subjects free of digestive symptoms or systemic disease (25 men and 25 women) and 50 patients (25 men and 25 women) diagnosed as having IBS using the Rome criteria [19], the latter comprising 30 with predominant constipation and 20

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with predominant diarrhoea. Members of the two groups were matched for age, and lacked antecedents of gastric surgery, alcohol intake of more than 40 g per day or drug treatment (including oral contraconceptives) during the 2 weeks before the study, or smoking during the 2 days before the study. In addition, systemic, endocrine and connective tissue-related diseases were ruled out with appropriate hematological and biochemical analyses. All subjects and patients had a body mass index within 20–25 kg/m^2. All women had a negative pregnancy test. Twenty-eight (56%) patients with IBS were diagnosed as having functional dyspepsia. All subjects and patients gave their written consent to participate in the study, which was approved by the Clinical Assays Committee of the University Hospital of Granada and carried out in accordance with the Declaration of Helsinki.

Method

The presence of antibody-IgG for *Helicobacter pylori* infection in gastric mucosa was investigated in all subjects and patients (Helico-G, Porton, Cambridge, UK). Two test of gastric emptying were done as described below.

Test 1. Gastric emptying of digestible solids and liquids. In accordance with a previously described procedure [20], at 0900 hours after and overnight fast of at least 8 h, all participants consumed two scrambled eggs cooked to a firm consistency in a teflon pan; each serving was labelled by injecting 22.3 MBq technetium-99m diethylene triamine penta-acetic acid (DTPA). Immediately thereafter, each subject drank 60 ml of orange juice labelled with 3.7 MBq indium 111 DTPA. The patients consumed the solid and liquid test meal in front of the gamma camera, and thereafter the total number of radioisotope counts in the abdominal cavity was recorded; this value was 100% of the food retained in the stomach at time = 0. The solid test meal contained 9.1 g protein, 4.6 g carbohydrates and 26.3 g fat, equivalent to a 260-kilocalorie meal.

Radioactivity emitted by the radioisotopes was measured with an Acticamera-CGR gamma camera connected to an Imag-7300-CGR computer. Acquisition time was 60 s at 0, 5, 15, 45, 75 and 105 min after ingestion of the test meal, in a 128×128 pixel resolution matrix. The pulse height analyser was set at the 140-keV photopeak with a 10% window for ^{99m}Tc and at the 247-keV photopeak with a 10% window for ^{111}In. The counts were measured with the subject supine (anterior projection) and pronoe (posterior projection) to avoid attenuation error. The images stored in the computer were observed, and the area of interest, comprising the gastric area, was outlined with the digitalising system's pencil to determine the number of counts in this area. The geometric mean of the values obtained in the anterior and posterior projections was used as the count value.

The proportion of the isotope remaining in the stomach was plotted against time as previously described [21]. Because the scanning intervals were so long, the fractional solid meal retention values were analysed using the function $y(t) = 1–(1–e^{-\kappa t})^{\beta}$. A power exponential curve was computer-fitted to the proportional gastric emptying data to obtain two representative indices, κ and β, and the $T_{1/2}$. In this equation, the $y(t)$ factor was the fractional meal retention at time t, κ was the gastric emptying rate in min^{-1}, t was the time interval in minutes, and β was the y-intercept extrapolated from the terminal portion of the curve. The unknown parameters κ and β were determined with a non-linear least square algorithm using the measured fractional meal retention [y (t)] versus time data (t).

The initial delay portion of the curve was characterised by a lag phase index, T_{lag}, which was numerically equal to ln β/κ, and was the time in minutes when the second derivative of the function became equal to zero. The κ index provided an estimate of the rate of emptying or the later rapid phase of the emptying curve; the β index provided an estimate of the shape of the curve or the earlier and more gradual phase of emptying. The measures used to analyse the liquid component were $T_{1/2}$ and the amount of tracer remaining 10 min after liquid meal ingestion. During the studies, the subjects remained seated but were allowed to move about over a distance of approximately 5 m. Gastroparesis was defined by values above or in the upper range of normality for at least three of the five parameters used to characterise GES (κ, β, $T_{1/2}$, $T_{lag, \%}$Tc remainig at 105 min) or one of two parameters used to characterise GEL ($T_{1/2, \%}$ In remaining at 10 min).

Test 2. Gastric emptying of indigestible solids (IDS). IDS were prepared according to the method previously described [20], from 16-F polyvinyl nasogastric tubing cut into 1-cm pieces that weighed approximately 40 mg. The pieces were filled with powdered barium sulphate and sealed, and each piece was placed in a gelatine (gastric fluid soluble) capsule of the type used for pharmaceutical preparations. The total volume of radiopaque IDS released in the stomach after the capsule dissolved was approximately 125 mm^3, and their density 0.43 mg/mm^3.

At least 48 h after the digestible solids and liquids test, all participants swallowed ten IDS capsules with a small amount of water after an overnight fast of at least 8 h. Supine abdominal radiographs were taken 4 h later. IDS capsules remaining in the stomach were counted successfully in 96% of the radiographs; when there was doubt, a lateral radiograph (obtained in 12% of the studies) was used to confirm the presence and location of IDS. In 4% of the examinations, the location of the IDS in the distal stomach or proximal duodenum could not be unequivocally determined; in these cases an intragastric position was arbitrarily assumed. For all radiological studies the genital region was shielded with lead. The total radiation received in the radiological study was approximately 0.4 mGy. At the time of the study we did not quantify the dose of radiation received during test 1 (nuclear medicine test).

All data showed a normal distribution except emptying rate (κ). We used the Mann-Whitney U test for non-paired samples. The rest of the data showed a normal distribution and we used Student's t test for comparisons of two samples. All statistical tests were two-tailed, and were evaluated at the 5% level of significance. All results were expressed as means ±SD (normal distribution) or median and interquartile range (non-normal distribution).

Results

Clinical data and *Helicobacter pylori* infection status for the control group and IBS patients are shown in Table 1. Three of the five parameters that define GES, and two of those that define GEL, were significantly lower in the control group than in patients with IBS, showing that the emptying of both solids and liquids was delayed in the latter group (Table 2, Fig. 1). Four hours after intake, IBS remained in the stomach in only two patients with IBS (both women). Thirty-two patients (64%) showed delayed GES, 29 (58%) delayed GEL, and two (4%) delayed GER. In the control group, GES and GEL were slower in women than in men (P<0.05). Among patients

Table 1. Clinical data for the control group and patients with IBS

	Controls	IBS
No.	50	50
Age (years)	35.6 ± 5.6	34.1 ± 7.4
Body weight (kg)	64.1 ± 5.7	63.5 ± 4.2
Body mass index (kg/m^2)	22.7 ± 1.2	23.5 ± 1.1
% patients Hp+ve	58	54
Smoking (*n* cigarettes/day)	11.2 ± 4.1	13.4 ± 5.7

Results expressed as mean ± SD
HP, *Helicobacter pylori*

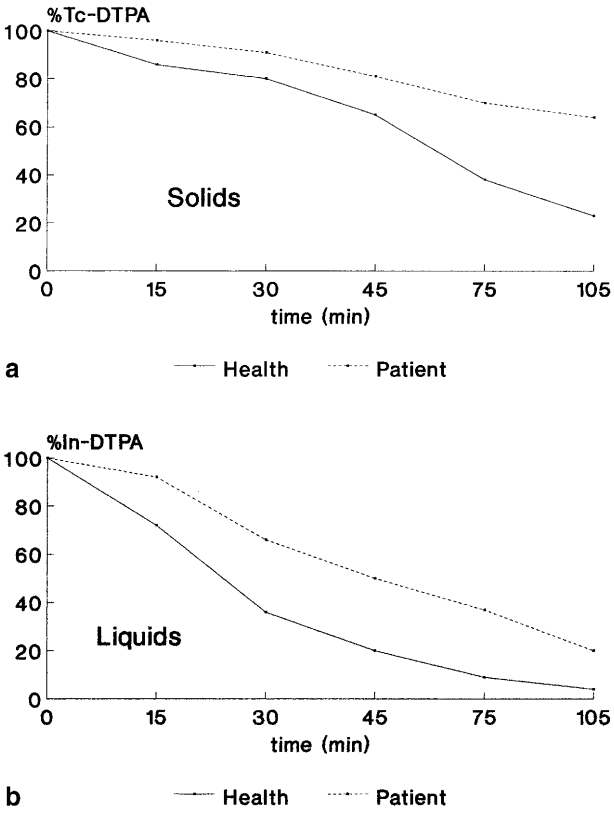

Fig. 1. Examples of typical emptying gastric curves of **a** solids and **b** liquids in health subjects and patients with IBS

with IBS, GES and GEL were also slower in women, although the difference in T_{lag} was not significant for GES. Emptying of solids and liquids was slower in both men and women with IBS in comparison with control men and women respectively (P<0.05). GES was slower in patients with predominant constipation than in patients with predominant diarrhoea (P<0.05), although GEL and GER were similar in both subgroups (Table 3).

Discussion

Irritable bowel syndrome is the most common digestive tract disorder, with a prevalence in the general population of 12–22% [1]. As already mentioned, aetiology and pathogenesis are unknown. Of the several causal factors suggested, some are also thought to be involved in dys-

Table 2. Analysis of the gastric emptying curve of digestible solids [according to the function: $y(t) = 1–(1–e^{-\kappa t})^{\beta}$] and liquids, and gastric emptying of indigestible solids

	Controls			*P*	IBS			*P*
	Men	Women	Overall		Men	Women	Overall	
No.	25	25	50		25	25	50	
Solids								
Emptying rate (κ)	–0.010 (8)	–0.045(7)	–0.028 (17)	NS	–0.021 (8)	–0.061 (9)	–0.051 (19)	NS
β	1.24 (0.26)	1.29 (0.25)	1.26 (0.30)	NS	1.28 (0.32)	1.32 (0.27)	1.30 (0.30)	NS
T_{lag} (min)	13.1 (4.3)	16.1 (5.1)	14.6 (4.7)	*	17.6 (3.0)	19.3 (4.8)	18.5 (4.3)	**, ***
$T_{1/2}$ (min)	52.8 (6.9)	62.8 (8.5)	57.8 (7.6)	*	58.9 (6.2)	68.2 (7.1)	63.6 (6.5)	*, **, ***
% isotope remaining at 105 min (%Tc_{105})	21.1 (8.0)	27.9 (10.4)	24.5 (9.9)	*	26.3 (8.0)	31.2 (9.3)	28.8 (10.6)	*, **, ***
No. with IDS capsules remaining at 4 h	0	0	0		0	2	2	
Liquids								
$T_{1/2}$ (min)	19.5 (8.6)	23.9 (6.5)	21.7 (7.3)	*	23.7 (7.4)	28.5 (8.7)	26.2 (7.2)	*, **, ***
% isotope remaining at 10 min (%In_{10})	68.5 (8.5)	72.8 (7.4)	70.7 (7.9)	*	73.5 (7.2)	78.4 (9.7)	76.0 (8.2)	*, **, ***

Results are expressed as the mean, with the standard deviation in parentheses, except for emptying rate (κ), which is expressed as the median, with the interquartile range in parentheses
* P<0.05, men vs women
** P<0.05, control vs IBS
*** P<0.05, men and women in the control group vs men and women with IBS, respectively

Table 3. Analysis of the gastric emptying curve of digestible solids and liquids, and gastric emptying of indigestible solids in patients with IBS with predominant constipation or predominant diarrhoea

	IBS-predominant constipation	IBS-predominant diarrhoea	*P*
No.	30	20	
Solids			
Emptying rate (κ)	–0.021 (12)	–0.048 (8)	NS
β	1.27 ± 0.31	1.32 ± 0.42	NS
T_{lag} (min)	21.3 ± 3.6	17.2 ± 4.3	*
$T_{1/2}$ (min)	65.1 ± 7.4	60.7 ± 5.3	*
% isotope remaining at 105 min (%Tc_{105})	34.0 ± 9.5	26.1 ± 6.7	*
No. with IDS capsules remaining at 4 h	2	0	–
Liquids			
$T_{1/2}$ (min)	27.6 ± 8.1	25.9 ± 6.7	NS
% isotope remaining at 10 min (%In_{10})	77.2 ± 7.6	75.3 ± 9.1	NS

Results are expressed as mean ±SD, except for emptying rate (κ), which is expressed as the median, with the interquartile range in parentheses
* $P<0.05$

pepsia report symptoms compatible with IBS, and from one-half to two-thirds of the patients with IBS also have dyspepsia [8, 9, 11, 12]; further, 50%–70% of patients with functional dyspepsia show gastrointestinal motility and gastric emptying disorders [10, 21]. Motor disorders, one of the most important etiological and pathogenic factors in IBS [2, 7], can affect segments of the digestive system other than the colon [5–7]. However, it is not known whether gastric emptying is impaired (as a further manifestation of a generalised motor disorder) in patients with IBS.

Of the small number of studies to analyse gastric emptying in patients with IBS some have failed to find alterations in GES in patients with IBS [13–16], whereas others have reported that GES [17, 18] and GEL [18] to be delayed. A high proportion of these studies were methodologically flawed because of the low number of subjects studied [13, 15–17] and because of failure to match subjects in different groups for age [14–16], sex [13, 14, 16–18], or body mass index [13–18] – all of which have been shown to vary with the rate of gastric emptying [22–27]. Another study did not match subjects for *H. pylori* infection [28]. Some studies evaluated gastric emptying by measuring a single parameter, $T_{1/2}$ [13–16], an approach that does not adequately characterise the complexity of the process [20, 21]. In the present study we accounted for all these factors by matching patient group and control group for age, sex, body mass index and *H. pylori* infection (although this was tested only as previous exposure to the germ, rather than current infection).

Like Van Wijk et al. [17] and Evans et al. [18], we found that GES was significantly delayed in patients with IBS. The difference was found for the group of patients as a whole, and for both men and women separately. GEL was also significantly slower in patients with IBS as a whole, and in men and women separately. These findings are similar to those reported by Evans et al. [18], who found that GEL was slower in patients with IBS, although these authors did not analyse men and women separately. Earlier studies showed that GES [25–27] and GEL [24, 25] were slower in women than in men; we also noted this "physiological gastroparesis", although to a lesser degree, in women with IBS. Cann et al. [14] and Van Wijk et al. [17] observed this difference between sexes, although other studies did not analyse the sex differences [13, 15, 16, 18].

Although we did not use gastrointestinal manometry, we assume that patients with IBS have a motor deficit in the fundus (GEL) and in the antrum (GES) [29]. We found no earlier studies of GER in patients with IBS, and thus cannot draw comparisons between our findings and those of earlier series. Indigestible solids remained in the stomach 4 h after intake in only two patients (both women). Because antral phase III of the myoelectric motor complex is responsible for moving IDS out of the stomach [30], this finding suggests that a small number of patients with IBS may have a disorder in fasting antral motility. If we had measured fasting gastric motility, we might have detected abnormalities in a larger number of patients, as GER is less sensitive than manometry and detects only major disorders. Several different manometric alterations have been found in the small intestine of patients with IBS during the fasting [2, 31, 32] and the postprandial phase [18]; however, the latter study found manometric disorders only in patients with delayed GES. Although it is not known to what degree intestinal dysmotility influences GER, our findings suggest that such influence is slight.

Patients with severe idiopathic constipation show delayed GES and GEL, but only 6 h after intake; emptying parameters before this time remain normal [33]. However, some studies have found gastroparesis for solids and liquids [34, 35], and although Bannister et al. [36] found normal GES in these patients, their study is of limited value as they measured only $T_{1/2}$. Fasting and postprandial manometric alterations in the stomach and small intestine have been reported in patients with idiopathic constipation [2, 31, 37, 38]. Many patients with IBS are constipated [1, 11, 19], and we found that GES was slower in patients with IBS and constipation than in their counterparts with diarrhoea, although GEL and GER were similar in the two subgroups. Small bowel transit time was found to be slower in patients with IBS and constipation than in patients with diarrhoea and in healthy control subjects [14, 16]. However, GES and GEL were normal in patients with IBS regardless of whether constipation or diarrhoea was predominant [14, 16, 18].

Like us, Van Wijk et al. found gastroparesis in patients with IBS and predominant constipation [17]. In addition, patients with IBS and delayed GES more often show postprandial and fasting dysmotility of the small intestine [18]. These findings appear to indicate that in comparison with patients who have predominant diarrhoea, patients with IBS and predominant constipation represent a subgroup with a more widespread motor disorder affecting the stomach and small intestine. Chronically constipated patients, regardless of whether they have IBS, therefore more frequently show evidence of a motor disorder that affects more proximal segments of the digestive tract, possibly as a result of prolonged ileal inhibition or rectal distension [39]. This would explain why disorders in one part of the digestive tract could influence motor and functional activity in other parts.

Although our findings may be of limited clinical use, they confirm that patients with IBS frequently have delayed GES and GEL; however, only a small proportion of our patients also had delayed GER. These results suggest that IBS and idiopathic gastroparesis are simply local expressions of a single more generalised disorder of the digestive tract [5–8, 11, 12, 18, 40]. The origin of gastroparesis in patients with IBS is unknown, although it may be related to a myogenic or a neurogenic alteration, or to both. Because manometric alterations in patients with IBS show normal or elevated amplitude and frequency in motor activity [2, 18, 31, 32], it has been suggested that the motor alteration is of (local or central) neurogenic rather than myogenic origin. Further evidence of a neurogenic origin is the absence of the normal patterns of integration between the fasting and the fed state [18]. Our data support this notion: although GES and GEL (postprandial or fed motility-dependent) were slowed, GER (fast motility-dependent) was normal in the most patients.

In 1928 Bockus et al. [41] suggested that IBS be caused by an imbalance in the autonomic nervous system. More recent studies have found that 27%–36% of all patients with IBS display autonomic neuropathy [42–44] of the sympathetic [45] or parasympathetic system [42], or of both [46]. The cause of this autonomic neuropathy is unknown, although the development of gastroparesis after certain viral infections has suggested a role for these pathogens [47]. Whether the motor disorder spreads to other parts of the digestive tract may depend on the degree of autonomic nervous system involvement, which may range from highly localised functional autonomic neuropathy with little neurogenic damage to chronic intestinal pseudoobstruction [34, 48].

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