INFLUENCE OF URSODEOXYCHOLIC ACID ON THE CHOLECYSTOKININ LEVELS IN PATIENTS WITH GASTRO-ESOPHAGEAL REFLUX DISEASE AND TYPE 2 DIABETES MELLITUS

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Diabetes mellitus (DM) represents a serious medical and social problem, due to its high prevalence, as well as severe complications that lead to early disability and mortality [11]. The experts from International Diabetes Federation (IDF) and World Health Organization (WHO) predict that by 2030 there are expected to more than 552 million patients with DM [12]. Moreover, up to 90% of these patients will be patients with type 2 DM. In addition, 183 million people with DM remain undiagnosed [4].

The increased interest towards gastro-esophageal reflux disease (GERD) is caused by the high prevalence of this disease with a permanent upward trend (~5% annual increase) [8]. Moreover, in some cases, extra-esophageal manifestations may come to the foreground in clinical findings [9]. In addition, in 25% of cases, GERD occurs along with extra-esophageal symptoms: bronchopulmonary, cardiac, otorhinolaryngopharyngeal, and dental [1,3,6,2].

Of particular interest is the study of the peculiarities of clinical findings and diagnostics of GERD in patients with DM. It is known that the pathogenesis of GERD with DM is based on the development of diabetic neuropathy, which causes disruption of the motor function of esophagus and stomach. Protective mechanisms are also disrupted, in particular, the antireflux barrier function of the gastroesophageal junction and the lower esophageal sphincter are weakened, the esophageal clearance and resistance of the esophagus mucosa are reduced, and timely emptying of stomach contents is disrupted [10,12]. The lesion of digestive organs in patients with DM is also associated with secretion dysregulation, inactivation of hormones and increments, electrolyte disruptions in patients with uremia and ketoacidosis, which can affect the normal movement of upper parts of the digestive system [5]. At the same time, the general pathogenetic mechanisms are not fully disclosed, as certain difficulties arise when choosing the tactics for treating patients with GERD with type 2 DM.

Aim of the research - to study the dynamics of cholecystokinin (CCK) level on the background of complex therapy using the ursodeoxycholic acid (UDCA) drug in patients with GERD with type 2 DM.

Material and methods. At the clinical site of the State Higher Educational Establishment "UzhNU" medical faculty propaedeutics of internal diseases department (gastroenterology and endocrinology department of the TRCH n. a. A. Novak, and the therapeutic department of the State Institution of the Territorial Medical Association of the Ministry of Internal Affairs of Ukraine in the Transcarpathian region) during 2016-2018, 68 patients with type 2 DM and GERD were examined. Among the examined patients, 38 were males (55.9%) and 30 were females (44.1%). Their average age was 48.5±6.3.

Depending on the clinical form of GERD, patients with type 2 DM were divided into two groups: group I included 42 (61.8%) patients with esophageal manifestations of GERD, and group II included 26 (38.2%) patients with extra-esophageal manifestations of GERD.

The control group comprised of 20 practically healthy individuals (12 males (60.0%) and 8 females (40.0%)). Their average age was 47.6±5.8.

All studies were performed with patients consent, and the methodology of their implementation were in line with the Helsinki Declaration of Human Rights of 1975 and its 1983 revised version.

Patients have underwent general clinical examinations in accordance with the local protocols. All examined patients were subject to anthropometric, general clinical, laboratory and instrumental research methods. An anthropometric study determined the body mass index (BMI), waist circumference (WC), hip circumference (HC) and calculated the waist / hip ratio (WHR = WC/HC). Based on the data obtained, the patients were distributed depending on the BMI in accordance with WHO recommendations, in which: BMI of 16.0 and less corresponded to a profound deficiency of body mass; 16.0-18.5 – insufficient body mass; 18.0-24.9 – normal body mass; 25.0-29.9 – excess weight; 30.0-34.9 – class I obesity; 35.0-39.9 – class II obesity; 40.0 and above – class III obesity (morbid obesity).

The diagnosis of type 2 DM was established according to IDF (2005) recommendations. The severity of type 2 DM was estimated by the level of glycosylated hemoglobin (HbA1c,%),

which was obtained using the chromogenic analysis on a Sysmex 560 apparatus (Japan) using Siemens reagents.

GERD diagnosis was established in accordance with the Unified Clinical Protocol criteria (Order of the Ministry of Health of Ukraine dated 31.10.2013, No. 943) taking into account patient complaints, data from endoscopic examination, etc. To confirm the diagnosis, the examined patients underwent fibro-esophagogastroduodenoscopy (FEGDS) using endoscopy equipment with Pentax EPM-3300 video processor with the use of flexible Pentax E-2430 and GIF-K20 fibroendoscopes, as well as daily pH monitoring (according to Prof. V.N. Chernobrow method). For the endoscopic examination of the degree of esophagus damage the Los Angeles classification (1998) was used. Helicobacter pylori (HP) infection was diagnosed in the examined patients using the rapid urease test (CLO-test), as well as C^{13}-urea breath test (IZINTA, Hungary). The examined patients also underwent ultrasound examination of the abdominal organs (HDI-1500 apparatus, USA) and electrocardiographic examination.

The blood serum cholecystokinin index was determined in patients with type 2 DM and GERD using enzyme-linked immunosorbent assay (ELISA) before and after the complex treatment using a test system from "Peninsula Laboratories" (USA).

The provision of medical care to patients with type 2 DM was carried out according to the clinical treatment protocols of the Ministry of Health of Ukraine and local protocols. To control the level of glucose in the blood serum, the examined patients were prescribed oral hypoglycemic drugs (metformin) on the background of dietary nutrition and lifestyle modification. Insulin therapy was performed when necessary. For HP-positive patients with GERD (groups I and II), standard triple anti-Helicobacter therapy was performed for 14 days in combination with Saccharomyces boulardii ("Enterol", Biocodex) medication: 2 capsules 2 times a day. Treatment with pantoprazole lasted up to 1 month, or longer if necessary. To normalize the work of the upper section of the gastrointestinal tract, itopride hydrochloride ("Ganaton", Abbot) was prescribed: 50 mg 3 times a day for 1 month. All examined patients with type 2 DM with GERD were prescribed rebamipide ("Mucogen", manufactured by McLeods Pharmaceuticals Limited): 100 mg 3 timers a day for 1 month. Also, all patients with type 2 DM with GERD underwent therapy using ursodeoxycholic adic (UDCA) medication ("Choleduxan", World Medicine) at a rate of 15 mg per kilogram of body mass. UDCA treatment lasted up to 6 months.

The analysis and processing of the patient examination results were carried out using the computer program "Statistics" for Windows v.7.0 (StatSoft Inc., USA) using parametric and non-parametric methods of evaluating the results obtained.

Results and discussion. Type 2 DM of medium severity type was observed in all the examined patients, which was characterized by fasting blood glucose not exceeding 8.5 mmol/L, and, after eating, - not higher than 10 mmol/L, and HbA1c did not exceed 9%.

The damage of the upper digestive system in the examined patients with type 2 DM before the treatment was clinically manifested by sour belching, lumps in the throat, and heartburn (esophageal manifestation of GERD in patients group I). After a detailed analysis, it was found that some patients with type 2 DM (20.6%) often complained on a sore throat, hoarseness, dry cough (extra-esophageal, namely otolaryngological manifestations of GERD in patients group II). 12 (17.6%) of patients with type 2 DM, who were also examined by a cardiologist, complained before the treatment on chest pains along the esophagus and cardiac abnormalities, which most often occurred after consumption of fatty, fried foods, carbonated drinks and coffee (extraesophageal – cardiological manifestations of GERD in patients of group II). Before the treatment, GERD was confirmed by FEGDS in all patients with type 2 DM.

Prior to treatment, a gastrointestinal hormone such as CCK was measured in the blood serum in both patient groups, as well as in healthy individuals (Table 1). Interestingly, a more profound increase in CCK level has been observed in patients with type 2 DM with extra-esophageal manifestations of GERD.

The use of UDCA medication as part of the complex treatment of patients with type 2 DM with GERD has at the end of the 1st month already led to a decrease tendency in CCK level of the examined groups, and, at the end of the 6th month, a significant decrease by 2.4 and 2.7 times respectively ($p<0.01$) was observed.

Before the treatment, an analysis of the results of anthropometric study showed that an excess in body mass or obesity of various degrees, which was manifested by an increase in BMI, was observed in all 68 patients with type 2 DM and GERD (Tables 2, 3).

Table 1. Dynamics of cholecystokinin level in blood serum in patients examined on the background of complex therapy using UDCA medication

Patients group	**Cholecystokinin level,** ng/mL		
	before treatment	**on the background of treatment**	
		1st month	**6th month**
Control group (n=20)	0.86±0.12		
Group I (n=42)	4.12±0.33*	3.89±0.21	1.74±0.28^
Group II (n=26)	5.03±0.19*	4.76±0.18	1.84±0.25^

*note: * $p<0.01$ - the difference between the indexes of patients from control group and groups I and II is significant; ^ $p<0.01$ - the difference between the indexes of patients from group I and II before and after the treatment is significant*

Table 2. Dynamics of anthropometric study indicators in patients with type 2 DM and GERD on the background of complex therapy using UDCA medication

Index	**Control group (n=20)**	**Examined patients with type 2 DM and GERD**			
		Group I (n=42)		**Group II (n=26)**	
		before treatment	**after treatment**	**before treatment**	**after treatment**
BMI, kg/m^2	21.43±3.22	36.42±4.29*	29.31±3.26	35.22±3.23*	27.41±2.22
WHR, r.u.	0.81±0.55	1.27±0.35	1.01±0.17	1.25±0.24	0.99±0.11

*note: the difference between the indexes in patients and the control group is significant - * - $p<0.05$*

Table 3. Distribution of examined patients -with type 2 DM and GERD based on the BMI and its dynamics during therapy

Index	Examined patients with type 2 DM and GERD			
	Group I (n=42)		**Group II** (n=26)	
	before treatment	**after treatment** (6th month)	**before treatment**	**after treatment** (6th month)
Normal weight (BMI: 18.0 – 24.9)		28.6%**	-	38.5%**
Overweight (BMI: 25.0 – 29.9)	31.0%	23.8%*	50.0%	26.9%*
Class I obesity (BMI: 30.0 – 34.9)	42.9%	28.6%*	34.6%	23.1%
Class II obesity (BMI: 35.0 – 39.9)	26.1%	1.0%	15.0%	11.5%

*note: * – p < 0,05; ** – p < 0,01 – the index in patients before and after treatment is significant*

Table 4. Dynamics of cholecystokinin level in blood serum in patients with type 2 DM and GERD on the background of complex therapy depending on BMI disorder

Index	**Cholecystokinin level,** ng/mL			
	Group I (n=42)		**Group II** (n=26)	
	before treatment	**after treatment** (6th month)	**before treatment**	**after treatment** (6th month)
Normal weight		0.92±0.18		0.94±0.12
Overweight	4.36±0.23	1,88±0,17^^	5.72±0.51*	2.15±0.26^^
Class I obesity	3.89±0.25	1.98±0.22^	4.39±0.37+	2.04±0.15^
Class II obesity	3.93±0.35	2.03±0.15^	4.47±0.48+	2.11±0.09^

*note: * - p < 0,001: difference between the indexes in overweight patients from groups I and II before the treatment is significant; + - p < 0.05: difference between the indexes of patients with overweight and class I and II obesity from group I before the treatment is significant; ^^ - p < 0.05, ^ - p < 0.01: difference between the indexes of patients from group I and II before and after the treatment is significant*

On the background of complex therapy with the use of UDCA medication in patients with type 2 DM with GERD, a pronounced positive effect on the BMI dynamics was established (Table 3). Already at the end of 1st month of treatment with the use of UDCA, a weight loss of 3-5 kg was established in the examined patients. A six month course of UDCA medication had a positive effect on the anthropometric indexes, mainly in patients with class I obesity and overweight patients.

We have analyzed the dynamics of CCK level in the examined patients depending on the degree of nutritional status disorder on the background of using complex treatment with the use of UDCA medication (Table 4).

A detailed analysis of the obtained data indicates an interesting consistency in changes of blood serum CCK level in patients with type 2 DM depending on the BMI established before the treatment, the maximum indexes in overweight patients in particular (especially patients with an extra-esophageal form of GERD, p<0.01). It should be noted that with an decrease in BMI, a significant decrease in CCK level was observed in patients of both groups, so far as its normalization in patients with body mass normalization.

In patients with a complex pathology (GERD with type 2 DM), a significant increase of CCK concentration in blood serum was established. It is know that the CCK regulates human's reaction to physiological acts, namely: it stimulates contractions of the gallbladder, participates in the regulation of mental tension, fear and pain, as well as suppresses nutritional motivation,.

Obviously, with type 2 DM on the background of altered metabolic processes in the organism, physiological reactions that are characteristic of the gastrointestinal hormone CCK are disrupted. At the same time, a high level of CCK can lead to an impaired motility of the upper digestive system with a formation of a pathological bile flow into the stomach and esophagus, as evidenced by the large number of patients with duodenogastric reflux (DGR) with an extra-esophageal form of GERD and type 2 DM. It is assumed that in patients with type 2 DM, an "expected" feeling of saturation, which is characteristic of an increased concentration of CCK, does not occur, which is evidenced by the high CCK index in patients with overweight and obesity on the background of GERD. At the same time, "unreasonable" feelings of shortness of breath, palpitations, pain and heaviness in the chest, and increase of blood pressure are formed, which are regarded as extra-esophageal manifestations of GERD with of type 2 DM.

The use of UDCA medication in the complex treatment of patients with type 2 DM is an efficient method for the correction of clinical and endoscopic symptoms of GERD, reduction of CCK level in these patients, as well as normalization of BMI.

Further research is needed in order to correctly understand the role of gastrointestinal hormones, namely CCK, in the formation of digestive organ lesions in patients with combined pathology on the background of type 2 DM, as well as to develop effective methods of their prevention and treatment.

Conclusions: 1. In patients with type 2 DM and GERD, an increase in blood serum CCK level is observed, especially in case of extra-esophageal form of reflux disease. 2. The maximum concentration of CCK in blood serum was revealed in overweight patients with type 2 DM in case of an extra-esophageal form of GERD. 3. The use of UDC medication in the complex treatment of patients with type 2 DM and GERD leads to a normalization tendency of blood serum CCK levels, as well as to a decrease in body mass in these patients.

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SUMMARY

INFLUENCE OF URSODEOXYCHOLIC ACID ON THE CHOLECYSTOKININ LEVELS IN PATIENTS WITH GASTRO-ESOPHAGEAL REFLUX DISEASE AND TYPE 2 DIABETES MELLITUS

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Of particular interest is the study of the peculiarities of clinical findings and diagnostics of gastroesophageal reflux disease (GERD) in patients with diabetes mellitus (DM).

The aim of the research - to study the dynamics of cholecystokinin (CCK) level on the background of complex therapy using the ursodeoxycholic acid (UDCA) drug in patients with GERD with type 2 DM.

68 patients with combination of type 2 DM and GERD were examined. The levels of CCK were studied in these patients, depending on the clinical forms of GERD, as well as their dynamics on the background of UDCA therapy.

More pronounced increase in the serum level of CCK in patients with combination of type 2 DM and extra-esophageal manifestations of GERD was observed. Decrease in the CCK level in 2,4 – 2,7 times was reached on the background of complex therapy with UDCA in patients with combination of type 2 DM and GERD ($p<0,01$).

In patients with type 2 DM and GERD, an increase in blood serum CCK level is observed, especially in case of extra-esophageal form of reflux disease. The maximum concentration of CCK in blood serum was revealed in overweight patients with type 2 DM in case of an extra-esophageal form of GERD. The use of UDC medication in the complex treatment of patients with type 2 DM and GERD leads to a normalization tendency of blood serum CCK levels, as well as to a decrease in body mass in these patients.

Keywords: type 2 diabetes mellitus, gastroesophageal reflux disease, cholecystokinin, ursodeoxycholic acid.

РЕЗЮМЕ

ВЛИЯНИЕ УРСОДЕЗОКСИХОЛЕВОЙ КИСЛОТЫ НА УРОВЕНЬ ХОЛЕЦИСТОКИНИНА У БОЛЬНЫХ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНЬЮ И САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Цель исследования - изучить динамику уровня холецистокинина на фоне комплексной терапии с использованием препарата урсодезоксихолевой кислоты у больных гастроэзофагеальной рефлюксной болезнью при сахарном диабете 2 типа.

Обследовано 68 больных сахарным диабетом (СД) 2 типа и гастроэзофагеальной рефлюксной болезнью (ГЭРБ). В сыворотке крови у обследованных больных СД 2 типа изучали уровни холецистокинина (ХЦК) в зависимости от клинических форм ГЭРБ, а также его динамику на фоне терапии урсодезоксихолевой кислотой (УДХК).

Выявлено более выраженное повышение уровня ХЦК в сыворотке крови у пациентов с СД 2 типа и внепищеводными проявлениями ГЭРБ. Снижение уровня ХЦК в 2,4-2,7 раза достигнуто на фоне комплексной терапии УДХК у пациентов с сочетанным СД 2 и ГЭРБ ($p<0,01$).

На основании проведенного исследования авторами сделаны выводы:

1. У больных СД 2 типа и ГЭРБ наблюдается повышение уровня ХЦК в сыворотке крови, особенно при внепищеводной форме рефлюксной болезни.

2. Максимальная концентрация ХЦК в сыворотке крови выявлена у больных СД 2 типа с избыточной массой тела при внепищеводной форме ГЭРБ.

3. Использование препарата УДХК в комплексной

терапии больных СД 2 типа и ГЭРБ приводит к нормализации уровня ХЦК в сыворотке крови и снижению массы тела.

რეზიუმე

ურსოდეოქსიქოლის მჟავას გავლენა ქოლეცისტოკინინის დონეზე პაციენტებში გასტროეზოფაგური რეფლუქსით და შაქრიანი დიაბეტი ტიპი 2-ით

ე.სირჩაკი, მ.დერბაკი, მ.სტანი, ო.პეტრიჩენკო

უჟგოროდის ეროვნული უნივერსიტეტი, მედიცინის ფაკულტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ქოლეცისტოკინინის დონის დინამიკის შეფასება ურსოდეოქსიქოლის მჟავას პრეპარატებით კომპლექსური მკურნალობის ფონზე პაციენტებში გასტროეზოფაგური რეფლუქსით და შაქრიანი დიაბეტი ტიპი 2-ით.

გამოკვლეულია 68 პაციენტი შაქრიანი დიაბეტი ტიპი 2-ით და გასტროეზოფაგური რეფლუქსური დაავადებით. შაქრიანი დიაბეტი ტიპი 2-ის მქონე პაციენტების სისხლის შრატში, გასტროეზოფაგური რეფლუქსური დაავადების კლინიკური ფორმებისაგან დამოკიდებულებით, გამოკვლეულია ქოლეცისტოკინინის დონე, ასევე, მისი დინამიკა ურსოდეოქსიქოლის მჟავათი თერაპიის ფონზე.

გამოვლენილია ქოლეცისტოკინინის დონის უფრო მეტად გამოხატული მატება შაქრიანი დიაბეტი ტიპი 2-ით პაციენტებში სისხლის შრატში გასტროეზოფაგური რეფლუქსური დაავადების არაეროზიული ფორმით. პაციენტებში შაქრიანი დიაბეტი ტიპი 2-ით და გასტროეზოფაგური რეფლუქსით ურსოდეოქსიქოლის მჟავათი კომპლექსური თერაპიის შემდეგ მიღწეულია ქოლეცისტოკინინის დონის შემცირება 2,4-2,7-ჯერ ($p<0,01$).

ჩატარებული კვლევის საფუძველზე ავტორები დაასკვნიან, რომ:

1. პაციენტებში შაქრიანი დიაბეტი ტიპი 2-ით და გასტროეზოფაგური რეფლუქსით აღინიშნება ქოლეცისტოკინინის დონის მატება სისხლის შრატში, განსაკუთრებით - რეფლუქსური დაავადების არაეროზიული ფორმის დროს;

2. ქოლეცისტოკინინის მაქსიმალური კონცენტრაცია სისხლის შრატში აღინიშნა პაციენტებში შაქრიანი დიაბეტი ტიპი 2-ით და სხეულის ჭარბი მასით რეფლუქსური დაავადების არაეროზიული ფორმის დროს;

3. ურსოდეოქსიქოლის მჟავას პრეპარატის გამოყენება პაციენტებში შაქრიანი დიაბეტი ტიპი 2-ით და გასტროეზოფაგური რეფლუქსური დაავადებით განსაზღვრავს ქოლეცისტოკინინის დონის ნორმალიზებას სისხლის შრატში და სხეულის მასის შემცირებას.