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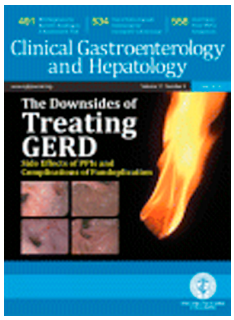

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Effects of Rome IV Definitions of Functional Dyspepsia Subgroups in Secondary Care

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Key words: dyspeptic patients, gastroduodenal questionnaire, “adapted” PDS group, overlapping PDS-EPS, postprandial pain, postprandial burning

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NEED TO KNOW

Background: The Rome III consensus subdivided functional dyspepsia into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). In clinical practice, using the Rome III subdivision results in overlap between PDS and EPS.

Findings: When the Rome IV subdivision is used, the overlap between PDS and EPS is limited.

The decrease of the overlap group is paralleled by an increase in the PDS group.

The PDS group is the largest subgroup in the Rome IV classification.

Implications for patient care: The Rome IV criteria should be used for analysis of patients with functional dyspepsia.

ABSTRACT

Background & Aims: Functional dyspepsia (FD) is subdivided into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) according to the Rome III consensus. In clinical practice, there is a major overlap between these subgroups. The Rome IV criteria included postprandially occurring symptoms in the PDS subgroup. We aimed to analyze the effects of the Rome IV criteria, compared to Rome III, on FD subgroups in patients recruited from secondary care.

Methods: Patients with FD (n=224; mean age, 43±1 years; 77% women) were recruited from secondary-care units in Belgium and filled out symptom questionnaires, allowing subdivision according to Rome III and Rome IV criteria and identification of postprandial symptoms. Symptom patterns and demographics were compared between the subgroups. Statistical analysis was performed using the t-test and Fisher's exact test.

Results: According to the Rome III criteria, 25% of participants had PDS, 8% had EPS, and 67% had an overlap. Postprandial fullness, early satiation, and bloating were present in significantly more patients in the PDS and overlap groups than the EPS group (P<.0001). A higher proportion of patients in the overlap group showed symptoms as postprandial epigastric pain and nausea than in the EPS group (both P≤.02). With the Rome IV criteria, the overlap group was reduced to 35%; 57% of patients were considered to have PDS and 8% to have EPS. Postprandial pain was significantly more prevalent in the PDS than in the EPS group (P≤.002), and postprandial nausea was significantly more prevalent in the PDS group than the overlap group (P=.007).

Conclusion: Compared to Rome III criteria, the Rome IV criteria significantly reduce the overlap between PDS and EPS groups. Studies are needed to determine if Rome IV subgroups are differently associated with psychological co-morbidities and treatment responses.

Key words: dyspeptic patients, gastroduodenal questionnaire, "adapted" PDS group, overlapping PDS-EPS, postprandial pain, postprandial burning

INTRODUCTION

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorder, with estimates of up to 21% population prevalence (1,2). The Rome III consensus defined FD as a condition characterized by symptoms, which were thought to originate from the gastroduodenal segment, in the absence of an organic, systemic or metabolic disease likely to explain the symptoms (3). In this consensus, only 4 symptoms were considered as cardinal FD symptoms: postprandial fullness, early satiation, epigastric pain, and epigastric burning. In addition, in order to optimize the management of FD, the Rome III consensus proposed a subdivision into meal-related FD or postprandial distress syndrome (PDS) and meal-unrelated FD or epigastric pain syndrome (EPS) (3,4). The PDS comprises FD patients who experience bothersome postprandial fullness after ordinary sized meals occurring at least several times a week and/or early satiation that prevents finishing a regular meal at least several times a week. The EPS includes patients experiencing epigastric pain or burning at least once a week. The pain is intermittent, not generalized or localized to other abdominal or chest regions, not relieved by defecation or passage of flatus and not related to gallbladder or sphincter of Oddi disorders.

Epidemiological studies after the Rome III consensus confirmed that both EPS and PDS existed as separate entities in the general population, with a minority of subjects in the overlap PDS-EPS group (4-7). However, in clinical practice, the separation between EPS and PDS was less clear, and the majority of patients was found in the overlap group presenting both EPS and PDS symptoms which of course hampers the applicability of the subdivision for clinical management (4,8,10). Although the PDS subgroup was defined as displaying “meal-related dyspeptic symptoms”, it focused only on postprandial fullness and early satiation. Several clinical observations revealed that many FD patients report postprandially occurring epigastric pain or nausea (11-14). When postprandial non-PDS symptoms such as epigastric pain and postprandial nausea are considered part of an “adapted” PDS group, a better separation from EPS is obtained (14). These principles have been applied to the Rome IV definitions, where PDS is now referring to all meal-related symptoms, to consider not only bothersome postprandial fullness and bothersome early satiation, but also postprandial epigastric pain or burning, epigastric bloating, excessive

belching, and nausea as part of the same spectrum (15). EPS is still defined as bothersome epigastric pain and/or bothersome epigastric burning, occurring at least one day a week (15). Based on our analysis, conducted on a secondary care patient population before the Rome IV consensus, this approach indeed has the potential to decrease the overlap between EPS and PDS. An analysis of prevalence of functional gastrointestinal disorders in the general population in 3 countries also supports this notion (16), but data from clinical practice are lacking.

The **aim** of this study was to evaluate the impact of the Rome IV criteria on the PDS, EPS subgroups and their overlap in secondary care, and in comparison with Rome III criteria. We hypothesize a better division in different FD subgroups with a lower percentage of patients in the overlap group and a higher proportion in the PDS subgroup based on Rome IV criteria, compared to Rome III.

MATERIALS AND METHODS

Patients

Patients, aged between 18 and 70 years old, presenting dyspeptic symptoms were recruited from eight gastroenterology secondary care sites in Belgium. Patients referred by their general practitioner to secondary care gastroenterology specialists or care levels, for epigastric symptoms with a negative endoscopy, filled out a symptom questionnaire. *H. pylori* positive patients or those receiving treatment for *H. pylori* eradication during the last 3 months were excluded from the study. Further, patients with diabetes mellitus, with a confirmed organic gastro-intestinal disorder or a concomitant major organic condition that may explain their digestive symptoms, or females who are pregnant or lactating were ineligible to participate. Patients presenting predominant symptoms of irritable bowel syndrome, daily symptoms of nausea, vomiting more than one day a month, daily symptoms of excessive belching, and predominant symptoms of gastro-esophageal reflux disease were excluded. Furthermore, patients with a former digestive surgery affecting the upper gut motility could not participate. The Research Ethics Committee UZ/KU Leuven approved this study and an informed consent was obtained from all patients prior to any study procedures being performed. The study was performed in accordance with the 1975 Declaration of Helsinki and the BMJ guidelines.

Study design

Patients with epigastric symptoms and a negative endoscopy at secondary care sites in Belgium filled out an adapted Rome III gastro-duodenal questionnaire, which contained additional questions regarding the relationship of symptoms and meal, allowing to make Rome IV subgroup diagnoses. Questions were available in Dutch or French according to the mother tongue of the patient.

Data analysis

After filling out the questionnaire, patients were subdivided into ‘pure’ PDS, ‘pure’ EPS and the overlapping EDS-PDS subgroups as per Rome III criteria for FD. The group with PDS was defined by postprandial fullness and/or early satiety. The EPS subgroup was characterized by epigastric pain and burning occurring at least several times a week. The occurrence and frequency of symptoms were compared between all subgroups.

A second analysis was performed on the same set of patients based on the Rome IV consensus, to include patients with postprandial symptoms of nausea and postprandial epigastric pain within the PDS subgroup. The presence and frequency of symptoms were analyzed and compared to the subgroups defined by Rome III.

Statistical analysis

The presence and severity of symptoms was defined and proportions of patients with symptoms were compared using Fisher’s exact test. Results are shown as mean ± standard deviation. Non-significant results are indicated as NS. Statistical analyses were performed using Graphpad. *P*-values <.05 were considered significant.

RESULTS

Patient selection

In this trial, 250 secondary care level dyspeptic patients were recruited from 8 sites in Belgium. The mean age of the patients was 43±1 years and 77% were women. Twenty-six patients did not meet the Rome criteria for functional dyspepsia, and were characterized by symptoms such as bloating (23%), nausea (5%), and belching (15%). These patients were excluded from the analysis, resulting in 224 FD patients used for analysis.

Symptom patterns

Ninety-one percent of all patients reported postprandial fullness at least several times a week. In addition, 76% of all patients reported bloating at least several times a week, followed by epigastric pain at least once a week (72%). Early satiation and epigastric burning were present in respectively 58% and 38% of all patients.

Subdivision according to Rome III criteria

Using the Rome III criteria, 25% of the patients were classified as pure PDS (postprandial fullness and/or early satiation several times a week with epigastric pain or burning occurring less than once a week) (figure 1). Their mean age was 43±3 years and 70% were women. Eight percent were considered pure EPS (epigastric burning and/or pain at least once a week without relevant postprandial fullness or early satiation) with a mean age of 49±4 years and 64% female predominance. Overlapping PDS-EPS, the largest subgroup, was found in 67% of all patients (42±1 years; 81% women).

As expected, the main symptoms of the Rome III FD-PDS group were postprandial fullness and early satiation at least several times a week, present in 96% and 69% respectively. In addition, 77% of the PDS subgroup experienced bloating at least several times a week. In line with the Rome III subgroup definitions, postprandial fullness, early satiation, and bloating were significantly more frequently reported in

the PDS and overlap groups (99% postprandial fullness, 60% early satiation, and 80% bloating) compared to the EPS group (0%, 0%, and 27%, all *P*<.001). The Rome III EPS group was characterized by epigastric pain (72%), which occurred significantly less frequently than in the Rome III overlap group (95%, *P*=.006). Epigastric burning was present in 56% of the EPS group and 48% of the overlap group (NS). In addition, postprandial pain was reported more often by the Rome III overlap group (76%) compared to the PDS and EPS groups (respectively 25% and 12%, *P*<.001).

Other reported gastrointestinal symptoms were nausea and belching. Nausea occurred at least several times a week in 36% of the PDS group and in 40% of the overlap group, which was significantly higher than in the EPS group (11%, *P*=.02). Belching appeared in a similar amount of patients in all groups (28% EPS, 25% PDS, 32% overlap, NS).

Subdivision according to Rome IV criteria

In a second analysis using the Rome IV definition, postprandially occurring epigastric pain was considered a symptom of the PDS group. All patients were divided into the three subgroups: PDS (57%, mean age 42±1.5 years, 78% women), EPS (8%, mean age 49±4.1 years, 64% women), and the overlap EPS-PDS group (35%, mean age 42+2.0 years, 78% women).

Within the PDS group, 98% reported postprandial fullness, which was similar to 99% in the overlap group (NS). Meanwhile, early satiation was reported significantly less frequently in the overlap group compared to the PDS group (49% vs. 71%, *P*=.003). PDS patients were characterized by a lower occurrence of epigastric pain compared to the overlap group (59 vs. 91%, *P*<.001). No significant difference was found in comparison with the EPS group (72%). Postprandial epigastric pain was reported less frequently by the EPS group (12%) compared to the PDS group (72%, *P*<.001) and the overlap group (53%, *P*=.002). Epigastric burning was present in 27, 56, and 52% of the PDS, EPS, and overlap groups respectively, with significant differences between PDS and EPS (*P*=.01) and the overlap (*P*<.001) groups.

In addition, the prevalence of upper abdominal bloating was higher in PDS and overlap patients (85% and 71%) compared to the EPS group (27%, *P*<.001 for both). The symptom occurrence rating for belching was similar in all groups, but the EPS group reported less nausea than the PDS and overlap patients (11% vs. 40%, *P*=.02 and vs. 37%, *P*=.05 respectively). However, postprandial nausea was reported more often in PDS patients compared to the overlap and EPS groups (51% vs. 31%, *P*=.007 and vs. 11%, *P*=.002 respectively).

The profiles of symptoms of all groups according to the Rome IV criteria are presented in figure 2.

DISCUSSION

The management of patients with FD, one of the most common gastrointestinal disorder, is hampered by the lack of treatments of proven efficacy (15,17-19). It has often been argued that FD is a heterogeneous condition, with variable underlying pathophysiology, and that this explains why it is so difficult to develop generally effective treatment approaches (20,21). Already since the earliest Rome classifications, FD subdivisions have been proposed, but most of them did not persist as epidemiological, therapeutic and scientific knowledge evolved (4,22-24).

The Rome III consensus and its subdivision into EPS and PDS generated a radical change from previous definition, narrowing down FD to 4 cardinal symptoms (3). Epidemiological studies confirmed the existence of EPS and PDS as defined by Rome III as separate entities in the general population, with modest overlap (4-7). However, in clinic samples, the overlap group was dominantly the most prevalent one (4,8-10,14). The Rome IV consensus adapted the PDS and EPS definitions, aiming at diminishing the overlap by consistently considering meal-related symptoms as PDS, regardless of the nature of the symptom (15).

We analyzed the impact of this change on the classification and symptom pattern of 224 FD patients recruited from eight secondary level care settings in Belgium. As expected based on the known FD epidemiology (1-7,15,16), patients were on average in their early forties and were predominantly women.

Using the Rome III definition, we confirmed earlier reports that the largest subgroup was the PDS-EPS overlap group (67%), followed by PDS alone (25%) and EPS alone (8%). If the management of the patients should be based on the FD subgroup, then the overlap group poses a major challenge and uncertainty: should they initially be treated as PDS, or as EPS, or should treatment for each of these entities be combined at the offset?

We already published that the overlap within the Rome III subdivision is significantly reduced when postprandial symptoms are considered to represent PDS (14). This was implemented in the Rome IV criteria, and in a previous study of our group in

tertiary care FD patients referred for gastric emptying testing, we confirmed that using Rome IV, the overlap group is significantly reduced, the pure PDS group becomes the dominant one and the size of the pure EPS group is unchanged (25). Similar findings were also reported at the general population level in a study in the USA, Canada and the UK (16). With the present study, which demonstrated the same in a secondary care FD population, it seems valid to state that the reduced overlap group and the enlarged PDS group are common effects of the Rome IV adaptation from Rome III.

Reducing the overlap group is not a goal in itself. One goal is to identify subgroups with a more homogeneous underlying pathophysiology. Our own study found no difference in prevalence of impaired gastric accommodation, delayed gastric emptying or hypersensitivity to gastric distention when FD patients were subdivided according to the Rome III consensus (12). Others reported similar findings (26,27). Whether a better separation of pathophysiological mechanisms can be obtained with the Rome IV approach remains to be studied.

A second goal is to identify subgroups with different treatment responses. The Rome III consensus proposed that the EPS group might respond best to proton pump inhibitors and the PDS group to prokinetic agents (3,17-19). However, this was only partially confirmed in prospective studies (28,29). Few studies have evaluated treatment responses in FD subgroups according to the Rome IV definitions. In a preliminary report of a placebo-controlled study with itopride, the best response was observed in the overlap group rather than in the pure PDS group according to Rome III (30). The features of this group seem to correspond to what would now be PDS according to Rome IV, with postprandial pain being part of the Rome IV PDS spectrum (15). Of course, many more studies are needed to substantiate the claim of superior clinical relevance of the Rome IV subgrouping.

Besides the clear need to further study the treatment response of the Rome IV PDS group, the not inconsiderable overlap group according to Rome IV, comprising around 1/3 of the patients in the current study, also needs to be analyzed in depth in terms of co-morbidity pattern and treatment response. This group has high prevalences of upper abdominal bloating and nausea, similar to those found in the pure PDS group and higher than in the Rome IV EPS group. These associations suggest that the overlap group according to Rome IV may in fact be more

reminiscent of PDS than EPS. While it is not inconceivable that these patients will also respond to prokinetics, it is also possible that additional features, such as the predominant symptom (24), the presence of weight loss (2, 21) or of psychosocial co-morbidities (3,5,15) will determine treatment responses. Prospective treatment outcome studies should evaluate these aspects in FD subgroups according to the Rome IV consensus.

Strengths of this study are the setting in the secondary care level, based on referral from general practitioners, and the use of a single questionnaire across different practices. Limitations are the relatively limited sample size in comparison with epidemiological studies (2, 10), and the setting where data were only collected in Belgium. A final limitation is the exclusion of *H. pylori* infected patients. However, recent studies have shown that these are only a small subset of the FD population in Belgium (12).

In conclusion, compared to the Rome III approach, the Rome IV classification of FD patients significantly diminishes the overlap group and renders PDS the largest subgroup. Hence, this classification is likely to be more useful in clinical practice for stratifying FD patients, but this needs confirmation in prospective outcome studies.

Tables

Table 1. Demographic and symptom characteristics of the patient population subdivided according to Rome III or Rome IV definitions.

	Rome III			Rome IV		
Subgroup	**Overlap**	**PDS**	**EPS**	**Overlap**	**PDS**	**EPS**
Proportion	67%	25%	8%	35%	57%	8%
Gender (f)	81%	70%	64%	78%	78%	64%
Age (years)	42±1	43±3	49±4	42±2	42±2	49±4
Symptom frequency	**Rome III**			**Rome IV**		
Postprandial fullness	99%	96%	0%	99%	98%	0%
Early satiation	60%	69%	0%	49%	71%	0%
Bloating	80%	77%	27%	71%	85%	27%
Nausea	40%	36%	11%	37%	40%	11%
Epigastric pain	44%	0%	72%	91%	59%	72%
Postprandial pain	76%	25%	12%	53%	73%	12%
Epigastric burning	48%	0%	56%	52%	27%	56%
Belching	32%	28%	25%	32%	31%	25%

Figures

Figure 1. Subgroup prevalence (upper panel) and symptom characteristics (lower panel) when applying the Rome III definitions for EPS and PDS.

Figure 2. Subgroup prevalence (upper panel) and symptom characteristics (lower panel) when applying the Rome IV definitions for EPS and PDS.

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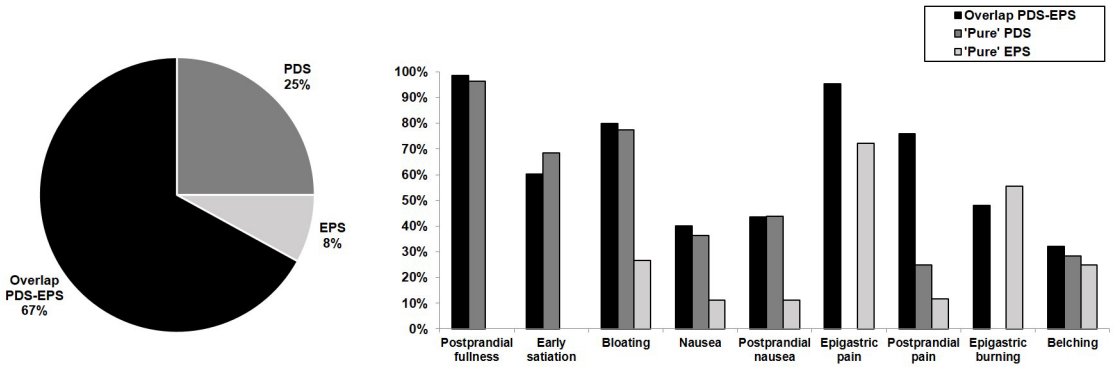

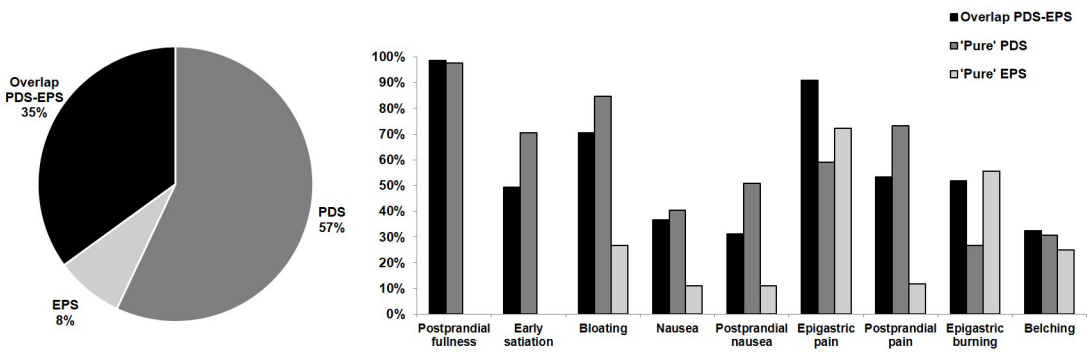

NEED TO KNOW

Background: The Rome III consensus subdivided functional dyspepsia into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). In clinical practice, using the Rome III subdivision results in overlap between PDS and EPS.

Findings: When the Rome IV subdivision is used, the overlap between PDS and EPS is limited.

The decrease of the overlap group is paralleled by an increase in the PDS group.

The PDS group is the largest subgroup in the Rome IV classification.

Implications for patient care: The Rome IV criteria should be used for analysis of patients with functional dyspepsia.