ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

The Role of Salivary Pepsin in the Diagnosis of Reflux

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G&H How sensitive and specific are the traditional diagnostic modalities for gastroesophageal reflux disease?

DS Modalities traditionally used for the diagnosis of gastroesophageal reflux disease (GERD) include the evaluation of symptoms, the proton pump inhibitor (PPI) test, endoscopy with biopsies, barium swallows, manometry, and reflux monitoring.

Symptoms are best evaluated with specific questionnaires, of which there are several, such as the Reflux Disease Questionnaire and the ReQuest Questionnaire. The sensitivity and specificity of these questionnaires for the evaluation of treatment in patients with GERD are in the range of 65% to 75%.

Performing a PPI test has also been proposed as a potential diagnostic modality in patients with GERD symptoms. The problem with this option is that there are other diseases that can respond to PPI treatment, such as dyspepsia and gastric inflammatory disorders; thus, patients who respond to a PPI test cannot be definitively identified as having GERD. Therefore, the specificity of this diagnostic modality is not very appropriate.

Endoscopy is highly specific because it diagnoses esophagitis, but it is not very sensitive because many patients with reflux symptoms may have nonerosive reflux disease. Biopsies can be used, but they are not specific or practical for the diagnosis of GERD. In patients with nonerosive reflux disease, it is possible to find dilation of intercellular spaces, or basal cell hyperplasia, but these are not specific findings; they are useful tools for distinguishing among functional heartburn, hypersensitive esophagus, and nonerosive reflux disease.

Reflux monitoring is the most widely used diagnostic technique for GERD and can be either catheter-based or wireless; 2 modalities are commonly used, pH metry and a combination of impedance and pH metry. In both cases, the sensitivity and specificity of the technique are 65% to 75% when the gold standard to consider is the presence of endoscopic lesions such as esophagitis.

Even though the current gold standard for the diagnosis of GERD is reflux monitoring, there remains a need for new techniques that are less invasive, cheaper, and less labor-intensive.

G&H How does laryngopharyngeal reflux differ from GERD?

DS Instead of having heartburn or regurgitation, some patients have other symptoms that may be related to gastroesophageal reflux. These extraesophageal symptoms might affect the larynx or pharynx and can provoke voice changes, sore throat, laryngitis, or even cough. This condition is known as laryngopharyngeal reflux (LPR). It is a clinical diagnosis in which reflux might be the cause of the symptoms; however, in many patients, it is often difficult to demonstrate a causal relationship between GERD and these symptoms.

G&H How is LPR typically diagnosed?

DS Otorhinolaryngologists have described different endoscopic patterns attributed to GERD (from edema to

erythema to ulceration). However, it is now well known that most of these patterns are nonspecific, and many of them can be observed in normal, asymptomatic individuals. Therefore, the endoscopic diagnosis of LPR is not very specific.

In addition to the difference in symptoms, patients with LPR very rarely have esophagitis or pathologic acid exposure in the distal esophagus.

It is difficult to diagnose LPR because of the lack of specificity of the diagnostic modalities. Many patients are treated with PPIs without an appropriate diagnosis and, therefore, often have very poor therapeutic outcomes. In general, the patients who respond better to treatment of LPR are those who also have typical reflux symptoms, such as heartburn and regurgitation, together with extra-esophageal symptoms. These individuals are more likely to respond to a high-dose PPI administered twice daily for at least 8 weeks.

Several modalities have been examined to improve the diagnosis of LPR, including reflux monitoring of the proximal esophagus and the pharynx with pH metry and impedance pH metry with impedance sensors located distal and proximal to the upper esophageal sphincter. These reflux monitoring modalities are very difficult to interpret in the context of LPR, and there is a high degree of interobserver variability, making the diagnosis very difficult. Other diagnostic modalities have also been tried, such as a specially designed pH sensor located in the pharynx. Unfortunately, this instrument has many artifacts and has been shown to provide an inaccurate diagnosis of LPR, particularly when validated against other measurements of reflux, such as pH metry and impedance pH metry.

Finally, the use of pepsin in saliva has also been proposed as a tool to diagnose LPR, based on recent findings that patients with LPR may have a significant concentration of pepsin in mucosal biopsies of the pharynx. Pepsin is able to remain in pharyngeal mucosa. In an alkaline environment, pepsin is inactive. However, with new acid reflux episodes, the molecule can be reactivated and can have proteolytic action, and perhaps it is involved in symptom generation.

G&H What research has been conducted on the use of salivary pepsin for the diagnosis of reflux?

DS There have been few studies and only very small case series on the use of salivary pepsin in the diagnosis of LPR. We recently studied patients with sore throat and identified a subgroup of patients in whom more than 2 diagnostic tests were positive, including impedance pH metry and the detection of pepsin. Follow-up with telephone interview demonstrated that these patients were the only ones who responded to PPI treatment. However, this study was very small, so further prospective, controlled research is still needed.

G&H How is salivary pepsin collected and used to diagnose reflux?

DS Several studies, which have been conducted in the United States, Italy, and most recently my own laboratory in the United Kingdom, have looked at the use of pepsin in saliva for the diagnosis of GERD. All have used a pepsin assay developed by Professor Dettmar from the United Kingdom. This technique is easy to use and has been evaluated over years; therefore, different cutoff thresholds for the diagnosis of pathologic reflux have been used in different publications.

In our recent study, we investigated not only the presence or absence of pepsin in saliva but also the concentration of pepsin in saliva as a factor for discriminating between healthy subjects and patients with reflux. We observed more than 100 normal subjects and 100 patients who had reflux with typical symptoms and pathologic pH metry. Pepsin was measured in saliva in the morning (after waking up), at noon during the first hour after lunch, and during the first hour after dinner. Almost one-third of normal subjects had a positive determination of pepsin in saliva, but in very low concentrations.

In contrast, when patients with reflux are pepsin-positive, the concentration is significantly higher, and most likely these samples were obtained in the postprandial period, both after lunch and after dinner, and much less likely in fasting or morning samples. Therefore, the most useful timing for the determination of pepsin in saliva was after meals. We know that a significant number of healthy subjects might have some positive samples, although in low concentrations, so the concentration cutoff used to determine pathologic samples was set at 200 ng/L. Using this cutoff, it was possible to distinguish 3 different types of patients with reflux: those who have increased acid exposure and a significant amount of pepsin in saliva; those with a hypersensitive esophagus, who have normal acid exposure, a positive association between symptoms and reflux, and often significant concentrations of pepsin in saliva; and those with functional heartburn, who have normal acid exposure, a negative association between symptoms and reflux, and very low concentrations of pepsin in saliva (a pattern similar to that observed in normal subjects).

G&H Have other cutoff values been used in studies?

DS A study in the United States by Dr Vaezi's group reported cutoff values for positivity that were different from ours. Endoscopy results were also included so that the presence or absence of esophagitis could be identified. The test had a significantly lower sensitivity for the detection of patients with esophagitis. Nevertheless, the

researchers acknowledged that the use of pepsin is noninvasive and inexpensive and has a potential future for the screening and diagnosis of reflux once the cutoff threshold can be determined in a large population, particularly one including patients with extraesophageal reflux symptoms and patients with reflux refractory to PPI treatment.

G&H What are the advantages and disadvantages of this test, compared with standard diagnostic tests for reflux?

DS A pepsin test is a noninvasive diagnostic option that can be performed in the clinician's office or in a very small laboratory in the clinic, and results can be obtained relatively fast (although we are currently recommending the use of samples obtained over 24 hours, which means that results cannot be obtained during the same visit). This technique can be assessed in pediatric patients, in whom invasive tests are not convenient.

In the studies that have been performed thus far, the sensitivity and specificity of the pepsin test are moderate, suggesting the possibility of false-positive and -negative results. Having said this, the sensitivity and specificity of this noninvasive test are in the same range as those of traditional diagnostic tests, including questionnaires and reflux monitoring. Therefore, the pepsin test should be used with caution, and clinicians should consider it in the context of clinical findings and other considerations, particularly the likelihood of the diagnosis of reflux, types of symptoms, previous response to PPIs, and previous endoscopy results.

G&H Based on the research conducted thus far, can this test be used in all patients with suspected reflux?

DS I think that this test is very promising. At the moment, I am aware of many otolaryngologists and clinics using pepsin in saliva, without clinical trial evidence or investigative protocols, to establish a diagnosis of LPR. I would like to propose a word of caution regarding this practice because there are no clinical trials to date with adequate controls, numbers of patients, and normal values for LPR that can be used to know when pepsin values should be considered diagnostic for LPR. It is very important to establish the same cutoff threshold in different laboratories. Furthermore, there are no outcome studies of treatment of LPR based on pepsin determinations in saliva. In other words, how good is this test at predicting the outcome of treatment with PPIs or with antireflux surgery? More research is also needed in patients with extraesophageal reflux symptoms such as LPR and in patients who are not responding to PPIs. Therefore, in my opinion, this technique is not yet ready for use in the clinical setting in patients with suspected LPR. As further research is currently underway in laboratories around the world, including my own, I am optimistic that in the near future we will be able to establish the role of this technique in the clinical diagnostic armamentarium for reflux.

Dr Sifrim's research studies on salivary pepsin were performed in collaboration with Technostics (the company that produces Peptest in the United Kingdom). However, the company was blinded at the time of sample analysis, and it did not participate in the statistical analysis and in the evaluation and interpretation of results.

Suggested Reading

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