Role of Acid and Bile in Esophageal Mucosal Damage

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Objective:
At the end of this presentation the participants will be able to:

1. Better understand the role of acid and DGER (bile reflux) in esophageal mucosal injury.
2. Know the limitation of pH monitoring in assessing DGER.
3. Understand the importance of a new bilirubin monitoring device and its utility in assessing DGER.
4. Treat DGER in patients with GERD and post-gastrectomy patients.

Reference:

1. Champion G, Richter JE, Vaezi MF, Singh S, Alexander R. Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology 1994; 107:747-754.
2. Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastroesophageal reflux in esophageal mucosal injury: a review of animal and human studies. Gastroenterology 1995; 108:1897-1907.
3. Vaezi MF, Richter JE. Role of acid and bile in gastroesophageal reflux disease. Gastroenterology 1996; 111:1192-1199.
4. Vaezi, MF, LaCamera EG, Richter JE. Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system. Am J Physiol 1994; 267:G1050-1057.
5. Vaezi MF, Richter JE. Contribution of acid and duodenogastroesophageal reflux to esophageal mucosal injury and symptoms in partial gastrectomy patients. Gut 1997; 41:297-302.
6. Vaezi MF, Sears R, Richter JE. Double-blind placebo-controlled cross-over trial of cisapride in postgastrectomy patients with duodenogastric reflux. Dig Dis Sci 1996; 41:754-763.

Introduction

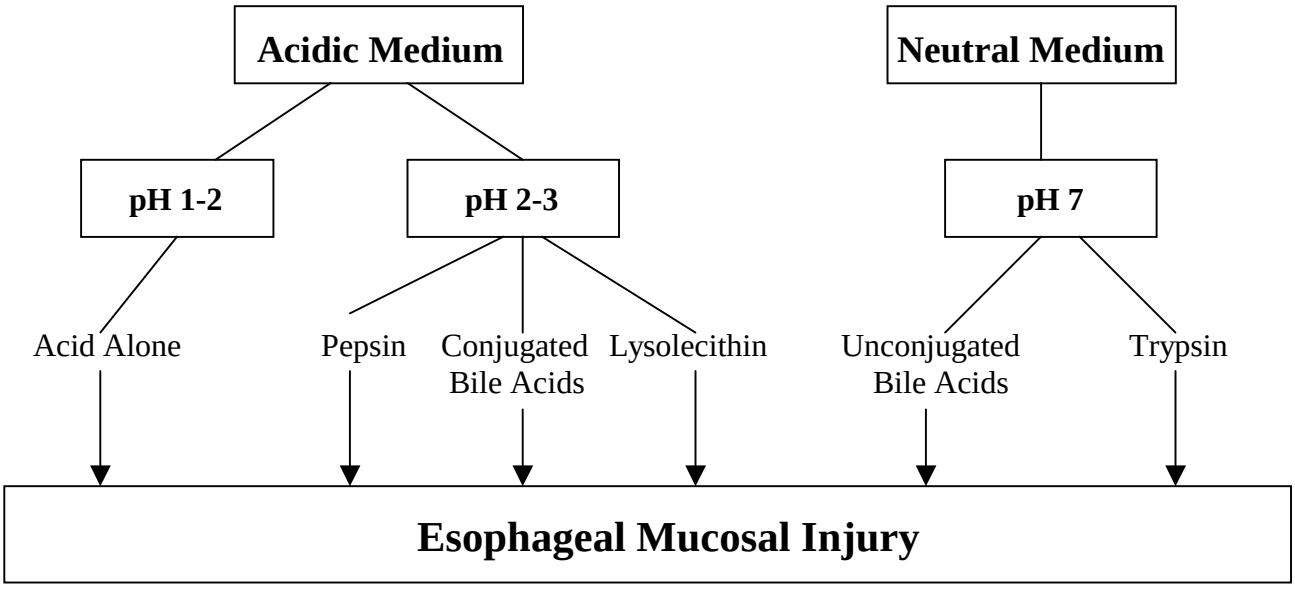
The term duodenogastroesophageal reflux (DGER) refers to regurgitation of duodenal contents through the pylorus into the stomach, with subsequent reflux into the esophagus. Previously, the terms "bile reflux" and "alkaline reflux" were used to describe this process. However, duodenal contents contain more than just bile and recent studies show that the term "alkaline reflux' is a misnomer since pH > 7 does not correlate with reflux of duodenal content (1-3).

Role of Acid and DGER in Esophageal Injury

Substantial experimental and clinical evidence strongly supports the importance of acid and pepsin in causing esophageal mucosal injury. Animal studies show that acid in combination with pepsin results in more severe injury to esophageal mucsoa than acid alone. Additionally, clinical studies show a relationship between severity of esophageal mucosal injury and acid reflux measured by 24-hour esophageal pH monitoring (2). However, the frequency and duration of acid exposure is not always predictive of the degree of esophageal mucosal injury, suggesting the importance of other factors, including DGER.

The role of individual components of duodenal material responsible for esophageal mucosal injury is well studied in animal experiments. These studies implicate conjugated bile acids and lysolecithin, a by product of hydrolysis of lecithin in bile by the pancreatic enzymes, in acidic pH values, while unconjugated bile acids and trypsin are more injurious in neutral pH values (Figure 1).

Figure 1



Extrapolating the results regarding the injurious effect of DGER from the animal data into humans is problematic. This is because there are no "gold standards" for detecting DGER in humans. Endoscopic observation of bile pool in humans is a poor marker of bile induced esophageal disease. Aspiration of gastric contents for measurement of bile acid and trypsin concentration, although helpful, represents only a short-term assessment of reflux of duodenal contents into the stomach occurring in a 24-hour period. Scintigraphic evaluation for DGER is stationary and results in radioactive exposure to patients and have shown conflicting results. Using pH > 7 ("alkaline reflux") as a marker for esophageal exposure to duodenal contents (DGER) has recently been shown to be an inaccurate means of detecting DGER. In fact, most esophageal pH > 7 is secondary to saliva or probe dysfunction.

Recently, a new fiberoptic spectrophotometer (Bilitec 2000) (Synectics, Stockholm, Sweden) was developed which detects DGER in an ambulatory setting, independent of pH. This system utilizes the optical properties of bilirubin, the most common pigment in bile. The basic working principal of this instrument is that an absorption near the wavelength of bilirubin implies the presence of bile, thus represents DGER. This instrument was extensively tested by several groups and shows a good correlation (r=0.82) between Bilitec readings and bile acid concentrations measurements of gastric aspirates (4).

Recent studies with this instrument in patients with acid reflux disease including patients with Barrett's esophagus have shed some light in better understanding the role of DGER in esophageal mucosal injury. These studies found a significant graded increase in both acid and DGER across the GERD spectrum with Barrett's patients having the highest measured acid and DGER. Furthermore, these studies found that simultaneous exposure to both acid and DGER was the most prevalent reflux pattern occurring in 95% of patients with Barrett's esophagus and 79% of GERD patients. Thus, these studies support the finding in animals, suggesting a possible synergy between acid and DGER in the development of esophagitis and Barrett's esophagus.

The role of DGER in producing esophageal mucosal injury, in the absence of acid reflux, was not clarified until recently. Studies in 32 partial-gastrectomy patients with reflux symptoms found increased DGER in 78% of patients (5). However, endoscopic esophagitis was only present in those with concomitant acid reflux, suggesting that DGER without acid reflux may cause symptoms but does not produce esophageal mucosal injury.

Bilitec is also used to assess the effects of drug therapy on DGER. Recent studies (1) found that aggressive acid suppression with omeprazole (20 mg BID) dramatically decreased both acid and DGER in patients with severe GERD. The decrease in DGER by omeprazole may be due to decreased gastric acidity and volume produced by omeprazole, resulting in decreased reflux of gastric contents. In partial-gastrectomy patients having upper GI symptoms due to non-acidic DGER, a recent randomized double-blind cross-over study (6) found that cisapride (20mg qid) significantly reduces both DGER measured by Bilitec and the associated upper GI symptoms.

Conclusion

Both animal and human studies strongly suggest that acid is the key factor in causing esophageal injury and Barrett's esophagus in patients with GERD. Studies using advanced techniques to identify DGER spectrophotometrically and independent of pH (Bilitec), however, suggest that duodenal contents often are present in the esophageal refluxate. The degree of esophageal exposure to acid and DGER showed a graded and similar increase from controls to esophagitis patients, with the highest value observed in patients with Barrett's esophagus. This close relationship raises the possibility that synergistic actions of acid, pepsin, and conjugated bile acids may be contributing to the development of Barrett's metaplasia and possibly even adenocarcinoma. Human studies show that DGER in non-acidic environment (i.e. partial gastrectomy patients) may cause symptoms but does not cause esophageal mucosal injury. Despite suggestions to the contrary by some surgical groups, aggressive acid suppression with proton pump inhibitors decreases both acid and DGER, perhaps by decreasing the volume of gastric contents available to reflux into the esophagus. Furthermore, the high intragastric and intraesophageal pH environment produced by proton pump inhibitors inactivates conjugated bile acids, the main DGER ingredients implicated in causing esophagitis. Thus, the proton pump inhibitors effectively heal esophagitis even in cases of severe reflux and Barrett's esophagus.