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Invited Commentary

Overlap Between GERD and Functional Esophageal Disorders—a Pivotal Mechanism for Treatment Failure

Ofer Z. Fass, MD[1]
Ronnie Fass, MD[2,*]

Address
[1]Department of Medicine, New York University Langone Health, New York, NY, USA
[*,2]Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University School of Medicine, 2500 MetroHealth Drive, Cleveland, OH, 44109, USA
Email: ronnie.fass@gmail.com

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Abstract

Refractory GERD is very common, and while many different underlying mechanisms have been identified, the main focus has remained on residual reflux (acidic or non-acidic). Recently, Rome IV introduced two new concepts with important impact on patients with refractory GERD. They include the introduction of the reflux hypersensitivity group and the proposal that GERD can overlap with a functional esophageal disorder. Recent studies have demonstrated that the latter affects approximately three quarters of the GERD patients who failed PPI once daily.

Gastroesophageal reflux disease (GERD) is defined as reflux of stomach contents into the esophagus resulting in troublesome symptoms [1]. It is a common disorder affecting 20% of the US population [2]. The prevalence of GERD is increasing, in part, due to rising obesity rates in the western world [3]. The cornerstone of medical management remains proton pump inhibitors (PPIs), which reduce gastric acid secretion and thus, improve symptoms and heal esophageal inflammation [4]. Despite their well-documented efficacy, up to 40% of GERD patients report continued symptoms on standard dose, once-daily therapy [5, 6].

Failure of PPI treatment in patients with documented GERD has been previously attributed to residual reflux due to insufficient acid suppression [7, 8]. While the need to achieve normalization of esophageal acid exposure for complete esophageal healing or resolution of GERD-related symptoms remains an area of controversy, studies have subsequently focused on non-acidic reflux as a leading underlying mechanism for PPI failure in GERD patients. A pivotal trial evaluating 144 GERD patients on PPI treatment with persistent symptoms using multichannel intraluminal impedance and pH monitoring demonstrated that 37% had a positive symptom index with non-acidic reflux and 11% with acidic reflux [9]. Thus, the study concluded that nearly half of the patients with PPI failure had residual reflux (either acidic or non-acidic), which was likely the cause of their symptoms. Further characterization of the residual reflux revealed a mixed liquid and gas composition with a high tendency to reach the proximal esophagus [8]. As a result, therapies targeting residual reflux were evaluated in patients who were unresponsive to PPI treatment. They included transient lower esophageal sphincter relaxation reducers, prokinetics, mucosal protective agents, endoscopic therapy, and anti-reflux surgery [10–12]. However, it has been demonstrated that the likelihood of patients with GERD to have an abnormal pH test on twice-daily PPI is 7% and the odds of a normal pH test are 11 times higher than in patients on once-daily PPI (OR = 11.4; 95% CI = 4.3–30.1 $P < 0.01$) [13]. In addition, symptomatic response of patients with GERD to PPI treatment is a poor indicator for successful normalization of esophageal acid exposure or complete healing of erosive esophagitis [14]. These findings suggest that factors other than abnormal levels of reflux (any type) drive symptoms in GERD patients who failed PPI treatment [15].

Comparison of reflux characteristics between GERD patients responding fully to once-daily PPI versus those who failed to respond, by using a combination of 24-h pH test and Billitec, revealed a similar distribution of duodenogastroesophageal and acidic reflux in both groups [16]. This suggested that abnormal levels of residual reflux are unlikely to be the cause for persistent symptoms in PPI treatment failure. Instead, esophageal hypersensitivity may be driving symptoms by increasing esophageal perception of lower intensity stimuli. Rohof et al. provided further evidence for this idea by evaluating 18 GERD patients; 9 PPI responders and 9 partial responders [17]. The authors found no difference in the rate of post-prandial reflux, pH of the gastric acid pocket, or position of the acid pocket between the two groups. Additionally, the permeability of the esophageal mucosa was similar in both groups. However, PPI partial responders had more reflux events that reached the proximal esophagus and increased mechanoreceptor sensitivity to balloon distension in both the upper and lower esophagus. This study established for the first time the presence of esophageal hypersensitivity in patients who did not fully respond to PPI treatment as compared to those who demonstrated complete symptom resolution. The authors proposed that PPI-resistant symptoms are most likely explained by increased reflux to the proximal esophagus in a hypersensitive esophagus. More recently, Abdallah et al. compared GERD patients who failed PPI once daily to those who were successfully treated with a similar dose of PPI, using

multichannel intraluminal impedance and pH monitoring [18]. The authors demonstrated no difference in reflux characteristics between the two patient groups, further supporting the hypothesis that other mechanisms besides lack of complete suppression of gastroesophageal reflux are responsible for patients' residual symptoms.

Rome IV introduced for the first time two separate functional esophageal disorders with heartburn as their predominant symptom [19]. They include functional heartburn, which was previously recognized as a functional esophageal disorder, and reflux hypersensitivity, which was previously considered a subgroup of nonerosive reflux disease (NERD) [20]. Both functional esophageal disorders are the main underlying mechanism for persistent heartburn despite twice-daily PPI in up to 90% of the patients [21, 22]. Furthermore, Rome IV also introduced another new concept, which was not mentioned in the previous Rome criteria, that functional esophageal disorders, specifically functional heartburn and reflux hypersensitivity, may overlap with GERD [19]. Rome IV emphasized that patients with documented GERD who failed PPI treatment likely have an overlap with a functional esophageal disorder. It is the latter that is responsible for patients' symptoms. This concept is a breakthrough in our understanding of the mechanisms that lead to persistent symptoms in GERD patients who are on PPI treatment. It also ties together the previous reports about esophageal hypersensitivity and psychological comorbidity as potential underlying mechanisms for failure of PPI treatment in GERD patients. The recent study by Abdallah et al. further helped to cement the overlap concept between GERD and functional esophageal disorders in PPI failure patients by demonstrating that 75% of the GERD patients who continued to have symptoms on once-daily PPI had an overlap with either functional heartburn (62.5%) or reflux hypersensitivity (12.5%) [18]. The authors concluded that most GERD patients who failed PPI treatment have an overlap with functional heartburn or reflux hypersensitivity, which are likely responsible for patients' lack of response to treatment.

In summary, recognizing that most PPI failure in patients with documented GERD is the result of an overlap with a functional esophageal disorder may improve our current management of this common clinical dilemma. Treatment that focuses on pain modulators, psychological intervention, or complimentary medicine techniques may be needed in addition to anti-reflux medications to provide full control of symptoms. Moreover, educating physicians from all disciplines, as well as patients, about the relationship between GERD and functional esophageal disorders may simplify the diagnostic process.

Compliance with ethical standards

Conflict of interest

Ofer Fass declares that he has no conflict of interest. Ronnie Fass declares that he is an advisor for Ironwood, Mecleri Therapeutics, Takeda and Chinoin, speaker for Ostrazeneca, Takeda, Cadilla and Diversitek and receive research money from Ironwood.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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