PATHOGENETIC SUBSTANTIATION
OF USING SELENIUM-CONTAINING DRUGS FOR THE CORRECT
DISORDERS OF THE BLOOD PLASMA FIBRINOLYTIC SYSTEM
IN PATIENTS WITH CHRONIC DIFFUSE LIVER DISEASES
AND EUTHYROID SYNDROME PATHOLOGY

Summary. The dynamics of the indices of fibrinolysis and cellular adhesion in patients with chronic diffuse liver diseases and euthyroid syndrome against the ground of administration of selenium-containing drugs, has been studied. The administration of selenium-containing drugs in a comprehensive therapy of patients with chronic diffuse liver diseases with disorders of thyroid homeostasis was found to improve the indices of the blood plasma fibrinolytic system, to reduce adhesive cellular properties and to increase total enzymatic activity of the blood plasma.

Key words: chronic diffuse liver diseases, disorders of thyroid homeostasis, cellular adhesion, fibrinolysis, selenium.

Introduction
Disorders of the endothelial participation in the regulation of fibrinolysis are an important link in pathogenesis of many diseases including chronic diffuse liver diseases (CDLD) [1, 2, 4]. Disorders of the local fibrinolysis are an important factor in the development and progressing of CDLD which can be caused by disorders of the liver circulation, and results in an increased release of thromboplastin, a powerful triggering factor of blood clotting, into the blood [5, 6].

In its turn, endothelial dysfunction causes occurring and progressing of thyroid homeostasis disorders [3], which is indicative of the necessity to elaborate effective methods of its correction.

Objective: to examine the dynamics of indices of the blood fibrinolytic activity and cellular adhesion in patients with chronic diffuse liver diseases against the ground of administration of a selenium-containing drug.

Materials and methods
28 patients with CDLD aged from 25 to 74 (an average age — 52.30 ± 6.09) were included into the study. There were 19 men (67.9 %) and 9 women (32.1 %), an average duration of the disease was 5.9 ± 1.3 years. The control group included 20 practically healthy individuals (an average age — 52.20 ± 12.15, 13 men (65.0 %) and 7 women (35 %) among them.

The diagnosis of chronic hepatitis (CH) was made in 13 individuals (46.4 %) with an average age of 49.60 ± 8.59. There were 7 men (53.8 %) and 6 women (46.2 %) among them, an average duration of the disease was 6.0 ± 2.1 years. A mild form of CH was found in 8 patients (28.6 %) and moderate form — in 5 patients (17.8 %).

Liver cirrhosis (LC) was diagnosed in 15 patients (53.6 %) with an average age of 55.00 ± 7.43. Men constituted 11 patients (73.3 %), women — 4 (26.7 %), an average duration of the disease was 5.7 ± 1.8 years. A mild form of LC was found in 9 patients (32.2 %) and moderate form — in 6 (21.4 %).

The study was conducted on the basis of the Department of Gastroenterology, Chernivtsi Regional Clinical Hospital.
CH and LC were verified on the basis of complaints, anamnesis, objective status, general laboratory methods of examination (general clinical blood and urine analyses, biochemical blood test — general bilirubin and its fractions, sublimate and thymol tests, ionogram, proteinogram, coagulogram). The activity of the following blood enzymes was examined: alaminaminotransferase (AIAT), aspartateaminotransferase (AsAT), gammaglutamyltransferase (GGT), alkali phosphatase (AP). The levels of urea, creatinine were detected in the blood as well as serum markers of hepatitis B and C viruses. Instrumental examinations were conducted (USD of the abdominal organs, esophageagogastroduodenofibroscopy (EGDFS)).

The degree of activity of CH and LC was found on the basis of clinical manifestations and biochemical signs — AIAT, AcAT activity, thymol test, bilirubin level in the blood [1, 2].

The degree of LC compensation was estimated by the criteria of C.G. Child and J.G. Turcotte (1964) in the modification of K.N.H. Pugh (1973). The levels of bilirubin, albumins, prothrombin were detected in the blood serum, the presence of ascites and encephalopathy was found [2].

The degree of portal hypertension was determined on the basis of varix dilatation of the lower esophageal portion, subcutaneous veins of the anterior abdominal wall, umbilical veins, splenomegaly, ascites and hepatic encephalopathy [1].

Inclusion criteria were: the age from 25 to 76, diagnosed CH and LC (of a mild and moderate activity) verified by means of clinical, laboratory and instrumental examinations, the basis of varix dilatation of the lower esophageal portion, subcutaneous veins of the anterior abdominal wall, umbilical veins, splenomegaly, ascites and hepatic encephalopathy [1].

The diagnosis of CDLD was made on the basis of carefully collected anamnesis, generally accepted complex of clinical-laboratory and instrumental methods of examination, detection of serum markers of viral hepatitis B and C, USD of the abdominal organs and thyroid gland.

All the patients were divided into two groups represented by their age, sex, degree of cytolysis activity and liver cirrhosis compensation. The first group (a comparative group) included 12 individuals afflicted with CDLD receiving a generally accepted therapy (diet No 5), hepatoprotectors, diuretics and detoxicants in case of need. The main group included 16 patients with CDLD receiving two selenium-containing drug capsules in the morning and in the evening against the ground of basic therapy during one month. The diagnosis of CDLD was made on the basis of carefully collected anamnesis, generally accepted complex of clinical-laboratory and instrumental methods of examination, detection of serum markers of viral hepatitis B and C, USD of the abdominal organs and thyroid gland.

The content of soluble intercellular adhesive molecule of the 1st type (ICAM-1) was detected by means of immune-enzymatic method using the commercial test-system of the «Diaclone» firm (France).

The total (TFA), non-enzymatic (NFA) and enzymatic fibrinolytic activity (EFA) of the citrate blood plasma was detected by means of azofibrin lysis (Simko Ltd., Ukraine). Peculiarities of thyroid homeostasis were studied by the content of free thyroxin (fT4), free thyriodothyronine (fT3) and thyroid-stimulating hormone (TSH) by means of immune-enzymatic method using the reagents «ImmuneFa-TTH», «IFA-SvT3» and «IFA-SvT4-1» (JSC «Immunotech») on the analyzer of immune-enzymatic reactions «Uniplan» calculating the coefficients fT3/fT4, fT4/fT3.

The results obtained were processed by means of Biostat program using Student t-criterion.

Results and discussion

Indicators studies of thyroid homeostasis at patients with CDLD established a probable reduction in fT4 and increase of the concentration in fT3 due to failure of peripheral monodeiodization against the increasing of thyroid stimulating pituitary function. As evidence of this assumption the probable reduction rate was observed in fT3/fT4, with a corresponding of indicator in fT4/fT3. However, in most of the examined cases the values of the studied parameters did not exceed the norm.

The level of ICAM-1 in the blood plasma of CDLD patients was 34.6 % higher (p < 0.001).

Examination of blood fibrinolytic activity detected a reliable decrease of TFA index on 20.2 % (p < 0.001) at the expense of reduced enzymatic portion of fibrinolysis (EFA on 45.5 %, p < 0.001). The index of non-productive NFA, being 35.2 % higher (p < 0.001) that of the control, increased against this ground.

Thus, CDLD patients demonstrate inhibition of fibrinolytic blood plasma activity occurring at the expense of inhibition of enzymatic fibrinolysis as well as compensatory increase of non-enzymatic fibrinolytic activity.

According to the data of correlation analysis the development of fibrinolytic system disorders in patients with dysmetabolism of thyroid hormones against the
грунт CDLD связан с гипотрийодтиронинемией и нарушениями функции тиреоидных гормонов.

Таким образом, эндотелиальная дисфункция, вызванная патологическими механизмами, таких как оксидантный стресс и увеличенное адгезионное свойство клеток, может инкапсулировать фибринолитическую активность крови у исследуемых пациентов.

Результаты лечения Triovit оказывают влияние на индексы адгезивных свойств и фибринолитической активности крови CDLD пациентов, как представлено в таблице 1.

Исследование динамики содержания ICAM-1 в крови выявило значительное уменьшение адгезивных свойств в основной группе. Этот индекс был на 10.3 % ниже (p < 0.001) в месячный период по сравнению с базовой терапией, и на 17.8 % ниже (p < 0.01) против Triovit (фиг. 1).

В 14 дней пациенты основной группы демонстрировали достоверное увеличение TFA на 13.7 % (p < 0.01), в месячный период — на 20.6 % (p < 0.001), в то время как в контрольной группе эти изменения были достоверными только в месячный период (p < 0.01) (фиг. 2).

После использования препаратов на основе селена наблюдалось уменьшение NFA на 10.0 % (p < 0.05) и 15.9 % (p < 0.01) в 2 недели и 1 месяц после лечения, в группе, получавшей только базовую терапию, NFA уменьшились на 8.1 % и 12.5 % (p < 0.01) соответственно.

Результаты проведенных исследований показали достоверное увеличение EFA в основной группе на 42.6 % (p < 0.001) и на 60.7 % (p < 0.001) в месячный период, в контрольной группе значимые изменения были только на 36.8 % (p < 0.01) и 54.4 % (p < 0.001) соответственно.

Таблица 1. Гомеостаз индексов пациентов с хроническими диффузными заболеваниями печени и нарушениями гомеостаза щитовидной железы в динамике лечения препаратами на основе селена (M ± m)

<table>
<thead>
<tr>
<th>Indices</th>
<th>Control group (n = 20)</th>
<th>Patients with chronic diffuse liver diseases and disorders of thyroid homeostasis</th>
<th>Patients with chronic diffuse liver diseases and disorders of thyroid homeostasis (n = 28)</th>
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<tr>
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<td>Basic treatment (n = 12)</td>
<td>Basic treatment + Triovit (n = 16)</td>
<td>Basic treatment</td>
</tr>
<tr>
<td>ICAM-1, ng/ml</td>
<td>259.60 ± 10.324</td>
<td>377.70 ± 16.08</td>
<td>338.70 ± 16.64</td>
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<td></td>
<td>p1 &lt; 0.001</td>
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<td>Total fibrinolytic activity, azofibrin mc mole/1 ml per 1 hour</td>
<td>1.630 ± 0.041</td>
<td>1.300 ± 0.042</td>
<td>1.520 ± 0.079</td>
</tr>
<tr>
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<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.05</td>
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<tr>
<td>Non-enzymatic fibrinolytic activity, azofibrin mk mole/1 ml per 1 hour</td>
<td>0.510 ± 0.019</td>
<td>0.720 ± 0.01</td>
<td>0.630 ± 0.016</td>
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<tr>
<td></td>
<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.001</td>
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<tr>
<td>Enzymatic fibrinolytic activity, azofibrin mk mole/1 ml per 1 hour</td>
<td>1.120 ± 0.051</td>
<td>0.570 ± 0.052</td>
<td>0.880 ± 0.077</td>
</tr>
<tr>
<td></td>
<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.001</td>
<td>p1 &lt; 0.05</td>
</tr>
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Примечания: n — количество наблюдений; p1 — вероятность изменений, принимая контроль за основу; p2 — вероятность изменений, принимая индекс до лечения за основу; p3 — вероятность изменений, принимая сравнительную группу за основу.
Thereby, administration of a selenium-containing drug in a comprehensive treatment of CDLD patients promotes decrease of cellular adhesive properties which is proved by reduced ICAM-1 expression. TFA increases against this ground at the expense of EFA increase.

Conclusions

1. Chronic diffuse liver diseases are accompanied by disorders of the blood plasma fibrinolytic system, functional endothelial state with inhibition of enzymatic fibrinolysis against the ground of increased expression of the 1st type intercellular adhesion molecule.

2. Addition of selenium-containing drug into the therapeutic complex of patients with chronic diffuse liver diseases and disorders of thyroid homeostasis results in the reduction of adhesive cellular properties (expression of the 1st type intercellular adhesion molecule) and the signs of disorders of the blood plasma fibrinolytic system (increase of enzymatic fibrinolytic activity).

The prospects of proceeding investigations will be further studies of pathogenetic peculiarities of thyroid homeostasis disorders under conditions of chronic diffuse liver diseases with the aim to find the mechanisms of their occurrence and progress and substantiation of the improved methods to correct and prevent the given pathology.

References


