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## PECULIARITIES OF STATE OF PROTECTION AND AGGRESSION FACTORS IN PATIENTS WITH DIABETES MELLITUS TYPE II AND GASTROESOPHAGEAL REFLUX DISEASE

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### Abstract

Diabetes mellitus is one of the most serious problems of the clinical medicine. This is determined by the fact that it is followed by multisystemic affects, as well as complications on the side of other organs and systems, among which a special place is occupied by gastroesophageal reflux disease. As for the combination and mutual influence of diabetes mellitus and gastroesophageal reflux disease, this issue has not been studied yet, the data of modern literature are not complete and quite contradictory.

**The aim of the study:** to investigate the state of the factors of aggression and protection of the oesophageal mucosa in patients with diabetes mellitus type II with concomitant gastroesophageal reflux disease without associated pathology.

**Method.** There were two groups of patients under observation. The first group included 45 patients with diabetes mellitus type II with concomitant gastroesophageal reflux disease (26 men and 19 women). The second group included 38 patients with gastroesoph-

ageal reflux disease without associated pathology – 20 men and 18 women. By sex, age, body weight, *Helicobacter pylori* infection, smoking and alcohol consumption, both groups were comparable. The surveillance program included determining the compensation ratio of carbohydrate metabolism and the state of the factor. The antioxidant protection factor was assessed by the level of catalase activity in the blood serum, as well as by the diameter of the celiac trunk and the blood flow velocity in it. Statistical processing of the obtained data was carried out with the aid of the program WINDOWS STATISTIKA 6.0. For all types of analysis, differences were considered statistically significant with  $p < 0.05$ .

**Results.** During the study, we found that in patients with diabetes mellitus type II with concomitant gastroesophageal reflux disease, as well as in patients with gastroesophageal reflux disease without associated pathology, the level of pH-metry was reduced, but with varying measures of confidence. At the same time, we found that patients with GERD without associated pathology had a decrease in the blood flow velocity in the celiac trunk. Concurrently, we ascertained that the decrease in the blood flow velocity in patients of both groups reduced the diameter of the celiac trunk.

**Conclusions.** In patients with diabetes mellitus type II, concomitant gastroesophageal reflux disease has a subtle clinical presentation that is affected by a significant decline in mucosal sealing protection factors. In patients with GERD without associated pathology, typical clinical manifestations, accompanied by inflammation, acid regurgitation and dyspepsia, are more vivid.

**Keywords:** diabetes mellitus type II, gastroesophageal reflux disease, level of pH-metry, factors of aggression and protection, oesophageal mucosa.

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## 1. Introduction

Diabetes mellitus (DM) remains one of the most serious problems of clinical medicine, which is determined by its high incidence, severity of complications, disability and heavy mortality [1, 2].

Every year the mortality rate of diabetic patients steadily increases, the incidence prognosis is about 5–7 % per year [3, 4].

In 2011, according to the European Diabetes Association, there were 266 million people in the world who suffered from diabetes mellitus, in addition, 4.6 million people died of this disease every year.

In Ukraine, more than 1.3 million people with diabetes mellitus are registered, which makes about 2 % of the total population of the country. At the same time, epidemiological studies have shown that the true incidence is 2-3 times higher [5, 6].

Already there are more than 260 million patients with diabetes mellitus in the world, which is 2.8 % of the world's population, and by 2025 their number will reach 300 million. In Russia, according to the World Health Organization, the number of people suffering from diabetes mellitus is also projected to rise from 4.6 million in 2000 to 5.3 million by 2030 [7, 8].

Such dynamics is caused by the fact that diabetes mellitus is accompanied by multisystemic affects, as well as early and frequent complications on the side of other organs and systems, including upper gastrointestinal, among which a special place is occupied by gastroesophageal reflux disease (GERD).

These concomitant diseases largely predetermine the course of diabetes mellitus and its complications and affect the life expectancy of the patient.

For today, the pathology of cardiovascular and renal systems in patients with diabetes mellitus has been studied fairly well, which is sufficiently reflected in numerous publications. However, the gastroenterological aspects of diabetes mellitus are much less studied.

As for the combination and mutual influence of diabetes mellitus and gastroesophageal reflux disease, this issue has not been studied much so far, the data of modern literature are not complete and are quite contradictory.

At the same time, clinical researches devoted to the study of the state of the oesophagus in patients with a combination of GERD and DM are few and do not give a complete answer to many questions on the formation and development of this comorbid pathology. In particular, there is no precise data on the incidence, peculiarities of the GERD course with various types of diabetes mellitus depending on the duration of its course and the nature of the hypoglycemic therapy. In addition, there has been no profound comparative analysis of changes in the secretory (acid-pro-

ducing) function of the gaster, the peculiarities of the state of metabolic processes with underlying gastroesophageal reflux disease, depending on the type of diabetes mellitus, which affect the pathogenetic mechanisms of GERD formation with underlying DM [12, 13].

All these facts of a few studies devoted to the investigation of the GERD formation mechanisms with underlying DM have not been fully clarified, and therefore require further investigation, which conditions this study.

**The aim of the study:** to investigate the state of the factors of aggression and protection of the oesophageal mucosa in patients with diabetes mellitus type II with concomitant GERD without associated pathology.

## 2. Materials and Methods

The study was conducted from 2016 to 2019 based on the Department of Therapy, Rheumatology and Clinical Pharmacology, the Gastroenterology Department of the Kharkiv City Student Hospital, as well as on the basis of the Endocrinology Department of the Kharkiv Regional Clinical Hospital.

There were two groups of patients under observation. The first group included 45 patients with diabetes mellitus type II with concomitant GERD (26 men and 19 women). The mean age of patients was  $46.4 \pm 3.1$  years; the body weight was  $63.2 \pm 2.8$  kg.

Patients of the first group in the clinical setting had in equal measure, along with the symptoms characteristic of DM, moderate acid regurgitation (in 25 patients, 55.5 %), dysphagia (in 22 patients, 48.8 %), and constantly appearing inflammation (in 23 patients, 51.1 %).

The studies were carried out in accordance with the Declaration of Helsinki; the procedures were approved by the local ethics committee of Kharkiv medical academy of postgraduate education, protocol No. 5, 12.11.2019. Informed consent for the participation was obtained from all the patients.

As a result of fibroadastroduodenoscopy, there were revealed hyperemia, oedema of the oesophageal mucosa and muscular fractures in the patients, in addition 33 patients had gastroesophageal reflux, and 12 (26.7 %) patients had multiple erosions of the oesophageal mucosa.

The second group (experimental) included 38 patients suffering from GERD without concomitant pathology – 20 men and 18 women, whose mean age was  $45.6 \pm 4.1$  years, and the body weight was  $62.7 \pm 3.1$  kg.

In patients with GERD without associated pathology, in the clinical setting the main symptoms in most patients were inflammation (in 33 patients, 86.9 %), acid regurgitation and dysphagia (in 26 patients, 78.9 %). Hyperaemia, muscular fractures and mucosal oedema of the lined lower oesophagus, revealed as a result of fibroadastroduodenoscopy, were less evident than in the patients of the first group, and gastroduodenal reflux was present in the majority of patients (in 24 patients, 73.6 %).

The level of infection of *Helicobacter pylori* in both groups was insignificant and reached I degree of dissemination in 67 patients (87 %) and II degree in 11 patients (13 %).

Thus, by gender, age, body weight, *Helicobacter pylori* infection, smoking and alcohol consumption, both groups were comparable.

Patients without additional concomitant pathology were taken for the study. All patients had no need for insulin; there were no complications of diabetes mellitus. The arterial pressure of patients of both groups did not exceed 135/85 mm. gt; the body mass index of all patients was within the normal range and made to  $21.3 \pm 1.9$  kg/m<sup>2</sup>.

The duration of the gastroesophageal reflux disease in both groups did not exceed 5 years, the severity of the symptoms was moderate, signs of Barrett's oesophagus and atrophy of the mucous membrane of the oesophagus and gaster were not revealed in fibroadastroduodenoscopy.

The diagnosis of GERD was determined according to the Montreal Consensus (2006), taking into account the clinical presentation and the data of the fibroadastroduodenoscopy.

The diagnosis of DM was confirmed in accordance with the criteria proposed by the WHO experts, including the presence of glycaemia more than 6.1 mmol/l in the fasted state.

The exclusionary criteria were presence of other organic diseases, including diseases of the digestive and endocrine systems, as well as the patient's refusal to participate in the study.

The examination program included determining the degree of compensation of carbohydrate metabolism by the level of glycosylated haemoglobin HbA1c by chromatographic method; the state of the aggression factor – according to the level of pH-metry in the body and antrum of the gaster.

To assess the gastric secretion we used a 24-hour pH-metry, carried out with the help of the Gastroscan-24 (Russia) by the standard procedure, since this procedure allows to measure the pH directly in the oesophagus and gaster, as well as the intragastric pH-metry, using special biolive pH-probes with antimony-calomel electrodes (antral and gastric) on the apparatus of IKJ-2 (gaster acid indicator) (production Ukraine) by a standard procedure, since this intragastric pH-metry allows to measure the pH directly in the gaster in the basal period, with continuous record of pH changes in different parts of the gaster and oesophagus.

The antioxidant protection factor (AOP) was assessed according to the level of the serum catalase activity determined with the aid of the standard set of IBL reagents (production Germany), as well as according to the diameter of the celiac trunk and the blood flow velocity in it, since the protective function of the oesophageal mucosa is provided by normal regeneration of the epithelium and adequate state of local blood flow [14, 15].

The local blood flow was assessed by the diameter of the celiac trunk and the blood flow velocity in it with the determination of PSV – peak systolic velocity and EDV – end-diastolic velocity by the pulsed wave Doppler sonography with colour mapping performed on the ALOKA SSD-750 (Japan) and ULTIMA pro-30 (production Ukraine).

15 practically healthy individuals of the same sex and age were used for the comparison.

Statistical processing of the data was carried out using the WINDOWS STATISTIKA 6.0 program. Comparison of the indices in the groups was carried out by the method of parametric statistics (*t* – Student's test). The interrelation between the indices in the groups was estimated using the Pearson correlation analysis (*r* is the correlation coefficient). Differences were rated with  $p < 0.05$  for all types of analysis of statistical significance.

### 3. Results

In the course of the study, we found that among patients with DM with concomitant GERD, as well as among patients with GERD without associated pathology, the level of pH-metry was reduced, although with varying degrees of reliability.

In particular, in patients with GERD without concomitant pathology, the pH-metry in the gaster was in the range from 0.5 to 1.0, in the antrum from 4 to 5.8, and on average its level ( $0.83 \pm 0.09$  and  $5.2 \pm 0.1$ ) in comparison with the group of healthy individuals for which the average level of pH-metry in the antrum was equal to  $1.62 \pm 0.05$  and in the gaster  $7.1 \pm 0.1$ , made statistically significant ( $p < 0.001$ ) difference.

In the group of patients with DM with concomitant GERD, the acidity indices both in the gaster (from 0.8 to 1.5) and in the antrum (5.8–7.0) were higher, and their average level ( $1.40 \pm 0.1$  and  $6.05 \pm 0.1$ ) with a lesser degree of reliability ( $p_2 < 0.05$ ) differed ( $p_1 < 0.05$ ) not only from the norm, but also from the group of patients with GERD without associated pathology ( $p_3 < 0, 05$ ). During daily pH monitoring, it was noted that the highest acidity values were recorded in morning hours 6.00–7.00 am (**Table 1**).

At the same time, we found that patients with GERD without associated pathology had a decrease in the blood flow velocity in the celiac trunk and amounted from 8 to 12 cm/sec. On average, the blood flow velocity decreased to  $10.7 \pm 1.06$  cm/sec, and which, in comparison with the control group, whose blood flow velocity in the celiac trunk was  $13.5 \pm 0.92$  cm/sec, the difference was statistically ( $p < 0.05$ ) reliable.

Among the patients with DM with concomitant GERD, the blood flow velocity in the celiac trunk decreased even more from 8 to 5 cm/sec, and on average dropped to  $6.9 \pm 0.82$  cm/sec, making a statistically significant difference not only when compared with the norm ( $p < 0.001$ ), but also with the average blood flow velocity of patients with GERD without associated pathology ( $p < 0.05$ ).

At the same time, there were no significant changes between PSV and EDV in both treatment groups (Table 2).

**Table 1**

Average parameters (table of gastric acidity) of pH-metry in patients with DM with concomitant GERD, in patients with GERD without associated pathology and in healthy individuals of the control group

pH-metry indices	Patients with DM with concomitant GERD n=45	Patients with GERD without associated pathology n=38	Control group n=20	p
In gaster	1.40±0.1	0.83±0.09	1.62±0.05	p <sub>1</sub> <0.05 p <sub>2</sub> <0.001 p <sub>3</sub> <0.01
In antrum	6.05±0.5	5.0±0.1	7.2±0.1	p <sub>1</sub> <0.05 p <sub>2</sub> <0.001 p <sub>3</sub> <0.05

Note: p<sub>1</sub> – degree of reliability of the difference between the group of patients with DM with concomitant GERD and the norm; p<sub>2</sub> – between the group of patients with GERD without associated pathology and the norm; p<sub>3</sub> – between the group of patients with DM with concomitant GERD and the group of patients without associated pathology

**Table 2**

Mean indices of the blood flow in the celiac trunk and the catalase activity in patients with DM with concomitant GERD and patients with GERD without associated pathology

Indices	Patients with DM with concomitant GERD, n=45	Patients with GERD without associated pathology, n=38	Control group, n=20	p
Diameter of the celiac trunk (cm)	0.59±0.05	0.76±0.05	0.93±0.07	p <sub>1</sub> <0.001 p <sub>2</sub> <0.05 p <sub>3</sub> <0.05
Blood flow velocity (cm/sec)	6.9±0.82	10.7±1.06	13.5±0.92	p <sub>1</sub> <0.001 p <sub>2</sub> <0.05 p <sub>3</sub> <0.001
Catalase (U/ml)	0.27±0.025	2.7±0.029	3.8±0.017	p <sub>1</sub> <0.001 p <sub>2</sub> <0.05 p <sub>3</sub> <0.001

Note: p<sub>1</sub> – the degree of reliability of the difference between the group of patients with DM with concomitant GERD and the norm; p<sub>2</sub> – between the group of patients with GERD without associated pathology and the norm; p<sub>3</sub> – between the group of patients with DM with concomitant GERD and the group of patients without associated pathology

Concurrently, we ascertained that the decrease in the blood flow velocity in patients of both groups reduced the diameter of the celiac trunk. Moreover, in patients with GERD without associated pathology (experimental group), the diameter of the celiac trunk was determined in the range from 0.4 to 0.8 cm, and on average its size (0.76±0.05 cm) was statistically significantly (p<0.05) smaller than in healthy individuals of the control group (0.93±0.07 cm).

In most patients with DM with concomitant GERD, the diameter of the celiac trunk was even smaller and on average its size (0.59±0.05 cm) was smaller not only in comparison with the norm (p<0.001), but also in comparison with the average data of the patients with GERD without associated pathology.

At the same time, we found that the greater microcirculatory disorders were in correlation with the decrease in the level of catalase activity.

In particular, in patients with GERD without associated pathology, the level of catalase activity was determined in the range from 2.12 U/ml to 3.23 U/ml, and on average its level was ( $2.7 \pm 0.029$ ) statistically significantly ( $p_2 < 0.05$ ) below the norm ( $3.8 \pm 0.017$ ).

At the same time, in the patients with concomitant GERD, the catalase activity dropped below 0.23 to 0.29 U/ml, and on average its level ( $0.268 \pm 0.01$ ) was statistically significantly not only lower than the norm ( $p_1 < 0.001$ ), but also lower than the average indices of the group of patients with GERD without associated pathology.

#### 4. Discussion

The questions of the comorbid course of diabetes mellitus type II and gastroesophageal reflux disease represent, on the one hand, great scientific and practical interest, and on the other hand, they remain open on several positions.

This way, some authors believe that there is no interrelation between diabetes mellitus and gastroesophageal reflux disease [16, 17], while other researchers note that diabetes mellitus type II and gastroesophageal reflux disease often accompany each other [18, 19], and that the prevalence of GERD symptoms among patients with diabetes mellitus type II is higher than in the general population [20].

In this regard, the obtained data show that there is a pathogenetic dependence between diabetes mellitus type II and gastroesophageal reflux disease, which is determined by the fact that diabetes mellitus has a direct effect on the reduction of regional blood flow and antioxidant activity indices, which are one of the basic factors of the oesophageal mucosa protection. At the same time, the pathogenetic effects of diabetes mellitus have less effect on the increase of the aggression mechanisms of the gastric juice.

A number of researchers concludes that gastroesophageal reflux disease can be considered as a regular complication of diabetes mellitus [21].

In this connection, our study shows that these statements do not always take place, as in the vast majority of our patients gastroesophageal reflux disease has been diagnosed before the onset of diabetes mellitus.

Some authors state that the degree of manifestation of GERD rises with the increase of duration and severity of the diabetes mellitus [15, 19].

In the context of our studies, this position is confirmed, as a connection, although not reliable, was established between the duration of the course of diabetes mellitus type II, the degree of its severity, and the severity of clinical manifestations of gastroesophageal reflux disease.

At the same time, the suggestion that one of the pathogenetic mechanisms of primary development of GERD against the background of diabetes mellitus may be neuropathy, since it is capable of causing motor dysfunction of the upper digestive tract, including disorders of the lower oesophageal sphincter regulation [13, 18], and needs further research. However, the interest in these processes of disorders of the regional blood flow, antioxidant protection processes, taking an active part in the regulation of motor function of the digestive tract, make it possible to talk about its legitimacy.

Thus, the changes we detected in the spectrum of the studied parameters and the presence of a close correlation between them undoubtedly indicate that diabetes mellitus has a direct effect on reducing the protective properties of the oesophageal mucosa and, to a lesser extent, on increasing the aggression of gastric juice, thereby creating favourable conditions for the initiation and formation of GERD with underlying diabetes mellitus.

Due to the fact that in patients with diabetes mellitus type II, which is characterized by inveterate course and disorders of all metabolic forms, affection of the oesophagus and accordingly formation of GERD with various forms of its manifestation (erosive or non-erosive) is a regular event. Therefore, in case of diabetes mellitus type II, even with the slightest suspicion of GERD, it is necessary to perform fibrogastroduodenoscopy for its early detection and timely treatment prescription.

#### 5. Conclusions

1. In patients with diabetes mellitus type II, concomitant gastroesophageal reflux disease has a mild clinical presentation due to a decrease in the secretion of the gastric mucosa and an

increase in acidity in it that occurs against the background of a significant decrease in mucosal barrier protection factors, which is indicated with a high degree of reliability by decrease in the catalase enzyme activity, deceleration of the blood flow velocity in the celiac trunk and narrowing of its diameter.

2. In patients with GERD without associated pathology, the typical clinical manifestations accompanied by inflammation, acid regurgitation and dyspepsia are more vivid and accompanied, with a greater degree of certainty, by increased gastric aggression (acidity).

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## A MULTI-MARKER MODEL FOR PREDICTING DECOMPENSATED HEART FAILURE IN PATIENTS WITH PRIOR ACUTE MYOCARDIAL INFARCTION

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### Abstract

**The aim of the study** was to assess the prognostic value of determining the plasma concentration of NT-proBNP and ST2 in the patients with decompensated HF and prior acute myocardial infarction and their combination in this category of patients.

**Materials and methods.** There were examined 120 patients with acute myocardial infarction and stage II A-B decompensated chronic HF according to the classification proposed by Vasylenko V. Kh. and Strazhesko M.D., NYHA functional class (FC) III–IV. The patients with Q-QS wave MI (60 individuals) and non Q MI (60 individuals) were divided into 4 groups depending on the treatment methods.

Study groups were homogenous by age, gender, disease severity, duration of the post-infarction period, clinical signs of decompensation, which served as a basis for inclusion of the patients in the study.

All the patients underwent the six-minute walk test in a quiet 30–50-m long hospital corridor in the morning. N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) and ST-2 were analyzed in all patients.

**Results.** Promising biomarkers of HF decompensation in the post-infarction period were studied. In the patients with prior Q-QS MI and decompensated HF, NT-proBNP level was (950.38±3.15) pmol/l ( $p<0.05$ ); in the patients with prior MI without signs of decompensated HF, it was (580.15±3.03) pmol/l ( $p<0.05$ ); in apparently healthy individuals, the level of NT-proBNP was found to be (111.20±3.47) pmol/l.

ST2 level was (14.80±1.61) ng/ml, (36.00±1.43) ng/ml and (49.22±1.40) ng/ml in the patients of Group 1, Group 2 and Group 3, respectively ( $p<0.05$ ).

Similar changes were found in patients with decompensated HF in postinfarction period after non Q MI.

**Conclusions.** The increase in plasma concentration of sST2 is associated with the activation of both neurohumoral and fibrous pathways and can help in detecting the patients with decompensated HF in the post-infarction period and predicting the risk of its development.

Our results confirmed the results of other multiple studies reporting ST2 in combination with NT-proBNP to be valuable tools for prognosing the development of decompensated HF in the patients with prior MI. ST2, alongside with NT-proBNP, is a promising biomarker to be included in the diagnostic panel for detecting acute HF and can provide additional information on risk stratification for such patients during hospitalization and at the time of discharge from the hospital.

**Keywords:** acute myocardial infarction, decompensated heart failure, biomarkers, NT-proBNP, ST2.

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