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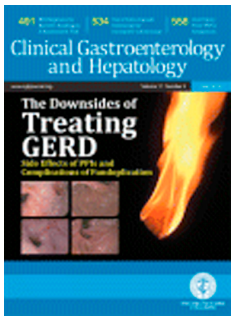

Analysis of Postprandial Symptom Patterns in Subgroups of Patients With Rome III or Rome IV Functional Dyspepsia

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Title: Analysis of Postprandial Symptom Patterns in Subgroups of Patients With Rome III or Rome IV Functional Dyspepsia

Short title: Postprandial symptom patterns in functional dyspepsia subgroups

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JT takes responsibility for the integrity of the work as a whole, from inception to published article. All authors approved the final version of the manuscript.

AUTHORS INVOLVED WITH THE MANUSCRIPT: JT, FC: study concept and design; JT, FC: acquisition of data; JT, TV, FC: analysis and interpretation of data; JT, TV, FC: drafting of the manuscript; critical revision of the manuscript.

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Abstract:

Background & Aims: Among patients with functional dyspepsia (FD), there is overlap in symptoms between those in the Rome III subgroups of postprandial distress syndrome (PDS) and those with epigastric pain syndrome (EPS). The Rome IV consensus proposed to incorporate all patients with postprandial symptoms into the PDS group. We aimed to evaluate the assessment of meal-related dyspepsia symptoms in patients with FD according to the Rome III vs Rome IV subdivisions.

Methods: Consecutive patients with FD referred for a gastric emptying test (n=96) were asked to fill out the Rome III gastroduodenal questionnaire, with questions on meal-related occurrence. Study participants underwent a gastric emptying breath test, during which the intensity of dyspeptic symptoms (fullness, bloating, belching, nausea, epigastric pain, and burning) was scored before and up to 4 hours after a meal. We analyzed the association between the Rome subdivision and symptom severity and pattern during the breath test.

Results: EPS According to Rome III, 10% had EPS alone, 29% PDS alone, and 61% overlapping EPS and PDS. The frequency of the symptoms reported in the Rome questionnaire associated with the intensity of the symptoms during the breath test in the PDS group and in the groups with PDS and EPS overlap, but not in the group with EPS. We adapted the definition of the PDS subgroup to include patients with meal-related non-PDS symptoms (Rome IV); this reduced the proportion of patients with overlap of EPS and PDS symptoms from 61% to 18% and in this group the association of symptoms with the meal was reduced.

Conclusions: In an analysis of patients with FD, a meal induced or exacerbated symptoms in most patients. The Rome IV criteria for PDS reduce the proportions categorized as having both PDS and EPS and identify a patient group whose symptoms are associated with the meals. University hospital of Leuven study no: S55426.

KEY WORDS: Rome classification, diagnostic, diagnosis, food

Need to Know

Background: Among patients with functional dyspepsia (FD), there is overlap in symptoms between those in the Rome III subgroups of postprandial distress syndrome (PDS) and those with epigastric pain syndrome (EPS). The Rome IV consensus proposed to incorporate all patients with postprandial symptoms into the PDS group.

Findings: In an analysis of patients with FD, found a meal to induce or exacerbate symptoms in 65% of patients. Questionnaires on meal-related symptoms help to accurately classify patients as PDS vs EPS.

Implications for Patient Care: Rome IV criteria for PDS reduce the proportions categorized as having both PDS and EPS and identify a homogenous group with meal-related symptoms.

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INTRODUCTION

Functional dyspepsia (FD) is defined as “the presence of symptoms thought to originate from the gastroduodenal region, in the absence of organic disease that is likely to explain the symptoms” (1). FD is a heterogeneous condition, with different underlying pathophysiological mechanisms, and this may also negatively impact on the efficacy of therapeutic interventions targeting a single mechanism (2).

Taking into account this heterogeneity and based mainly on expert opinion, the Rome III consensus subdivide FD into Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS) to guide the diagnostic and therapeutic approach of FD patients (3). PDS is characterized by meal-related symptoms such as early satiation and postprandial fullness. EPS is characterized epigastric pain or burning which are considered meal-unrelated symptoms.

Clinic samples of FD patients display a large overlap between PDS and EPS, which hampers the usefulness of the subdivision. Clinical observations and preliminary questionnaire studies indicated that an important subgroup of FD patients reports postprandially occurring symptoms of epigastric pain or nausea (4-6). Previously, we proposed an adaptation on the FD subgroup definition by considering postprandial non-PDS symptoms epigastric pain and nausea as part of the “adapted” PDS group, as this generated a better separation of PDS and EPS (7). This was implemented in the Rome IV consensus, where other postprandially occurring symptoms are now also categorized as PDS symptoms. However, elaborating on this potentially improved subdivision requires more detailed studies of the relationship between symptoms and meal ingestion in the respective groups.

The main aim of this study was to evaluate in detail the relationship of dyspepsia symptoms to meal ingestion in FD patients subdivided according to the Rome III and the Rome IV subdivisions. The first objective of this study was to explore the meal-relationship of the symptoms and its impact in the different FD subgroups as defined by Rome III. The second aim was to test the ability of reducing the PDS/EPS overlap by taking into account meal-related non-PDS symptoms in the PDS population, as defined by Rome IV.

METHODS

All authors had access to the study data and reviewed and approved the final manuscript.

Patient selection and general study design

Consecutive dyspeptic patients referred for a gastric emptying test were asked to fill out the Rome III gastroduodenal questionnaire with supplementary questions as previously reported (8-10). FD Diagnoses was done an expert gastroenterologist. Patients were excluded if the failed to fill out the questionnaire adequately, if they had abnormal findings on upper GI endoscopy, and if they had a history of upper digestive surgery, diabetes, coeliac disease, inflammatory bowel disease or predominant symptoms of other disorders such as IBS, GERD, dysphagia or globus.

Patients were properly informed about the study and provided witnessed written informed consent. The study was approved by the ethics committee of Leuven University Hospitals in Belgium (EC study number S55426) and was performed in accordance to Good Clinical Practice (GCP) guidelines.

Exploratory analysis of supplementary questions on postprandial symptoms

Supplementary document includes the description on the three supplementary questions on postprandial epigastric pain and nausea.

Rome III and IV subgroup classification

The Rome III criteria subdivide FD patients into Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS). Finally, the overlapping EPS-PDS subgroup was comprised of patients with both PDS and EPS symptoms according to Rome III definitions.

The Rome IV classification identified PDS and EPS on similar grounds, but also considered postprandial epigastric pain and postprandial nausea as PDS symptoms. See supplementary documents.

Gastric emptying (GE) breath test

The gastric emptying breath test is a standard diagnostic tool to measure gastric emptying rate in patients with dyspeptic symptoms (11, 12). The gastric emptying breath test protocol is summarized in the supplementary documents.

Data and statistical analysis

Patients were first subdivided into EPS and PDS subgroups according to the Rome III classification, and then according to the Rome IV classification, the latter taking into account the meal-relationship of non-PDS symptoms, as previously reported (18).

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The severity of meal-related dyspeptic symptoms was defined as the sum of the severity scores at every time point for fullness, epigastric pain, epigastric burning, nausea and bloating, recorded during the breath test after the ingestion of a standardized meal. The cumulative meal-related dyspepsia symptom severity was compared between groups using a Mann–Whitney test for non-parametric analysis of unpaired non-normally distributed data.

Spearman correlation testing and concordance correlation coefficient was used to study the relationship between the reported frequency of a symptom (Rome III) and the severity of that symptom during the breath test.

The time course of the severity of the symptoms during the breath test was studied for the entire FD population as well as for the different subgroups. The average time course of symptoms after the meal was compared to the symptoms reported before the meal. The maximal score and the time to reach maximal score was calculated and the area under the curve (AUC) was assessed for each symptom. The area under the curve gives an additional perspective on meal-related symptom severity as it sums the severity scores for a given symptom over the 4-hours postprandial time segment. Severity scores of the symptoms over time were compared using One-way Anova, Friedman test with repeated measures and post-hoc Dunn testing. Spearman correlation was used to quantify the meal-relationship characteristics determined by the supplementary meal-related questions and the severity of the symptoms during the breath test. In addition, the relationship between the severity of dyspepsia symptoms and the GE rate was evaluated.

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RESULTS

Entire patient population.

Dyspepsia patient population

168 patients (67% females, 44.9±1.2 years old and a BMI of 27.7±2.2 kg.m^2) who were referred for a GE breath were evaluated. Of these, 110 patients (72% females, 44.9±1.6 years old, 27.3±2.5 kg.m^{-2}) were characterized as FD (Table 1 and supplementary Table 1).

Meal-related symptom association in FD

During the breath test, the symptom scores were measured before (time point 0) and up to 240 min after ingestion of a standard meal. Immediately after the meal, all symptoms increased compared to baseline, except for belching. Repeated measures Friedman test was significant for all symptoms ($p< 0.0005$). The AUC was highest for fullness, followed by bloating, epigastric pain, nausea, belching and burning. Postprandial fullness (maximal score:1.82±0.12; AUC:134.9±8.0 min and bloating (maximal score:1.30±0.12; AUC:110.6±6.5 min) increased rapidly after meal ingestion to reach a peak intensity at time point 30 min for and at time point 45 min for belching (maximal score:1.05±0.1; AUC: 84.9±4.3 min) followed by a gradual decrease, in the case of fullness even below baseline. The scores for epigastric pain (T_{max}:60 min; maximal score: 1.18±0.13; AUC:107.4±2.9 min), nausea (T_{max}:75 min; maximal score:1.09±0.14; AUC:94.2±2.2 min) and burning (T_{max}:105 min ; maximal score: 0.99±0.13; AUC: 81.9±3.8 min) increased significantly from baseline directly after the meal but reached a maximal score from one hour or later after ingestion. The elevated symptom intensity score was maintained until the end of the measurement period (Figure 1).

Most patients (65%) reported the symptoms to be aggravated or triggered by the meal ("yes" to the first supplementary question). The meal-related symptom score was significantly higher in this group and the BMI was lower compared to the non-meal related subgroup (75.9±9.1 vs. 107.3±8.3; p=0.02 and 25.4±0.9 vs. 23.6±0.5 kg.m-2; p=0.1). In patients with reported aggravation of symptoms by the meal, a significant correlation was found between symptom frequency responses on the Rome questionnaires and the severity measured after the meal for all symptoms (supplementary table 2). In the group who did not report aggravation after a meal, a significant correlation was found for postprandial fullness, nausea and bloating (supplementary table 2).

Meal-related symptom and gastric emptying rate in FD

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GE was delayed in 20% of the patients and accelerated in 3% of the patients. The half emptying time was not correlated to the total dyspepsia symptom score reported during the GE test (r=0.05, p=0.64). Nausea is generally associated with delayed GE in idiopathic gastroparesis (13). A weak correlation was found between the gastric half emptying time and the frequency of nausea in the Rome III questionnaire (r= 0.20; p=0.04), but not between the half emptying time and the severity of nausea during the breath test (r=0.12; p=0.20).

Subdivision according to Rome III definitions

Rome III subdivision and meal-relationship

Of the 96 included FD patients, 9 were classified as EPS alone, 29 as PDS alone and 58 as overlapping EPS and PDS according to the Rome III consensus (see Table 1 and supplementary figure 1). More than 70% of the patients in the Rome III-defined "pure" PDS and overlap subgroup reported the symptoms to be aggravated by the meal (supplementary Table 3).

In the PDS subgroup, the frequency of nausea, epigastric burning and belching in the last 3 months correlated with the severity of these symptoms during the breath test. This was not the case for bloating and epigastric pain (Table 3). The EPS subgroup did not show any correlation between the reported frequency of dyspepsia symptoms on the Rome questionnaire and severity scores of those symptoms during the breath test. In contrast, in the overlap PDS/EPS subgroup symptom frequency as defined by the Rome III for all symptoms was significantly correlated to the meal-related symptom severities assessed after the breath test standardized meal (Table 2).

The time course of the severity of the symptoms during the GE test was compared between the different subgroups. In the PDS group symptom intensities increased after the meal (Figure 2A and Table 3). In the PDS group, a significant time effect was observed for bloating ($p< 0.0001$), postprandial fullness ($p< 0.0001$) belching ($p< 0.0001$) and borderline for burning ($p=0.05$) compared to baseline. Time effects for nausea ($p=0.61$) and epigastric pain ($p=0.91$) were not significant.

In the EPS subgroup, repeated measures Friedman test showed that bloating ($p< 0.0001$), postprandial fullness ($p< 0.0001$) and burning ($p< 0.001$) significantly changed over time after the meal, while for nausea ($p=0.26$), epigastric pain ($p=0.63$) and belching ($p=0.39$) this was not significant (Figure 3B and Table 4).

The PDS and the overlap group showed strikingly similar symptom patterns (Figure 3A and Table 4). In this subgroup, all symptoms showed a significant time effect using the repeated measures Friedman test ($p< 0.0001$) (Figure 2C and Table 3).

Meal-related symptoms and gastric emptying rate according to the Rome III subdivision

For PDS patients according to the Rome III subdivision, GE half time was 85.2±5.1 minutes (14% delayed). It was 75.4±7.0 minutes (0% delayed) for the EPS alone and 90.4±5.9 min (23% delayed) for the overlap subgroups. There were no significant differences between the half GE time of these subgroups ($p=0.25$, Kruskal Wallis test).

A modest correlation between the half emptying time and the cumulative dyspepsia severity score ($r=0.36$; $p=0.006$) and nausea ($r=0.31$, $p=0.02$) was observed in the overlap subgroup. For PDS, however, no significant association was observed for the GE $T_{1/2}$ time and the nausea ($r=-0.14$; $p=0.49$) or cumulative dyspepsia symptom score ($r=-0.29$; $p=0.14$). No correlation was found between the symptom scores and GE test results ($r=0.16$; $p=0.68$) in the EPS subgroup.

Subdivision according to Rome IV definitions

Rome IV subdivision and meal-relationship

Patients were subdivided as previously described, and in line with the Rome IV consensus (5,18). The Rome IV-defined PDS population included 70 patients (73%; 77% females, 43.1±2.1 years old, BMI 27.4±3.5 $Kg.m^2$) and the overlap EPS/PDS subgroup was reduced to 17 patients (18%; 53 % females, 45.9±3.7 years old, BMI 29.2±6.6 $Kg.m^2$). The pure EPS subgroup was not altered from the Rome III subdivision (9%) (Supplementary figure 1).

Most Rome IV-defined “pure” PDS (82%) answered “yes” to the meal-related symptom questions. In the overlap PDS-EPS subgroup, this was 47% (compared to 72% using the Rome III subdivision) (supplementary Table 3).

In the PDS subgroup, the symptom frequency on the Rome questionnaire was significantly correlated to the severity of meal-related symptoms for all symptoms. In the Rome IV PDS/EPS overlap subgroup, a significant correlation was only found for epigastric burning and belching, and a borderline significance was found for nausea (Table 2).

The time course of the severity of the symptoms during the GE test in the PDS subgroup continued to show a relationship to the ingestion of the meal (Figure 3). Repeated measures Anova showed that all symptoms changed over time after the meal ($p< 0.001$). In the Rome IV overlap group, the severity of the symptoms was only significantly increased for postprandial fullness and belching ($p< 0.0001$), but not for the other symptoms.

Meal-related symptoms and gastric emptying rate according to the Rome IV subdivision

According to the Rome IV subdivision, GE was delayed in 23% of the PDS subgroup (average: 93.4±5.0 min), in 0% of the EPS subgroup (average: 75.4±7.0 min) and in 7% of the overlap PDS/EPS subgroup (average: 71.1±6.3 min). Not significant correlation of the half emptying time with the meal-related dyspepsia symptom severity scores PDS subgroup ($r=0.16$; $p=0.17$), or for the Rome IV overlap PDS/EPS subgroup ($r=0.27$; $p= 0.29$) was observed.

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DISCUSSION

The Rome III consensus proposed subdivide FD patients with meal-related FD symptoms (PDS) and patients with meal-unrelated FD symptoms (EPS). Epidemiological studies supported the existence of these subgroups as separate entities (3). However, in patients coming to medical attention, a major overlap between both groups was found, which hampered the usefulness of the subdivision. Previously, we have reported that an important subgroup of FD patients reports non-PDS symptoms which are mainly occurring postprandially, and that their recognition may help to reclassify FD patients outside the overlap subgroup into the meal-related subgroup (4-6). These and other observations have led to a change in subdivision criteria for the Rome IV consensus.

In the present study we further analysed the impact of the changes made in the Rome IV subdivision for FD on the relationship of individual dyspepsia symptoms to meal ingestion. This analysis was performed in FD patients undergoing a GE test during which the occurrence and severity of 6 epigastric symptoms were systematically quantified after the ingestion of the standardized empting test meal. We compared the time course and relationship of the meal-related symptoms to the Rome III and Rome IV-defined subgroups of FD.

The 65% of FD patients who reported this were characterized by a higher symptom severity score after a standardized meal. Furthermore, in those patients reporting triggering of symptoms by a meal, a good correlation was found between the frequency of dyspepsia symptoms on the Rome III questionnaire and the symptom intensities recorded after the standardized breath test meal, supporting the validity of a simple question to adequately identify a group of FD patients with meal-related symptoms.

After subdividing FD patients (Rome III), the frequency of symptoms in the PDS and in the overlap PDS/EPS group correlated well with the meal-related symptom intensities scored after ingestion of the standardized meal. In these groups, most of the dyspepsia symptoms peaked shortly after the meal, with the exception of bloating in the PDS subgroup. Bloating is also frequently associated with lower gastrointestinal disorders, such as IBS, and hence can originate from other parts than the gastroduodenal region. Consequently, the Rome consensus considers bloating not a cardinal symptom, but an accessory symptom that may coexist in FD provided that it is not relieved by a bowel movement. In the present study, patients did report bloating as a frequent and bothersome symptom, but patients with

predominant IBS symptoms were excluded, potentially decreasing an impact of lower GI symptoms.

In the EPS subgroup (Rome III), no correlations were found between the Rome questionnaire with the additional meal-related questions and the postprandial symptom severity scores, confirming the lack of relationship of EPS symptoms to ingestion of the meal. The EPS symptom severity profile showed clear differences from the PDS and PDS/EPS overlap subgroups, suggesting a different pathophysiological basis for symptom generation. Indeed, while PDS is mainly considered a disorder of motor control, EPS has been related to gastric and duodenal (acid, mechanical distention) hypersensitivity (10, 14, 15), *H. pylori* infection (16) and low grade inflammation and increased mucosal permeability in the duodenum (17-20).

We have previously proposed an adaptation of the Rome subgroups definition which considers postprandially occurring epigastric pain part of the PDS subgroup, in order to reduce the overlap subgroup (7). Furthermore, the Rome IV consensus now recognizes postprandial pain and nausea part of PDS. In the present study, 53% of the FD patients had overlapping PDS/EPS symptoms (Rome III), and by revising the subdivision, the PDS/EPS overlap group decreased to 18%. In this Rome IV based PDS/EPS overlap subgroup, the relation of meal-related symptom severity with the symptoms reported in the Rome questionnaire became less significant, and only the severity of nausea and epigastric pain increased significantly from baseline to one hour after the meal.

Finally, the relationship and separation between FD and idiopathic delayed GE continues to be a topic of intense debate. Both conditions share symptom pattern, pathophysiological alterations and a therapeutic approach with prokinetic drugs (21, 22). In the present study, in line with several previous observations (23-25), the severity of symptoms was inconsistently and poorly associated to the GE rate in FD as a group or in the different subgroups, suggesting that delayed GE is not the primary mechanism underlying meal-related symptoms.

Taken together, these data support the hypothesis that FD symptoms are generated differently in EPS compared to especially the Rome IV PDS subgroup. Previously, Vanheel *et al*. demonstrated that the time course of dyspeptic symptom generation is probably related to the location of the meal in the gastroduodenal region (5). In line with this concept, our data support the hypothesis that symptoms in the Rome IV PDS population are originating from

the stomach, while symptoms in the Rome IV EPS and possibly also the Rome IV overlap group may originate from the duodenum or jejunum.

As many studies, this study has some limitations. The Rome questionnaire is based on symptom frequency of at least the previous 3 months, while during this study, the gastric emptying test with a standardized meal was used as an acute trigger for symptoms, of which the severity was scored. The Rome questionnaire may therefore be more susceptible to recall bias. The meal during the gastric emptying test is extremely standardized, but it may not be representative for the patient's daily diet and hence have a less relevant symptom inducing effect. The patients may also experience different symptoms or severities compared to what occurs during their regular diet. Finally, the number of EPS patients is small, but this is in line with previous studies which have also shown that EPS is a less prominent subgroup (3, 7, 25-27). Furthermore, the focus of the current analysis was on the overlap group, rather than the EPS group, and the overlap group according to Rome III was the biggest subgroup.

In conclusion, this study confirms that the meal plays an important role in the triggering or aggravation of symptoms in FD. Using the Rome IV consensus definitions, taking into account the meal-related symptoms, substantially reduces the overlap between EPS and PDS, with a proportionate increase of the Rome IV PDS group. The symptoms of Rome IV EPS patients and of Rome IV overlap subgroup patients lack a clear link to the meal suggesting a different pathophysiological mechanism.

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FIGURE LEGENDS

Figure 1.Time Course of symptom severity scores in all FD patients (n=110).

Figure 2. Time course of the severity score of (a) PDS, (b) EPS and (c) overlap PDS/EPS symptoms.

Figure 3. Time course of (a) the “adapted” subdivision of PDS patients and (b) the overlap PDS/EPS subgroup.

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TABLES

Table 1: Symptom characteristics of FD patients.

Table 2. Symptom frequency correlated to symptom severity (Rome III and Rome IV)

Table 3. Overview of symptoms characteristics during the GE test in the different subgroups (Rome III and Rome IV).

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SUPPLEMENTARY FIGURES AND TABLES

Supplementary Figure 1. Overview of proportions of FD subgroups as predefined by Rome III and by Rome IV criteria.

Supplementary Table 1. Diagnosis in the patient population referred for a GE breath test.

Supplementary Table 2: Association between frequency score on the Rome III questionnaire and the severity score during the GE test. FD patients (n=96) were subdivided dependent to their answers to the first supplementary question “Is your epigastric pain or discomfort frequently triggered or aggravated by the meal?” *NS: no significant (p>0.05)*

Supplementary Table 3. Prevalence of answered supplementary questions, maximal severity score (0-4) and symptoms characteristics during the breath test per subgroup. Questions:

1. Presence of symptoms usually triggered or aggravated by the meal (answer: “yes” or “no”);
2. Frequency at epigastric pain triggered or aggravated by the meal (answer: 0 “not present” to 5 “always”
3. Frequency at nausea was triggered or aggravated by the meal (range 0-5 as above).

*A score of 3 (“often”) was accepted as indicative of a meal-relationship.

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Table 1. Symptom characteristics of FD patients; Rome III subdivision.

Dyspeptic symptom	Functional dyspepsia (n=96)	Rome III PDS (n=29)	Rome III EPS (n=9)	Rome III Overlap (n=58)
Age (years)	43.9±1.7	40±2.9	46.2±5.9	45.4±2.2
Gender (% female)	74%	69%	89%	61%
BMI ($Kg.m^2$)	27.5±2.8	24.5±1.1	25.5±1.6	29.2±4.5
Postprandial fullness	91%	100%	0%	100%
Early satiation	63%	62%	0%	72%
Upper abdominal bloating	80%	93%	0%	86%
Nausea	58%	55%	44%	62%
Postprandial nausea	51%	31%	0%	36%
Epigastric pain	71%	0%	100%	100%
Postprandial epigastric pain	51%	0%	0%	71%
Epigastric burning	35%	24%	56%	38%
Excessive belching	59%	54%	44%	62%
Heartburn	47%	38%	78%	59%
Delayed gastric emptying time ($T_{1/2}$>109 min)	18%	14%	0%	23%

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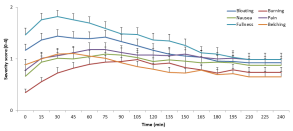
Table 3. Correlation (Pearson R) between frequency score on the Rome questionnaire and the severity score (Area under the curve during 4 hours postprandial severity scores at 15 minute intervals) during the GE test in Rome III and Rome IV FD subgroups. Statistically significant correlations are shown in a grey shaded cell.

Rome III FD subgroups			Rome IV FD subgroups		
Rome III PDS (n=29)	**r**	**p-value**	**Rome IV PDS (n=70)**	**R**	**p-value**
Bloating	0.14	NS, p=0.46	**Bloating**	0.37	0.0017
Nausea	0.68	<0.0001	**Nausea**	0.61	<0.0001
Epigastric pain	0.13	NS, p=0.51	**Epigastric pain**	0.59	0.0001
Epigastric burning	0.43	0.02	**Epigastric burning**	0.69	0.0001
Belching	0.38	0.04	**Belching**	0.50	0.0001
Rome III EPS (n=9)	**R**	**p-value**	**Rome IV EPS (n=9)**	**r**	**p-value**
Bloating	0.57	NS, p=0.12	**Bloating**	0.57	NS, p=0.12
Nausea	0.29	NS, p=0.44	**Nausea**	0.29	NS, p=0.44
Epigastric burning	-0.2	NS, p=0.64	**Epigastric burning**	-0.2	NS, p=0.64
Belching	0.37	NS, p=0.31	**Belching**	0.37	NS, p=0.31
Rome III Overlap PDS/EPS (n=58)	**R**	**p-value**	**Rome IV overlap PDS/EPS (n=17)**	**R**	**p-value**
Fullness	0.45	0.0004	**Fullness**	0.45	NS, p=0.07
Bloating	0.47	0.0002	**Bloating**	0.26	NS, p=0.31
Nausea	0.58	<0.0001	**Nausea**	0.48	0.05
Epigastric pain	0.39	0.003	**Epigastric pain**	-0.08	NS, p=0.73
Epigastric burning	0.73	<0.0001	**Epigastric burning**	0.54	0.03
Belching	0.56	<0.0001	**Belching**	0.52	0.03

Table 3. Overview of symptoms characteristics during the GE test in the different subgroups (Rome III and Rome IV subdivision).

	Fullness	Bloating	Pain	Nausea	Belching	Burning
Rome III PDS						
Maximum	1.7±0.2	1.2±0.2	0.6±0.2	0.9±0.2	1.3±0.2	0.6±0.2
Time to max (min)	30	30	15	60	45	30
AUC	35.7±1.9	24.1±1.5	13.5±0.4	21.5±0.7	26.5±1.4	14.2±0 .7
Rome III = Rome IV EPS						
Maximum	1±0.3	0.9±0.4	1±0.4	0.3±0.2	1.1±0.3	1.7±0.5
Time to max (min)	15	15	60	165	15	135
AUC	3.2±0.7	1.5±0.6	5.9±0.5	1.0±0.3	6.8±0.3	9.1±0.8
Rome III Overlap PDS-EPS						
Maximum	2.0±0.2	1.8±0.2	1.6±0.2	1.4±0.2	1.1±0.2	1.1±0.2
Time to max (min)	30	75	75	75	45	105
AUC	90.1±4.5	84.7±3.1	79.5±1.6	68.6±1.9	47.7±2.2	50.1±2 .3
Rome IV PDS						
Maximum	2.0±0.2	1.6±0.2	1.4±0.2	1.3±0.2	1.2±0.2	1.0±0.2
Time to max (min)	30	75	60	75	45	105
AUC	109.9±5.4	92.0±3.7	83.1±1.7	77.1±1.9	63.6±2.7	54.9± 2.4
Rome IV Overlap PDS-EPS						
Maximum	1.4±0.3	1.3±0.3	0.8±0.3	1.0±0.2	1.1±0.3	0.8±0.2
Time to max (min)	15	75	210	90	60	105
AUC	17.9±1.0	17.9±0.6	11.1±0.5	11.4±0.7	11.8±0.8	9.6±0. 6



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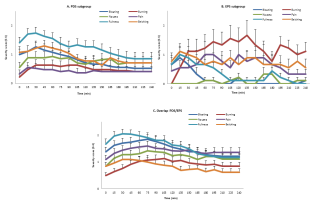

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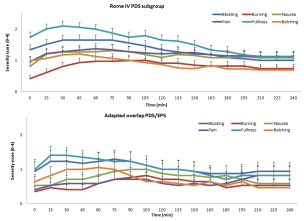

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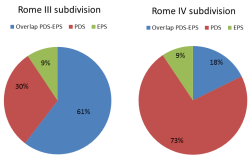

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Supplementary Table 1. Diagnosis in the entire patient population referred for a GE breath test.

Diagnosis	Number	%
Functional dyspepsia	110	65%
Reflux esophagitis	14	8%
History of upper digestive surgery	12	7%
Esophageal motility disorder	10	6%
Predominant IBS	7	4%
Diabetes	7	4%
Barrett's esophagus	2	1%
Other	6	4%
Total number of patients	168	

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Supplementary Table 2. Correlation (Pearson R) between frequency score on the Rome III questionnaire and the severity score (Area under the curve during 4 hours postprandial severity scores at 15 minute intervals) during the GE test. FD patients (n=96) were subdivided depending on their answers to the first supplementary question "Is your epigastric pain or discomfort frequently triggered or aggravated by the meal?" Statistically significant correlations are shown in a grey shaded cell. *NS: not significant (p>0.05).*

Answer to first supplementary question (meal relationship of symptoms)	**"Yes"** (n=69)		**"No"** (n=27)	
Severity vs. Frequency	**R**	**p-value**	**R**	**p-value**
Fullness	0.43	0.0002	0.54	0.01
Bloating	0.41	0.0005	0.45	0.04
Nausea	0.69	<0.0001	0.42	0.02
Epigastric pain	0.64	<0.0001	-0.21	NS, 0.4
Epigastric burning	0.68	<0.0001	0.40	NS, 0.09
Belching	0.54	<0.0001	0.36	NS, 0.09

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Supplementary Table 2: Responses to supplementary postprandial questions per subgroup.

	1.Meal-related symptoms	2.Postprandial epigastric pain	3.Postprandial nausea
Rome III PDS	79%	28%	45%
Rome III = Rome IV EPS	44%	0%	33%
Rome III Overlap	72%	71%	57%
Rome IV PDS	82%	69%	59%
Rome IV overlap	47%	0%	29%

Questions:

1. Presence of symptoms usually triggered or aggravated by the meal (answer: “yes” or “no”);
2. Frequency at epigastric pain triggered or aggravated by the meal (answer: 0 “not present” to 5 “always”
3. Frequency at nausea was triggered or aggravated by the meal (range 0-5 as above).

*A score of 3 (“often”) was accepted as indicative of a meal-relationship.

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Supplementary documents

Exploratory analysis of supplementary questions on postprandial symptoms

The supplementary questions consisted of a) a general question about the presence of epigastric pain or discomfort and whether this was usually triggered or aggravated by the meal (answer: “yes” or “no”); b) if present, the frequency at which epigastric pain was triggered or aggravated by the meal (answer: 0 “not present” to 5 “always”; c) if present, the frequency at which nausea was triggered or aggravated by the meal (range 0-5 as above). A score of 3 (“often”) or higher was accepted as indicative of a meal-relationship.

Rome III subgroup classification

All FD patients presenting for the gastric emptying breath test were classified into subgroups based on the characteristics (frequency) of their dyspeptic symptoms, using the Rome III criteria (1). Patients were classified as having “pure” PDS symptoms if they reported bothersome postprandial fullness and/or early satiation occurring after normal-sized meals at least several times per week in the absence of EPS symptoms. “Pure” EPS patients included those patients reporting epigastric pain and/or burning at least once per week in the absence of PDS symptoms. Finally, the overlapping EPS-PDS subgroup comprised patients with both PDS and EPS symptoms according to Rome III definitions.

Rome IV subgroup classification

In this approach, PDS was identified as above, but Patients reporting meal-related symptoms other than early satiation and postprandial fullness, such as postprandial epigastric pain and postprandial nausea more than once per week, were classified as belonging to the Rome IV PDS group (2).

Gastric emptying breath test

The gastric emptying breath test is a standard diagnostic tool to measure gastric emptying rate in patients with dyspeptic symptoms (3, 4). Breath tests were done

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after an overnight fast, without the patient taking drugs that may interfere with gastric emptying rate or epigastric symptom occurrence.

Patients ingested a standardized solid meal that consisted of 60 g of white bread, an egg, the yolk of which was doped with 74 kBq of ^{14}C octanoic acid sodium salt (DuPont, NEN Research, Boston, MA, USA) and 300 mL of water. The meal was consumed within a five minute period. The total caloric value of the test meal was 250 kCal

After eating, patients provided a breath sample and scored the severity (0: absent - 4: very severe) of 6 epigastric symptoms (fullness, bloating, nausea, epigastric pain, burning, and belching) every 15 minutes until 4 hours postprandially.

The breath samples were collected in sample tubes and gastric emptying rate was analyzed by determining the exhaled $^{14}CO_2/\ ^{12}CO_2$ ratio. Radiation was determined by liquid scintillation counting (Packard Tri-Carb Liquid Scintillation Spectrometer, model 3375, Packard Instrument Company, Downers Grove, IL, USA). Delayed gastric emptying was defined as a half emptying time (T ½) of more than 109 minutes and accelerated gastric emptying as a half emptying time (T ½) of 30 minutes or less (3, 4).

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Rome III Functional dyspepsia subdivision in PDS and EPS: recognizing symptoms that reduce overlap.

Protocol number: SubgroupOverlap
Protocol version: 1
S-number: S55426

Principal Investigator: Prof. Dr. Jan Tack

Date: 28/03/2013

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PROTOCOL SYNOPSIS

Academic study	**Logistic device under study** Rome III Questionnaire for symptom assessment in FD
Title of Protocol: Rome III Functional dyspepsia subdivision in PDS and EPS: recognizing postprandial symptoms reduces overlap.	
Protocol Number: **Version 1, 28/03/13**	**Indication:** FD subgroups symptoms
Project Design: Non-commercial, non-interventional, monocentric study	
Primary Objective: To investigate whether taking into account the relationship of postprandial symptoms to meal ingestion may help to improve separation between EPS and PDS.	
Patient Population: Patients with functional dyspepsia symptoms	
Number of Patients: 50	
Criteria for Evaluation: **Primary Endpoint:** identification of PDS and EPS subgroups by means of the ROME III questionnaire and improve their separation **Main Criteria for Inclusion:** 1. Patients with a diagnosis of functional dyspepsia 2. Patients that previously underwent a gastric emptying breath test 3. Patients aged between 18 and 70 years inclusive 4. Male or female patients **Main Criteria for exclusion** 1. Patients with any condition which, in the opinion of the investigator, makes the patient unsuitable for entry into the study 2. Patients with any major psychiatric disorder (including those with a major psychosomatic element to their gastrointestinal disease), depression, alcohol or substance abuse in the last 2 years 3. Patients presenting with predominant symptoms of irritable bowel syndrome (IBS) or of gastro-esophageal reflux disease (GERD) 4. Patients suffering from diabetes type 1 or type 2	

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BACKGROUND

Functional gastrointestinal disorders are highly prevalent conditions with major health and economic impact (1, 2). Functional dyspepsia (FD) is one of the most prevalent functional disorders, and is defined by Rome III consensus as the presence of symptoms thought to originate from the gastroduodenal region, in the absence of organic disease that is likely to explain the symptoms (3). It has been argued that FD is in fact a heterogeneous condition, with different underlying pathophysiological mechanisms contributing to the symptom pattern (4). The most relevant candidate pathophysiological mechanisms identified to date include delayed or rapid gastric emptying, impaired gastric accommodation and hypersensitivity to gastric distension (5-7). The heterogeneity is also likely to affect efficacy of therapeutic interventions aimed at a single specific mechanisms.

Taking into account this heterogeneity, the Rome III consensus proposed to subdivide FD into Postprandial Distress Syndrome (PDS), characterised by meal-related symptoms such as early satiety and postprandial fullness and Epigastric Pain Syndrome (EPS) characterised by epigastric burning and epigastric pain. This subdivision was based mainly on expert opinion, and was also proposed to serve as a guide for the diagnostic and therapeutic approach to FD patients (3,8). In support of the EPS-PDS subdivision, population-based studies found a good separation between PDS and EPS (9-11). In contrast, in clinic samples large overlap of PDS and EPS in up to 50% was found, and it is evident that this significantly impacts on the usefulness of the subdivision (12-14). In addition, the Rome III subdivision separated belching and nausea from FD symptoms into separate categories of belching and nausea/vomiting disorders (3). Here again, major overlap could be found (12, 14-16).

Conceptually, the Rome III subdivision aimed at distinguishing meal-related FD symptoms (PDS) from meal-unrelated FD symptoms (EPS). Through their wording, the PDS symptoms of early satiation during meal intake, and postprandial fullness are inherently linked to meal ingestion. In contrast, the concept of not being related to meals for the EPS symptoms of epigastric pain and epigastric burning is not explicitly used. Clinical observations and preliminary questionnaire studies showed that an important subgroup of FD patients indicated epigastric pain that occurred mainly postprandially. In addition, an important proportion of patients with overlapping nausea or belching disorders indicated that these symptoms occurred mainly postprandially. There are other subgroups who indicate that epigastric pain or nausea are mainly occurring between meals. We hypothesize, therefore, that taking into account relationship of pain or nausea (and perhaps belching) to meal ingestion may allow to better classify some of the patients with overlapping functional gastroduodenal disorders into meal-related or meal-unrelated FD categories.

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PROJECT OBJECTIVES

The aim of our studies is to evaluate whether detailed evaluation of functional gastroduodenal symptoms and especially their relationship to meal ingestion allows to propose a subdivision with less overlapping between the FD syndromes than with the current Rome III subdivision.

PROJECT DESCRIPTION

Patients showing FD symptoms will be contacted (by phone, by e-mail, during consultation or at endoscopy) and ask to fill in the ROME III questionnaire.

The information given by the ROME III questionnaire will be used to separate the FD patients in 3 subgroups: epigastric pain syndrome (EPS), postprandial distress syndrome (PDS) and the overlapping group of EPS-PDS. Moreover, preceding information achieved from previous diagnose studies will be reviewed and associated to the symptom pattern of these patients subgroups.

PATIENT NUMBER AND ELIGIBILITY

Patient Numbers

A minimum of 50 patients will be recruited in this study. However, this sampling is exploratory.

Inclusion and exclusion criteria

For this study we will follow the following Inclusion/ exclusion criteria:

Criteria for Inclusion:

1. Patients with a diagnosis of functional dyspepsia
2. Patients that previously underwent a gastric emptying breath test
3. Patients aged between 18 and 70 years inclusive
4. Male or female patients

Criteria for exclusion

1. Patients with any condition which, in the opinion of the investigator, makes the patient unsuitable for entry into the study
2. Patients with any major psychiatric disorder (including those with a major psychosomatic element to their gastrointestinal disease), depression, alcohol or substance abuse in the last 2 years
3. Patients presenting with predominant symptoms of irritable bowel syndrome (IBS) or of gastro-oesophageal reflux disease (GERD)
4. Patients suffering from diabetes type 1 or type 2

PATIENT INFORMATION AND INFORMED CONSENT

Prior to any study procedure being performed, patients must provide witnessed written informed consent.

Information about the study will be given to the patient both verbally and in writing. The written patient information sheet will explain the objectives of the study, its potential risks and benefits. The patient should have adequate time to read the information sheet and to ask questions to the investigator. The investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient should not enter the study.

If a patient agrees to participate, he/she will be asked to sign and date an informed consent form which will be kept by the investigator.

COMPLIANCE WITH THE PROTOCOL

The study will be performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local laws and regulations as recommended by the European Community.

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STATISTICAL METHODS/DATA ANALYSIS

Sample Size Justification

At least 50 FD patients will be necessary to first make a good EPS and PDS subdivision and then properly analyze the different meal-related non-PDS symptoms that may help improve the subgroup separation.

Study Populations

All evaluable patients who respected the protocol and fully completed the questionnaires will be considered for the analysis.

Statistical Analysis hypothesis

Hypothesis testing will consist on the identification of postprandial symptoms to reduce the overlapping between PDS and EPS FD subgroups.
Therefore, we will use different models to correlate postprandial symptoms to meal ingestion.

STUDY MANAGEMENT AND DATA COLLECTION

The protocol and informed consent form will be submitted to the CTC and the Ethical Committee.
All documentation pertaining to the study will be kept by the K.U.Leuven according to the local regulations.

USE OF INFORMATION

Patient Confidentiality and Data Protection

The site will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

Final Report and Publication Policy

At the conclusion of the study, after the data are analysed, the Principal Investigator will write a final clinical study report. It is anticipated that the results from this study will be published.

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Need to Know

Background: Among patients with functional dyspepsia (FD), there is overlap in symptoms between those in the Rome III subgroups of postprandial distress syndrome (PDS) and those with epigastric pain syndrome (EPS). The Rome IV consensus proposed to incorporate all patients with postprandial symptoms into the PDS group.

Findings: In an analysis of patients with FD, found a meal to induce or exacerbate symptoms in 65% of patients. Questionnaires on meal-related symptoms help to accurately classify patients as PDS vs EPS.

Implications for Patient Care: Rome IV criteria for PDS reduce the proportions categorized as having both PDS and EPS and identify a homogenous group with meal-related symptoms.

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