PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

ELSEVIER

World J Gastroenterol 2005;11(20):3122-3126
World Journal of Gastroenterology ISSN 1007-9327

• *BRIEF REPORTS* •

Maximum tolerated volume in drinking tests with water and a nutritional beverage for the diagnosis of functional dyspepsia

Aldo Montaño-Loza, Max Schmulson, Sergio Zepeda-Gómez, Jose Maria Remes-Troche, Miguel Angel Valdovinos-Diaz

Aldo Montaño-Loza, Max Schmulson, Sergio Zepeda-Gómez, Jose Maria Remes-Troche, Miguel Angel Valdovinos-Diaz, Department of Gastroenterology, Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran, Vasco de Quiroga # 15, Tlalpan. CP 14000, México DF
Co-first-authors: Aldo Montaño-Loza and Max Schmulson
Co-correspondents: Aldo Montaño-Loza
Correspondence to: Dr. Miguel Angel Valdovinos-Diaz, Department of Gastroenterology, Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran, Vasco de Quiroga # 15, Tlalpan. PC 14000, Mexico City, Mexico. mavaldo@quetzal.innsz.mx
Telephone: +5573-34-18 Fax: +56550942
Received: 2004-10-09 Accepted: 2004-12-20

Abstract

AIM: Recently, drinking load tests with water or nutritional beverages have been proposed as diagnostic tools for functional dyspepsia (FD), therefore we sought to reproduce if these tests can discriminate between FD patients and controls in a Mexican population.

METHODS: Twenty FD-Rome II patients were matched by age and gender with 20 healthy controls. All underwent both drinking tests at a 15 mL/min rate, randomly, 7 d apart. Every 5 min within each test, four symptoms were evaluated (satiety, bloating, nausea and pain) by Likert scales. Maximum tolerated volume (MTV) was defined as the ingested volume when a score of 5 was reached for any symptom or when the test had to be stopped because the patients could not tolerate more volume. Sensitivity and specificity were analyzed.

RESULTS: FD patients had higher symptom scores for both tests compared to controls (water: $t = 4.1$, $P = 0.001 < 0.01$; Nutren®: $t = 5.2$, $P = 0.001 < 0.01$). The MTV for water and Nutren® were significantly lower in FD (water: 1014±288 *vs* 1749±275 mL; $t = 7.9$, $P = 0.001 < 0.01$; Nutren®: 652±168 *vs* 1278±286 mL; $t = 6.7$, $P = 0.001 < 0.01$). With the volume tolerated by the controls, the percentile 10 was determined as the lower limit for tolerance. Sensitivity and specificity were 0.90, 0.95 for water and 0.95, 0.95 for Nutren® tests.

CONCLUSION: A drinking test with water or a nutritional beverage can discriminate between FD patients and healthy subjects in Mexico, with high sensitivity and specificity. These tests could be used as objective, noninvasive, and safe diagnostic approaches for FD patients.

Key words: Functional dyspepsia; Water and nutrient drinking load tests; Maximum tolerated volume

Montaño-Loza A, Schmulson M, Zepeda-Gomez S, Remes-Troche JM, Valdovinos-Diaz MA. Maximum tolerated volume in drinking tests with water and a nutritional beverage for the diagnosis of functional dyspepsia. *World J Gastroenterol* 2005; 11(20): 3122-3126
http://www.wjgnet.com/1007-9327/11/3122.asp

INTRODUCTION

Functional dyspepsia (FD) is the second most common functional gastrointestinal disorder, after irritable bowel syndrome[1]. This condition is characterized by chronic, recurrent pain or discomfort in the upper abdomen in the absence of any organic or structural disorder[2]. Its prevalence ranges between 5% and 20% in the general population worldwide[3-7]. The pathogenesis of this entity is complex and it has been related to alterations in gastric motility[8,9] visceral hypersensitivity[10,11] and psychological factors[12]. A significant number of FD patients have a diminished or absent gastric fundic accommodation and this is related with satiety and weight loss[6,7,13]. Also, about 40% of patients with FD have hypersensitivity to mechanical distention that may cause pain, abdominal discomfort, bloating and satiety[14]. Methods to evaluate gastric accommodation and hypersensitivity such as a barostat[15] are invasive, expensive and not readily available, as well as imaging studies to evaluate accommodation such as ultrasound[16,17], SPECT imaging[18] and nuclear medicine studies which also require expertise[19,20]. Yet, the diagnosis of FD is based on symptoms and "lack of organic disease", including a normal upper endoscopy. Therefore the absence of an objective finding increases uncertainty in these patients[21]. Recently, a rapid liquid drinking test with water or a nutritional beverage (Nutridrink) have been used to discriminate FD patients from normal subjects and to identify the presence of hypersensitivity and diminished gastric accommodation[18,22]. These tests can be performed in a short period of time, are of low cost and have no adverse effects. Therefore we sought to reproduce the clinical usefulness of the drinking tests with water and a nutritional beverage to discriminate FD patients from healthy controls and to investigate their sensitivity and specificity.

MATERIALS AND METHODS

Patients

In a prospective controlled study, 20 consecutive patients

with FD fulfilling the Rome II[2] diagnostic criteria (pain or abdominal discomfort centered in the upper abdomen, at least for 12 wk, not necessarily consecutive, in the last 12 mo, with a normal upper gastrointestinal endoscopic examination and absence of any other systemic disease), who consulted a Functional Bowel Disorders and Motility Clinic were included. Upper endoscopies were performed within 3 mo prior to the study. The patients suspended all antisecretory medications including H_2 blockers and proton pump inhibitors, antacids, prokinetics or visceral analgesics, 1 wk prior to the protocol. All patients signed an informed consent and the protocol was approved by the Institutional Committee for Human Research.

Controls

Patients were matched by gender and age (±5 years) with 20 healthy volunteers (controls), recruited from advertisement, without any digestive symptoms and not fulfilling the Rome II criteria for FD, nor any past history of systemic diseases, gastrointestinal surgeries, erosions or ulcers seen on previous upper endoscopic examination or any other imaging study, and who were not taking any medications.

Methods

Drinking tests with water and a nutritional beverage: After an overnight fast of 8 h, patients arrived at the Motility Unit of the Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran of Mexico City, an academic referral center. They were randomized to begin either with water or the nutritional beverage (Nutren®, Nestle; 1.5 kcal/mL, 51% carbohydrates, 33% lipids, and 16% proteins). Water and Nutren® were ingested at a predetermined rate of 15 mL/min as reported elsewhere[15]. Every 5 min within each drinking test symptoms such as satiety, bloating, nausea and epigastric pain were evaluated by using Likert scales from 0 to 5: 0 = without sensation, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe. When a score of 5 was reached for any of the symptoms, or when the subjects could not tolerate any more volume, the tests were stopped and the total ingested volume (mL) was recorded. The maximum tolerated volume (MTV) was defined as the total ingested volume, after the test was stopped. All subjects were asked to score the same symptoms, 1 and 2 h after the tests were completed. Sensitivity and specificity for the drinking tests to discriminate FD from healthy controls were analyzed, considering the Rome II criteria for FD (symptom criteria and a normal endoscopy) as the gold standard for FD diagnosis.

Statistical analysis

The ratings within each 5 min during the test and at the two follow-up periods were analyzed. For each symptom, a score was obtained by the summation of all the ratings within each test divided by the time in minutes of the length of the drinking test and multiplied by 100 (to correct for those who drank longer and had more scores to add up). A total score was obtained by adding all the individual symptom scores. Also, the ratings for each symptom at the follow-up periods were added to obtain the 1 and 2 h scores for water and Nutren®.

Frequencies were expressed in percentages and compared by using Fisher exact test. Symptoms scores and volumes were expressed as mean±SD for each group (FD patients and controls) and comparisons were done by using the *t* test. A $P \leqslant 0.05$ was considered statistically significant. The Pearson (*r*) test was used to establish correlations of the MTV between both drinking tests. The SPSS version 10.0 for Windows was used for the data analysis.

RESULTS

Table 1 depicts age, gender and body mass index (BMI) characteristics of FD patients and controls. There was no statistical difference between the two groups in relation to the BMI.

Table 1 Baseline characteristics

	FD patients (n = 20)	Controls (n = 20)	P
Age (yr)	34±15	31±9	NS
Gender (M/F)	4/16	4/16	NS
BMI (kg/m^2)	23±2.8	23±2.3	NS

BMI: body mass index.

Symptoms

During both tests, the most frequent symptoms reported by FD patients and controls were bloating and satiety. The frequency of symptoms reported during the water test was (FD patients and controls, %): satiety 100 and 65 ($\chi^2 = 5.5$, $P = 0.02<0.05$), bloating 90 and 55 ($\chi^2 = 4.5$, $P = 0.03<0.05$), nausea 65 and 25 ($\chi^2 = 4.9$, $P = 0.02<0.05$), and epigastric pain 45 and 15 ($\chi^2 = 2.9$, $P = 0.08$, NS). Similarly, the frequency of symptoms for the Nutren® test was: satiety 100 and 90 ($\chi^2 = 0.35$, $P = 0.5$, NS), bloating 100 and 70 ($\chi^2 = 4.2$, $P = 0.03<0.05$), nausea 75 and 25 ($\chi^2 = 8.1$, $P = 0.004<0.01$), and epigastric pain 55 and 15 ($\chi^2 = 5.3$, $P = 0.02<0.05$).

FD patients had significantly higher scores for satiety, bloating and pain in the water test, and also significantly higher scores for satiety, bloating, nausea and pain in the Nutren® test (Tables 2 and 3).

Table 2 Symptom scores for the water test

	Bloating	Nausea	Satiety	Pain	Total
FD patients	31.1±16.9	17.8±22.5	41.5±20.5	26.1±27	90.4±11.8
Controls	6.8±7.7	7.5±5.2	12.5±11.1	2.0±2.8	28.8±3.7
P	<0.001	NS	<0.001	<0.001	<0.001

Note: symptoms are shown as mean ± SD.

Table 3 Symptom scores for the Nutren® test

	Bloating	Nausea	Satiety	Pain	Total
FD patients	51.5±18.8	45.5±23.4	76.9±47.1	13.2±14.7	186.7±26.1
Controls	19.4±7.4	15.3±8.6	25.2±9.2	4.2±2.9	64.1±8.9
P	<0.001	<0.001	<0.001	<0.01	<0.001

Note: symptoms are shown as mean ± SD.

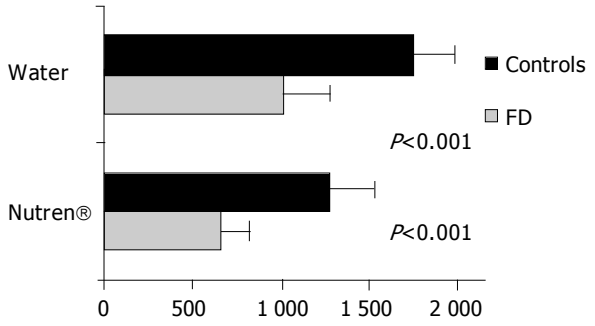

Figure 1 Maximum tolerated volumes of water and Nutren® in healthy controls and FD patients. FD: Functional Dyspepsia.

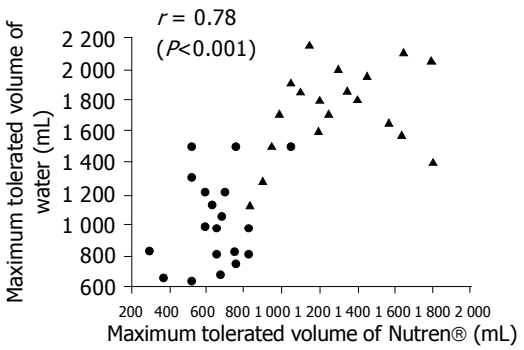

Figure 2 Correlation of maximum tolerated volume (MTV) between water and Nutren® tests in FD patients (●) and healthy controls (▲).

At the 1 h follow-up evaluation for the water test, the symptom scores reported by the FD patients were higher than those reported by controls (9.1±3.2 *vs* 2.9 ± 1.5, $t = 5.6$, $P = 0.001<0.01$). At the 2 h follow-up evaluation, FD patients reported a symptom score of 4.5±4.2, while none of the controls reported any symptoms ($t = 4.9$, $P = 0.001<0.01$). For the Nutren® test, FD patients had significantly higher scores than controls at the 1 and 2 h follow-ups (1 h: 14.3±2.5 *vs* 2.3±0.58, $t = 3.1$, $P = 0.001<0.01$; 2 h: 5.9±1.9 *vs* 1.4±0.84, $t = 2.7$, $P = 0.01<0.05$).

Maximum tolerated volume (MTV)

There were no statistically significant differences in the MTV according to gender both for water (males: 1587±466 mL *vs* females: 1 380±472 mL) and the Nutren® test (males: 1 125±577 mL *vs* females: 935±352 mL).

The MTV for water and Nutren® was significantly lower in FD patients (water: 1 014±288 *vs* 1 749±275 mL; $t = 7.9$, $P = 0.001<0.01$; Nutren®: 652±168 *vs* 1 278±286 mL; $t = 6.7$, $P = 0.001<0.01$; Figure 1). With the volume tolerated by healthy controls, we determined the percentile 10 as the lower limit of the normal range for drinking tolerance. That is ⩾1 200 mL for females and ⩾1 400 mL for males in the water test, and ⩾900 mL for females and ⩾1 200 mL for males in the Nutren®.

Considering these limits, 18 out of 20 patients with FD had abnormal results (lower tolerated volume) for the water test compared to only one control, and 19 FD patients had lower tolerated volumes in the Nutren® test compared to one of the healthy controls. The sensitivity and specificity of the drinking test with water was 0.90 (CI 95% 0.69-0.97) and 0.95 (CI 95% 0.76-0.99), respectively. For the Nutren® test, sensitivity and specificity was 0.95 (CI 95% 0.76-0.99), and 0.95 (CI 95% 0.76-0.99), respectively.

Correlation between both drinking tests

There was a significant correlation in the MTV between the water and the Nutren® tests ($r = 0.78$, $P = 0.001<0.01$; Figure 2).

DISCUSSION

In the current study we evaluated two drinking load tests [water and a nutritional beverage (Nutren®)] in Mexican patients with FD and healthy controls, and we have shown that more than 85% of the patients have a decreased tolerance for drinking capacity. In addition, we found that both tests induced dyspeptic symptoms such as bloating, nausea, satiety and epigastric pain more frequently in patients than in controls, and the first ones reported the symptoms earlier and with lower ingested volumes. Also, when compared to the Rome II criteria (symptom criteria and negative upper endoscopy) as the gold standard for diagnosing FD, the sensitivity and specificity for the water and Nutren® drinking tests have shown that both are useful tools to discriminate patients from healthy subjects. These results reproduced the data reported by other groups. In an Italian study using a water load test, the maximum tolerated volume was significantly lower in FD patients than controls and scores for satiety, pain, nausea, fullness and bloating were higher for the latter ones[19]. Another study found that a caloric drinking test distinguished FD patients with or without early satiety[23]. Using mineral water at a rate of 100 mL/min in a Nordic population, maximal water intake was significantly lower in FD patients than healthy controls[22].

Several possibilities can explain the above findings. Using transabdominal ultrasound, Gilja *et al*[16], reported that in response to a soup meal, FD patients had smaller sizes and higher emptying fractions of the proximal stomach and they reported more symptoms than controls. Tack *et al*[15], reported that this impaired gastric accommodation to a meal was found in 40% of patients with FD and was associated with symptoms of early satiety in a multivariate analysis. Previously, Boeckxstaens *et al*[23], reported that FD patients had a lower drinking capacity for both water and a caloric liquid, compared to healthy volunteers or patients with mild dyspeptic symptoms, and that FD patients developed significantly more symptoms than the healthy volunteers after both tests. In contrast to our findings, they also reported that compared to women, men consumed significantly more water and Nutridrink®, a nutritional beverage with the same composition as the Nutren® used in our study. Finally, in their study, drinking capacity did not predict impaired fundic accommodation or visceral hypersensitivity.

The speed of liquid ingestion in the oral load tests is controversial and may explain the differences among the studies. Boeckxstaens *et al*[23], tested water and Nutridrink® at a fast ingestion rate of 100 mL/min, and showed a diminished tolerance for liquid ingestion only in 50% of FD patients. In a more recent study, Tack *et al*[11], showed that a

liquid ingestion of a caloric drink at a speed of 15 mL/min induced symptoms of satiety in FD patients, and a significant correlation existed between the amount of calories ingested during the satiety testing and the amplitude of the gastric accommodation. The same group of researchers found that the gastric accommodation is a slow-onset reflex presenting in a gradual manner and reaching its maximal relaxation 15 min after ingestion of a meal[14].

The duration of the rapid drinking test is clearly lower than the time required for full development of the accommodation reflex[24].

Based on the above data, in the current study we used the predetermined speed of liquid ingestion of 15 mL/min. The maximum ingested volume of a nutritional drink depends on the balance between mechanisms that increase the gastric volume (fundic relaxation) and the negative feedback that slows gastric emptying and induces symptoms after a meal. In the absence of nutrients, other mechanisms that limit liquid ingestion in FD patients should be considered. The gastric and duodenal distention may trigger vaso-vagal reflexes that result in proximal gastric relaxation and induction of satiety and fullness[25-27]. The vaso-vagal reflexes could also be activated during a test with water. In our study, the finding of a greater tolerance of water volume ingestion than that of a nutritional drink by healthy volunteers suggests that the feedback mechanisms induced by nutrients are activated before the reflexes are induced by distention[28-30]. Interestingly, our patients with FD had similarly low water and nutritional beverage tolerated volumes, suggesting a decreased threshold for the activation for both reflexes[31,32].

The gastric accommodation disturbances[11,33,34] and proximal gastric mechanical distention hypersensitivity[35,36] are recognized as the most important pathogenic mechanisms in FD. The gastric barostat test is considered the "gold standard" for the evaluation of the proximal gastric accommodation in response to a meal; however, this is an invasive, time-consuming, and not readily available test. There is a need of less expensive, non-invasive and highly available diagnostic tests for FD that can provide an objective diagnosis to the patients. Whether an abnormal fundic relaxation in response to a meal, an abnormal distribution of the gastric contents, or gastric hypersensitivity are the causes of dyspeptic symptoms in response to a drinking load test, is unknown. Furthermore, hypersensitivity in functional dyspepsia is associated with abnormal gastric accommodation[18-22] and hyperalgesia, and cofactors of this hypersensitivity are likely to be wall tension and the function of visceral afferents[10,32,35]. The high percentage of FD patients with impaired drinking capacity in our study, supports a multifactorial component in symptoms generation, and together with the high sensitivity and specificity, for discriminating FD from healthy controls by using the Rome II criteria, including symptoms and a negative endoscopy as the gold standard for diagnosis, provides a simple test for patients with a disease where the absence of an objective diagnosis, creates anxiety and a continuous search for an answer.

In Mexico, functional gastrointestinal disorders are the main reason for consulting a gastroenterologist, with FD being the second most frequent disorder following IBS[4]. Lydeard and Jones have reported that FD patients seeking health care are more preoccupied that their symptoms might be related to cancer compared to those who do not consult[37]. Effective well-founded reassurance that no serious disease is present is an important outcome of medical intervention, but patients consider that medical explanations are not sufficient to clarify the nature of their condition and negative results of paraclinical investigations may be taken as "bad news" driving patients to keep consulting in search of an objective diagnosis. Anxiety has been found to be an independent factor associated with health-care seeking in FD[38]. Other psychosocial factors including abnormal illness attitudes and beliefs have been found to characterize those patients who seek help versus those that do not[39]. Furthermore, physicians also lack confidence in their functional diagnosis. In a British study, clinicians reported confidence in 63-91% of their organic diagnosis compared to only 48% of FD diagnosis[40]. This difference was related to the possibility of an objective confirmation of organic disease by using paraclinical investigations. The absence of confidence in functional diagnosis may drive clinicians to order more investigations that may increase the anxiety and the fear of a more serious disorder in functional patients. Therefore, a drinking loading test may be a potential tool for an objective diagnosis in patients consulting for FD.

Both drinking tests caused more symptoms in patients with FD than in healthy controls. In the future, it would be useful to find which test (water or nutritional beverage) has a more diagnostic importance. Meanwhile, we considered that both are easy to perform, available, safe, non-invasive and useful to discriminate FD patients from healthy volunteers. Furthermore, these tests could be used in future studies to evaluate the effect of new treatments in the management of postprandial symptoms in patients with FD.

In conclusion, a drinking load test with water or a nutritional beverage at a slow drinking rate of 15 mL/min, can discriminate FD patients from controls in a simple, non-invasive, safe and available manner. Our findings in a group of Mexican patients with FD, are in accordance with previously reported studies. The gastric distention produced by the volume of water or nutritional beverage reproduces the symptoms of FD and suggests a multifactorial origin for symptom generation, including impairment in gastric sensitivity and proximal accommodation. The current data supports the potential usefulness of liquid loading tests to provide FD patients with an objective diagnosis in a disease with otherwise no objective diagnostic data rather than clinical criteria, and with a potential use in the evaluation of future treatments.

REFERENCES

1 **Chang L.** Review article: epidemiology and quality of life in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2004; **20** Suppl 7: 31-39
2 **Talley NJ,** Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; **45** Suppl 2: II37-II42
3 **Agréus L**. The epidemiology of functional gastrointestinal disorders. *Eur J Surg Suppl* 1998; **583**: 60-66
4 **Huerta I,** Valdovinos MA, Schmulson M. Irritable bowel syn-

drome in Mexico. *Dig Dis* 2001; **19**: 251-257
5 **Gschossmann JM,** Haag S, Holtmann G. Epidemiological trends of functional gastrointestinal disorders. *Dig Dis* 2001; **19**: 189-194
6 **Locke GR.** Prevalence, incidence and natural history of dyspepsia and functional dyspepsia. *Baillieres Clin Gastroenterol* 1998; **12**: 435-442
7 **Kawamura A,** Adachi K, Takashima T, Yuki M, Ono M, Kinoshita Y. Prevalence of irritable bowel syndrome and its relationship with Helicobacter pylori infection in a Japanese population. *Am J Gastroenterol* 2001; **96**: 1946
8 **Talley NJ,** Silverstein MD, Agréus L, Nyrén O, Sonnenberg A, Holtmann G. AGA technical review: evaluation of dyspepsia. American Gastroenterological Association. *Gastroenterology* 1998; **114**: 582-595
9 **Bredenoord AJ,** Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003; **1**: 264-272
10 **Feinle-Bisset C,** Vozzo R, Horowitz M, Talley NJ. Diet, food intake, and disturbed physiology in the pathogenesis of symptoms in functional dyspepsia. *Am J Gastroenterol* 2004; **99**: 170-181
11 **Tack J,** Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. *Gastroenterology* 2001; **121**: 526-535
12 **Fischler B,** Tack J, De Gucht V, Shkedy ZI, Persoons P, Broekaert D, Molenberghs G, Janssens J. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. *Gastroenterology* 2003; **124**: 903-910
13 **Tack J,** Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; **127**: 1239-1255
14 **Tack J,** Demedts I, Dehondt G, Caenepeel P, Fischler B, Zandecki M, Janssens J. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* 2002; **122**; 1738-1747
15 **Tack J,** Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**: 1346-1352
16 **Gilja OH,** Hausken T, Wilhelmsen I, Berstad A. Impaired accommodation of proximal stomach to a meal in functional dyspepsia. *Dig Dis Sci* 1996; **41**: 689-696
17 **De Schepper HU,** Cremonini F, Chitkara D, Camilleri M. Assessment of gastric accommodation: overview and evaluation of current methods. *Neurogastroenterol Motil* 2004; **16**: 275-285
18 **Kim DY,** Delgado-Aros S, Camilleri M, Samsom M, Murray JA, O'Connor MK, Brinkmann BH, Stephens DA, Lighvani SS, Burton DD. Noninvasive measurement of gastric accommodation in patients with idiopathic nonulcer dyspepsia. *Am J Gastroenterol* 2001; **96**: 3099-3105
19 **Tossetti C,** Salvioli B, Stanghellini V, Cogliandro L, Cogliandro R, Marra MG, De Giorgio R, Mazzotta E, Zamboni P, Corinaldesi R. Reproducibility of a water load test in healthy subject's symptom profile compared to patients with functional dyspepsia. *Gastroenterology* 1999; **116**(S): A 336
20 **Cuommo R,** Sarnelli G, Grasso R, Alfieri M, Niccolai E. Early satiety in functional dyspepsia: validity of a caloric drinking test and relation to gastric emptying dyspepsia. *Gastroenterology* 1999; **116**(S): A142
21 **Simrén M,** Tack J. Functional dyspepsia: evaluation and treatment. *Gastroenterol Clin North Am* 2003; **32**: 577-599
22 **Strid H,** Norstrom M, Sjober J, Simren M, Svedlund J, Abrahamsson H, Bjornsson ES. Impact of sex and psychological factors on the water loading test in functional dyspepsia. *Scand J Gastroenterol* 2001; **36**: 725-730
23 **Boeckxstaens GE,** Hirsch DP, van den Elzen BD, Heisterkamp SH, Tytgat GN. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. *Gastroenterology* 2001; **121**: 1054-1063
24 **Tack J.** Drink tests in functional dyspepsia. *Gastroenterology* 2002; **122**: 2093-2094; author reply 2094-2095
25 **Azpiroz F,** Malagelada JR. Perception and reflex relaxation of the stomach in response to gut distention. *Gastroenterology* 1990; **98**: 1193-1198
26 **Ladabaum U,** Koshy SS, Woods ML, Hooper FG, Owyang C, Hasler WL. Differential symptomatic and electrogastrographic effects of distal and proximal human gastric distension. *Am J Physiol* 1998; **275**: G418-G424
27 **Coffin B,** Azpiroz F, Guarner F, Malagelada JR. Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. *Gastroenterology* 1994; **107**: 1345-1351
28 **Barbera R,** Feinle C, Read NW. Abnormal sensitivity to duodenal lipid infusion in patients with functional dyspepsia. *Eur J Gastroenterol Hepatol* 1995; **7**: 1051-1057
29 **Feinle C,** Meier O, Otto B, D'Amato M, Fried M. Role of duodenal lipid and cholecystokinin A receptors in the pathophysiology of functional dyspepsia. *Gut* 2001; **48**: 347-355
30 **Samsom M,** Verhagen MA, vanBerge Henegouwen GP, Smout AJ. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. *Gastroenterology* 1999; **116**: 515-520
31 **Vingerhagen S,** Hausken T, Gilja OH, Berstad A. Influence of a 5HT1 receptor agonist on gastric accommodation and initial transpyloric flow in healthy subjects. *Neurogastroenterol Motil* 2000; **12**: 95-101
32 **Koch KL,** Hong SP, Xu L. Reproducibility of gastric myoelectrical activity and the water load test in patients with dysmotility-like dyspepsia symptoms and in control subjects. *J Clin Gastroenterol* 2000; **31**: 125-129
33 **Thumshirn M,** Camilleri M, Saslow SB, Williams DE, Burton DD, Hanson RB. Gastric accommodation in non-ulcer dyspepsia and the roles of *Helicobacter pylori* infection and vagal function. *Gut* 1999; **44**: 55-64
34 **Salet GA,** Samsom M, Roelofs JM, van Berge Henegouwen GP, Smout AJ, Akkermans LM. Responses to gastric distension in functional dyspepsia. *Gut* 1998; **42**: 823-829
35 **Mertz H,** Fullerton S, Naliboff B, Mayer EA. Symptoms and visceral perception in severe functional and organic dyspepsia. *Gut* 1998; **42**: 814-822
36 **Lemann M,** Dederding JP, Flourie B, Franchisseur C, Rambaud JC, Jian R. Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. *Dig Dis Sci* 1991; **36**: 1249-1254
37 **Lydeard S,** Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. *J R Coll Gen Pract* 1989; **39**: 495-498
38 **Hu WH,** Wong WM, Lam CL, Lam KF, Hui WM, Lai KC, Xia HX, Lam SK, Wong BC. Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. *Aliment Pharmacol Ther* 2002; **16**: 2081-2088
39 **Koloski NA,** Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am J Gastroenterol* 2001; **96**: 1340-1349
40 **Cann PA,** Gleeson MH, Robinson TJ, Wicks AC. Assessing dyspepsia in general practice. *Br J Clin Pract* 1994; **48**: 263-267

Science Editor Guo SY **Language Editor** Elsevier HK