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INFLUENCE OF COMPLEX TREATMENT ON THE FUNCTIONAL STATE OF THE HEPATOBILIARY SYSTEM IN PATIENTS WITH DIABETES MELLITUS

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Liver damage in diabetes mellitus is of particular interest, since this factor significantly affects the course of the disease, the level of compensation and prognosis of the underlying disease.
The aim. *To study the effect of complex treatment using ursosan on the functional state of the hepatobiliary system in patients with diabetes mellitus.*
Materials and methods. *The study included 30 patients with type 1 diabetes mellitus and 48 patients with type 2 diabetes. According to the duration of diabetes, patients were divided into three subgroups:*
a) up to five years; b) 5–10 years; c) more than 10 years.
The number of patients was: 1a group – 13, 1b group – 10, 1c group – 7 people; Group 2a – 23, 2b group – 13, 2c group – 10 people. The control group consisted of 23 apparently healthy people. Ursosan was prescribed at a dose of 10–12 mg per 1 kg of body per day for 6 months. Clinical laboratory and instrumental research methods were used to study the functional state of the liver and gallbladder.
Research results. *After the course of treatment with Ursosan, patients with diabetes mellitus showed normalization of protein, pigment, enzymatic metabolism and, to a lesser extent, lipid metabolism in the liver, which led to an improvement in cellular metabolism and redox processes, providing a stable course of diabetes.*
Conclusions. *A 6-month course of treatment with Ursosan in diabetic patients promotes long-term diabetes compensation. Patients during treatment have a decrease in cytolysis syndrome indicators (alanine aminotransferase (AlAT), aspartate aminotransferase (AsAT), lactate dehydrogenesis (LDH)) by about 1.5 times in all 3 indicators compared to the indicators before treatment. The same trend was observed in terms of gamma-glutamine transferase (GGT) and alkaline phosphatase (ALP)*
Keywords: *diabetes mellitus, hepatobiliary system, ursodeoxycholic acid, ultrasound, alanine aminotransferase, aspartate aminotransferase*

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1. Introduction

Diabetes mellitus (DM) has become a global health problem that threatens to reach pandemic levels by 2030 [1, 2].

Metabolic disorders in DM lead to changes in the functional activity of all organs and systems, including the hepatobiliary system (its pathology in DM is less studied). DM is one of the diseases in which the liver is damaged more and more seriously; therefore, the treatment of this organ is of particular interest, since its damage significantly affects the course of the disease, the level of compensation and the prognosis of the disease [3–5].

To achieve a positive result in the treatment of patients with DM, modulation of treatment should be aimed not only at correcting carbohydrate, lipid and protein metabolism, but also at combating secondary immunodeficiency.

It is known that ursodeoxycholic acid – UDCA (drug Ursosan), which is a hydrophilic non-toxic acid formed under the influence of bacterial enzymes from 7-keto-lithocholic acid entering the liver from the small intestine – is of great importance in the treatment of liver diseases from various groups of drugs. While taking the drug, the hydrophobic enterohepatic circulation of bile acids decreases, their toxic effect on the membrane of hepatocytes and the epithelial membrane of the bile ducts is prevented [6]. UDCA has antioxidant effects and attenuates cholestasis-induced immunosuppression. It has been scientifically proven that UDCA has hepatoprotective, anticholestatic, immunostimulating, hypocholesterolemic, hypolipidemic, litholytic and anti-apoptotic effects. UDCA has a therapeutic effect in non-alcoholic steatohepatitis, primary biliary cirrhosis, hepatopathies of pregnant women. Prescribing UDCA is warranted in patients with cholestasis-related liver disease [7, 8].

Taking into account the above, **the aim of the work** was to study the effect of complex treatment with Ursosan on the functional state of the hepatobiliary system in patients with diabetes mellitus.

2. Materials and methods of the research

The work was carried out in 2009–2015, within the framework of the scientific program of the Department of Internal Medicine-2 of the Azerbaijan Medical University.

The results of the therapeutic action of Ursosan were studied in 30 patients with type 1 DM and 48 patients with type 2 DM. According to the duration of diabetes, patients were divided into three subgroups: a) up to five years; b) 5–10 years; c) more than 10 years. The number of patients was: 1a group - 13, 1b group – 10, 1c group – 7 people; 2a group – 23, 2b group – 13, 2c group – 10 people. The control group consisted of 23 apparently healthy people.

The consent of the ethical commission at the Azerbaijan Medical University was obtained for the study (protocol No. 9 dated June 25, 2009). The work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All study participants were preliminary informed about all types of upcoming examinations and treatment, the patients received written consent to participate in this work.

Ursosan was prescribed at a dose of 10–12 mg per 1 kg of body per day for 6 months. After a 6-month course of treatment with Ursosan, the patients were assessed for the clinical course of diabetes, blood serum biochemical parameters, the functional state of the liver, and the functional state of the biliary system (BS).

The function of the gallbladder and the state of the liver were studied in dynamics 8–12 weeks after treatment with Ususan according to the data of dynamic ultrasound.

The patient's history, glycemic parameters before treatment and treatment tactics for diabetes mellitus (repeated counselling, drugs used, dosage dynamics, treatment results) were assessed. The diagnosis was made considering the severity of the disease, the compensatory stage of carbohydrate metabolism, and the presence of micro- and macrovascular complications of DM.

All patients included in the study were examined at the beginning and 6 months after treatment according to the following parameters: dynamics of blood glucose levels (according to laboratory tests and self-monitoring data), complete blood count, complete urinalysis, biochemical blood test, liver ultrasound. When determining the severity of diabetes mellitus, the criteria of the clinical protocol adopted by the Ministry of Health of the Republic of Azerbaijan on June 12, 2009 were used.

To determine the status of carbohydrate metabolism, to verify the diagnosis of DM, we determined the average daily amount of fasting glucose in the blood serum, the amount of glycated hemoglobin (HbA_{1c}), and the excretion of microalbumin in the urine.

When studying the functional state of the liver in patients with DM, attention was paid to their appetite, dyspepsia (dry mouth, bitterness, nausea, vomiting), pain in the right hypochondrium.

Indices of lactate dehydrogenesis (LDH) and gamma-glutamine transferase were determined by an optimized kinetic method using a ready-made kit of reagents from Vital Diagnostics SPb (Olveks Diaqnostikum). Alkaline phosphatase (ALP) levels were assessed with the Olsey Diagnosticum using the Bessie and Lowry methods. Bilirubin levels were determined using the Vital Diagnostics SPb diagnostic kit according to the Van den Berg method. Alanine aminotransferase (AlAT) and aspartate aminotransferase (AsAT) levels were assessed by the Reitman və Frankel method using the Bio-LA-Test diagnostic kit.

Total cholesterol was determined using the CHOLESTEROL liquicolor test system (CHOD – PAP method). The total protein was determined by the biuret method using the "General Protein Agat" device (LLC "Agat-Med"). Plasma albumin was determined using the ALBUMIN FS kit (ZAO "DIAKON-DS").

The metabolism of liver pigments was assessed by the level of total bilirubin and its components in the blood serum (Endrashik, 1936). The ability of the liver to synthesize protein was studied by the turbometric method according to the level of total protein in the blood and its main fractions. A thymol test was performed.

The glucose level in capillary blood was determined by the glucose oxidase method using a standard GOD-POD Gluosis kit (Kope, Finland).

Determination of the amount of glycated hemoglobin in the blood serum was carried out by the immunoburbometric method. Its volume was expressed as a percentage of total hemoglobin and was determined by the colorimetric method. Lyophilized concentrated serum Serum Hp and Serum HN (Cormay, Poland) were used to standardize the results.

The amount of total cholesterol and triglycerols in the blood serum was determined enzymatically using a standard Cormay kit (Poland). High-density lipoprotein (HDL) levels were determined after precipitation of low-density lipoprotein (LDL) in the supernatant using a standard kit from Cormay (Poland).

The determination of β-lipoproteins was carried out by the enzymatic method using a standard kit from Cormay (Poland).

The amount of low-density lipoproteins (LDL) was determined according to W. Friedewald's formula by an indirect calculation method (Friedewald W. T. et al., 1972): Chol LDL (mg/dl) = total Chol – total Chol HDL – TG / 5 Chol LDL (mmol/l) = total Chol – Chol HDL – TG / 2.2.

Ultrasound of the liver and gallbladder was performed according to the method of A.G. Zubovsky (1986). In the study of the liver, the following was studied: the size and thickness of the right and left lobes, their borders, edges, exostructure, exogenousness, the state of the intrahepatic and extrahepatic bile ducts, veins, vascular pattern; when examining the gallbladder, the following were also studied: size, width, wall thickness, shape bile ducts, contents of the gallbladder.

Ultrasound was performed on an ALOKA apparatus using transmitters with a frequency of 1000 MHz.

The drug of choice in the treatment of patients with DM was ursodeoxycholic acid (UDCA) – Ursosan. Indications for the appointment of this drug are liver steatosis, steatohepatitis, or colloidal destabilization of bile. It should be noted that the drug Ursosan was prescribed in addition to the main treatment.

Statistical processing of the obtained data was carried out on a computer according to the generally accepted method Statistica 6.0, Microsoft Excel software pack-

age. During the analysis of the results, the mean (M), standard error (m) were determined, the statistical significance of the difference between the two mathematical indicators was determined by the Student's t test, and the statistical significance of the difference between the two mathematical indicators, the frequencies were determined by Fisher's exact test. The difference between the compared indicators, $p<0.05$, was taken for statistical accuracy.

3. Research results and their discussion

During the study, the functional state of the liver and biliary system was studied in patients with diabetes mellitus after a course of treatment with ursodeoxycholic acid (the drug Ursosan).

When assessing the clinical effectiveness of therapy, it should be noted that the positive effect of Ursosan, first of all, manifested itself in a decrease in asthenovegetative, pain and dyspeptic syndromes. On average, in 64 (81.8 %) patients by the end of the fourth week after the start of taking the drug, weakness, decreased ability to work, fatigue decreased significantly. Dull pain and heaviness in the right hypochondrium, nausea and bitterness in the mouth significantly decreased. There were practically no side effects when taking the drug in this study.

At the next stage of the study, the biochemical parameters of the blood serum of patients after the treatment with ursosan were analyzed (Table 1).

Table 1

Biochemical parameters of blood serum of patients with diabetes mellitus after a 6-month course of treatment with Ursosan

Indicators	Healthy (n=23)	Before treatment (n=78)	After treatment (n=78)	p
AlAT (mmol/h ml)	0.80±0.12	0.92±0.08	0.66±0.05	0.001
AsAT (mmol/h ml)	0.72±0.18	0.86±0.01	0.57±0.04	0.001
LDH (U/l)	188.0±7.4	328.0±29.4	242.0±20.4	0.001
ГГТ (U/l)	26.8±7.8	48.2±4.5	34.3±5.2	0.001
ALP (U/l)	92.5±2.3	146.2±6.8	96.5±7.5	0.001
Total cholesterol (mmol/l)	4.1±0.18	6.1±0.57	4.3±0.8	0.001
Triglycerols (mmol/l)	1.5±0.12	3.1±0.53	2.4±0.34	0.001
HDL (mmol/l)	1.02±0.09	0.84±0.16	1.1±0.41	0.001
LDL (mmol/l)	2.8±0.23	4.9±1.2	3.2±0.2	0.001
Total bilirubin (μmol/l)	12.6±0.42	15.6±0.62	14.2±0.43	0.001
Bound bilirubin (μmol/l)	3.2±0.58	3.8±0.72	3.3±0.58	0.01
Total protein (g/l)	75.4±5.6	78.2±5.7	77.4±5.2	0.362
Albumin (%)	56.3±2.4	54.7±3.8	56.0±3.5	0.028
Globulins a1 (%)	6.1±0.23	4.8±0.32	5.5±0.38	0.001
Globulins a2 (%)	8.3±0.22	7.6±0.48	6.4±0.42	0.001
Globulins β (%)	10.8±0.6	12.7±1.3	11.9±1.2	0.01
Globulins γ (%)	18.5±0.6	22.5±1.8	18.2±1.3	0.001
Globulins γ (abs., g/l)	12.5±4.2	16.8±4.6	14.1±4.3	0.001
Thymol test (Un.)	2.7±0.28	3.15±0.32	1.84±0.13	0.001
β-lipoproteins (mmol/l)	4.5±5.2	5.23±2.5	4.68±2.3	0.001

Note: p – statistical significance in relation to indicators before treatment

As can be seen from this Tab. 1, the indicators of cytolysis syndrome (AlAT, AsAT, LDH) during treatment decreased by about 1.5 times in all 3 indicators compared with the indicators before treatment. The same trend was observed for the GGT and ALP indicators.

Analyzing the parameters of lipid metabolism before and after treatment, it should be noted that the levels of total cholesterol, LDL, HDL and triglycerols showed a tendency towards normalization.

Thus, after the course of treatment with Ursosan in patients with DM, normalization of protein, pigment, enzymatic metabolism and, to a lesser extent, lipid metabolism in the liver was observed, which led to an improvement in cellular metabolism and redox processes, providing a stable course of DM.

The results of ultrasound showed that after the course of treatment with Ursosan, the volume of the gallbladder changed over time. A particularly clear dynamics of changes in the volume of the gallbladder after treatment was observed in the short-term course of diabetes (subgroups 1a and 2a) – here it significantly decreased in almost all patients but remained high compared to the control group. Only in subgroup 1a, the volume of the gallbladder did not differ statistically significantly from the control group ($p> 0.05$) (Table 2).

Significant dynamics of the gallbladder volume was also observed in subgroups 1b and 2b, where it was reduced in most patients – statistically significantly lower than the initial mean. In patients with diabetes for more than 10 years (subgroups 1c and 2c), the volume of the gallbladder changed moderately, although the majority of patients with type 1 and 2 DM showed a decrease in its volume. With a long course of diabetes mellitus (subgroups 1b, 1c and 2b, 2c) after the course of treatment with Ursosan, the volume of the gallbladder in patients with type 1 DM remained 1.3 times, in patients with type 2 DM – 1.5 times higher than in the control group.

An improvement in the contractile function of the gallbladder was also confirmed by ultrasound data – in most patients with diabetes up to 10 years, a significant decrease in the degree of hypotension was observed.

After the course of treatment with Ursosan, the hypotension of the sphincter of Oddi persisted (especially in diabetes with a duration of more than 5 years), which is most likely due to the incomplete restoration of the contractile ability of the gallbladder.

Thus, almost all patients with type 1 and 2 diabetes mellitus had a pronounced choleretic effect of Ursosan, which led to a significant improvement in the clinical condition of patients. The data of ultrasound examination of the liver after treatment with Ursosan in diabetes mellitus are presented in Table 3.

Table 2

Dynamics of gallbladder volume according to ultrasound data after a course of treatment with Ursosan

Parameters	Subgroups	Group 1 (DM 1 type) (n=30; a=13; b=10; c=7)		Group 2 (DM 2 type) (n=48; a=23; b=13; c=10)	
		Before treatment	After treatment	Before treatment	After treatment
Gallbladder volume, ml	A	44.6±3.8	41.5±2.9 p=0.028	58.2±5.4	50.8±4.3 p=0.0001
	Б	58.3±4.2	50.4±3.7 p=0.003	64.3±5.6	58.4±4.7 p=0.008
	C	60.7±4.6	56.8±3.2 p=0.096	72.5±5.4	68.7±4.6 p=0.084
	Control group (n=23)	40.4±4.9			

Note: p – statistical significance of the difference in comparison with the indicators before treatment

Table 3

Dynamics of the liver in patients with diabetes mellitus according to ultrasound data after a course of treatment with Ursosan

Parameter	DM 1 type (n=30)			DM 2 type (n=48)		
	Before treatment (abs., %)	After treatment (abs., %)	p	Before treatment (abs., %)	After treatment (abs., %)	p
Echogenicity: Normal	18 (60.0±8.94)	26 (86.7±6.21)	0.039	22 (45.8±7.19)	35 (72.9±6.41)	0.012
High	12 (40.0±8.94)	4 (13.3±6.21)		26 (54.2±7.19)	13 (27.1±6.41)	
Echostructure: homogeneous	7 (23.3±7.72)	9 (30.0±8.37)	0.771	–	2 (4.2±2.88)	
relatively homogeneous	13 (43.3±9.05)	15 (50.0±9.13)	0.796	22 (45.8±7.19)	37 (77.1±6.07)	0.003
heterogeneous	10 (33.3±8.61)	6 (20.0±7.30)	0.382	26 (54.2±7.19)	9 (18.8±5.63)	0.0005
Density: compacted	9 (30.0±8.37)	6 (20.0±7.30)	0.552	16 (33.3±6.80)	11 (22.9±6.07)	0.364
unconsolidated	21 (70.0±8.37)	24 (80.0±7.30)		32 (66.7±6.80)	37 (77.1±6.07)	
Contours and edges:clear, smooth	30 (100 %)	30 (100 %)		100	100	
Unsmooth	–	–		–	–	
Dimensions: Right lobe: Increased	4 (13.3±6.21)	2 (6.7±4.55)	0.671	12 (25.0±6.25)	7 (14.6±5.09)	0.306
Left lobe: Increased	3 (10.0±5.48)	1 (3.3±3.28)	0.995	13 (27.1±6.41)	8 (16.7±5.38)	0.323
Bile ducts and veins: expanded	2 (6.7±4.55)	1 (3.3±3.28)	1.0	4 (8.3±3.99)	2 (4.2±2.88)	0.677
not expanded	28 (93.3±4.55)	29 (96.7±3.28)		44 (91.7±3.99)	46 (95.8±2.88)	
Vascular pattern: Retained	25 (83.3±6.80)	27 (90.0±5.48)	0.480	11 (22.9±6.07)	28 (58.3±7.12)	0.007
Depleted	5 (16.7±6.80)	3 (10.0±5.48)		37 (77.1±6.07)	20 (41.7±7.12)	

Note: p – statistical significance of the difference in comparison with the indicators before treatment

As can be seen from Table 3, ultrasound examination of the liver after treatment revealed the following changes. The study of the exogenousness of the liver in the group of patients with type 1 DM showed that normal exogenity was found in 86.0±2.3 % of patients, its relatively homogeneous echo structure – in 31.0±5.2 % of patients, no dilatation of the bile ducts and veins – in 98.0±1.7 % of cases, the preservation of the vascular pattern – in 91.0±2.4 %, which indicates a positive therapeutic effect of Ursosan.

As for patients with type 2 DM, after a 6-month course of treatment with Ursosan, according to ultrasound data, the exogeneity and exostructure of the liver normalized, the size of the right and left lobes decreased, the vascular pattern increased ($p < 0.01$).

4. Discussion of research results

The study once again confirmed the efficacy of Ursosan as a hepatoprotective and anticholestatic drug. Taking it for 6 months improved the functional state of the hepatobiliary system in most patients with type 1 and type 2 diabetes. The dynamics of the studied subjective and objective indicators indicates that the course of treatment with Ursosan has a significant positive effect on the state of the digestive system, which, to a certain extent, can contribute to the improvement of the clinical course of diabetes. These results are consistent with the results of a number of studies [7, 8] to study the hepatoprotective and anticholestatic effect of Ursosan.

After the course of treatment with Ursosan, in the study of biochemical parameters of liver function tests, an increased synthesis of albumin ($p<0.05$) and a decrease in the level of globulins responsible for inflammatory processes in the liver parenchyma, especially β- and γ-globulins ($p<0.01$), were noted, which manifested itself in a significant improvement in the ability of the liver to synthesize protein. Normalization of the levels of both total and conjugated (combined) bilirubin ($p<0.01$) was observed, which indicates the suppression of the early inflammatory response of reticulendothelial and parenchymal cells responsible for the uptake, conjugation and excretion of bilirubin from the bile ducts. In our study, a decrease in the amount of alkaline phosphatase and GGT was noted, which indicates the prevention of signs of intrahepatic cholestasis against the background of fatty hepatosis. The cytolytic syndrome also decreased due to the normalization of aminotransferase activity, which, like the above results, was proved by the results of the authors who studied the effect of Ursosan on the liver in individuals with various pathologies [9].

An improvement in lipid metabolism was observed. At the same time, the levels of cholesterol, LDL, HDL and triglycerols did not change significantly during treatment, although a tendency towards normalization of these parameters was noted. Similar data were obtained earlier by other researchers [10, 11].

After the course of treatment with Ursosan, according to the ultrasound examination of the liver in both type 1 DM and type 2 DM, the exogenity and exostructure of the liver normalized ($p<0.05$), the size of the right and left lobes decreased, and the vascular pattern increased. Data on patients with type 2 diabetes are consistent with the work of Yu. M. Vakrushev et al. [12]. We have not come across data on the study of ultrasound after a course of Ursosan in patients with type 1 DM in the available literature.

Clear dynamics of changes in the volume of the gallbladder during ultrasound after a course of treatment with Ursosan was most pronounced with a short duration of diabetes (up to 5 years) – in this case, it decreased in almost all patients, but remained high compared to the control group ($p<0.05$). A significant decrease in the degree of hypotension was observed in most patients with diabetes mellitus lasting up to 10 years ($p<0.01$). We did not find data on the study of ultrasound parameters of the gallbladder in patients with diabetes mellitus with its different duration after a course of Ursosan, but there are works [13, 14] that prove the positive effect of Ursosan on ultrasonographic dimensions of the gallbladder and its choleretic effect.

In general, the high efficiency of our proposed treatment with Ursosan in patients with type 1 and type 2 diabetes mellitus is ensured by the integration of the pharmacological effect of the drug, its ability to enhance the pharmacological potential of drugs aimed at treating the underlying disease, and, practically, the absence of its side effects.

Study limitations. The study did not include patients with diabetes mellitus with infectious, autoimmune liver diseases, alcoholic lesions, benign and malignant liver tumors.

Prospects for further research. The authors suggest that the use of Ursosan for a longer period (over 6 months), and, possibly, permanently throughout life, will prevent the occurrence of functional liver disorders in diabetic patients with a short history of the disease, and with a long duration of the disease, avoid more severe complications of the hepatobiliary system. This assumption requires additional research.

5. Conclusions

1. A 6-month course of treatment with Ursosan in patients with DM by the end of the fourth week contributed to a significant decrease in dull pain and heaviness in the right hypochondrium, nausea and bitterness in the mouth, as well as a decrease in weakness, and an increase in work capacity in 81.8 % of patients.

2. 6-month course of treatment with Ursosan in patients with DM contributed to a decrease in cytolysis syndrome indicators (AlAT, AsAT, LDH), as well as in GGT and ALP indicators by about 1.5 times compared with those before treatment.

3. Ultrasound examination of the liver in the group of patients with type 1 DM showed normalization of the exogenousness of the liver, preservation of the vascular pattern and no dilatation of the bile ducts and veins in most patients ($p<0.01$), which indicates a positive therapeutic effect of 6-month treatment with Ursosan.

4. Ultrasound examination of the liver in the group of patients with type 2 DM also indicates the normalization of the exogenous and exostructure of the liver, a decrease in the size of the right and left lobes of the organ, an increase in the vascular pattern ($p<0.01$), which proved the effectiveness and adequacy of the therapy used.

5. The greatest efficacy of Ursosan in relation to changes in the volume of the gallbladder during ultrasound is observed in patients with diabetes up to 5 years of age ($p<0.05$).

Conflict of interests

The author declares there is no conflict of interests.

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