Revenge of the NERDs: Cadherin Fragments Differentiate Functional Heartburn from Non-erosive Reflux Disease

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Published online: 12 January 2018
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To the Editor,

Due to the ever-increasing use of proton pump inhibitors (PPI), the therapeutic front line in gastroesophageal reflux disease (GERD) has changed. The successful healing of esophagitis, an elusive therapeutic target a mere 25 years ago, has been eclipsed by new considerations, with emphasis now being focused on symptom resolution, in particular, heartburn. Moreover, patients with heartburn are a heterogeneous group, including subpopulations with different mechanisms responsible for their symptoms. Patients with GERD symptoms such as heartburn either have increased esophageal acid exposure with (erosive esophagitis; EE) or without (non-erosive reflux disease; NERD) erosions, or with normal acid exposure with acid hypersensitivity (functional heartburn; FH) [1]. Although EE is readily diagnosed, the distinction between patients diagnosed with NERD and those with FH can be difficult despite being highly clinically relevant: the first group mostly benefits from pharmacological suppression of acid secretion or from surgical anti-reflux therapy, whereas in the second group, prolonged therapy with proton pump inhibitors (PPI) and anti-reflux surgery are unnecessary and possibly harmful and should thus be assiduously avoided. Until now, the missing piece in this puzzle has been the existence of a biomarker useful to differentiate patients with NERD from FH and to predict the response to PPI therapy.

Patients with NERD have for long been considered poor responders to PPIs. Nonetheless, a meta-analysis emphasized that the previously reported low response rate in NERD was

likely the result of biased studies that included patients with non-GERD-related upper gastrointestinal symptoms [2].

Twenty-four-hour esophageal pH monitoring is useful to define the etiology of heartburn symptoms. Recently, the addition of impedance, which recognizes fluid reflux, along with pH monitoring has enhanced the ability to detect patients with FH [3]. Nevertheless, these techniques have some intrinsic limitations: (a) esophageal acid exposure time presents a physiological day-to-day variability due to variations of dietary habits and physical activity; (b) symptoms reported during single-day monitoring are often absent or few, decreasing the reliability of reflux association indexes; and (c) patients are often uncomfortable and adopt a more sedentary lifestyle, reducing the frequency of reflux-provoking activities. These limitations could be particularly relevant to patients with NERD who frequently have weakly acidic (pH 4–7) reflux during 24-h pH monitoring, as opposed to patients with EE who generally have strongly acidic (pH < 4) reflux [4].

Ultrastructural studies [5–7] have demonstrated a widening of the intercellular junctions between cells in the esophageal epithelium in patients with NERD, with limited data supporting corresponding increased paracellular permeability to solutes, which was hypothesized to be due to acid damage to the intercellular junctional complex. Since the zonula adherens, a structure integral to maintaining the integrity of the tight junction between cells, is composed partly of cadherins, the presence of E-cadherin cleaved into carboxy (C)-terminal fragments (CTFs) and amino (N)-terminal fragments (NTFs) is likely associated with the increased junctional damage and increased paracellular permeability in patients with NERD [8].

In this issue of *Digestive Diseases and Sciences*, Jovov et al. [9] reported a study of twenty-nine NERD patients with heartburn occurring at least 3 days/week. Esophageal biopsies for western blot (WB) analysis of CTF expression were obtained at baseline, whereas blood samples for NTF analysis were acquired before and after a course of PPI therapy.

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Two different control groups were used: one was recruited in order to measure CTF expression in biopsies of the esophageal epithelium and the second group was recruited to evaluate serum concentrations of NTFs of by enzyme-linked immunoabsorbent assay (ELISA). The authors reported that fragments of E-cadherin were present in the esophageal mucosa in 93% of patients. In the treatment cohort, 83% of patients were either full or partial responders and 17% were non-responders to PPI. Yet, the only two patients with biopsies negative for CTFs were both responders to PPI and the biopsies all non-responders to PPI were positive for CTFs. Although at baseline, concentrations of serum NTFs were similar between the treatment cohort and the control group, NTF concentrations in responders (complete or partial) were significantly higher than in non-responders and in controls. Moreover, NTF concentrations post-treatment decreased in 75% of complete and partial responders.

After 4 weeks of PPI therapy, NTF concentrations were significantly reduced in the responders while remaining unchanged in the non-responders and in the controls. The authors concluded that an absorbance value for serum NTFs of ≥ 0.228 AU may be useful in differentiating between these patient groups. Moreover, the concentrations of serum NTFs in PPI-responsive patients declined after treatment, but remained the same as controls for the 5 PPI non-responsive subjects.

The information of this pilot study could be used to determine when PPI therapy could be tapered or stopped in responders and help predict the risk of symptom relapse. Still, despite being a pilot study, there are limitations, as reported by the authors. In particular, the sample size was small, only pre-treatment CTF concentrations were obtained, and a correlation of esophageal acid exposure (as determined by 24-h pH monitoring on or off therapy) with NTF concentrations was not used.

This pilot study generates an interesting hypothesis, that if confirmed in clinical trials with larger patient cohorts, could offer an appealing translational potential. In particular, the putative biomarker may help determine when a PPI may be tapered or discontinued without the immediate risk of

relapse. For those with heartburn not responsive to empiric PPIs, particularly at a double/high dose, normal NTF concentrations would support the conclusion that the symptoms were unrelated to acid-reflux disease, adding confidence that PPI therapy could be safely discontinued.

Finally, an objective serum biomarker that differentiates NERD from FH, and assesses the response to PPI treatment with high sensitivity, could become in the future and inexpensive, predictive, and relatively safe means to differentiate NERD from FH.

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