

ORIGINAL ARTICLE

CHANGES IN SERUM SOMATOSTATIN AND GASTRIN LEVELS IN PATIENTS AFTER CHOLECYSTECTOMY AND GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

The aim: To study of changes in the level of serum gastrin (GN) and somatostatin (SST) in patients with GERD after ChECT and determined their characteristics from clinical forms of GERD.

Materials and methods: 64 patients with different clinical forms of GERD were examined. The patients with GERD were divide into 2 clinical groups. Group 1 included 34 patients with GERD after ChECT, among them there were 14 males (41.2 %) and 20 females (58.8 %), with the average age of 40.2 ± 3.2 years. Group 2 consisted of 30 patients with GERD without ChECT. Among them there were 18 males (60.0 %) and 12 females (40.0%), with the average age of 38.9 ± 4.7 years. All patients were tested for serum SST and GN level by enzyme-linked immunosorbent assay (ELISA).

Results: In all patients with GERD of both group there was a significant increase in the level of serum SST. At the same time, a more higher indicators have been established in 2 Group of patients (increase up to 0.702 ± 0.029 pg / ml – $p < 0.01$). Noteworthy is the change in the level of SST in the serum in both groups of the examined patients depending on the clinical form of GERD, with the maximum increase in patients with atypical manifestation of GERD. The analysis of the level of GN in blood serum indicates its decrease in the examined patients. In this case, the most pronounced changes were found in patients with extraesophageal clinical signs of GERD.

Conclusions: 1. In patients after ChECT gastroesophageal reflux disease often has atypical symptoms (mostly cardiac and bronchopulmonary forms in 45.0% and 25.0 % of examend patients). 2. There was detected an increase in the level of blood SST of patients with GERD while there was observed a decrease in the GN indicator in the serum, especially in its atypical forms. 3. Duodenogastric reflux is often diagnosed during endoscopic examination of patients with GERD after cholecystectomy. At the same time, its severity correlates with the level of SST in blood serum ($r=0.76$; $p<0.01$ in the typical form and $r= 0.72$; $p<0.05$ in the atypical clinical form of GERD).

KEY WORDS: gastroesophageal reflux disease; esophageal, extraesophageal manifestations of gastroesophageal reflux disease; cholecystectomy; somatostatin; gastrin

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INTRODUCTION

Diseases of the gallbladder are common and costly. The best epidemiological screening method to accurately determine point prevalence of gallstone disease is ultrasonography. Many risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics [1].

Gallstones are common and lead to significant morbidity, mortality, and health care utilization in the United States and worldwide. More than 20 million people in the United States have ultrasound-detected gallbladder disease. There were an estimated 1.8 million ambulatory care visits with an all-listed gallstone diagnosis in 2004 and rates were relatively stable over time.

There were 622,000 overnight hospitalizations with an all-listed gallstone diagnosis in 2004. Hospitalization rates declined by 40% from 1991 due to the shift to outpatient laparoscopic cholecystectomy. There were 2,155 deaths with gallstones as underlying or other cause in 2004 and mortality rates fell between 1979 and 2004 by 70%. Based on data from the National Survey of Ambulatory Surgery conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, gallstone disease resulted in 503,000 laparoscopic cholecystectomies in 2006 [2, 3].

In this case, cholecystectomy (ChCET) does not solve the problem if we talk about patients with gallstone disease, because the removal of the gallbladder does not rid patients of those processes that led to the formation

of a calculus in the biliary tract. After performing ChCET, new clinical symptoms remain or, on the contrary, appear, which is part of the concept of post-olecystectomy syndrome. Postcholecystectomy syndrome is manifested through various symptoms, inter alia, damage to the upper parts of the gastrointestinal tract. Notably, the symptoms are more pronounced if ChCET surgery has been performed on the functioning gallbladder.

Gastroesophageal reflux disease (GERD) is a common digestive disease based on pathological gastroesophageal (GE) reflux, which occurs due to esophageal cardia insufficiency and impaired barrier function of the lower esophageal sphincter. The prevalence of GERD in Western populations over the past 30 years has a clear tendency to increase and varies from 10.0 % to 30.0%. The relevance of GERD is also due to the presence of both typical and atypical (bronchopulmonary, cardiac, dental, otolaryngological) clinical manifestations that complicate the diagnosis of GERD [4, 5].

The study of various biologically active substances that can play a role in the formation of gastroesophageal reflux disease (GERD) in patients with combined pathology, including damage to the biliary system, is important, extremely problem of modern clinical medicine.

THE AIM

The aim of the study was to study of changes in the level of serum gastrin (GN) and somatostatin (SST) in patients with GERD after ChECT and determined their characteristics from clinical forms of GERD.

MATERIALS AND METHODS

64 patients with different clinical forms of GERD were examined. The examined patients were hospitalized in Gastroenterology and Surgery Departments of Municipal Non Profit Enterprise "Transcarpathian Regional Clinical Hospital named After Andrii Novak" of Transcarpathian Regional Council, and patients who were on outpatient observation by family doctors at the place of residence in the period of 2020-2023. The patients with GERD were divide into 2 clinical groups. The 1 Group included 34 patients with GERD after ChECT, among them there were 14 males (41.2 %) and 20 females (58.8 %), with the average age of 40.2 ± 3.2 years. Group 2 consisted of 30 patients with GERD without ChECT. Among them there were 18 males (60.0 %) and 12 females (40.0%), with the average age of 38.9 ± 4.7 years.

The control group included 30 healthy individuals: 14 males (46.7 %) and 16 females (53.3 %) without lesions of the musculoskeletal system and upper gastrointestinal tract. The average age was 40.3 ± 4.1 years.

All studies were performed with the consent of patients, and their methodology was in line with the Helsinki Declaration of Human Rights of 1975 and its revision in 1983, the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine.

All the examined patients were subject to general clinical, anthropometric, instrumental, and laboratory tests. Ultrasound examination of the abdominal cavity was performed on all patients according to generally accepted method. Standard and biochemical blood serum tests have been performed to determine the functional state of the liver, lipid metabolism indexes and carbohydrate metabolism indexes.

The diagnosis of GERD at observed patients was established according to the criteria of the unified clinical protocol (order of the Ministry of Health of Ukraine dated 31.10.2013 № 943) taking into account complaints, endoscopic examination data, etc. To confirm the diagnosis, the examined patients underwent fibroesophagogastroduodenoscopy (FEGDS) using endoscopy equipment Pentax ERM-3300 video processor and flexible fiber endoscopes Pentax E-2430, GIF-K20. The Los Angeles (LA) classification (1998) was used for endoscopic assessment of the degree of damage to the esophagus [6].

All patients were tested for serum somatostatin (SST) level (using Human Somatostatin EIA-1 Kit test system No. 1.03930004301 from Ray Biotech) and serum gastrin (GN) level (using Gastrin-EIA test kit Cat. No CS001 30) by enzyme-linked immunosorbent assay (ELISA).

The criteria for inclusion in the study were: clinical symptoms of GERD (typical and atypical), changes in the mucose of the esophagus, characteristic of GERD, during FEGDS, cholecystectomy in anamneses.

The exclusion criteria were as follows: non-erosive form of GERD, Barrett's esophagus functional or organic changes of the upper parts of the gastrointestinal tract, Helicobacter pylori positive patients.

The analysis and processing of the results of the examinations was performed by the computer program Statistics for Windows v.10.0 (StatSoft Inc, USA) using parametric and non-parametric methods for evaluating the results.

RESULTS

Complaints of digestive organs characteristic of GERD (typical esophageal manifestations) were more often found in patients of 2 Group – 56.7 % of the examined patients ($p < 0.05$), while patients of 1 Group were more often diagnosed with atypical manifestation of GERD – 58.8 % of the examined patients ($p < 0.05$). The leading clinical manifestation of the upper digestive tract lesions in patients of 2 Groups was acid regurgitation, heartburn, dysphagia and sore throat.

Table I. Clinical manifestations of GERD in the examined patients

Symptoms	1 Group of patients (n=34), %	2 Group of patients (n=30), %
Typical manifestation of GERD	(n=14), 41.2 %	(n=17), 56.7 %*
Atypical manifestation of GERD	(n=20), 58.8 %*	(n=13), 43.3 %
Cardiac	45.0 %*	30.8 %
Bronchopulmonary	25.0 %	46.2 %**
Otolaryngological	20.0 %	15.3 %
Dental	20.0 %**	7.7 %

Note: the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - $p < 0.05$; ** - $p < 0.01$.

Table II. The nature of endoscopic changes in the examined patients

Endoscopic manifestations	Examined patients			
	1 Group (n=34)		2 Group (n=30)	
	Typical manifestation of GERD (n=14)	Atypical manifestation of GERD (n=20)	Typical manifestation of GERD (n=17)	Atypical manifestation of GERD (n=13)
Reflux esophagitis (severity according to LA classification):				
LA-A	14.3 %	15.0 %	29.4 % **,++	15.4 %
LA-B	50.0 % **	30.0 %	47.1 % *	30.8 %
LA-C	28.6 %	35.0 % *	23.5 %	46.1 % *,^
LA-D	7.1 % +	20.0 % **,^	-	7.7 % *
DGR	71.4 % *,++	60.0 % ^^	23.5 %	30.8 % *
CE	28.6 % ++	25.0 % ^^	5.9 % *	-

Note: the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - $p < 0.05$; ** - $p < 0.01$; the difference between the indicators in patients of 1 and 2 Groups with typical manifestation of GERD is significant: + - $p < 0.05$; ++ - $p < 0.01$; the difference between the indicators in patients of 1 and 2 Groups with atypical manifestation of GERD is significant: ^ - $p < 0.05$; ^^ - $p < 0.01$.

Atypical manifestation of GERD in patients of both groups were more often manifested by cardiac, bronchopulmonary masks. At the same time, there was a difference: patients of 1 Group (after ChECT) more often had cardiac of GERD (45.0 % of subjects - $p < 0.05$), while patients without ChECT were more often diagnosed with bronchopulmonary form of GERD (46.2 % of examined patients - $p < 0.01$). The dental "mask" of GERD was more diagnosed in 1 Group (20.0 % of subjects - $p < 0.01$). The results are shown in Table I.

At endoscopic examination in all patients of both groups it was manifested by gastroesophageal reflux and reflux esophagitis (RE) of varying severity (Table II).

It was noted that in the group of patients after ChECT with typical manifestation of GERD, the severity of reflux-esophagitis (RE) more often corresponded to LA-B, while in patients with atypical manifestation - more often - LA-C (at 35.0 % patients - $p < 0.05$). The same tendency was observed in patients of 2 Group. Attention was drawn to the high frequency of duodenogastric reflux (DGR) in patients of 1 Group (71.4% and 60.0% of patients with typical and atypical manifestations of GERD, respectively), against 23.5% - 30.8% in patients

of 2 Group. Signs of candida esophagitis are also more often found in patients of 1 Group.

In all patients with GERD of both group there was a significant increase in the level of serum SST. At the same time, a more higher indicators have been established in 2 Group of patients (increase up to 0.702 ± 0.029 pg / ml - $p < 0.01$) - table III. Noteworthy is the change in the level of SST in the serum in both groups of the examined patients depending on the clinical form of GERD, with the maximum increase in patients with atypical manifestation of GERD.

The analysis of the level of GN in blood serum indicates its decrease in the examined patients. In this case, the most pronounced changes were found in patients with extraesophageal clinical signs of GERD.

Correlation analysis established the relationship between serum SST and a decrease in serum gastrin - table IV. There was established dependence between the change in the SST level and the severity of endoscopic changes in reflux esophagitis (mainly LA-B and LA-C) in patients of both groups. A correlational dependence was identified between the somatostatin indicator and the severity of DGR only in patients of the first group.

Table III. Levels of somatostatin and indicators of calcium metabolism in the blood serum of the examined patients of the examined patients

Examined patients	Indicator	
	SST, pg/mL	GN, pg/mL
Control group (n=30)	0.423±0.015	75.30±2.16
1 Group: (n=34)	0.626±0.018 ¥	51.34±0.22 ¥
Typical manifestation of GERD (n=14)	0.584±0.033	56.13±0.25 ++
Atypical manifestation of GERD (n=20)	0.652±0.021	42.16±0.18
2 Group: (n=30)	0.702±0.029 ¥¥,*	40.15±0.26 ¥¥,*
Typical manifestation of GERD (n=17)	0.687±0.032 +	42.50±0.18
Atypical manifestation of GERD (n=13)	0.731±0.028 ^	38.10±0.24 ^

Note: the difference between the indicators in patients of 1 and 2 Groups and the control group is significant: ¥ - p <0.05; ¥¥ - p <0.01; the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - p <0.05; the difference between the indicators in patients of 1 and 2 Groups with typical manifestation of GERD is significant: + - p <0.05; ++ - p <0.01; the difference between the indicators in patients of 1 and 2 Groups with atypical manifestation of GERD is significant: ^ - p <0.05.

Table IV. Comparison of the level of somatostatin with level of gastrin in the serum and endoscopic changes of the examined patients depending on the clinical form of GERD

Indicator	SST level			
	Examined patients			
	1 Group (n=34)		2 Group (n=30)	
	Typical manifestation of GERD	Atypical manifestation of GERD	Typical manifestation of GERD	Atypical manifestation of GERD
GN	r= 0.62; p<0.05	r= 0.78 p<0.01	r= 0.70; p<0.05	r= 0.92; p<0.01
LA-B	r= 0.80; p<0.01	-	r= 0.78; p<0.051	-
LA-C	r= 0.56; p<0.05	r= 0.88; p<0.01	r= 0.60; p<0.05	r= 0.90; p<0.01
DGR	r= 0.76; p<0.01	r= 0.72; p<0.05	-	-

Thus, in patients with after ChCET GERD is often manifested by atypical clinical symptoms. Examination of serum SST and GN level indicates its increase with the most pronounced deviation from the norm in atypical form of GERD. In this case, a correlation was found between the increase in serum SST level and the decrease in the level of PGN in serum.

DISCUSSION

Scientific research of pathogenetic mechanisms of GERD formation at patients with comorbid states is carried out. Particular interest are studies aimed at determining the effect of biologically active substances on the tonus of the lower esophageal sphincter, which affect the formation of GERD.

Peptides of nervous origin (somatostatin, substance P, endorphins, enkephalins) were found in cells that produce hormones of the gastrointestinal tract, and cholecystokinin, gastrin were found in the central nervous system and nerve fibers; this confirms the close connection of the digestive and nervous systems. Spontaneous motor activity of the smooth muscles of the

digestive tract is caused by their automaticity [7]. The effects of irritation of the autonomic nerves depend on the initial condition of the muscles, the frequency and strength of the irritation. Humoral substances regulate motility by directly affecting myocytes or neurons of the digestive tract [8, 9]. Thus, biologically active substances, neuropeptides play a leading role in maintaining the normal synchronous functioning of the organs of the digestive system, providing the balance within the acid formation system.

The obtained results indicate high levels of somatostatin in blood serum of the patients with GERD after undergoing cholecystectomy. At the same time, the level of somatostatin correlates with the level of gastrin in blood serum of, particularly, patients with atypical clinical signs of GERD. The revealed relationship between neuropeptides and the expression of DGR in patients with GERD after cholecystectomy also enables one to speak about their involvement in forming lesions of the upper parts of the gastrointestinal tract after performing cholecystectomy. The data obtained make it possible to recommend a more detailed clinical analysis connected to identifying atypical forms of GERD

in patients after they underwent cholecystectomy, as well as to take measures aimed at their prevention and treatment. Notably, further research in this area is needed for a more accurate understanding of pathogenetic mechanisms underlying the damage to other organs of the digestive system after cholecystectomy.

CONCLUSIONS

1. In patients after ChECT gastroesophageal reflux disease often has atypical symptoms (mostly cardiac

and bronchopulmonary forms in 45.0 % and 25.0 % of examined patients).

2. There was detected an increase in the level of blood SST of patients with GERD while there was observed a decrease in the GN indicator in the serum, especially in its atypical forms.
3. Duodenogastric reflux is often diagnosed during endoscopic examination of patients with GERD after cholecystectomy. At the same time, its severity correlates with the level of SST in blood serum ($r=0.76$; $p<0.01$ in the typical form and $r=0.72$; $p<0.05$ in the atypical clinical form of GERD).

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Conflict of interest:

The Authors declare no conflict of interest.

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