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# 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.

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CH and LC were verified on the basis of complaints, anamnesis, objective status, common 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: alaninaminotranspherase (AlAT), aspartateaminotranspherase (AsAT), gammaglutamyltranspherase (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, esophagogastroduodenofibroscopy (EGDFS)).

The degree of activity of CH and LC was found on the basis of clinical manifestations and biochemical signs — AlAT, 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, informed written concern of the patient to participate in the study.

Patients with decompensated LC (III degree of hepatic-cellular failure, hypoalbuminemia less than 30 %, III–IV degree of hepatic encephalopathy, resistant ascites, systemic hypotension), chronic hepatitis of a viral etiology, Wilson's disease, congenital $\alpha_1$-antitripsin insufficiency ($\alpha_1$-inhibitor of proteinases), idiopathic (genetic) hemochromatosis, autoimmune hepatitis, diabetes mellitus, III–IV degree of chronic heart failure with ejection fraction of the left ventricle less than 45 %, acute disorders of the cerebral circulation and acute coronary syndrome, psychic disorders, residents of the III–IV zones of radiation contamination, individuals during pregnancy or lactation period or those receiving oral contraceptives, with any acute inflammatory processes, other concomitant decompensated diseases or acute conditions able to affect the results of the study, were excluded from the investigation.

The diagnosis of CDLD was made on the basis of anamnesis, generally accepted complex of clinical-laboratory and instrumental investigation methods, USD of the abdominal organs. Patients with chronic hepatitis and cirrhosis of a viral etiology, Wilson — Konovalov disease, congenital insufficiency of α-antitripsin (α-inhibitor of proteinase), idiopathic (genetic) hemochromatosis, autoimmune hepatitis were excluded from the study.

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 ($fT_4$), free thriiodothyronine ($fT_3$) and thyroid-stimulating hormone (TSH) by means of immune-enzymatic method using the reagents «ImmuneFa-TTH», «IFA-Sv$T_3$» and «IFA-Sv$T_4$-1» (JSC «Immunotech») on the analyzer of immune-enzymatic reactions «Uniplan» calculating the coefficients $fT_3/fT_4$, $fT_4/fT_3$.

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 $fT_3$ and increase of the concentration in $fT_4$ 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 $fT_3/fT_4$ with a corresponding of indicator in $fT_4/fT_3$. 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

ground of CDLD is connected with hypotriiodthyroninemia and conversion disorders of free thyroid hormones.

Thus, endothelial dysfunction caused by pathological mechanisms such as oxidant stress and increased cellular adhesion is likely to inhibit fibrinolytic blood activity in the examined patients.

The results of Triovit effect upon the indices of cellular adhesion and fibrinolytic blood plasma activity of CDLD patients are presented in the table 1.

Examination of the dynamics of ICAM-1 content in the blood serum detected more considerable decrease of the cellular adhesive properties in the main group. This index was 10.3 % lower ($p < 0.001$) in a month against the basic therapy, and 17.8 % lower ($p < 0.01$) against Triovit administration (fig. 1).

In 14 days the patients of the main group demonstrated a reliable increase of TFA index on 13.7 % ($p < 0.01$), in a month — on 20.6 % ($p < 0.001$), at the same time in the comparative group these changes were reliable only in a month after the treatment ($p < 0.01$) (fig. 2).

After selenium-containing drug use NFA reduction on 10.0 % ($p < 0.05$) and 15.9 % ($p < 0.01$) was registered 2 weeks and 1 month after the treatment, in the patients treated by means of basic therapy only — on 8.1 % and 12.5 % ($p < 0.01$).

The result of the therapy conducted was a reliable increase of EFA in the main group 2 weeks after the initiation of therapy on 42.6 % ($p < 0.001$) and on 60.7 % ($p < 0.001$) in a month, in the comparative group — on 36.8 % ($p < 0.01$) and 54.4 % ($p < 0.001$) respectively.

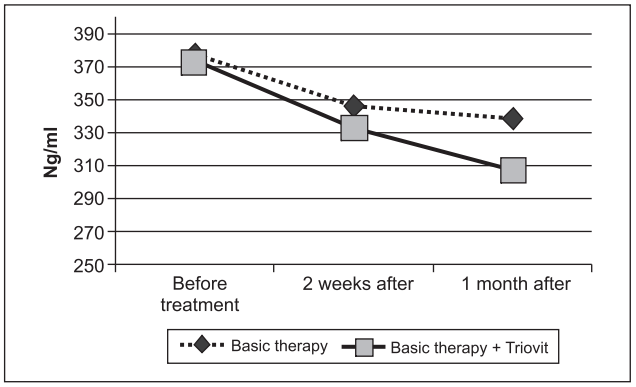


***Figure 1. Dynamics of the content of the 1st type intercellular adhesion molecules (ICAM-1) in the blood serum of patients with chronic diffuse liver diseases and disorders of thyroid homeostasis in the course of treatment***

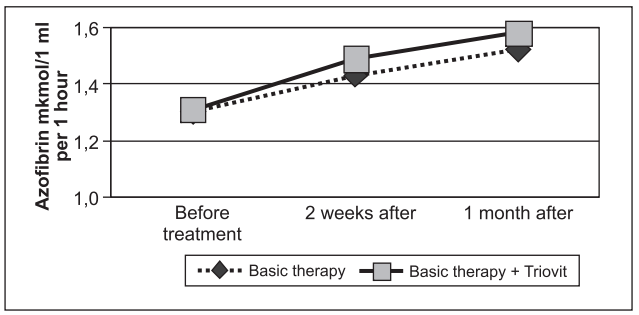


***Figure 2. Dynamics of the total fibrinolytic activity of the blood plasma in patients with chronic diffuse liver diseases and disorders of thyroid homeostasis in the course of treatment***

***Table 1. Homeostasis indices of patients with chronic diffuse liver diseases and disorders of thyroid homeostasis in the dynamics of treatment with selenium-containing drug (M ± m)***

| Indices | Control group (n = 20) | Patients with chronic diffuse liver diseases and disorders of thyroid homeostasis (n = 28) | | | |
|---|---|---|---|---|---|
| | | Basic treatment (n = 12) | | Basic treatment + Triovit (n = 16) | |
| | | Before treatment | After treatment | Before treatment | After treatment |
| ICAM-1, ng/ml | 259.600 ± 10.324 | 377.70 ± 16.08<br>$p_1 < 0,001$ | 338.70 ± 10.64<br>$p_1 < 0.001$<br>$p_2 < 0.05$ | 374.10 ± 14.68<br>$p_1 < 0.001$ | 307.50 ± 9.54<br>$p_1 < 0.01$<br>$p_2 < 0.01$<br>$p_3 < 0.05$ |
| Total fibrinolytic activity, azofibrin mcmol/1 ml per 1 hour | 1.630 ± 0.041 | 1.300 ± 0.042<br>$p_1 < 0.001$ | 1.520 ± 0.079<br>$p_1 > 0.05$<br>$p_2 < 0.01$ | 1.310 ± 0.031<br>$p_1 < 0.001$ | 1.580 ± 0.055<br>$p_1 > 0.05$<br>$p_2 < 0.001$<br>$p_3 > 0.05$ |
| Non-enzymatic fibrinolytic activity, azofibrin mkmol/1 ml per 1 hour | 0.510 ± 0.019 | 0.72 ± 0.01<br>$p_1 < 0.001$ | 0.630 ± 0.016<br>$p_1 < 0.001$<br>$p_2 < 0.01$ | 0.690 ± 0.028<br>$p_1 < 0.001$ | 0.580 ± 0.011<br>$p_1 < 0.001$<br>$p_2 < 0.01$<br>$p_3 < 0.05$ |
| Enzymatic fibrinolytic activity, azofibrin mkmol/1 ml per 1 hour | 1.120 ± 0.051 | 0.570 ± 0.052<br>$p_1 < 0.001$ | 0.880 ± 0.077<br>$p_1 < 0.05$<br>$p_2 < 0.001$ | 0.610 ± 0.052<br>$p_1 < 0.001$ | 0.980 ± 0.035<br>$p_1 < 0.05$<br>$p_2 < 0.001$<br>$p_3 > 0.05$ |

***Notes: n — number of observations; $p_1$ — probability of changes considering the control; $p_2$ — probability of changes concerning the index before treatment; $p_3$ — probability of changes concerning the comparative group***

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


*1. Еремина Е.Ю. Факторы риска прогрессирования хронических гепатитов и циррозов печени / Е.Ю. Еремина // Эксперимент. и клин. гастроэнтерол. — 2008. — № 6. — С. 101-106.*

*2. Ивашкин В.Т. Клиническая гепатология сегодня и завтра / В.Т. Ивашкин, А.О. Буеверов // Рос. журн. гастроэнтерол., гепатол., колопроктол. — 2005. — Т. 12, № 1. — С. 4-9.*

*3. Карпов Ю.А. Эндотелий — новая мишень для лечебного действия ингибитором ангиотензинпревращающего фермента / Ю.А. Карпов // Терапевт. арх. — 2004. — Т. 76, № 6. — С. 94-97.*

*4. Лазебник Л.Б. Роль оксида азота (NO) в этиопатогенезе некоторых заболеваний органов пищеварения / Л.Б. Лазебник, В.Н. Дроздов, Е.Н. Барышников // Эксперимент. и клин. гастроэнтерол. — 2005. — № 2. — С. 4-11.*

*5. Cytokine-induced monocyte adhesion to endothelial cells involves platelet-activating factor: Suppression by conjugated linoleic acid / A.A. Sneddon, E. McLeod, K.W. Wahle, J.R. Arthur // Biochimica et Biophysica Acta-Molecular and Cell Biology of Lipids. — 2006. — Vol. 761. — P. 793-801.*

*6. Hodge A. Coagulopathy in liver disease: The whole is greater than the sum of its parts / A. Hodge, P. Crispin // J. of Gastroenterol. and Hepatol. — 2010. — Vol. 25, № 1. — P. 1-2.*


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### ПАТОГЕНЕТИЧНЕ ОБГРУНТУВАННЯ ЗАСТОСУВАННЯ СЕЛЕНОВМІСНИХ ПРЕПАРАТІВ У КОРЕКЦІЇ ПОРУШЕНЬ СИСТЕМИ ФІБРИНОЛІЗУ ПЛАЗМИ КРОВІ У ХВОРИХ НА ХРОНІЧНІ ДИФУЗНІ ЗАХВОРЮВАННЯ ПЕЧІНКИ ІЗ СИНДРОМОМ ЕУТИРЕОЇДНОЇ ПАТОЛОГІЇ


**Резюме.** Вивчено динаміку показників фібринолізу та клітинної адгезії у хворих на хронічні дифузні захворювання печінки із синдромом еутиреоїдної патології на тлі використання селеновмісного препарату. Установлено, що селен у комплексній терапії хворих на хронічні дифузні захворювання печінки із порушенням тиреоїдного гомеостазу сприяє оптимізації показників системи фібринолізу плазми крові, дозволяє істотно зменшити адгезивні властивості клітин та підвищити сумарну ферментативну активність плазми крові.


**Ключові слова:** хронічні дифузні захворювання печінки, тиреоїдний гомеостаз, клітинна адгезія, фібриноліз, селен.


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### ПАТОГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ ИСПОЛЬЗОВАНИЯ СЕЛЕНСОДЕРЖАЩИХ ПРЕПАРАТОВ В КОРРЕКЦИИ НАРУШЕНИЙ СИСТЕМЫ ФИБРИНОЛИЗА ПЛАЗМЫ КРОВИ У БОЛЬНЫХ ХРОНИЧЕСКИМИ ДИФФУЗНЫМИ ЗАБОЛЕВАНИЯМИ ПЕЧЕНИ С СИНДРОМОМ ЭУТИРЕОИДНОЙ ПАТОЛОГИИ


**Резюме.** Изучена динамика показателей фибринолиза и клеточной адгезии у больных хроническими диффузными заболеваниями печени с синдромом эутиреоидной патологии на фоне использования селенсодержащего препарата. Установлено, что селен в комплексной терапии больных хроническими диффузными заболеваниями печени с нарушением тиреоидного гомеостаза способствует оптимизации показателей фибринолиза плазмы крови, позволяет существенно уменьшить адгезивные свойства клеток и повысить суммарную ферментативную активность плазмы крови.


**Ключевые слова:** хронические диффузные заболевания печени, тиреоидный гомеостаз, клеточная адгезия, фибринолиз, селен.