Complications of Gastroesophageal Reflux Disease

Role of the Lower Esophageal Sphincter, Esophageal Acid and Acid/Alkaline Exposure, and Duodenogastric Reflux

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The factors contributing to the development of esophageal mucosal injury in gastroesophageal reflux disease (GERD) are unclear. The lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and the presence of excessive duodenogastric reflux (DGR) was evaluated in 205 consecutive patients with GERD and various degrees of mucosal injury (no mucosal injury, n = 92; esophagitis, n = 66; stricture, n = 19; Barrett's esophagus, n = 28). Manometry and 24-hour esophageal pH monitoring showed that the prevalence and severity of esophageal mucosal injury was higher in patients with a mechanically defective lower esophageal sphincter ($p < 0.01$) or increased esophageal acid/alkaline exposure ($p < 0.01$) as compared with those with a normal sphincter or only increased esophageal acid exposure. Complications of GERD were particularly frequent and severe in patients who had a combination of a defective sphincter and increased esophageal acid/alkaline exposure ($p < 0.01$). Combined esophageal and gastric pH monitoring showed that esophageal alkaline exposure was increased only in GERD patients with DGR ($p < 0.05$) and that DGR was more frequent in GERD patients with a stricture or Barrett's esophagus. A mechanically defective lower esophageal sphincter and reflux of acid gastric juice contaminated with duodenal contents therefore appear to be the most important determinants for the development of mucosal injury in GERD. This explains why some patients fail medical therapy and supports the surgical reconstruction of the defective sphincter as the most effective therapy.

GASTROESOPHAGEAL REFLUX DISEASE is a common foregut disorder with an estimated prevalence of 0.36% and accounts for approximately 75% of esophageal pathology.[1] Complications of gastroesophageal reflux disease such as esophagitis, stricture, or Barrett's esophagus occur in about 50% of patients when increased esophageal exposure to gastric juice is documented by 24-hour esophageal pH monitoring.[2] A mechanically defective lower esophageal sphincter and ingredients in the refluxed juice, for example, gastric acid, pepsin, pancreatic enzymes, and bile acids, have been implicated as factors predisposing to the development of these complications. Considerable differences of opinion exist, however, in regard to the relative importance of each of these factors.[3–7]

The mechanical characteristics of the lower esophageal sphincter and esophageal exposure to acid gastric juice can easily be measured with manometry and esophageal pH monitoring, but the measurement of esophageal exposure to gastric juice alkalinized by duodenogastric reflux has been difficult in the past. We have recently shown that duodenogastric reflux can be quantified with 24-hour gastric pH monitoring and appears to be related to increased esophageal exposure to alkalinity pH > 7 recorded on esophageal pH monitoring.[8–11]

Using esophageal manometry and combined 24-hour esophageal and gastric pH monitoring, we evaluated the relationship between the mechanical characteristics of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and excessive duodenogastric reflux to the prevalence and severity of esophageal mucosal injury, in other words, esophagitis, stricture, or Barrett's esophagus, in gastroesophageal reflux disease.

Patients and Methods

Study Population

The study population consisted of 50 normal healthy volunteers and 205 consecutive patients with gastroesophageal reflux disease (GERD) documented by an in-

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creased esophageal exposure to gastric juice on 24-hour esophageal pH monitoring. A third group consisted of 67 consecutive patients with foregut symptoms from a cause other than GERD as shown by a normal esophageal pH record. Fifty-four of the 272 patients had previous foregut surgery (pyloroplasty or antrectomy, n = 12; proximal gastric vagotomy, n = 7; cholecystectomy, n = 35). All subjects had standard manometry to determine the mechanical characteristics of the lower esophageal sphincter and 24-hour esophageal pH monitoring to quantify esophageal acid and alkaline exposure. Twenty-four–hour gastric pH monitoring was performed simultaneously with esophageal pH monitoring to assess duodenogastric reflux in 25 of 50 volunteers, 152 of 205 patients with GERD, and all symptomatic patients without GERD. All patients also had an upper gastrointestinal endoscopy. Of the 205 patients with GERD, macroscopic esophagitis was seen in 66 (grade 1 in 32 patients, grade 2 in 20 patients, grade 3 in 14 patients), a stricture in 19, and Barrett's esophagus in 28 patients. The remaining 92 of 205 patients with GERD had no evidence of esophageal mucosal injury on endoscopy. Of the 67 patients without GERD, mucosal erythema was present in five. None of the patients without GERD had a stricture or Barrett's esophagus.

The normal volunteers were assessed after history, physical examination, and barium swallow had excluded the presence of any foregut pathology. All volunteers gave written informed consent. Demographic data of the study groups are shown in Table 1.

Standard Manometry of the Lower Esophageal Sphincter

Standard manometry was performed after an overnight fast using a single-catheter assembly consisting of five polyethylene tubes bonded together with five lateral openings placed at 5-cm intervals from the distal end of the catheter and oriented radially around the circumference. The catheters were perfused with distilled water at a constant rate of 0.6 mL/minute, using a pneumohydraulic low compliance perfusion pump (Arndorfer Medical Specialties Inc, Greendale, WI). Overall length, abdominal length, in other words, length below the respiratory inversion point, and resting pressure of the lower esophageal sphincter were measured with a station pull-through technique as previously described.[4] Based on the values obtained in the 50 normal subjects, a mechanically defective sphincter was defined as having one or more of the following characteristics: an average resting pressure of less than 6 mmHg, an average length of less than 2 cm, or an average length exposed to the positive-pressure environment of the abdomen of less than 1 cm. These values were below the 2.5th percentile for the normal range of sphincter pressure and overall length and below the 5th percentile for abdominal length.[4]

TABLE 1. *Demographic Data*

	No.	M/F	Age (yr)	
			Mean	Range
Normal volunteers	50	20/30	35.2	23–71
Patients, no GERD	67	32/35	50.4	16–78
Patients with GERD				
No mucosal injury	92	45/47	45.6	16–69
With mucosal injury				
Esophagitis	66	35/31	46.9	17–72
Stricture	19	12/7	59.1	17–78
Barrett's	28	19/9	52.7	25–76

GERD, gastroesophageal reflux disease.

Outpatient 24-hour Esophageal and Gastric pH Monitoring

Outpatient 24-hour esophageal and gastric pH monitoring was performed simultaneously using two combined Ingold glass electrodes, each with a built-in reference electrode (Model 440 M4, Ingold, Switzerland). The probes were calibrated in standard buffer solutions at pH 7 and 1 before and after the study. Only recordings with an electrode drift of less than 0.2 pH units over the 24-hour monitoring period were accepted. Both electrodes were passed transnasally through the same nostril. The esophageal pH electrode was placed 5 cm above the upper border of the lower esophageal sphincter, and the gastric pH electrode was placed 5 cm below the lower border of the lower esophageal sphincter (Fig. 1). The electrodes were connected to a portable digital data recorder that stored pH readings of both probes every 6 seconds (Synectics, Irving, TX). After placement of the probes, the subjects were sent home and instructed to remain in the upright or sitting position until they retired for the night, to perform normal daily activity but to avoid strenuous exertion, and to follow a diet restricted to three meals composed of food with a pH between 5 and 6. Only water was permitted between meals. A diary was kept of food and fluid intake, symptoms experienced during the monitored period, the time the supine position was assumed in preparation for sleep, and the time of rising in the morning. All medications known to interfere with foregut motor or secretory function were stopped at least 48 hours before the study.

The amount of esophageal exposure to gastric juice (pH < 4) was quantified using a composite scoring system.[2] A patient was considered to have increased esophageal exposure to gastric juice, in other words, gastroesophageal reflux disease, if the composite score exceeded the 95th percentile of the 50 normal volunteers.[12] For purposes of comparison between the groups, the cumulative exposure of the esophagus to acid was expressed as per cent time

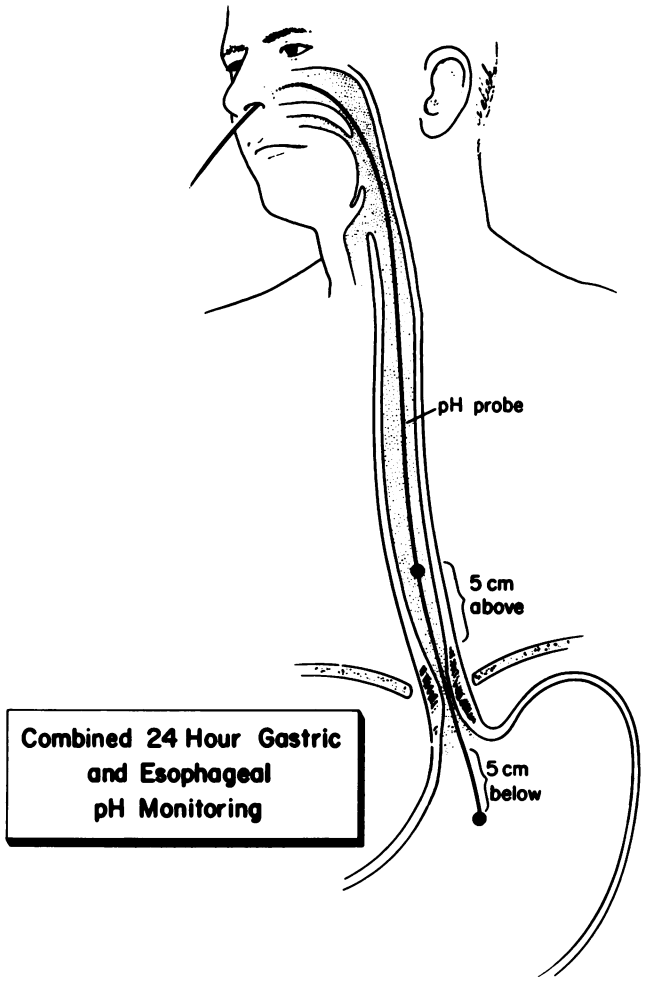

FIG. 1. Combined esophageal and gastric pH monitoring showing position of the probes in relation to the lower esophageal sphincter.

the pH was below 4 during the study period and defined as abnormal when it exceeded 4.45% (95th percentile of the normal volunteers). The cumulative exposure of the esophagus to alkalinity was expressed as per cent time the pH was above 7, and defined as abnormal when it exceeded 17.7% (95th percentile of the normal volunteers).

The 24-hour gastric pH record was evaluated for evidence of excessive duodenogastric reflux. To quantify alkaline duodenogastric reflux the gastric pH record was divided into the upright period, the supine period, the prandial pH plateau period, and the postprandial pH decline period. For each of these periods, the following parameters were calculated:

(1) The pH frequency distribution, in other words, the percentage time the gastric pH was at the pH intervals 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and >7.
(2) The frequency of pH changes, in other words, the incidence of pH movements from a lower into a higher pH interval.
(3) The duration of pH exposure expressed as the longest time the pH remained at a pH interval during the monitoring period
(4) Duration-frequency of pH exposure expressed as the number of times the pH remained at a pH interval for longer than 5 minutes.

Using discriminate analysis, we have previously shown that a scoring system based on 16 of these parameters could completely differentiate the gastric pH record of normal volunteers from patients with classic duodenogastric reflux disease. When applied prospectively, this scoring system was superior to DISIDA scanning with cholecystokinin stimulation in the diagnosis of excessive duodenogastric reflux and detected the disease with a sensitivity of 90% and a specificity of 100%.[8,9] The entire analysis of the esophageal and gastric pH records was performed by an IBM-compatible personal computer and analyzed using commercially available software (Gastrosoft, Irving, TX).

Endoscopy

Upper gastrointestinal endoscopy was performed in all patients by the senior author (TRD), who was unaware of the results of manometry and pH monitoring at the time of endoscopy. The presence of esophagitis was recognized by mucosal erythema (grade 1), linear erosions and friability (grade 2), or coalescent erosions, the so-called cobblestone mucosa (grade 3).[3] An esophageal stricture was identified by the inability to pass a 12-mm endoscope with ease. Biopsies were performed on all strictures to exclude malignancy and dilated to 50 Fr. before manometry and pH monitoring. There was an interval of at least 1 week between dilatation and esophageal function test. Barrett's esophagus was diagnosed by histologic documentation of columnar epithelium lining the esophagus at least 3 cm above the endoscopic gastroesophageal junction.[11]

Statistics

Esophageal acid and alkaline exposure were compared between groups using standard statistical analysis for nonparametric data sets (Wilcoxon rank-sum test). The prevalence of a mechanically defective sphincter, increased esophageal acid and acid/alkaline exposure, and the frequency of complications of GERD were compared between groups using the Fisher's exact test of proportion. A p-value < 0.05 was considered as significant. Unless otherwise stated, all data are expressed as mean ± standard error of the mean.

Results

A mechanically defective lower esophageal sphincter was present in 112 of 205 (55%) patients with increased esophageal exposure to gastric juice, compared with 10 of 67 (14.8%) patients with a normal esophageal pH record ($p < 0.01$). In patients with GERD, in other words, increased esophageal exposure to gastric juice, the prevalence of a mechanically defective sphincter increased with the severity of mucosal injury and was significantly higher in patients with esophagitis (65%), stricture (89%), and Barrett's esophagus (93%), as compared with patients with increased esophageal exposure to gastric juice but no mucosal damage (28%) ($p < 0.01$, Fig. 2).

As shown in Figure 3, the mean esophageal acid exposure (pH < 4) in patients with GERD increased progressively with the severity of mucosal injury. Compared with GERD patients with no mucosal injury, however, esophageal acid exposure was significantly increased only in patients with Barrett's esophagus ($p < 0.01$). When the pH records of these patients were analyzed for esophageal alkaline exposure, the per cent time pH > 7 was higher in GERD patients with esophagitis, stricture, or Barrett's esophagus, as compared with GERD patients with no mucosal injury, patients without GERD, or normal volunteers ($p < 0.05$).

The prevalence of increased esophageal alkaline exposure, in other words, the per cent time pH was above 7, exceeding the 95th percentile of normal, was 11% (22/205) of patients with GERD (Fig. 4). Sixteen of these 22 patients had previous foregut surgery that would increase the probability of excessive duodenogastric reflux (pyloroplasty, n = 2; antrectomy, n = 2; cholecystectomy, n = 12). The prevalence of complications of GERD (esophagitis, stricture, or Barrett's esophagus) was significantly higher in the 22 patients with acid/alkaline reflux (86%) as compared with those with only acid reflux (51%, $p < 0.01$) (Fig. 5). In GERD patients with only acid reflux, complications were more frequent in those with a mechanically defective lower esophageal sphincter (28.1% *versus* 73.4%; $p < 0.01$). Complications were almost always present in patients with a mechanically defective sphincter and acid/alkaline reflux (94.4%, $p < 0.01$) (Fig. 6).

The severity of complications progressively increased from patients with a normal lower esophageal sphincter and only acid reflux, to patients with a defective sphincter and acid/alkaline reflux (Fig. 7). Patients with a normal lower esophageal sphincter were more apt to have the complication of esophagitis ($p < 0.01$), whereas those with a mechanically defective sphincter were more likely to have a stricture or Barrett's esophagus ($p < 0.01$), particularly so in those with acid/alkaline reflux.

The origin of increased esophageal alkaline exposure was evaluated in individuals who had simultaneous esophageal and gastric pH monitoring. In these individuals, gastric pH monitoring showed excessive duodenogastric reflux in 14 of 67 (21%) patients without GERD and 44 of 152 (29%) patients with GERD, but in none of the normal volunteers. Of the 58 patients with excessive

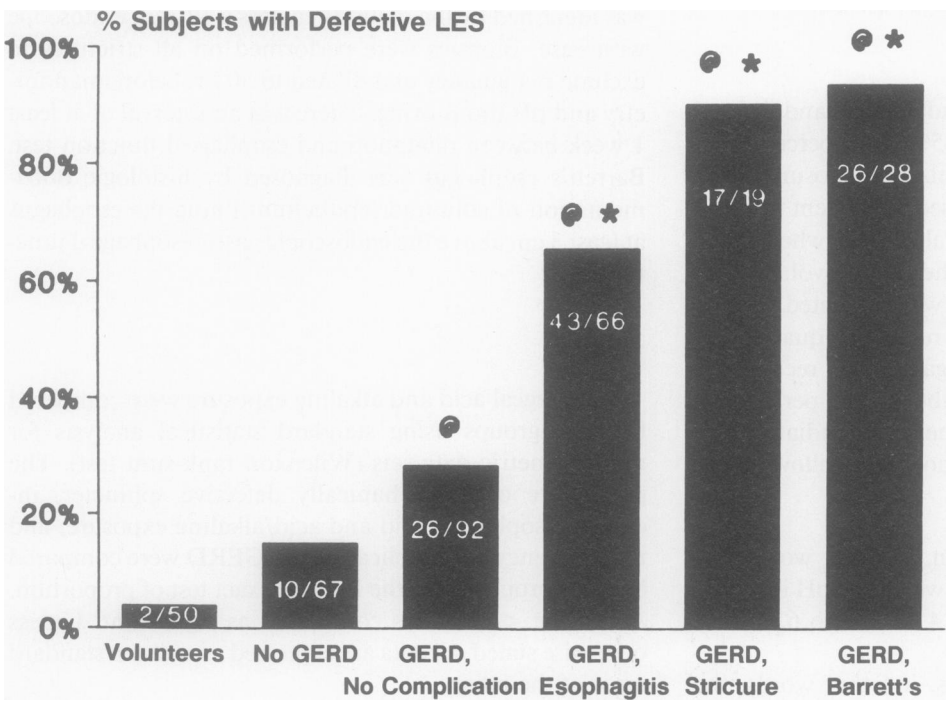

FIG. 2. Prevalence of a mechanically defective LES in the study groups. * $p < 0.01$ *vs.* patients without GERD and patients with GERD but no complication. @ $p < 0.01$ *vs.* subjects without GERD.

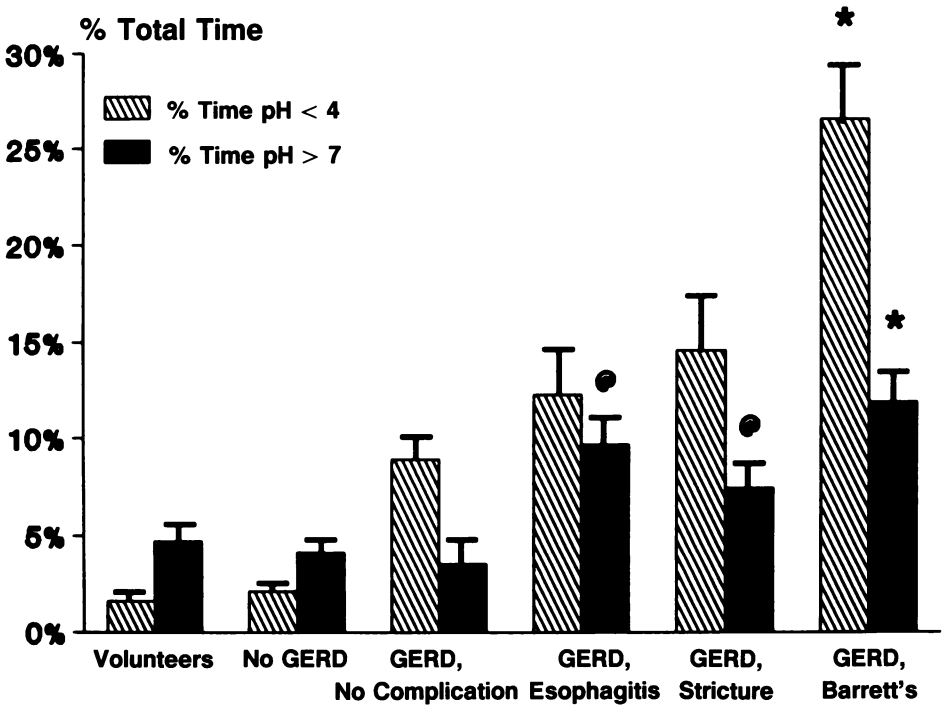

FIG. 3. Esophageal acid and alkaline exposure in the study groups expressed as percentage total time pH < 4 and pH > 7. * $p < 0.01$ *vs.* GERD patients with no complication. @ $p < 0.05$ *vs.* GERD patients with no complication.

duodenogastric reflux on gastric pH monitoring, 30 had previous foregut surgery (pyloroplasty, n = 4; truncal vagotomy and antrectomy, n = 7; cholecystectomy, n = 19). As shown in Figure 8, there were no significant differences in the prevalence of excessive duodenogastric reflux between patients without GERD (21%) and patients with GERD and no mucosal injury (20%) or esophagitis (28%). The prevalence of excessive duodenogastric reflux was, however, higher in patients with a stricture (41%, $p = 0.07$) and patients with Barrett's esophagus (46%, $p < 0.05$) as compared with those with GERD and no mucosal injury.

There was no difference in esophageal alkaline exposure (pH > 7) between normal volunteers, patients without GERD with and without excessive duodenogastric reflux, and patients with GERD but no excessive duodenogastric reflux (Fig. 9). Esophageal alkaline exposure was, however, significantly higher in patients with GERD and excessive duodenogastric reflux as compared with all other groups (Fig. 5, $p < 0.05$).

Discussion

Refluxed acid gastric juice is generally regarded as the major damaging agent in GERD. In contrast to this belief, the current study shows that the prevalence and severity of the complications of GERD, in other words, esophagitis, stricture, and Barrett's esophagus, are directly related to the presence of a mechanically defective sphincter and an increased esophageal exposure to both acid and alkalinity. Furthermore, combined esophageal and gastric pH monitoring showed that the alkaline component in these patients is due to excessive reflux of duodenal contents

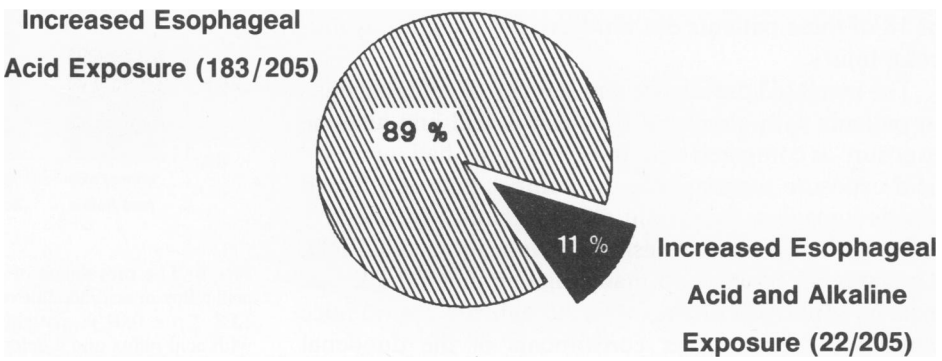

FIG. 4. Prevalence of only acid reflux and combined acid/alkaline reflux in 205 consecutive patients with GERD.

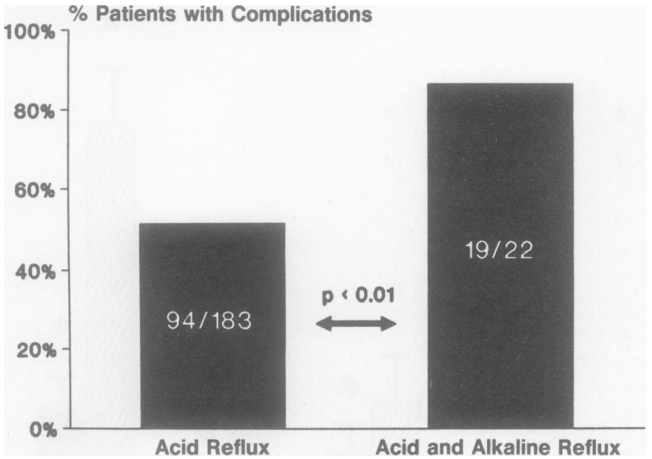

FIG. 5. Prevalence of complications in patients with GERD with only acid reflux or combined acid/alkaline reflux.

through the stomach into the distal esophagus. These findings suggest that the mechanical characteristics of the lower esophageal sphincter and reflux of acid gastric juice contaminated with duodenal contents are the most important determinants for the development of mucosal injury in patients with GERD.

The prevalence of a mechanically defective sphincter increased progressively with increasing severity of the complications of GERD. Although it is tempting to ascribe the loss of sphincter function to the presence of inflammation or tissue destruction, the observation of a defective sphincter in 28% of the GERD patients without mucosal injury suggests that the mechanical defect of the sphincter is primary and not due to inflammation or tissue damage.

It is easy to visualize that in the presence of a mechanically defective lower esophageal sphincter, large volumes of gastric juice can reflux into the esophagus and overwhelm the normal clearance mechanism of the esophagus. In the current study, this was not only associated with an increased prevalence of complications but also a shift toward a greater severity of mucosal injury. This was particularly so in patients with a combination of a mechanically defective lower esophageal sphincter and increased esophageal acid/alkaline exposure, in that 78% of these patients had a stricture or Barrett's esophagus and only 1 of 18 of these patients did not have any esophageal mucosal injury.

The increased prevalence and severity of complications in patients with abnormal esophageal acid and alkaline exposure as compared with those who only had increased acid exposure suggests that the composition of refluxed gastric juice is as important as a mechanically defective sphincter in the pathogenesis of complications of GERD. The presence of an abnormally high esophageal alkaline exposure (pH >7) implies that the refluxed gastric juice contained bile or other constituents of the duodenal juice.[13-15] Measurement of esophageal alkaline exposure with pH monitoring is less dependable, however, than the measurement of esophageal acid exposure. An increase in the per cent total time the pH is above 7 in the distal esophageal can be due to the presence of dental infection, which increases the salivary pH, ingestion of food with pH > 7, or the presence of esophageal obstruction that results in static pools of saliva with bacterial overgrowth and a rise in esophageal luminal pH. To avoid these errors, special precautions were taken. Patients' diets during the test were restricted to a list of foods with pH between 4 and 7. Each patient was inspected for dental and oral condition, and all strictures were dilated before manometry and pH studies to prevent pooling of saliva above the stricture. Technical factors also can artificially increase the measured esophageal alkaline exposure. These include the use of antimony probes, the drift of an unstable electrode, or errors in calibration. We therefore used glass electrodes in all studies rather than antimony electrodes, which can be unstable in alkaline pH ranges, and electrodes were checked in buffered solutions before and after each test to assure proper calibration and the absence of drift. Assiduous attention to these factors gives us confidence that the measured episodes of alkalinity in the esophagus do represent reflux of gastric juice contaminated with alkaline duodenal contents.

Duodenogastroesophageal reflux has been implicated as the source of increased esophageal alkalinity in the past, and the potential detrimental effect of duodenal contents on esophageal mucosa has been shown in animal models and humans.[13-18] Our study shows that esophageal alkaline exposure is increased in patients with GERD and

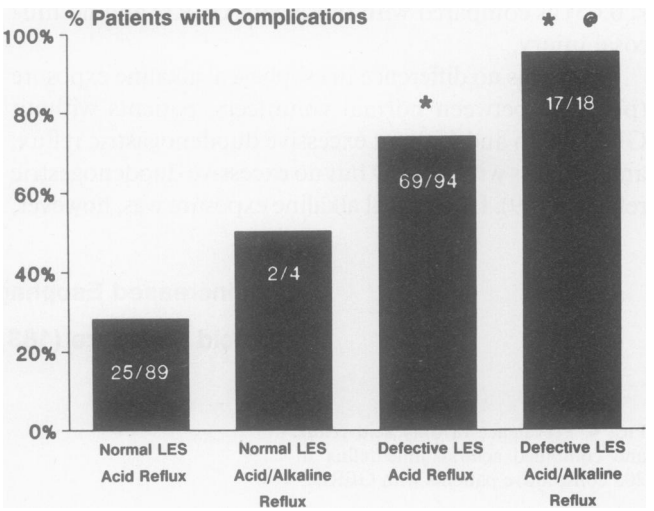

FIG. 6. The prevalence of complications in patients with GERD and acid reflux or acid/alkaline reflux with or without a mechanically defective LES. * $p < 0.01$ *vs.* patients with normal LES. @ $p < 0.05$ *vs.* patients with acid reflux and a defective LES.

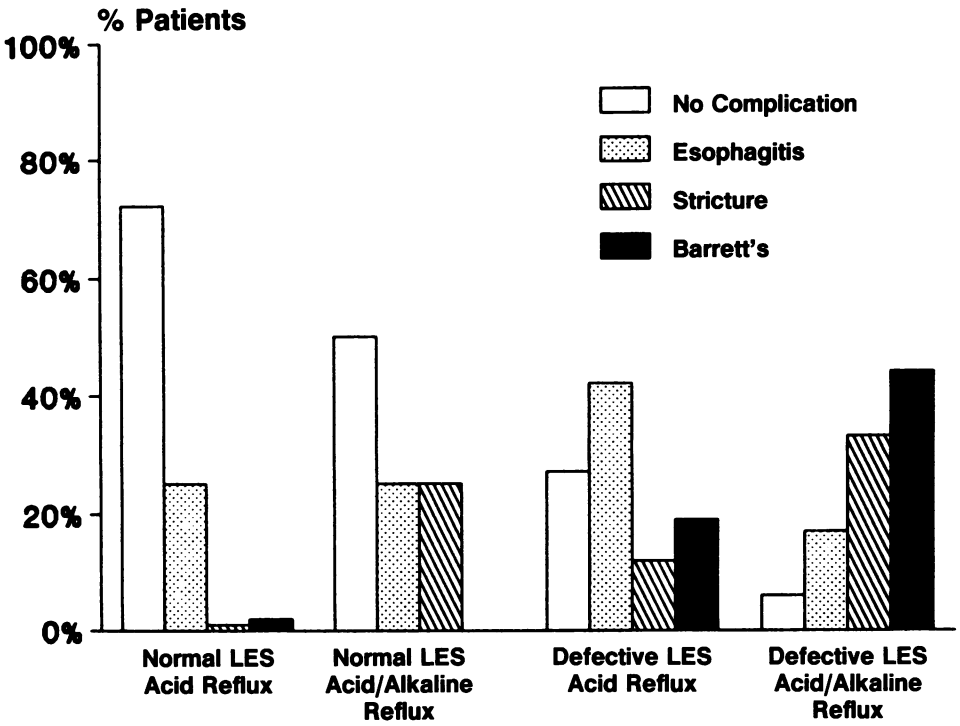

FIG. 7. The severity of complications in patients with GERD and acid reflux or acid/alkaline reflux with and without a mechanically defective LES.

evidence of excessive duodenogastric reflux and that excessive duodenogastric reflux is more frequent in patients with severe complications of GERD as compared with those with no mucosal injury. This indicates that the complications of GERD are due to the reflux of both acid and alkaline gastric juice, with the latter being of duodenal origin. Of interest is that a significant number of patients with excessive duodenogastric reflux had previous foregut surgery that would promote the condition. The most common of these was cholecystectomy, which results in a continuous flow of bile into the duodenum and hence excessive reflux of duodenal contents into the stomach.

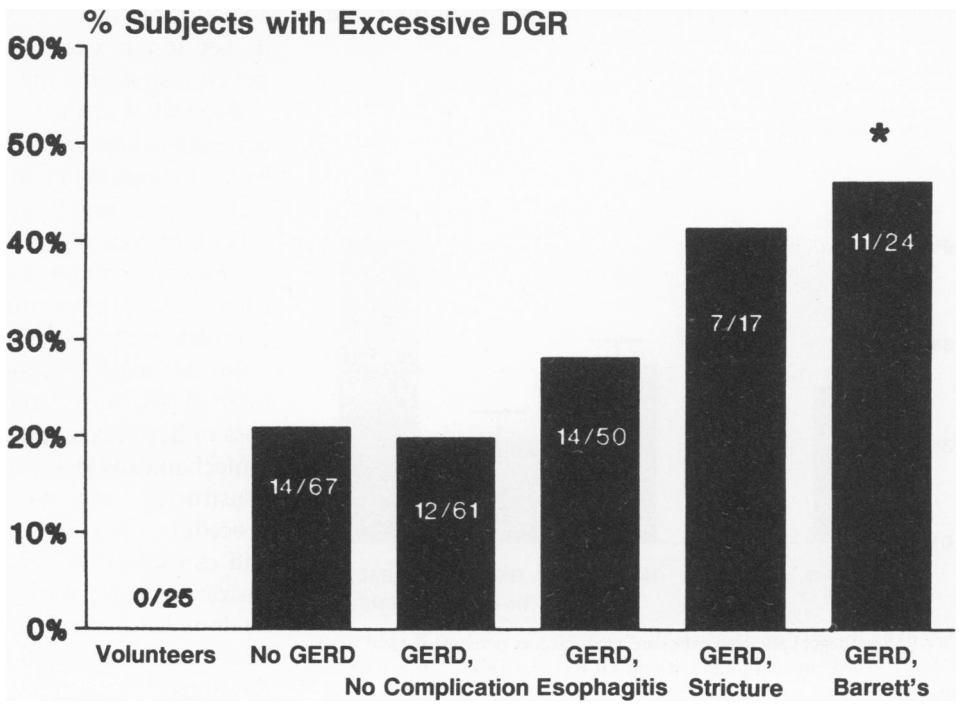

FIG. 8. Prevalence of excessive DGR in the study groups. * $p < 0.05$ *vs.* patients with GERD with no complication and patients without GERD.

Of importance is that excessive duodenogastric reflux can also occur primarily, as seen in 28 patients of the current study who did not have previous foregut surgery.

For alkaline duodenal juice to reach the distal esophagus, it has to cross the acidic gastric environment (Fig. 10), which in most instances results in neutralization of the alkaline reflux. Only in situations of excessive duodenogastric reflux will the reflux of gastric contents into the esophagus result in an increased esophageal exposure to pH above 7. Lesser degrees of duodenogastric reflux mix with gastric acid and result in a pH of gastric juice indistinguishable from the normal luminal pH of the esophagus. In this situation, the reflux of gastric juice into the esophagus cannot be detected by pH monitoring. Consequently the increased esophageal exposure to a pH > 7 recorded on 24-hour esophageal pH monitoring represents "the tip of the iceberg" of duodenogastroesophageal reflux. If this is so, duodenogastroesophageal reflux may have even a larger role in the development of complications of GERD than that shown in the current study.

The potentially injurious ingredients of duodenal juice are bile acids or activated pancreatic enzymes like trypsin, lipase, and carboxypeptidase, all of which can produce epithelial changes when incubated with strips of esophageal mucosa.[19] Their presence in the esophagus can be conclusively proved only by direct measurement over a prolonged period. Attempts have been made to do this using a variety of aspiration techniques, but the measurements are complicated by technical problems and the dilutional effect of large amounts of saliva. Consequently, the results of these studies are conflicting.[20-22] The elegant perfusion studies of Johnson and Harmon[7] and the *in vitro* experiments of Kivilaakso et al.[18] do support the clinical observations in the current study. Their experiments showed that both acid and bile can produce esophageal mucosal barrier abnormalities, such as changes in potential difference, hydrogen ion reflux, and permeability defects, yet neither alone nor combined could they produce morphologic lesions consistent with clinical esophagitis. When the enzymes pepsin or trypsin were present in physiologic concentrations, however, significant gross and microscopic esophagitis resulted, depending on the pH of the perfusate. Trypsin therefore may be a major injurious agent in an alkaline refluxate, and pepsin in an acid refluxate. It appears that the pH of the refluxed juice dictates which enzyme, if present, would be the injurious agent by providing the optimal pH range for its activity, that is, a pH of 2 to 5 for pepsin and 5 to 8 for trypsin. In either case, the current study suggests that the esophageal exposure to alkaline or acidic gastric contents can be measured by esophageal pH monitoring using the hydrogen ion as a tag, even though the hydrogen ion may not be responsible for esophageal mucosal injury.

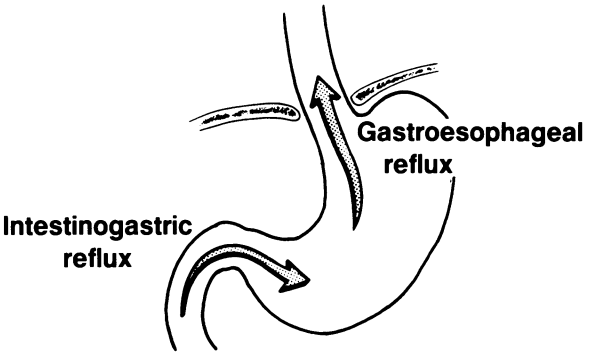

FIG. 10. Intestinogastroesophageal reflux in patients with GERD.

Regardless of the underlying physiologic abnormality, current medical therapy of GERD is aimed at suppressing its acid component. In patients with a mechanically defective lower esophageal sphincter, this approach allows other components of the refluxate such as duodenal secretions, pancreatic secretions, and bile to continue to cause tissue destruction. This may explain why even complete suppression of acid secretion fails to heal severe reflux esophagitis in most patients,[23] allows the development of strictures,[24] and progression of the columnar mucosa in Barrett's esophagus.[25] In patients with GERD and a mechanically defective lower esophageal sphincter, reconstruction of a functional sphincter by an antireflux procedure therefore provides the only rational therapy and can effectively and definitely abolish reflux of any gastric content in more than 90% of patients.[26] This should be done before the loss of esophageal contractility that is known to occur once a stricture or Barrett's esophagus develops.[27]

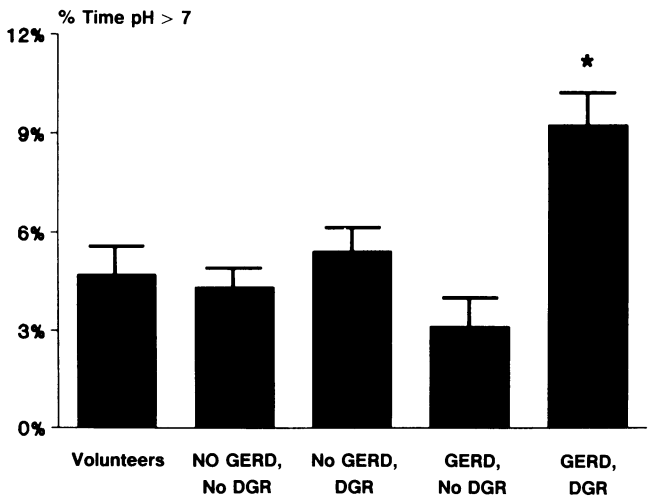

FIG. 9. Esophageal alkaline exposure expressed as percentage total time pH > 7 in patients with and without GERD and DGR. * $p < 0.05$ *vs.* all other groups.

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