

POINT OF VIEW

Defining functional dyspepsia

Fermín Mearin¹ and José Luis Calleja²

¹*Instituto de Trastornos Funcionales y Motores Digestivos. Department of Digestive Diseases. Centro Médico Teknon. Barcelona, Spain.* ²*Department of Gastroenterology and Hepatology. Hospital Universitario Puerta de Hierro. Universidad Autónoma de Madrid. Madrid, Spain*

ABSTRACT

Dyspepsia and functional dyspepsia represent a highly significant public health issue. A good definition of dyspepsia is key for helping us to better approach symptoms, decision making, and therapy indications. During the last few years many attempts were made at establishing a definition of dyspepsia. Results were little successful on most occasions, and clear discrepancies arose on whether symptoms should be associated with digestion, which types of symptoms were to be included, which anatomic location should symptoms have, etc. The Rome III Committee defined dyspepsia as "a symptom or set of symptoms that most physicians consider to originate from the gastroduodenal area", including the following: postprandial heaviness, early satiety, and epigastric pain or burning. Two new entities were defined: a) food-induced dyspeptic symptoms (postprandial distress syndrome); and b) epigastric pain (epigastric pain syndrome). These and other definitions have shown both strengths and weaknesses. At times they have been much too complex, at times much too simple; furthermore, they have commonly erred on the side of being inaccurate and impractical. On the other hand, some (the most recent ones) are difficult to translate into the Spanish language.

In a meeting of gastroenterologists with a special interest in digestive functional disorders, the various aspects of dyspepsia definition were discussed and put to the vote, and the following conclusions were arrived at: dyspepsia is defined as a set of symptoms, either related or unrelated to food ingestion, localized on the upper half of the abdomen. They include: a) epigastric discomfort (as a category of severity) or pain; b) postprandial heaviness; and c) early satiety. Associated complaints include: nausea, belching, bloating, and epigastric burn (heartburn). All these must be scored according to severity and frequency. Furthermore, psychological factors may be involved in the origin of functional dyspepsia. On the other hand, it has proven very difficult to establish a clear correlation between symptoms and pathophysiological mechanisms.

Key words: Dyspepsia. Functional dyspepsia. Definition. Functional digestive disorders.

Received: 22-09-11.

Accepted: 22-09-11.

Correspondence: Fermín Mearin. Department of Digestive Diseases. Instituto de Trastornos Funcionales y Motores Digestivos. Centro Médico Teknon. C/ Vilana, 12. 08022 Barcelona, Spain.
e-mail: mearin@dr.teknon.es

Mearin F, Calleja JL. Defining functional dyspepsia. *Rev Esp Enferm Dig* 2011; 103: 640-647.

INTRODUCTION

Dyspepsia (and functional dyspepsia) represents a highly relevant public health issue with a substantial personal, professional, healthcare, financial, and social impact. It affects a huge number of people in the general population, is a common cause of work absenteeism, and entails enormous direct and indirect costs (1).

The prevalence of dyspepsia among the general population varies according to the criteria involved in its definition, and the method used to obtain such information. The mean prevalence as estimated from studies in several countries is around 25%, but oscillates between 8 and 54% (2-4). Dyspeptic symptoms are slightly more common in women, and usually decrease with age. In Spain dyspepsia represents 8.2% of visits to primary care clinics, and up to 40% of visits to gastroenterologists (5). However, only 50% of dyspepsia patients are supposed to seek medical help. The fact of visiting a clinic or otherwise is associated with symptom severity, fear of having a serious disease (particularly cancer), older age, anxiety, and lower socioeconomic status.

In 75% of dyspepsia cases upper GI endoscopy reveals no relevant lesions subsidiary of specific therapy (4). However, these patients with functional dyspepsia have a substantial decrease in quality of life.

IMPORTANCE OF A FUNCTIONAL DYSPEPSIA DEFINITION

Let us start from the beginning. What is a definition and what is it for? The *Real Academia Española* defines definition (no redundancy here) as a "proposition or formula

by means of which a sufficient set of properties is provided to univocally designate an object, individual, group or idea"; in addition, "a definition must be clear and accurate". This is why a good definition of dyspepsia allowing a better approach of complaints, decision making, and treatment indications is so important.

Words are what they mean and what people understand by them. In this respect, physicians have been for centuries (with absolute intent) extremely poor communicators, always trying to use the most complex terms and most confusing words to identify symptoms and diseases. Therefore, it is only logical that patients –and at times even we among ourselves– do not understand. And this is precisely what happens with the term "dyspepsia", which is obscurely used despite being most common in gastroenterology and primary care clinics because there is no consensus regarding its meaning. The *Real Academia Española* defines dyspepsia as "laborious, imperfect digestion that is chronic in nature" (not bad; we physicians did much worse for years). This definition is based on the etymology of the term dyspepsia, which is composed of the Greek words "dys" (bad or difficult) and "peptos" (to boil or digest). Therefore, its strict meaning would be "bad digestion". However, the term dyspepsia is currently used to denote symptoms or groups of symptoms not necessarily related to digestion.

Some physicians use the term dyspepsia to refer to any digestive discomfort, others use it to denote ingestion-triggered symptoms, and yet for others is a synonym of peptic ulcer disease. Moreover, it is not uncommon for some professionals to label as "dyspeptic" patients where no cause accounting for their complaints can be found, or more specifically when a psychological cause is held responsible for them. Such disparity in the use of one term is confusing, difficult medical communication, and leads to diagnose with one same syndrome patients with different symptoms of varying etiology.

The issue is further compounded when the meanings of dyspepsia –or its translated equivalents– are compared between different languages. For instance, it is interpreted differently by Scandinavian *versus* Latin physicians and patients. Therefore, clearly defining what we are talking (and writing) about and establishing concepts and criteria to ease up mutual understanding seems crucial. In this paper we have tried to sum up the current status of this issue, including the contributions of the Rome III consensus conference. In addition, the conclusions obtained in a consensus conference on dyspepsia are introduced. Time will tell if this is the right path to follow, but this will not be the last consensus or paper attempting to elucidate the huge complexity underlying this 9-letter word, dozens of meanings, and millions of affected subjects.

DEFINITIONS OF FUNCTIONAL DYSPESPSIA TO DATE

In the last few years many attempts at establishing a definition of dyspepsia were carried out. On most occasions

results were rather poor, and clear discrepancies have arisen regarding whether symptoms should be related to digestion, which type of symptoms should be included, the anatomical site of complaints, etc. Of course, this confusion results not only from the difficulties entailed by the definition itself but also from our vast lack of understanding regarding the pathophysiological mechanisms of dyspepsia.

In 1988 Talley and Phillips defined dyspepsia as "Chronic or recurrent pain or discomfort in the upper abdomen, or nausea, which may or may not be related to ingestion" (6). However, in that time other definitions were used, including "Pain in the upper abdomen or retrosternal area, heartburn, nausea, vomiting, or other symptoms attributable to the upper GI tract" (7) or "Episodic or persistent abdominal symptoms that either patients or doctors think are due to changes in the proximal digestive tract" (8).

Shortly afterwards the so-called "Rome" committees were established and, following a number of attempts, dyspepsia was defined in 1991 (Rome I criteria) and 1999 (Rome II criteria) as "Any pain or discomfort in the central upper abdomen" (9). This definition was certainly short and concise but not excessively explanatory. Nevertheless, it added some useful aspects: for instance that discomfort refers to a non-painful adverse sensation such as bloating, early satiety, distension or nausea; that symptoms may be on-going or intermittent whether related with ingestion or otherwise; and that heartburn should not be considered a dyspepsia symptom proper given its considerable specificity for gastro-esophageal reflux disease (GERD). Even so, the term "discomfort" is rather confusing both in Spanish and in English as it may be perceived as mild pain (quantitative difference) or a non-painful complaint (qualitative difference). Furthermore, "discomfort" is no Spanish word, and it is best translated as "molestia" or "incomodidad".

The Rome III committee recommends the following dyspepsia definition: "A symptom or set of symptoms that most physicians consider as originating in the gastroduodenal region" (10); and fortunately, in order to somewhat elucidate the issue, it adds: "... and these symptoms include postprandial heaviness, early satiety and epigastric pain or burning". The committee particularly highlights the differentiation between epigastric burning (considered a dyspeptic symptom) and heartburn (considered a GERD symptom), even though both complaints may overlap and some patients with functional dyspepsia also have gastroesophageal reflux (11).

A CLASSIFICATION OF DYSPESPSIA

Classically dyspepsia has been divided up into ulcerous and non-ulcerous dyspepsia according to its etiology. However, this classification seems not adequate enough since ulcer disease is only one among the potential organic causes of dyspeptic complaints. Other possibilities include gastric cancer or erosive duodenitis, among digestive causes, and a host of extradigestive etiologies. Dyspepsia is more appropriately categorized into organic and non-organic or functional dys-

pepsia. This separation is useful from a practical standpoint albeit the division between organic and functional may on occasion be quite arbitrary and depend on the depth of the study performed. Another key category of dyspepsia emerges here: non-investigated dyspepsia. Thus, to clear up things, dyspepsia may be classified into three different types:

1. Dyspepsia with an identified organic or metabolic cause in such a way that improvement in the underlying condition results in improved or eliminated dyspeptic symptoms. Causes include peptic ulcer disease, gastric cancer, biliopancreatic disorders, and drug-related etiologies.
2. Dyspepsia with no identifiable explanation for symptoms. It is the so-called functional dyspepsia, also known by other names such as non-organic dyspepsia, idiopathic dyspepsia, and essential dyspepsia.
3. Dyspepsia where no studies –basically upper GI endoscopy– have been performed yet in order to establish a potential organic character. This category is not uncommon as a full work-up is not absolutely necessary for many patients when age criteria are unmet and no alarm symptoms exist. Since symptom characteristics are not specific enough to tell organic dyspepsia from functional dyspepsia, the preferred approach should be the use of an appropriate label such as non-investigated dyspepsia.

In turn, attempts have been made at classifying functional dyspepsia according to its predominant pathogenetic mechanism: slow gastric emptying, changes in postprandial fundal relaxation, and visceral hypersensitivity. A correlation between such changes and specific symptoms has been suggested. Thus, an association has been unveiled between slow gastric emptying and fullness, nausea or vomiting (12), between fundal relaxation changes and early satiety or weight loss (13), and between gastric visceral hypersensitivity and epigastric pain or belching (14). However, this pathophysiological classification remains insufficiently accurate or useful, major overlapping exists between groups, some symptoms are associated with several mechanisms, and stability over time is unknown.

FUNCTIONAL DYSPEPSIA DEFINITION

Functional dyspepsia is defined as that which cannot be attributed to structural changes, metabolic conditions, or alcohol and drugs, and that presumably relates to upper GI tract function disorders or abnormal patient perception (9). However, physicians often diagnose with functional dyspepsia patients who have no dyspepsia or even no GI condition at all.

CURRENT DIAGNOSTIC CRITERIA FOR FUNCTIONAL DYSPEPSIA (ROME III)

In their 2006 report the Rome III committee proposed to define functional dyspepsia at two levels (10) –a general one

mainly for clinical use, no excessively different from previously used criteria, and a more specific definition for pathophysiological studies and therapy trials where two new entities are defined: a) ingestion-induced dyspeptic symptoms (postprandial distress syndrome or PDS); and b) epigastric pain (epigastric pain syndrome or EPS). This subdivision results from the fact that, while many patients with dyspepsia show ingestion-induced or ingestion-exacerbated symptoms, complaints set in for other individuals while fasting.

Functional dyspepsia definition

1. A bothering sensation of postprandial fullness, early satiety, epigastric pain, or epigastric burning.
2. No evidence of structural conditions (including on upper GI endoscopy) that might account for complaints.

Postprandial distress syndrome (PDS) definition

1. A bothering sensation of postprandial fullness after a standard-volume meal, at least several times a week; or
 2. An early sensation that prevents patients from normally ending a meal, at least several times a week.
- Support criteria:
- Upper abdominal bloating, postprandial nausea, or excessive belching may be present.
 - May coexist with EPS (epigastric pain syndrome).

Epigastric pain syndrome (EPS) definition

1. Pain or burning on the epigastrium, at least moderate in severity, with a minimum frequency of once per week.
2. Pain is intermittent.
3. Non-generalized or localized in other abdominal or thoracic regions.
4. Defecation or gas passing provides no relief.
5. Does not meet biliary pain criteria.
6. Pain may be burning in nature but not retrosternal.
7. Pain is commonly induced or relieved by food ingestion but may occur while fasting.
8. May coexist with PDS (postprandial distress syndrome).

These criteria should be present for the last 3 months and have begun at least 6 months prior to diagnosis.

2011 CRITICISMS OF THE ABOVE DEFINITIONS

The definitions for dyspepsia and functional dyspepsia so far have shown both benefits and drawbacks. In some cases they were too complex, in other instances they were excessively simple (e.g., “symptoms that patients or physicians believe to result from changes in the proximal GI

tract”); in addition, they commonly erred in being too inaccurate and impractical.

On the other hand, some definitions (those more recently issued) are not easily translated into Spanish. Thus a problem with dyspepsia definitions according to Rome I and Rome II criteria was the qualitative definition between pain and discomfort, which may also be interpreted as quantitative variants of one and the same symptom (with pain being more severe than discomfort); this seems to be the case in Spanish. Furthermore, no data support that visceral pain is mediated by different pathways or stronger stimuli as compared to complaints considered as “discomfort” (15). Moreover, in the classification of functional dyspepsia according to Rome III the term “postprandial distress syndrome” is difficult to understand and nearly impossible to recall (and use) by general practitioners. The word “distress”, translated as “distrés”, is alien to Spanish, and its proper translations (“dolor, angustia o aflicción”) are irrelevant.

KEY ASPECTS IN A DEFINITION OF DYSPESPSIA

Differentiating between specific symptoms, associated symptoms, and excluding symptoms is key for an adequate definition of dyspepsia. Other aspects should also be assessed, including the influence of psychological factors and the association of complaints with ingestion or lack thereof. Determining their location and establishing key criteria on the frequency of symptoms and the time since their onset is essential. Agreement on how symptoms should be graded according to intensity is also necessary. As symptoms are nonspecific establishing which patients should undergo tests to rule out other conditions, and which studies should be performed, is also mandatory. In turn, given the wide heterogeneity of patients with functional dyspepsia, an assessment should be made on whether pathophysiological mechanisms explaining specific symptoms are present.

CONSENSUS DECISIONS TO DEFINE FUNCTIONAL DYSPESPSIA

On February 10, 2011 a meeting of gastroenterologists was held in Madrid with a special interest in functional digestive disorders, where the various aspects of a dyspepsia definition as mentioned in the above section of this paper –and summarized in the conclusions below– were discussed and put to the vote.

CLINICAL ASPECTS

Specific symptoms

The following were unanimously endorsed: a) epigastric discomfort (as a severity category) or pain; b) post-

prandial heaviness; and c) early satiety. Other symptoms such as nausea, epigastric burning or abdominal bloating were suggested by some participants but were not accepted as specific dyspepsia symptoms.

The term “discomfort” in Spanish, used to translate the English term discomfort, has traditionally been controversial, as it was interpreted as mild pain or a different symptomatic complex including other non-painful symptoms such as fullness, early satiety, bloating, or even nausea.

Rome II criteria suggested a subdivision of patients with functional dyspepsia according to the presence of pain or discomfort. This classification has been severely criticized because of the difficult distinction between pain and discomfort, the high number of patients that simply will not fit in either category, and the absence of symptom stability even for short periods of time.

During the session discomfort was accepted as a grade of pain severity even though it was recognized that fullness or bloating are often labeled as pain depending on cultural, linguistic, and even educational factors.

Postprandial heaviness is understood as an unpleasant sensation of prolonged persistence of food inside the stomach.

Early satiety is defined as the feeling of having a full stomach shortly after starting a meal, disproportionate with the ingested amount of food, and preventing patients from ending that meal.

Associated symptoms

The following were unanimously endorsed:

1. Nausea, defined as an unpleasant sensation of urge to vomit.
2. Belching: the ingestion of air while eating is a normal physiological phenomenon, as is the release of some amount of gas as a result of transient relaxation in the lower esophageal sphincter. It may only be considered a symptom when excessive and troublesome. In the Rome II criteria it was recognized as an unusual symptom in patients with dyspepsia that could be related to a need to alleviate gastric distension in some patients. Anyway, Rome III criteria recognize it as a common symptom of varying etiology. Some studies find in patients with aerophagia an unconscious ingestion of air that enters the esophagus and is rapidly expelled towards the oral cavity, never reaching the stomach (16).
3. Abdominal distension must be visible and different from heaviness, which is a subjective term.
4. Epigastric burning. Most participants discussed the difficulties implied in telling epigastric burning from heartburn. In the Rome III criteria a sensation of epigastric burning is not considered to be heartburn unless it radiates toward the retrosternal area. In the past, the presence of heartburn or acidic regurgitation was considered sufficient to define dyspepsia, but these complaints are now recognized as key symptoms in the diagnosis of gastroesophageal reflux disease.

Excluding symptoms

No symptom was found that could rule out a diagnosis with dyspepsia as of itself.

Psychological component

There is clear evidence of an association of dyspepsia with psychological disorders. The mechanism of this association is unclear, as is whether they share some common predisposing factors.

All participants in the conference endorsed that any definition of dyspepsia should recognize that psychological factors (anxiety, depression, somatization) and/or a disrupted response to physical or psychological stress may be involved in its origin.

Relation to ingestion

Rome III criteria, in contrast with the previous ones, consider two patient subgroups according to the relations of symptoms to food ingestion. Patients categorized within the epigastric pain syndrome meet the general criteria of functional dyspepsia and also exhibit intermittent epigastric pain or moderate epigastric burning at least once a week; from a pathophysiological standpoint these symptoms result from excessive visceral hypersensitivity (17). Patients included in the so-called postprandial distress syndrome meet the general criteria of functional dyspepsia and also have feelings of fullness or early satiety several times a week, which on occasion prevents them from ending their meal; from a pathophysiological perspective these symptoms mainly result from an accommodation disorder, a gastric emptying disorder, or both (17).

In the ensuing discussion most attendants found the relationship between symptoms and food ingestion irrelevant, and recognized that any symptom in a patient with dyspepsia may or may not be related to food ingestion. Therefore, in contrast to Rome III criteria, including this aspect in a definition of dyspepsia seems inappropriate.

LOCALIZATION

The term upper hemiabdomen was unanimously chosen to define where dyspepsia is localized. Some participants suggested the addition of "particularly in the epigastrium" for increased specificity.

The term epigastrium is defined as the area comprised between the distal sternum and the navel, limited on both sides by the prolongation of the midclavicular line downwards.

TIME FACTORS

Overall dyspepsia—though not functional dyspepsia—may be categorized as acute or chronic. For a definition of functional dyspepsia according to Rome III criteria symptoms should develop at least 6 months before diagnosis and be present during the last 3 months.

SEVERITY

It was unanimously decided that functional dyspepsia should be graded according to symptom severity and frequency. The grading scale should include the terms mild, moderate, and severe. This grading should be carried out according to symptom impact on patient quality of life. A number of studies have shown that this disorder—which is considered a benign disease—significantly reduces quality of life for involved patients. In a study performed in Spain on the impact of various diseases on quality of life that included over 2,800 patients, functional GI disorders were seen to reduce the physical component as much as other disorders such as hypertension, ulcerative colitis, and hepatitis C. Furthermore, when the mental component was assessed a higher impact was unveiled as compared to hypertension or diabetes mellitus (18).

Numerous questionnaires allow assessing the impact of functional dyspepsia on quality of life, including the "Dyspepsia Related Health Scales" (DRHS), which has been validated in Spanish (19). This assessment of quality of life should also be present in clinical studies assessing the potential effectiveness of a given therapy for patients with dyspepsia, perhaps not replacing but certainly supplementing the standard overall improvement and symptom reduction scales.

EXCLUSION DIAGNOSIS

Functional dyspepsia represents a clinical diagnosis, and other diseases should be ruled out. The expert panel decided to divide the need to rule out other diseases up into absolute and relative indications. There is an absolute indication for the exclusion of other disorders in patients with alarm signs or symptoms such as significant weight loss, recurrent vomiting, progressive dysphagia, and gastrointestinal bleeding. The indication is relative for patients older than 50, and depends upon symptom duration and response to treatment.

WORK-UP FOR EXCLUSION

Most experts considered upper GI endoscopy and laboratory testing essential for all patients where other disorders should be ruled out. Upper GI endoscopy allows a detailed study of the gastroduodenal mucosa and the exclusion of most of the significant structural disorders. A barium study is not

indicated as it is usually less sensitive and specific than endoscopy.

Some conference attendants considered the performance of a breath test for lactose intolerance and anti-transglutaminase antibodies levels for patients with associated abdominal distension. Most participants did not accept abdominal ultrasounds as a key test for the study of patients with dyspeptic symptoms given its low diagnostic yield in the absence of clinical or laboratory data suggesting a biliopancreatic disease. Furthermore, the mere presence of bile stones is seemingly not associated with the onset of dyspepsia-related manifestations

TECHNIQUES FOR A DEFINITIVE DIAGNOSIS

No specific diagnostic tests are available for functional dyspepsia. Tests such as gastric emptying measurement, barostat for visceral sensitivity, and satiety testing may be useful for research but not so in daily practice.

RELATION TO PATHOPHYSIOLOGICAL MECHANISMS

Rome III criteria categorize functional dyspepsia according to the relationship of symptoms with food ingestion, and suggest that heterogeneity in symptoms may correspond to different pathophysiological mechanisms. Gastric emptying is slower in patients with dyspepsia *versus* healthy controls, but its specific relation to symptoms within the so-called postprandial distress syndrome, including postprandial heaviness or early satiety, is controversial, and cannot be clearly established (20). All these aspects were evaluated during the conference, and it was concluded that a clear correlation between symptoms and pathophysiological mechanisms is both ineffective and difficult to establish from a practical standpoint.

CONCLUSION: CONSENSUS DEFINITION

Dyspepsia is defined as a set of symptoms, whether associated with food ingestion or otherwise, that are localized on the upper hemiabdomen and include: a) epigastric discomfort (as a severity category) or pain; b) postprandial heaviness; and c) early satiety. Associated symptoms include: nausea, belching, abdominal distension, and epigastric burning. They should all be graded regarding severity and frequency.

In addition, in the case of functional dyspepsia, the fact that psychological factors may be involved in its origin should be recognized. Difficulties in establishing a clear correlation between symptoms and pathophysiological mechanisms are acknowledged.

There is an absolute indication for the exclusion of organic disorders in patients with alarm signs or symp-

toms such as severe weight loss, recurrent vomiting, progressive dysphagia, or gastrointestinal bleeding evidence. This indication is relative for patients over 50 years of age depending on symptom duration and response to treatment. In such cases upper GI endoscopy and laboratory testing are due. No specific diagnostic tests are available for functional dyspepsia.

PHYSICIANS WHO TOOK PART IN THE CONSENSUS CONFERENCE

Coordinators: Fermín Mearin (Clínica Teknon, Barcelona), José Luis Calleja (Hospital Universitario Puerta de Hierro, Madrid).

Participants: Miguel Bixquert (Hospital Arnau de Vilanova, Valencia), Vicente Cervera (Hospital Arnau de Vilanova, Valencia), Ángel González Galilea (Hospital Reina Sofía, Córdoba), Pedro Hergueta (Hospital Universitario Virgen Macarena, Sevilla), Maribel Herrero (Hospital de Jerez), Carlos Jiménez (Hospital Infanta Cristina, Badajoz), Francisco Jorquera (Hospital de León), Magdalena Llabrés-Roselló (Hospital Son Dureta, Palma de Mallorca), Ramiro Macenlle (Hospital del Chou, Orense), Carlos Martín de Argila (Hospital Universitario Ramón y Cajal, Madrid), Antonio López Higuera (Hospital Morales Messeguer, Murcia), José Luis Martín Lorente (Hospital General Yagüe, Burgos), Concepción Muñoz (Hospital de Toledo), Manuel Ramos (Hospital Juan Ramón Jiménez, Huelva), Ana Ruiz Guinaldo (Hospital de Jerez), Jordi Serra (Hospital Germans Trias i Pujol, Badalona), María Poca (Hospital Santa Creu y Sant Pau, Barcelona), Manuel Sánchez Gili (Hospital de Bellvitge, Barcelona), Manuel Suárez (Hospital de San Rafael, La Coruña), Javier de Teresa (Hospital Ruiz de Alda, Granada).

ACKNOWLEDGMENTS

The coordinators and participants are grateful to Recordati España, SA for their financial support regarding the meeting logistics.

REFERENCES

1. Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil* 2008;(Supl. 1):121-9.
2. Heading RC. Prevalence of upper gastrointestinal symptoms in the general population: a systematic review. *Scand J Gastroenterol Suppl* 1999;231:3-8.
3. Stanghellini V. Three month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl* 1999;231:20-8.
4. Moayyedi P, Mason J. Clinical and economic consequences of dyspepsia in the community. *Gut* 2002;Suppl. 4:iv10-2.

5. Caballero Plasencia AM, Sofos Kontoyannis S, Martín Ruiz JL, Valenzuela Barranco M. La prevalencia de dispepsia en España. *Med Clin (Barc)* 1994;103:717.
6. Talley NJ, Phillips SF. Non-ulcer dyspepsia: Potential causes and pathophysiology. *Ann Intern Med* 1988;108:865-79.
7. Colin-Jones DG, Bloom B, Bodemar G, Crean G, Freston J, Gugler R, et al. Management of dyspepsia: Report of a working party. *Lancet* 1988;1:576-9.
8. Barbara L, Camilleri M, Corinaldesi R, Crean GP, Heading RC, Johnson AG, et al. Definition and investigation of dyspepsia. *Dig Dis Sci* 1989;34:1272-6.
9. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada J-R, Tytgat GNJ. Functional gastroduodenal disorders. *Gut* 1999; (Supl.45):37-42.
10. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. Functional gastroduodenal disorders: a working team report for the Rome III consensus on functional gastrointestinal disorders. *Gastroenterology* 2006;130:1466-79.
11. Tack J, Caenepeel P, Arts J, Lee KJ, Sifrim D, Janssens J. Prevalence of acid reflux in functional dyspepsia and its association with symptom profile. *Gut* 2005;54:1370-6.
12. Sarnelli G, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003;98:783-8.
13. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998;115:1346-52.
14. Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. *Gastroenterology* 2001;121:526-35.
15. Vandenberghe J, Vos R, Persoons P, Demyttenaere K, Janssens J, Tack J. Dyspeptic patients with visceral hypersensitivity: sensitization of pain specific or multimodal pathways? *Gut* 2005;54:914-9.
16. Hemmink GJ, Weusten BL, Bredenoord AJ, Timmer R, Smout AJ. Aerophagia: excessive air swallowing demonstrated by esophageal impedance monitoring *Clin Gastroenterol Hepatol* 2009;7:1127-9.
17. Miwa H, Watari J, Fukui H, Oshima T, Tomita T, Sakurai J, et al. Current understanding of pathogenesis of functional dyspepsia. *J Gastroenterol Hepatol* 2011;26(Supl. 3):53-60.
18. Mearin F, Balboa A, Calleja JL. What patients with functional digestive disorders complain about? *Gastroenterology* 2008;134(Supl. 1):A-425.
19. Ruiz M, Vilasante F, León F, González-Lara V, González C, Crespo M, et al. Cuestionario sobre calidad de vida asociada a dispepsia. Adaptación española y validación del cuestionario Dyspepsia Related Health Scale. *Med Clin (Barc)* 2001;117:567-73.
20. Samelli G, Caenepeel P, Geypens B, Janssens J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003;98:783-8.