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ASSESSMENT OF INFLUENCE OF DUODENOGASTRIC REFLUX ON COURSE OF GASTROESOPHAGEAL REFLUX DISEASE

This article shows the role and significance of duodenogastric bile reflux in patients with gastroesophageal reflux disease. Intraesophageal and intragastric pH-metric investigations, as well as biochemical studies of gastric contents were carried out. Antacid dysfunction of the stomach as a result of hypergastrinemia is conditioned by biochemical characteristics of duodenogastric bile refluctant which contains high concentrations of toxic bile acids, trypsin, lysolecithin, as well as by high phospholipase activity of refluctant, and by the reduction of such factors of cytoprotection as sIgA and phospholipids. Duodenogastric reflux in gastroesophageal reflux disease often develops because of the presence of associated biliary and pancreatic pathologies with bacterial overgrowth syndrome.

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Introduction

According to the conclusion of the leading experts at the 4th World Gastroenterology week, gastroesophageal reflux disease (GERD) is considered as a polysymptomatic disease which characterized by primary motility disorders of the esophagus and weakening of antireflux barrier resulting in prolonged spontaneous contact of esophageal mucosa with gastric acidic contents (Barry et al., 2000).

However, the evidence of last decades suggests that damage of esophageal mucosa occurs not only at gastric juice hyperacidity, but also at its higher pH values. Further, this has allowed identification "acidic" and "alkaline" variants of GERD. According to researchers (e.g., Buyeverov et al., 2006), at last variant of disease the degree of damage of esophageal mucosa may be more significant because of both the toxic effects of bile acidic salts and observable thus more severe motor disorders. While not denying the importance of acid factor in the pathogenesis of GERD, this circumstance requires a comprehensive study of the nature of influence of "alkaline" variant of gastroesophageal reflux (GER) on the course of disease and the factors contributing to the development of this variant of GERD.

The purpose of research is to study comparatively the nature of duodenogastric refluctant and associated biliary and pancreatic pathologies in the course of GERD.

Materials and methods

We investigated 54 patients (21 males and 33 females at the average age of 36.3±7.5 years old) with GERD. The diagnosis was made on the basis of specific complaints, medical history, clinical and laboratory data, as well as results of endoscopy. For the clinical assessment of GERD manifestations we used the Likert scale. Endoscopy of the esophagus was carried out by the standard technique using device of "Olimpus" company (Japan). Intragastric pH value was studied by the transendoscopic, topographic method using pH acidogastrometer "AGM-03" ("Istok-sistema," Fryazino).

The presence of duodenogastric reflux (DGR) in the case of absence of daily pH monitoring and endoesophageal bilemetry was determined by endoscopic pattern and bile concentration in gastric juice. Endoscopic criteria for DGR established by Sablin et al.

(2002) and Belousov et al. (2005) were the following: doorkeeper gaping, bile regurgitation from the duodenum to the stomach, and the presence of bile in the stomach. DGR was evaluated biochemically by the concentration of bilirubin in the gastric juice using a spectrophotometer at a wavelength of 420nm, as well as by the activity of phospholipase A_2 enzyme by the method of Kazaryan et al. (1990), the spectrum of bile acids by the method of Ivanov (1973), and phospholipid fractions by the method of Keyts (1975).

The concentration of secretory immunoglobulin A (IgA) was measured by the radial immunodiffusion method. The presence of bacterial overgrowth syndrome (BOS) was determined by the respiratory and hydrogen tests with lactulose. The results of 10 practically healthy individuals were control. The data obtained were processed by the method of variational statistics.

Results of research and discussion

All patients with GERD were divided into two comparative groups of observation. The first group included 24 patients with "alkaline" variant of GERD who were diagnosed symptoms of DGR. The second observation group included 30 patients with "acidic" variant of GERD without symptoms of biliary reflux. Table 1 demonstrates clinical dynamics of GERD in the investigated groups.

TABLE 1. CLINICAL DYNAMICS OF GERD IN THE INVESTIGATED GROUPS OF PATIENTS

Symptoms	Scores on the Likert scale	
	1group	2 group
Heartburn	3.5±0.4	3.2±0.3
Eructation	3.9±0.2	2.7±0.3*
Regurgitation	2.6±0.2	1.8±0.2*

Notes: * - Significant differences between the groups. Scores on the Likert scale are the following: The symptom does not trouble; Causes some anxiety (can be ignored); Troubles moderately (no effect on the daily activity and at night); Troubles considerably (during the night and the day); Troubles very considerably, constantly violates activity during the day and does not allow have a sleep (rest)

The diagnosis of GERD was confirmed by the results of endoscopy and bilemetry of gastric juice. It is necessary to note that the term "alkaline" variant of GERD was used as conditional since the pure alkali variant of GERD with pH above 7.0 was observed only in two patients, and in other cases we dealt with mixed variants of GERD. 13 patients in the first group had endoesophagitis. 11 patients were made a diagnosis erosive variant of GERD of class A and B by the Los Angeles classification. The catarrhal variant of GERD was presented in 21 patients of the second group.

The erosive form of GERD of class A and B was determined in 9 patients. The hiatal hernia of diaphragm was revealed in 7 patients of the first group and 3 patients of the second one. At endoscopy, 19 (79.2%) patients of the first group noted the doorkeeper gaping, 12 (50%) patients - erosions of the gastric antrum, and 18 (75%) patients had visible bile reflux. In the first group of patients such changes in the stomach at gastric endoscopy were not revealed.

Topical gastric pH-metry conducted showed significantly lower pH in the antrum of patients in the first group, compared to pH of the second group of patients (Table 2).

TABLE 2. INTRAGASTRIC PH VALUES IN PATIENTS WITH GERD

Patients group	The body of the stomach	The antrum of the stomach
1 group	1.2±0.06	2.6±0.25
2 group	1.3±0.08	4.7±0.15*

Note: * - Significant differences between the groups

The study of bilirubin in gastric juice showed that in patients of the first group the concentration of bilirubin in bile was 4.8±0.2 mg%, while in the second group it was 1.2±0.04 mg% (vs. 1.0±0.07 mg% in control group). The investigation of phospholipase activity in gastric juice showed that the activity of phospholipase A_2 enzyme in patients of the first group was equal to 72.4±6.8 nmol/min/mg of protein, whereas in the second and control groups of investigated the activity of this enzyme in gastric juice was not identified. The determination of bile acids in gastric juice showed that in patients of the first and second groups their concentrations were 5.8±0.3 mg% and 1.3±0.05 mg%, respectively (vs. 1.2±0.03 mg% in control group). The study of the spectrum of bile acids in bile by thin layer chromatography determined that bile acids in bile were in conjugation with glycine and taurine. At the same time, it should note the fact that the first group of patients had lower content of primary hydrophilic and high content of secondary hydrophobic bile aids, compared with those in the second and control groups.

The study of phospholipid content in gastric juice showed that in patients of the first group it was significantly lower than in the second and control groups.

The study of phospholipid fractions revealed that patients of the first group had significantly higher levels of highly toxic pool of lysophosphatidylcholine (LPC) fraction and significantly low levels of phosphatidylcholine (PC) fraction, in comparison with the second group of patients. At the same time, there were no significant differences in the contents of sphingomyelin (SPM) fractions, phosphatidylethanolamine (PEA) and other small fractions (cardiolipin, phosphatidylserine, phosphatidic acid) (Table 3).

TABLE 3. PHOSPHOLIPID SPECTRUM IN GASTRIC JUICE OF PATIENTS WITH GERD

Patients group	LPC, g/l	SPM, g/l	PC, g/l	PEA, g/l	Other fractions, g/l
1 group	0.31±0.015	0.48±0.02	1.99±0.11	1.35±0.07	0.36±0.02
2 group	0.12±0.015*	0.52±0.015*	3.12±0.12*	1.10±0.06	0.40±0.025

The investigation of the content of local cytoprotection factor sIgA showed a similar pattern (Figure 2). Its amount in the gastric juice of patients with GERD associated with DGR was significantly below similar fraction in patients with GERD and healthy individuals.

BOS was diagnosed in 14 (58.3%) of 24 patients in the first group by the respiratory "hydrogen" test. This test was negative in all patients of the second group.

The presence of associated pathology (comorbidity) was noted in the first group as the Oddi sphincter dysfunction in 8 (33.3%) patients, biliary pancreatitis in 11 (45.8%), chronic hepatitis in 4 (16.6%), and gallbladder dyskinesia in 4 (16.6%) patients, respectively. Generally, the comorbidity of the hepatobiliary system and pancreas was observed in 22 patients of the first group in the form of isolated and/or combined variants. Only in 5 patients of the first group was noted the presence of dyskinesia of the gallbladder in a mild degree. Such extraesophageal manifestations as form of bronchial asthma associated with GERD with nocturnal attacks were found in 2 (8.3%) patients, posterior laryngitis in 4 (16.6%) and chronic cough in 3 (12.5%) patients, respectively, of the total amount of extraesophageal complications in the first group (n=9; 37.5%). Among the total amount of the second group of patients (n=44; 13.2%), chronic cough was noted in 1 (3.3%) patient and posterior laryngitis in 2 (6.6%) patients, respectively.

Thus, our research has shown the presence of a certain amount of bile in gastric juice in GERD without associated DGR. However, by the quantitative contents of bilirubin and bile acids, it is comparable with those of healthy individuals that may be regarded as a physiological process. Additionally, the presence of bile components whose concentrations are significantly higher than in healthy individuals with predominance of hydrophobic bile acids and pancreatic content, as well as endoscopic changes in the form

of doorkeeper gaping and reduction of cytoprotection factors should be recognized as a pathological sign as DGR.

Studies have shown that in the presence of DGR in patients with GERD were noted lower pH values in the antrum. In this case, along with the presence of alkali duodenogastric refluctant, the damage of mucous membrane of the gastric antrum under aggressive exposure of toxic bile acids and trypsin, with the high phospholipase activity, as evidenced by the reduction of such factors of cytoprotection as sIgA and phospholipids, play the major role.

As Osadchuk et al. (2004) noted an initial link of pathological effect of the duodenal contents in duodenogastroesophageal reflux is known to be disturbance of protective mechanisms of mucous membrane of the esophagus. The bile as a component of duodenal contents is a natural detergent which is soluble for lipid membranes of the superficial epithelium. As a result of bile acids action the esophageal mucosa loses the protective covering and is easily damaged by the aggressive gastric juice and duodenal contents with pancreatic juice. The bile inhibits mucosa-forming, breaks the synthesis of prostaglandins in the mucosa, and renders a direct cytotoxic effect on the mucous membrane. Particularly, the most pronounced damaging effect on esophageal mucosa have bile acidic salts deconjugated under the influence of hydrochloric acid the contents of which were higher in patients with "alkaline" variant of GERD in our study. According to our data, aggressive properties of pancreatic juice presented in the duodenogastric refluctant were conditioned by the increased activity of Ca+-dependent metalloenzyme - phospholipase A_2, and by associated with the activity of this enzyme the most toxic for surrounding membrane structures lysophosphatidylcholine (LPC). Accordingly, the severity of clinical picture of "alkaline" variant of GERD depends on the aggressive effects of hydrochloric acid and duodenogastric refluctant.

The underlying reasons for duodenogastric reflux in our study were often presented by concomitant diseases of the hepatobiliary system and pancreas. The pathology of the biliary system and pancreas is known to be often complicated by BOS in the small intestine that was confirmed by our research. Logically, one can assume that the bacterial growth with excessive gasification in the intestine may provoke the development of duodenal hypertension syndrome and regurgitation of bile and trypsin in the duodenal lumen.

Duodenogastric bile reflux is not only a consequence of motility disturbance of gastroduodenal zone. It may initiate motility disturbances of the stomach and the esophagus as well, transferring excitation to vagus nerve fibers. Hence, there are "local" manifestations of the esophagus due to "distant" changes in the biliary system in the "alkaline" variant of GERD which has more severe course than the "acidic" variant.

Summary

Our conclusions so far are based on a limited number of studies. For creation of evidence-based fundamentals more in-depth investigations using daily pH monitoring are required. However, we can recommend therapy aimed at preventing regurgitation of duodenogastric content in the stomach and the esophagus, in addition to antisecretory therapy, for the treatment of patients with GERD associated with DGR.

Conclusion

By the degree of damage of the esophageal mucosa, "alkaline" variant of GERD has more severe course with more frequent erosive lesions and extraesophageal manifestations than "acidic" variant of the disease.

The presence of deconjugated bile acids, lysophosphatidylcholine, along with hydrochloric acid in the refluctant, as well as high phospholipase activity in gastric juice are the underlying reasons of defeat of the esophageal mucosa in the "alkaline" variant of GERD.

Duodenogastric reflux in GERD often develops because of the presence of associated biliary and pancreatic pathologies with BOS symptoms.

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