Serum pepsinogen levels in patients with erosive form of Gastroesophageal reflux disease.

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Abstract
We studied levels of pepsinogen I and II in blood serum in 80 patients with erosive form of gastroesophageal reflux disease. Increasing concentrations of pepsinogen in 2.3 times and increasing the ratio of pepsinogen I to pepsinogen II in 40 patients was detected. Which was associated with a higher degree gradation of erosive lesions of the esophagus and acid reflexes prevalence. Higher concentrations of pepsinogen II in serum was diagnosed in 40 patients, and the results of 24-hour pH monitoring in lower part of esophagus have been registered in them as acidic and alkaline reflexes. The growth levels of P II and reducing the ratio of P I/II indicates admission composition to reflux components of duodenal content. Drugs ursodeoxycholic acid and itopride in combination with basic therapy significantly improve the condition of the patient and quickly reach the clinical effect. Pantoprazole in double doses is effective antisecretory drug that twice reduces the night reflux and provides rapid decrease of the main clinical manifestations of GERD.

Keywords: Gastroesophageal reflux disease, pepsinogen-I, pepsinogen II, pantoprazole, ursodeoxycholic acid, itopride

1. Introduction
Gastroesophageal reflux disease (GERD) is defined as the condition where reflux of stomach contents causes troublesome symptoms and/or complications [12]. During the last two decades, when GERD was defined by symptoms of at least weekly heartburn and/or acid regurgitation, its prevalence was approximately 20% in Western countries whereas its prevalence was less than 5% in Eastern countries [4]. Effective acid clearance plays a vital role in protection of the esophagus from potential injury. Knowing that acid and pepsin are damaging to the esophagus, the duration of acid exposure correlates with the severity of GERD. On average, reflux patients have acid clearance times that are two to three times longer than those of normal controls [9, 13]. Clearance of gastric refluxate from the esophagus occurs via two mechanisms: primary large volume clearance by esophageal peristalsis, and salivary buffering of the residual acid in the distal esophagus. Defects in either of these mechanisms promote GERD.

Reflex of duodenal contents has also been implicated in the pathogenesis of GERD. Recent evidence indicates that duodenogastric reflux may cause reflux symptoms but must coexist with acid and pepsin to induce esophageal injury [2]. A recent study by Sears and Richter found aggressive acid suppression with omeprazole 20 mg twice daily to dramatically reduce the amount of gastroduodenal reflux as measured by bilirubin absorbance [1]. Despite definitive evidence implicating pepsin and HCl as the most significant aggressive factors in GERD, it is important to realize that the amount of exposure does not always correlate directly with the amount of esophageal injury. Other variables like salivary and esophageal protective factors probably account for the variability of esophageal damage in patients with GERD. These salivary and esophageal protective factors are influenced by pepsin and HCl.

The role of pepsin in GERD has been well studied in animals and humans. In 1969, Goldberg concluded that the combination of HCl and pepsin was responsible for injury to the intact feline esophagus [7]. In this study, esophageal damage occurred with either a very high concentration of acid (pH 1.0 - 1.3), or lower acid concentrations (pH 1.6 - 2.0) in the presence of pepsin. No esophageal injury was noted at pH > 2.3. Therefore, although high concentration of acid alone could cause esophagitis.

Gastrin and pepsinogens are representative biomarkers that influence the gastric physiology and thus reflect the functional state of the gastric mucosa [8]. Human pepsinogen consists of
two biochemically and immunologically different isozymes: pepsinogen I and pepsinogen II. Pepsinogen (P) I is produced by the chief and mucous neck cells in the fundic glands. P II is produced by not only the chief and mucous neck cells in the fundic glands but also by the cells in the pyloric glands and Brunner’s glands. As Ps are secreted by chief cells in the gastric mucosa, their serum levels may reflect the mass and/or turnover of those cells in the mucosa. It was reported that measuring these markers in the serum thus allows gastric pathologies such as atrophic gastritis, functional dyspepsia and abnormalities in acid secretion to be detected [6, 11]. The progression of gastric atrophy leads to a gradual decrease in the level of P I while the level of P II remains fairly constant [3].

2. Material and Methods
The study involved 82 patients with GERD who were treated at the University Clinic of Ivano-Frankivsk National Medical University aged 19 to 64 years (mean age M ± 37.6), including 37 women and 45 men. And 10 healthy volunteers.

The study included patients with the symptoms of heartburn, which occurred mainly in the evening or during the day, acidic belching, pain in the epigastrum and chest, appetite disturbance. Patients did not receive any treatment before examination.

The initial diagnosis of GERD was based on the patient’s history or on the responses to a questionnaire, on the results of a detailed assessment of the clinical picture, endoscopic study of esophagus, stomach and duodenum using apparatus company “Olympus” GIF-XPE. 24-hour pH monitoring of the lower part of the esophagus was performed by apparatus “MyLab™50”, X-ray of the stomach.

By endoscopy, all the study subjects were diagnosed as RE(+) or RE(-) subjects according to the Los Angeles classification [10]. RE was defined as the presence of mucosal breaks: grade LA-A, -B, -C, or -D based on the Los Angeles classification. For patients who had GERD symptoms more than 10 years Lugol chromoendoscopy was conducted. Lugol’s iodine solution was sprayed onto the esophageal surface, followed by evaluation of the staining pattern. When Lugol-unstained streaks were observed at chromoendoscopy, biopsy specimens were obtained from unstained streaks and from adjacent stained mucosa. Histologic evaluation included basal cell hyperplasia, papillary length, and cellular infiltration.

Fasting serum was analysed for pepsinogen I, pepsinogen II using specific EIA Tests Kits (GastroPanel; Biohit, Plc, Finland).

The Data were collected and entered into the personal computer. Statistical analysis were done using Windows software program Microsoft Excel 2010, Statistica 8. Arithmetic mean, standard deviation for categorized parameters, chi-square test was used while for numerical data, t-test was used to compare two groups. The level of significance was 0.05. Also to determine the reliability of the data was used Spearman’s correlation test.

Criteria for exclusion were insufficient data (on age, sex, height, weight or laboratory data), history of upper gastrointestinal surgery, or intake of gastric acid inhibitors (histamine H2-receptor antagonists or proton pump inhibitors).

3. Results and Discussion
During chromoendoscopy two patients had Barrett’s esophagus, so they were not included in our study (Picture 1, 2). Based on the results of 24-hour pH monitoring, endoscopy, chromoendoscopy, and ELISA analysis, we divided patients into two groups of 40 people each. The first group consisted of patients with erosive esophagitis, the prevalence of alkaline reflux and slow gastric motility. The second group consisted of patients with erosive esophagitis, the prevalence of acid reflux (mainly at night time) and normal or accelerated gastric motility. Each group was divided into two groups (A and B) of 20 people in each. I A group patients got proton pump inhibitor pantoprazole 40 mg in the morning, prokinetic iotropide 50 mg 3 times daily and ursodeoxycholic acid 250 mg at nighttime. I B group got basic therapy IPP pantoprazole 40 mg a day. II A group patients got pantoprazole 40 mg two times a day. And patients of II B group got pantoprazole 40 mg a day according to the protocol. The course of treatment lasted 1 month.

Before treatment in the first group patients elevated levels of P I in serum were diagnosed (I A group 33.9±8.9 µg/l, I B group 32.1±4.3 µg/l, p<0.05 (in healthy volunteers 11.5±1.0 µg/l)). During 24-hour pH monitoring of the lower part of the esophagus in these patients were diagnosed both acid (I A group 7.7% of total time, I B group -8.9%), and alkaline refluxes (I A group 19.2 %, I B group -17.6 %), p<0.05. Between P I levels and number of alkaline reflux was installed direct strong correlation link (r=0.95, p<0.05 ) (Picture 3). At the same time reduced the ratio of PI / PII in this group was detected (I A group 4.9±0.7, I B group 5.6±0.8, in healthy volunteers 13.2±1.0), p<0.05. According to Los Angeles classification in 18 patients were diagnosed esophagitis grade A, in 18 patients grade B and in 3 patients grade C. Low PI/PII ratio and step reduction of the first of them against a background of rising concentrations of a second can confirm the development of atrophic gastritis and the emergence of alkaline refluxes [3]. Increasing levels of P I in 2.3 times (II A group 247.41±30.0 µg/l, II B group 230.2±16.9 µg/l, in healthy volunteers 106.0±9.9 µg/l ) was diagnosed in patients of the second group, p<0.05. In this case, it’s high concentration was associated with more severe esophagitis (in 4 patients was diagnosed endoscopic grade LA- A, in 20 patients grade LA-B, in 10 patients C and in 6 patients grade D ). In these patients had increased ratio PI/PII (II A group 28.6±2.6, II B - 25.8±3.3, p<0.05). According to the results of 24-hour pH monitoring of the lower part of the esophagus they had predominated acid refluxes with pH< 4 (II A group 32.29 % of total time, II B group 36.16%). By Spearman’s correlation test revealed a strong direct correlation (r = 0.75, p <0.05) between P I levels and number of acid refluxes (Picture 4). These data are consistent with the results of research of L. R. Lundell et al. [10] about higher acid reflux into the esophagus and its duration at higher levels of pepsinogens.

After treatment a significant reduction of P II was noted in patients of I A group ( from 33.9±8.9 to 16.9±4.1 µg/l) and less intensive reduction in I B group ( from 32.1±4.3 to 24.8±2.4 µg/l), p<0.05. The number of alkaline refluxes reduced in normal levels in patients of I A group (from 19.2±2.4 to 4.3±0.8 % of total time), and remained practically unchanged in II B group (from 17.6±3.1 to 18.1±4.6%). Increasing the ratio PI/ PII closer to the norms was observed in patients of I A group (from 4.9±0.7 to 10.1±1.2) and less intensive growth in I B group (from 5.6±0.8 to 8.4±1.4), p<0.05 (Picture 5). After treatment in patients of the second group were reducing levels of P I (II A group 247.4±30.0 to 164.9±20.9 µg/l and II B group 230.2±16.9 to 202.4±10.3 µg/l), p<0.05. The ratio of PI/ PII dropped closer to standards in the II A group (from 28.6±2.6 to 14.1±2.6) and with less intensity
decreased in group II B (from 25.8±3.3 to 21.2±1.4), p<0.05. According to the results of 24-hour pH monitoring of the lower part of the esophagus in two groups decreased numbers of acid refluxes were found (IIA group from 32.29±3.8 to 0.7±0.01% of total time, IIB group from 36.16±4.2 to 5.3±0.8%), p<0.05.

Picture 1: Endoscopic picture of Barrett’s esophagus.

Picture 2: Endoscopic picture of Barrett’s esophagus.
Picture 3: Direct strong correlation link between P II levels and number of alkaline refluxes.

Picture 4: Direct strong correlation link between P I levels and number of acid refluxes.
4. Conclusions
Studying the levels of pepsinogen I and II not only provides information about the glands of the stomach. It also confirms the fact that the presence of a high concentration of them in the body is accompanied by a more significant injury of the esophagus. The growth levels of PII and reducing the ratio of P I/II indicates admission composition to reflux components of duodenal content. Drugs ursodeoxycholic acid and itopride in combination with basic therapy significantly improve the condition of the patient and quickly reach the clinical effect. Proton pump inhibitors significantly reduce the night reflux and provide rapid decrease of the main clinical manifestations of GERD, including heartburn and healing of erosions.

5. References

Picture 5: The ratio of the PI, PII, PI / PII in patients of I group on the backdrop of treatment. *p<0.05.