

What Is the Profiles for Predicting Treatment Responsiveness in Gastroesophageal Reflux Disease?

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Summary

Gastroesophageal reflux disease (GERD) has a high prevalence and an increasing incidence. Traditionally, 24-hour ambulatory pH monitoring has been recognized as a standard diagnostic test for GERD. However, compared with pH-alone monitoring, combined esophageal pH-impedance monitoring allows detection and characterization of all types of reflux episodes as well as their extent to the proximal esophagus.¹ Previous studies with 24-hour ambulatory pH monitoring have demonstrated that patients with normal acid exposure have the lowest rate of response to proton pump inhibitors (PPIs) and patients with a positive symptom-reflux association have a better response to PPIs.²

This study was performed in 100 patients with typical GERD symptoms (heartburn and/or regurgitation) from 3 university hospitals.³ Among these patients, 48 patients had functional dyspepsia and 36 had irritable bowel syndrome. Patients were considered as responders to PPI therapy if they had fewer than 2 days of mild symptoms per week while receiving a standard or double dose of PPI treatment for at least 4 weeks. Patients were

considered to be non-responders if they had more than 2 days of mild symptoms per week while receiving a standard or double dose of PPI treatment for at least 4 weeks. Forty-three patients were considered as PPI responders and 57 as non-responders. All responders and non-responders were referred for 24 hour pH-impedance monitoring in order to demonstrate the presence of pathologic GER. Esophageal impedance-pH monitoring was performed using a Sleuth Multi-channel Intraluminal Impedance ambulatory system (Sandhill Scientific, Highland Ranch, CO, USA). Both clinical and reflux parameters were taken into account for analysis.

The authors demonstrated that the factors associated with the absence of response were absence of esophagitis ($P = 0.050$), body mass index (BMI) of $\leq 25 \text{ kg/m}^2$ ($P = 0.004$) and functional dyspepsia (FD) ($P = 0.001$). However, no reflux pattern associated with PPI failure was demonstrated by 24 hour pH-impedance monitoring. They performed analysis in different subgroups of patients. In patients who reported symptoms during the recording ($n = 85$), the factors associated with PPI failure were BMI $\leq 25 \text{ kg/m}^2$ ($P = 0.004$), FD ($P = 0.009$) and irritable bowel syndrome (IBS) ($P = 0.045$). In patients who docu-

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mented GERD ($n = 67$), the factors associated with PPI failure were absence of esophagitis ($P = 0.040$), FD ($P = 0.003$), IBS ($P = 0.012$) and $BMI \leq 25 \text{ kg/m}^2$ ($P = 0.029$). Therefore, they concluded that absence of esophagitis, presence of functional digestive disorders and $BMI \leq 25 \text{ kg/m}^2$ were strongly associated with PPI failure. And no reflux pattern demonstrated by 24 hour pH-impedance monitoring is associated with response to PPIs in patients with GERD symptoms.

Comment

They classified all patients into 2 groups (responder and non-responder). However, there was no standardization of PPI therapy equally to all patients. There were also patients referred for refractory symptoms that appeared to be adequately controlled after treatment optimization (increase dose, change of PPI and dosing time) and therefore considered to be responders. In other words, there were a different kind, dose and dosing time of PPIs even in the same group.

The combined multichannel intraluminal impedance/pH-monitoring is considered as the most sensitive tool for assessing all types of gastroesophageal reflux (acidic, weakly acidic and weakly alkaline), their composition, proximal extent, duration and clearing. However, despite the use of this technology, the multivariate analysis taking into account both clinical and physiological parameters could not identify any reflux pattern associated with PPI failure. Previous studies showed that proximal migration was associated with symptomatic reflux in PPI-refractory non-erosive reflux disease patients.⁴ But, the authors failed to demonstrate that patients with a high rate of proximal reflux events were less likely to respond to PPI therapy. And also, they could not demonstrate any predictive value of symptom-reflux association analysis with regard to response to PPI therapy, whereas, in the literature, both symptom index and symptom association probability have been shown to be associated with favorable outcome.² However, these indices from the pH-impedance monitoring may be complementary to the 'quantitative' evaluation of reflux, so there is still room for pH-monitoring in patients with refractory GERD.

The authors showed that body mass index $\leq 25 \text{ kg/m}^2$ was a crucial factor of inadequate response to PPIs. Previous 2 studies showed that patients with lower BMI had observed poorer treatment responses by physician.^{5,6} The mechanisms by which BMI may influence the response to PPIs remain to be elucidated. Actually, high BMI has been clearly associated with the develop-

ment of reflux symptoms and complications through different mechanisms such as increased transient lower esophageal sphincter relaxation rate, gastric esophageal pressure gradient and esophagogastric junction disruption, that is, separation of lower esophageal sphincter and crural diaphragm leading to hiatal hernia.⁷⁻⁹ So, this discrepancy requires further study.

In this study, functional digestive disorders such as functional dyspepsia and IBS were independent factors of PPI failure even in patients with documented GERD. It may be hypothesized that the presence of functional digestive disorders and refractory GERD share the same underlying mechanism such as increased visceral hypersensitivity. However, they did not assess the psychosocial status such as level of anxiety or quality of life for the patients.

In conclusion, this study is the first outcome study in which the patterns of gastroesophageal reflux were determined by 24 hour pH-impedance monitoring off PPI. No reflux pattern associated with PPI failure was demonstrable by 24 hour pH-impedance monitoring performed off therapy. In contrast, clinical factors such as absence of esophagitis, presence of functional digestive disorders, and BMI of $\leq 25 \text{ kg/m}^2$ were strongly associated with PPI failure.

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