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REVIEW

# Overlap of functional heartburn and gastroesophageal reflux disease with irritable bowel syndrome

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## Abstract

Several studies indicate a significant degree of overlap between irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD). Likewise, both functional heartburn (FH) and IBS are functional digestive disorders that may occur in the same patients. However, data establishing a solid link between FH and IBS are lacking, mainly because the clinical definition of FH has undergone substantial changes over the years. The available literature on the overlap between GERD or FH and IBS highlights considerable heterogeneity in terms of the criteria and diagnostic procedures used to assess heartburn and IBS. In particular, several epidemiological studies included patients with concomitant IBS and GERD without any attempt to distinguish FH (as defined by the Rome Ⅲ criteria) from GERD *via* pathophysiological investigations. Independent of these critical issues, there is preliminary evidence supporting a significant degree of FH-IBS overlap. This underscores the need for studies based on updated diagnostic criteria and accurate pathophysiological classifications, particularly to distinguish FH from GERD. This distinction would represent an essential starting point to achieving a better understanding of pathophysiology in the subclasses of patients with GERD and FH and properly assessing the different degrees of overlap between IBS and the subcategories of heartburn.The present review article intends to appraise and critically discuss current evidence supporting a possible concomitance of GERD or FH with IBS in the same patients and to highlight the pathophysiological relationships between these disorders.



**Key words:** Functional gastrointestinal disorders; Gastroesophageal reflux disease/Gastro-oesophageal reflux disease; Irritable bowel syndrome; Acidity (esophageal); Hypersensitivity

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) are gastrointestinal disorders that affect a large portion of the general population and have a relevant impact on quality of life and health care costs. Although these disturbances affect different regions of the digestive tract, it has been noted that they may occur in the same patient. In addition, recent studies have shown a concomitance between functional heartburn

(FH) and IBS. This finding is not completely unexpected because FH and IBS are both functional digestive disorders (FDDs), and the possibility of an overlap among different FDDs has been largely acknowledged[1]. Indeed, there is mounting evidence that FDDs consist of a number of heterogeneous syndromes characterized by various gastrointestinal symptoms with no evident organic cause found upon clinical investigation[2].

Based on the above considerations, the hypothesis of an association between FH and IBS deserves careful attention and investigation. However, data establishing a solid link between FH and IBS are lacking, most likely because the disorders' clinical definitions have undergone to significant variations over the years, and their pathophysiology remains poorly understood.

The present article intends to provide a review of current evidence supporting a possible clinical and pathophysiological relationship between GERD/FH and IBS.

## DEFINITIONS

To properly address the relationship between GERD/FH and IBS, it is important to preliminarily clarify some definitions of GERD, as patients affected by FH have been often included in this category in both past and recent clinical investigations.

### GERD

GERD develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms, with or without mucosal damage and/or complications[3]. A subcategory of GERD patients that displays reflux-related symptoms in the absence of erosive esophagitis at endoscopy is considered to have non-erosive reflux disease (NERD)[3]. Pathophysiological studies conducted *via* pH monitoring and, more recently, impedance-pH monitoring (MII-pH) have demonstrated that there are two main types of NERD patients: those with abnormal acid reflux and those with physiological acid exposure time (AET). In the latter group, patients showing a close temporal relationship between symptoms and acid or non-acid reflux episodes have been defined as having a "hypersensitive esophagus" and should be considered within the spectrum of GERD[4,5]. When the association between symptoms and physiological reflux is lacking, patients can be classified as having FH, which is defined in the next section.

### FH

The Rome Ⅱ criteria for functional esophageal disorders defined FH as an episodic retrosternal burning in the absence of pathological gastroesophageal reflux, pathology-based motility disorders, or structural alterations[6]. In 2006, the Rome Ⅲ committee modified the definition of FH as the occurrence of chronic retrosternal burning in the absence of either GERD or histopathology-based esophageal motility disorders. In particular, according to Rome Ⅲ criteria, heartburn should be reported as having persisted over the previous 3 mo, with a symptom onset dating to at least 6 mo before the diagnosis[7]. To exclude GERD, patients must undergo upper digestive endoscopy; in the absence of esophagitis, ambulatory pH monitoring should also be performed[4]. A lack of correspondence between symptoms and reflux episodes, together with normal acid exposure in the distal esophagus, would suggest a diagnosis of FH. Such a diagnosis could be further substantiated by the outcome of a therapeutic trial with a proton pump inhibitor (PPI); although it is not specific, an unsatisfactory response to acid inhibition is likely to have a negative predictive value in support of GERD[8].

A recent study suggested that, to be diagnosed with FH, patients should have a normal upper endoscopy, a normal AET in the distal esophagus and a negative symptom association with both acid and non-acid reflux[5].

The evaluation of the latter condition is possible only with MII-pH monitoring, which is able to recognize both acid and non-acid reflux. However, it must be considered that, to date, the exact role of non-acid reflux in the pathophysiology of symptoms in untreated GERD patients has been minimally evaluated. Therefore, the findings reported by Savarino *et al*[5] should be viewed as preliminary in nature and should be substantiated by further studies before undergoing a critical assessment by consensus committees.

### IBS

According to the Rome Ⅲ criteria, IBS is a functional bowel disorder in which recurrent abdominal pain or discomfort is associated with defecation and/or changes in bowel habits. In particular, abdominal pain or discomfort is associated with two or more of the following characteristics: improvement with defecation and onset associated with a change in the frequency and/or form of stool. The predominant stool pattern allows the classification of IBS into four clinical variants: with constipation; with diarrhea; mixed; and unsubtyped[9].

## GERD/FH AND IBS OVERLAP

To date, several studies have reported a certain degree of overlap between GERD and IBS that cannot be explained solely by chance[10-13]. By contrast, epidemiological data regarding the possible concomitance of FH and IBS in the same patient are lacking.

In the last two decades, the assessment of the epidemiological and clinical features of IBS has gained considerable attention. At present, the overall prevalence of IBS ranges from 10% to 20% of adults and adolescents, and it predominantly affects young (20-45 years old) females[14,15]. Population-based studies suggest that GERD, defined by at least weekly heartburn and/or regurgitation, is a common condition, with a prevalence of 10%-20% in Western populations[16]. Several studies have shown that up to 70% of patients complaining of heartburn have NERD; 30%-50% of NERD patients display nor-

mal 24-h esophageal pH monitoring[17], and approximately 60% of these patients show a negative relationship between symptoms and acid reflux events[4]. More recent studies conducted with MII-pH in NERD patients suggest an FH prevalence ranging from 19% to 26%[5]. Very little is currently known about gender prevalence among patients with FH, although the condition seems to be more common in women[18].

The identification of a clinical overlap between FH and IBS is complicated by the fact that most studies have usually evaluated the concomitance of IBS and heartburn, irrespective of whether the latter was related to GERD or FH. In particular, most data have been collected *via* epidemiological studies conducted using validated questionnaires and endoscopy, without any pathophysiological attempt to discriminate GERD patients from FH patients. In this context, we were interested in performing an in-depth analysis of the overlap between GERD/FH and IBS by conducting a search of the available literature.

### Literature search

We identified the published studies to include in our review *via* an electronic search of three bibliographical databases: PubMed (1966-2011), EMBASE (1980-2011) and the Cochrane Library (2000-2011). Only studies that were designed as randomized-controlled, cross-sectional and case-control were included in our analysis. The search was performed by two investigators using the string "(reflux OR heartburn OR GERD OR GORD OR gastroesophageal reflux OR PPI OR 24-h pH) AND (IBS)". A restriction was placed to collect articles in English only. The initial search yielded 371 titles of studies that were published as either full text papers or abstracts of scientific meetings, and all of the studies were screened by all authors to determine their eligibility. Based on our inclusion criteria, we selected 45 studies, which were used for an in-depth analysis of the prevalence of GERD/FH in patients with IBS and vice versa. In addition, the criteria and diagnostic procedures used to assess the presence of heartburn and IBS were recorded.

### Prevalence of GERD/FH in patients with IBS

Twenty-three studies evaluated the prevalence of GERD/FH in subjects with a previous diagnosis of IBS[10,12,19-39]. The details are shown in Table 1. The overall mean prevalence of GERD was 37.5%, although there was remarkable variability, with values ranging from 11% to 79%. Five studies assessed IBS according to the Manning criteria, 4 studies according to the Rome I criteria, 8 studies according to the Rome Ⅱ criteria, and 6 studies according to the Rome Ⅲ criteria. In 18 studies, IBS was diagnosed *via* a symptom questionnaire; in 4 studies, organic diseases were excluded with imaging techniques and laboratory tests; in 1 study, only laboratory tests were performed. In comparison, GERD was diagnosed *via* a symptom questionnaire in 18 studies and a symptom questionnaire combined with upper endoscopy in 3 studies. In 2 studies, pathophysiological evaluations *via* esophageal manometry and pH-metry/MII-pH were performed in addition to the symptom questionnaire and upper endoscopy[20,39]. Overall, in patients with IBS, NERD was slightly more prevalent (42%) than erosive reflux disease (ERD, 38%). One study conducted in accordance with Rome Ⅲ criteria estimated an FH prevalence of 59% among patients with IBS[39].

### Prevalence of IBS in patients with GERD/FH

Thirty-two articles investigated the prevalence of IBS in subjects with a previous diagnosis of GERD/FH[10,12,23,25,26,31,32,35,36,38-60]. The details are shown in Table 2. In GERD patients, the overall mean prevalence of IBS was 36%, although there was considerable variability, as shown by values ranging from 8% to 71%. In 3 studies, IBS was diagnosed according to the Manning criteria (mean prevalence: 34.4%); in 8 studies, it was diagnosed according to the Rome I criteria (mean prevalence: 41.4%); in 10 studies, it was diagnosed according to the Rome Ⅱ criteria (mean prevalence: 38.1%); in 8 studies, it was diagnosed according to the Rome Ⅲ criteria (mean prevalence: 31.9%); in 3 studies according to the ReQuest criteria (mean prevalence: 37.3%). In all studies, IBS was diagnosed *via* a symptom questionnaire. However, in one study, hematological and stool examinations were also performed to exclude organic diseases[26]. In comparison, GERD was diagnosed *via* a symptom questionnaire in 18 studies and *via* a symptom questionnaire combined with upper endoscopy in 7 studies. In 7 studies, esophageal pathophysiological studies (*i.e.*, manometry and pH-metry) were performed in addition to the symptom questionnaire and upper endoscopy. Overall, IBS was more prevalent in patients with NERD (41%) than in those with ERD (23.9%). Two studies, which evaluated FH in accordance with the Rome Ⅲ criteria, estimated prevalences of 39%[56] and 61.4% for IBS[39]. In the first study, heartburn was investigated *via* pH-metry, while the latter used MII-pH testing.

### Discussion

Large population-based studies have used validated questionnaires to investigate a possible association between GERD and IBS and have suggested that GERD can affect a considerable proportion of patients with IBS[22,27,28] or vice versa[43,49]. However, few studies specifically address the issue of overlap between FH and IBS, mainly because the definition of FH has varied substantially throughout the years. Indeed, the definition of FH has been greatly modified from the Rome Ⅱ criteria (in which the definition of FH included all NERD patients with negative pH-metry) to the Rome Ⅲ criteria (in which FH is defined as a functional esophageal disorder unrelated to GERD and characterized by negative pH-metry, the lack of a relationship between symptoms and reflux events, and the lack of symptom improvement after a trial of PPI therapy).

Notably, most of the available data on the association between IBS and GERD were collected in the context

**Table 1 Prevalence of gastroesophageal reflux disease/functional heartburn in irritable bowel syndrome patients**

| IBS patients (*n*) | IBS criteria | Diagnostic investigations of IBS | GERD prevalence | FH prevalence | Diagnostic investigations of heartburn | Ref. |
|---|---|---|---|---|---|---|
| 101 | Manning | S, HE, Sg, BE, BT, UE, SBB, BC, LE | 25% | Not evaluated | SQ | Svedlund *et al*[19] |
| 25 | Manning | S, Sg, SC, HE, BE | 28% (daily)<br>52% (weekly) | Not evaluated | S, UE, OM, pH (wireless) | Smart *et al*[20] |
| 100 | Manning | S, LE, HE, BE | 30% | Not evaluated | SQ | Whorwell *et al*[21] |
| 350 | Modified manning | SQ | 79% | Not evaluated | SQ | Jones *et al*[22] |
| 546 | Modified manning | Postal SQ | 46.5% | Not evaluated | Postal SQ | Kennedy *et al*[23]1 |
| 146 | Rome I | S, PE, AU, HE, UE or BE (patients older than 50 yr) | 28% | Not evaluated | S, UE | Stanghellini *et al*[24] |
| 68 | Rome I | SQ | 3% | Not evaluated | SQ | Hu *et al*[25]1 |
| 68 | Rome I | Phone SQ | 11% | Not evaluated | Phone SQ | Cheung *et al*[12]1 |
| 52 | Rome I | S, SC, HE | 38% (ERD)<br>42% (NERD) | Not evaluated | S, UE | Camacho *et al*[26]1 |
| 76 (IBS-C)<br>45 (IBS-D) | Rome II | SQ | 32.9%<br>40.9% | Not evaluated | SQ | Talley *et al*[27] |
| 3880 | Rome II<br>Rome I<br>Manning | Phone SQ | 21% | Not evaluated | Phone SQ | Hungin *et al*[28] |
| 662 | Rome II | SQ | 25% | Not evaluated | SQ | Si *et al*[29] |
| 517 | Rome II | SQ | 40% | Not evaluated | SQ | Balboa *et al*[30] |
| 95 | Rome II | SQ | 21% | Not evaluated | SQ | Lee *et al*[31]1 |
| 40 | Rome II | SQ | 20% | Not evaluated | SQ | Hori *et al*[32]1 |
| 164 | Rome II | SQ | 43% | Not evaluated | SQ | Johansson *et al*[33] |
| 113 | Rome II | SQ | 49.6% | Not evaluated | SQ | Schmulson *et al*[34] |
| 252 | Rome III | Postal SQ | 32.9% | Not evaluated | Postal SQ | Jung *et al*[10]1 |
| 1419 | Rome III<br>Rome II | SQ | 63.6% | Not evaluated | S, UE | Yarandi *et al*[35]1 |
| 381 | Rome III | SQ | 16% | Not evaluated | SQ | Kaji *et al*[36]1 |
| 1336 (in 1996)<br>799 (in 2006) | Rome III<br>Rome II<br>Manning | Postal SQ | 60.5%-71.9% | Not evaluated | Postal SQ | Olafsdottir *et al*[37] |
| 381 | Rome III | SQ | 16% | Not evaluated | SQ | Fujiwara *et al*[38]1 |
| 46 | Rome III | SQ | 41.3% | 59% | S, UE, OM22, MII-pH | Martinucci *et al*[39]1,2 |

[1]Articles listed in both Tables 1 and 2; [2]Abstract only (publication type). GERD: Gastroesophageal reflux disease; FH: Functional heartburn; IBS: Irritable bowel syndrome; S: Symptoms; SQ: Symptom questionnaire; PE: Physical examination; HE: Hematological examinations; BE: Barium enema; BC: Bacteriological culture; SC: Stool culture; BT: Lactose/lactulose breath test; AU: Abdominal ultrasonography; UE: Upper endoscopy; LE: Lower endoscopy; SBB: Small-bowel biopsies; Sg: Sigmoidoscopy; OM: Esophageal manometry; pH: pH-metry; MII-pH: pH impedance monitoring; ERD: Erosive reflux disease; NERD: Nonerosive reflux disease.

of epidemiological studies, which were conducted on patients with heartburn using validated questionnaires and upper endoscopy without the use of any reliable pathophysiological investigation to discriminate FH (according to the Rome Ⅲ criteria) from GERD.

As mentioned above, only two studies have evaluated the concomitance of FH and IBS. Lee *et al*[56] examined 95 patients with heartburn by endoscopy, pH-metry, PPI test, and psychological characteristics. The patients were classified using the Rome Ⅲ criteria; therefore, FH was diagnosed based on physiological AET, a negative association between symptoms and reflux, and a negative PPI test in patients without erosive esophagitis. A higher prevalence of IBS was recorded in FH patients (39%) than in ERD (17%) or NERD (23%) patients. Furthermore, anxiety was more prevalent in FH patients than in NERD patients. Recently, we examined 92 patients with heartburn (without esophageal mucosal breaks found upon upper endoscopy) *via* pH-MII to assess, in accordance with Rome Ⅲ criteria, the prevalence of NERD subgroups and FH in two groups of patients: those with and those without IBS. For each subject, we evaluated the AET, number of reflux episodes, correlation between symptoms and refluxes, and subjective response to PPI therapy. FH was found in 59% (27/46) of the patients with IBS, compared with 37% (17/46) of the patients without IBS ($P < 0.05$), indicating a higher prevalence of FH in IBS patients. In comparison, IBS was found in 39.6% (19/48) of the patients with NERD and in 61.4% (27/44) of the patients with FH, suggesting that in IBS patients, FH was more common than NERD was[39]. Although data from these two pioneering studies are not sufficient to support the concept that FH and IBS can occur in the same patient, they underscore the need for future investigations based on updated diagnostic criteria.

## PATHOPHYSIOLOGICAL SIMILARITIES IN GERD, FH AND IBS

Previous studies dealing with the overlap between GERD

**Table 2 Prevalence of irritable bowel syndrome in gastroesophageal reflux disease/functional heartburn patients**

| GERD patients (*n*) | FH patients (*n*) | Diagnostic investigations of heartburn | IBS prevalence | IBS criteria | Diagnostic investigations of IBS | Authors |
|---|---|---|---|---|---|---|
| 910 | Not evaluated | Postal SQ | 19% | Manning | Postal SQ | Kennedy *et al*[23]1 |
| 80 | Not evaluated | SQ | 36.7%-45.1% | Manning | SQ | Chey *et al*[40]2 |
| 34 (ERD)<br>67 (NERD) | Not evaluated | S, UE | 36% (in ERD)<br>35% (in NERD) | Manning | SQ | Nojkov *et al*[41] |
| 643 | Not evaluated | SQ | 42% | Rome I | SQ | Locke *et al*[42] |
| 35 | Not evaluated | SQ | 71% | Rome I | SQ | Pimentel *et al*[43] |
| 79 | Not evaluated | SQ | 3% | Rome I | SQ | Hu *et al*[25]1 |
| 457 | Excluded | S, UE, OM, pH | 49% | Rome I | SQ | Zimmerman *et al*[44] |
| 79 | Not evaluated | Phone SQ | 13% | Rome I | Phone SQ | Cheung *et al*[12]1 |
| 326 (NERD) | Excluded | S, UE, pH | 48.5% | Rome I | SQ | Hershcovici *et al*[45] |
| 326 (NERD) | Excluded | S, UE, pH | 49% | Rome I | SQ | Zimmerman *et al*[46] |
| 41 (ERD)<br>45 (NERD) | Not evaluated | S, UE | 48.7% (in ERD)<br>48.8% (in NERD) | Rome I | S, SC, HE | Camacho *et al*[26]1 |
| 3318 | Not evaluated | SQ | 36.7%-45.1% | Rome II | SQ | Bueno *et al*[47]2 |
| 102 | Excluded | S, UE, OM, pH | 32.4% | Rome II | SQ | Raftopoulos *et al*[48] |
| 3318 | Not evaluated | SQ | 27% | Rome II | SQ | Guillemot *et al*[49] |
| 263 | Not evaluated | S, pH | 35% | Rome II | SQ | De Vries *et al*[50] |
| 111 (ERD)<br>113 (NERD) | Excluded | S, UE, OM, pH. | 15.3% (in ERD)<br>44.2% (in NERD) | Rome II | SQ | Wu *et al*[51] |
| 238 | Not evaluated | SQ | 60.9% | Rome II | SQ | Nasseri-Moghaddam *et al*[52] |
| 67 | Not evaluated | SQ | 27% | Rome II | SQ | Lee *et al*[31]1 |
| 16 | Not evaluated | SQ | 50% | Rome II | SQ | Hori *et al*[32]1 |
| 92 | Not evaluated | SQ | 62% | Rome II | SQ | Rey *et al*[53] |
| 102 (ERD)<br>163 (NERD) | Excluded | S, UE, OM, pH | 20.6% (in ERD)<br>39.9% (in NERD) | Rome II | SQ | Wu *et al*[54] |
| 411 | Not evaluated | Postal SQ | 20.2% | Rome III | Postal SQ | Jung *et al*[10]1 |
| 344 | Not evaluated | SQ | 51.7% | Rome III | SQ | Solhpour *et al*[55] |
| 36/95 (ERD)<br>36/95 (NERD) | 23/95 | S, UE, OM, pH | 17% (in ERD)<br>23% (in NERD)<br>39% (in FH) | Rome III | SQ | Lee *et al*[56] |
| 207 | Not evaluated | SQ | 29.5% | Rome III | SQ | Kaji *et al*[36]1 |
| 286 (ERD)<br>74 (NERD) | Not evaluated | S, UE | 11.2%<br>41.9% | Rome III | SQ | Noh *et al*[57] |
| 2658 | Not evaluated | S, UE | 33.9% | Rome III<br>Rome II | SQ | Yarandi *et al*[35]1 |
| 207 | Not evaluated | SQ | 29.5% | Rome III | SQ | Fujiwara *et al*[38]1 |
| 48/92 (NERD) | 44/92 | S, UE, OM22, M II-pH | 39.6% (in NERD)<br>61.4% (in FH) | Rome III | SQ | Martinucci *et al*[39]1,2 |
| 1181 (ERD)<br>694 (NERD) | Not evaluated | S, UE | 12.7% (in ERD)<br>18.3% (in NERD) | ReQuest | SQ | Mönnikes *et al*[58] |
| 6810 | Not evaluated | SQ | 60% | ReQuest | SQ | Fass *et al*[59]2 |
| 257 | Not evaluated | SQ | 58% | ReQuest | SQ | Bardhan *et al*[60] |

[1]Articles listed in both tables 1 and 2; [2]Abstract only (publication type). GERD: Gastroesophageal reflux disease; FH: Functional heartburn; IBS: Irritable bowel syndrome; S: Symptoms; SQ: Symptom questionnaire; PE: Physical examination; HE: Hematological examinations; BE: Barium enema; BC: Bacteriological culture; SC: Stool culture; BT: Lactose/lactulose breath test; AU: Abdominal ultrasonography; UE: Upper endoscopy; LE: Lower endoscopy; LEB: Lower endoscopy and biopsies; SBB: Small-bowel biopsies; Sg: Sigmoidoscopy; OM: Esophageal manometry; pH: pH-metry; MII-pH: pH impedance monitoring; ERD: Erosive reflux disease; NERD: Nonerosive reflux disease.

and IBS have proposed that visceral hypersensitivity, motility dysfunctions, and central neural mechanisms can be the main common pathophysiological mechanisms[11,13,61]. However, following the release of Rome Ⅲ criteria, an increasing number of studies have indicated the importance of a careful categorization of GERD patients *via* pathophysiological investigations to better appreciate the degrees of overlap between IBS and reflux symptoms in various subgroups of patients[39,56,62,63]. Accordingly, this section intends to appraise and critically discuss the available evidence supporting a pathophysiological relationship among GERD, FH and IBS. When attempting such a difficult task, two important points must be carefully considered: (1) In previous studies, GERD and IBS patients have been investigated to determine their pathophysiological and clinical features, while FH patients constitute a "new entity" for which pathophysiological studies are urgently required; and (2) Most of the available literature on the pathophysiology of FH addresses patients who were identified using old criteria (*i.e.*, criteria that have since been replaced by the Rome Ⅲ classification) that also identified NERD patients with normal esophageal AET. Even when these issues are kept in mind, IBS and FH, as well as IBS and GERD, appear to share some pathophysiological features that need to be carefully considered.

### *Visceral hypersensitivity*

Most FDD patients display a reduced pain or discomfort threshold in response to visceral stimulation, implying that they might perceive a stimulus as uncomfortable or painful at significantly lower intensity than normal subjects would[64]. Such increased sensitivity can be usually documented throughout the whole gastrointestinal tract, suggesting diffuse, rather than site-dependent, involvement[65].

Studies aimed at gaining pathophysiological insights irrespective of the dominant digestive disorder have extensively investigated visceral hypersensitivity to a variety of stimuli (*e.g.*, acid perfusion, balloon distension, electrical stimulation) within both IBS[66] and GERD[63]. In particular, current data suggest that NERD patients displays equivalent or increased degrees of visceral hypersensitivity as compared with ERD, but may have lower levels than those shown by patients with functional esophageal disorders (*i.e.*, FH/chest pain of presumed esophageal origin). According to recent advances in basic science, three main mechanisms are believed to underlie visceral hypersensitivity (*i.e.*, peripheral sensitization, central sensitization and psychoneuroimmune interactions), and all of these have been documented in NERD patients[63]. Nevertheless, these factors' respective roles and degrees of involvement in the pathophysiology of FH remain to be established, particularly in the light of the Rome Ⅲ criteria. To verify whether FH patients have visceral hypersensitivity and to assess whether this feature is a common trait in IBS patients, some studies have investigated the presence of esophageal sensitivity to chemical or mechanical stimuli in FH and/or IBS patients.

Rodriguez-Stanley *et al*[67] reported that 89% of patients with FH (Rome Ⅱ) experienced abnormal responses to intraesophageal acid perfusion (Bernstein test), esophageal balloon distension, or both. In repeated studies using either esophageal balloon distension or electrical stimulation, patients with FH (Rome Ⅱ) have consistently demonstrated a lower perception threshold for pain or discomfort compared with patients with erosive esophagitis and/or abnormal 24-h esophageal pH monitoring[68,69]. Recently, Thoua *et al*[62] observed that patients with NERD had higher sensitivity to esophageal acid exposure than did ERD patients and controls, and this hypersensitivity was most pronounced with proximal esophageal acid exposure. Moreover, FH patients (Rome Ⅲ) were more hypersensitive to excess acid exposure than NERD patients were. Of note, these authors carefully selected patients with unequivocal reflux, taking care to exclude those with minor mucosal breaks, and the condition of hypersensitivity was found to be independent from motility changes[62]. Yang *et al*[70] found that cortical evoked potentials latencies induced by balloon distension were shorter in FH patients (Rome Ⅱ) than in controls before acid perfusion, and such perfusion decreased the latencies and increased their amplitude in FH patients, but not in controls. These findings suggest that dysfunctions of visceral neural pathways and/or alterations in cortical processing might generate and mediate esophageal hypersensitivity in FH.

Consistent with the notion that visceral hypersensitivity is not site-specific, Costantini *et al*[71] reported that during esophageal provocative testing (balloon distension and bethanechol administration), IBS patients displayed a lower threshold for esophageal symptoms compared with healthy volunteers, without any evident alteration of esophageal motility or decrease in esophageal basal pressure. In line with these observations, Trimble *et al*[72] demonstrated that IBS patients had a lower rectal sensory threshold for pain compared with healthy controls and that IBS patients displayed concomitantly lower sensory thresholds for both esophageal perception and discomfort evoked by balloon distension.

Whether the types of sensory dysfunctions previously detected in FH patients (Rome Ⅱ)[68] can also be observed in FH patients diagnosed in accordance with Rome Ⅲ criteria remains to be established. When investigating this issue, it must be considered that at present, there is not a unanimous consensus on how to define and measure the condition of lowered visceral threshold. A further critical issue is that visceral thresholds for different stimuli do not necessarily display parallel alterations. In this context, some relevant questions still await conclusive answers: (1) Which is the most meaningful index of an altered sensory threshold? (2) Can different stimuli be regarded as equivalent in nature? and (3) Considering day-to-day variations in the occurrence of symptoms, is there also a day-to-day variation in the underlying biological abnormalities responsible for these symptoms? Overall, great caution will be required in future studies addressing the pathophysiological meaning of visceral hypersensitivity in GERD/FH and/or IBS.

### *Motility dysfunction*

Motor abnormalities might represent a common pathophysiological mechanism between GERD and IBS[61]. Consistent with this concept, some authors speculate that an overall dysfunction of smooth muscle throughout the GI tract might explain the overlap between IBS and GERD[22].

Of note, the pattern of esophageal motility has been shown to differ between ERD and NERD patients[73], while no significant differences have been found in LES pressure or contraction amplitude when comparing FH patients (Rome Ⅲ) to NERD patients with pathological AET[62]. In unclassified subjects complaining of heartburn, Bhalla *et al*[74] observed that acid infusion elicited an increase in symptom sensitivity in concomitance with a perturbation of esophageal contractility, as revealed by a greater increase in contraction amplitude, contraction duration, muscle thickness, and the incidence of sustained esophageal contractions during the second acid infusion in comparison with the first one.

To date, the possible contribution of motility dysfunction to the pathophysiology of FH remains unclear; however, while studying 12 unclassified subjects with heartburn using 24-h pH-metry, synchronized pressure

recording and high-frequency intraluminal ultrasound imaging of the oesophagus, Pehlivanov *et al*[75] highlighted a close correlation between heartburn episodes (whether associated with acid reflux or not) and abnormally long longitudinal muscle contraction durations. This motor correlate might also be relevant to a better understanding of the pathophysiological bases of heartburn perception in FH patients, but it has been documented only by a preliminary investigation and requires additional studies to be confirmed. Likewise, whether esophageal and bowel motor abnormalities occur concomitantly in patients with overlapping GERD/FH and IBS is currently unclear, and studies addressing this issue are required.

### Central neural mechanisms

In FH patients, heartburn has been proposed to originate from factors other than luminal stimuli[68]. It has been speculated that central neural mechanisms related to psychological comorbidity (anxiety, depression and stress) could modulate esophageal perception and make patients prone to perceiving low-intensity esophageal stimuli as painful[69]. In particular, anxiety has been implicated as a factor that may modulate the degree of sensitization to esophageal acid testing[76].

Johnston *et al*[77] studied 101 patients with heartburn using esophageal pH monitoring. The subjects who showed no correlation between symptoms and refluxes displayed significantly higher levels of trait anxiety compared with patients with a positive correlation. Along the same line, Rubenstein *et al*[78] observed that in subjects with heartburn, esophageal sensation to both acid perfusion and mechanical distension was associated with increased levels of psychiatric distress and a diagnosis of IBS.

According to Posserud *et al*[79], no clear relationship between pain threshold and IBS symptoms (severe pain, bloating and diarrhea) has been convincingly established, and other mechanisms, including central nervous ones, are likely to play a relevant role. In line with this contention, Elsenbruch *et al*[80] observed that IBS patients can indeed experience a higher severity of distension-induced pain and overall discomfort despite unaltered rectal sensory thresholds, suggesting that the perception of visceral stimuli could be influenced by emotional factors. In contrast, it remains unclear what psychological factors are relevant for visceral hyperalgesia in IBS patients and how they may interact with biological mechanisms, such as peripheral/central neuroendocrine and immune processes[66].

Another aspect that deserves attention addresses the possible impact of sleep disorders on the pathophysiology of FDD symptoms. Jung *et al*[10] observed that self-reported insomnia and frequent abdominal pain represent two risk factors for IBS-GERD overlap compared with IBS or GERD alone. In addition, a positive association has been found between the severity of IBS symptoms and the severity of sleep disturbances. However, the pathophysiological mechanisms underlying this association are only partly understood. One possibility is that sleep disorders induce visceral hyperalgesia, thus amplifying the patient's perception of gastrointestinal symptoms[81,82].

### Response patterns to drugs that modulate visceral pain

Pathophysiological similarities among GERD, FH and IBS might reflect similarities in their response patterns to the drugs that influence common pathophysiological mechanisms. According to the Rome Ⅲ criteria, FH patients' symptoms do not improve with PPI therapy. Consistent with this criterion, even before Rome Ⅲ, some authors reported that adding or switching PPIs to a visceral pain modulator [(*i.e.*, tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs)] might induce beneficial effects in FH patients (Rome Ⅱ)[83]. Peghini *et al*[84] were the first to report that imipramine can reduce esophageal pain perception in healthy male volunteers. Clouse *et al*[85] investigated the effects of low-dose trazodone in patients with symptomatic esophageal dismotility and obtained a significantly greater global symptom improvement compared with placebo. Broekaert *et al*[86] observed that citalopram lowered chemical and mechanical esophageal sensitivity in healthy subjects without altering motility. Likewise, in a randomized placebo-controlled study, citalopram 20 mg/d was found to be effective in a selected group of patients with hypersensitive esophagus (*i.e.*, normal AET, positive SI)[87]. Overall, the current evidence, although preliminary in nature, suggests that SSRIs may exert beneficial effects in lowering esophageal sensitivity to chemical and mechanical stimuli. These observations encourage the performance of studies aimed at assessing the efficacy of SSRIs in patients with esophageal hypersensitivity. In this regard, it is interesting to note that antidepressants (*e.g.*, TCAs and SSRIs) have been found more effective than placebo in IBS treatment, as indicated by a recent review and meta-analysis of randomized controlled trials[88]. Thus, based on current knowledge, it can be tentatively speculated that visceral hypersensitivity might be a common trait among patients with esophageal hypersensitivity and/or IBS and that such an underlying pathophysiological condition might explain the beneficial responses to antidepressants in both these disorders. Overall, a critical appraisal of current evidence highlights the need for future clinical studies aimed at assessing the possible transverse beneficial actions of drugs in patients with concomitant ERD, NERD or FH and IBS. To date, it can be hypothesized that antidepressants have a beneficial role as visceral pain modulators.

## CONCLUSION

In the present review, we have attempted to appraise and critically discuss whether the current literature supports an association between GERD and IBS and between FH and IBS. Our literature search highlights a high heterogeneity in terms of both the criteria and diagnostic procedures used to investigate the presence of heartburn

and IBS. In particular, most of the current epidemiological data do not rely on a formal diagnostic assessment of IBS and/or GERD; rather, the studies generally evaluated these disorders *via* symptom questionnaires. Another critical issue is the inclusion of patients with concomitant IBS and GERD without any attempt to distinguish FH from GERD using pathophysiological investigations. Indeed, a very few small studies have documented an actual concomitance of FH and IBS. The main reason for this paucity of data stems from the fact that, until the release of the Rome Ⅲ criteria, FH was not regarded as a distinct entity and was included in the same category as GERD. Moreover, most of current pathophysiological data refer to FH patients as defined by criteria older than the Rome Ⅲ classification. Accordingly, clear evidence of an association between IBS and FH, as defined by the Rome Ⅲ criteria, is presently lacking.

Independent of these critical issues, there is some evidence, though scarce and preliminary, of the concomitance of FH and IBS. In support of this contention, some studies have shown that FH and IBS may share common pathophysiological mechanisms, such as visceral hypersensitivity, and that drugs that act as visceral pain modulators (such as antidepressants) may exert beneficial effects on both disorders when tested in separate trials.

Overall, current knowledge about the GERD/FH and IBS overlap needs to be expanded *via* investigations based on updated diagnostic criteria, more accurate pathophysiological classifications, and careful categorization of patients with heartburn. To achieve these goals, future epidemiological and pathophysiological studies should be designed to properly assess the presence and extent of overlaps linking IBS with FH and various subgroups of GERD patients. In this context, it is also expected that a better pathophysiological characterization of heartburn will foster the identification of therapeutic strategies that target the common pathogenic mechanisms underlying FH and IBS.

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