

Significance of Endothelial Dysfunction in the Development of HCV Etiology Chronic Hepatitis and Liver Cirrhosis

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Abstract The disruption of intragepatic hemodynamics is a key factor in the pathogenesis and progression of liver diseases, particularly liver cirrhosis and chronic hepatitis. This hemodynamic alteration leads to endothelial dysfunction, a condition that triggers the release of biologically active substances impacting the balance between pro-coagulant and anticoagulant factors. Such an imbalance contributes to a pro-thrombotic state in the liver, which exacerbates intrahepatic fibrosis, cellular apoptosis, and other degenerative changes, accelerating disease progression. This abstract explores the significance of endothelial dysfunction as both a cause and consequence in chronic liver disease, highlighting its role as a potential target for therapeutic intervention aimed at preventing or slowing the advance of cirrhosis. Addressing endothelial damage may thus offer new avenues for treatment strategies, improving outcomes for patients with chronic liver disease.

Keywords Liver cirrhosis, Hepatitis, Endothelial dysfunction, Endothelin-1, sICAM-1, Willebrand factor

1. Introduction

Endothelial cells of liver sinusoids not only act as a barrier between the sinusoids and the liver parenchyma, but are also actively involved in the inflammatory reaction, enhancing adhesion and antigen production, eliminating anti-inflammatory agents and producing inflammatory mediators [11].

At the same time, the effect of endothelium on aggregation is related to the production of prostacyclin and nitric oxide. The mechanism of action of prostacyclin and nitric oxide is the release of calcium ions from platelets, which reduces the aggregation function of platelets. The anticoagulant effect of the endothelium is related to the production of endogenous heparins, tissue thromboplastin inhibitor, tissue plasminogen activator, thrombomodulin, antithrombin III. Endothelial dysfunction predicts the pathogenesis of a number of diseases. Nowadays, the pathogenetic role of endothelial dysfunction is recognized and it is an important link in the development of cardiovascular diseases, diabetes, bronchial asthma, oncological diseases, intoxication, infections. The function of the vascular endothelium is important in treatment and prevention practices, which leads to the emergence of a new strategic concept of vascular medicine [9].

Endothelial cells are damaged under the influence of immune complexes, inflammatory mediators, and viruses. Coagulation factors of the hemostasis system are produced by endothelial cells and hepatocytes, which ensure the

interdependence of liver function and vascular endothelium. Endothelial dysfunction, which is the cause of many pathological processes, develops in liver diseases. Endothelial damage leads to the production of biologically active substances, which disrupts the balance between the synthesis of coagulation and anticoagulant factors. In endothelial dysfunction, the balance between production of vasodilation, angioprotective, prothrombotic and proliferative factors is disturbed [5].

Violation of the functional state of the endothelium leads to an increase in the cytolytic process in the liver. Von Willebrand factor, which is an indicator of the hemostasis system, increases in liver cirrhosis. Hollestelle M.J. study showed that the amount of Von Willebrand factor in the plasma increases by 10 times during the decompensation stage of liver cirrhosis. This number of platelets helps to compensate for their reduced adhesion function [3].

In patients with liver cirrhosis, binding of platelets to Willebrand factor is reduced by 50%, which increases the risk of hemorrhagic complications. [2]. Regardless of the etiology, the activity of Willebrand factor is much higher in chronic diffuse liver diseases [7].

Many factors of blood coagulation are synthesized by endothelial cells and hepatocytes, so the liver and endothelium have an effect on hemostasis. In chronic diffuse liver diseases, the spectrum of biologically active substances produced by the endothelium changes, which leads to an imbalance between the synthesis of prothrombotic and antithrombotic, dilatant and spastic factors. As a result, the synthesis of vasoconstrictors and procoagulants increases, which leads to vessel spasm. As a result of long-term exposure to a harmful

factor, the endothelium begins to cause a number of systemic pathological processes (inflammation, thrombosis, etc.) [1].

Death and fibrosis of the liver parenchyma in patients with cirrhosis of the liver combined with repeated thrombosis or hypercoagulation thrombotic complications (in the portal vein system, mesenteric veins, liver veins, veins of limbs, pulmonary embolism); causes the development of porto-pulmonary syndrome (lung endothelial dysfunction, microvascular thrombosis in the lungs). Thrombosis of the portal vein occurs in 0.6–26% of patients with liver cirrhosis. The prevalence of portal vein thrombosis increases with advancing liver disease [4].

Hypercoagulation associated with chronic liver disease can lead to liver parenchymal damage and death. In the last ten years, laboratory diagnostics of hemostasis and fibrinolysis system in chronic diffuse liver diseases have undergone significant changes. Standard complex tests for detection of hemostasis diseases lose their diagnostic value in this group of patients [10].

The problem of predicting hemorrhagic syndrome in liver cirrhosis with the help of modern laboratory tests remains open. There is no standard strategy for the treatment and prevention of hemorrhages in chronic diffuse liver disease. Randomized controlled trials are needed to evaluate laboratory tests in predicting bleeding or thrombosis in patients with cirrhosis.

2. Materials and Methods

Data were collected from patients treated with chronic hepatitis and cirrhosis of the liver in the departments of hematology and hepatobiliary pathology of the 1st clinic of the Tashkent Medical Academy in 2020-2023. Special attention was paid to the medical history of the disease, objective data and laboratory indicators.

Patients in the main group were divided into the following groups:

1. Main (first) group (n=20) – chronic hepatitis of HCV etiology without receiving antiviral therapy;
2. Main (second) group (n=30) – chronic hepatitis of HCV etiology receiving antiviral therapy of sofosbuvir and velpatasvir;
3. Main (third) group (n=20) - liver cirrhosis of HCV etiology without receiving antiviral therapy;
4. Main (forth) group (n=30) - antiviral therapy of Sofosbuvir and Velpatasvir patients with liver cirrhosis receiving therapy.

Immunoenzyme studies in Mindray BA96A (China) spectrophotometer, Shanghai Coon Koon Biotech Co. Ltd (China) was conducted using reagents.

The Immunoenzyme examination method aims to identify anti-platelet summar antibodies as well as endothelial dysfunction markers.

Method principle: nonconcurrent is a 2-step immunoenzyme analysis, in Step 1, platelet antibodies in the sample are combined with immobilized antigens at the bottom of the tablet luges. In Step 2, the color change of the combined antibodies is caused by the conjugate celebrated with peroxidase. Sequence of execution of the analysis. The desired strip and luges were separated from the tablet, and 30 minutes were left in the room layout. A washer solution was prepared that would be needed: distilled water was added to the washer liquid in the volume, which came in the instructions. A working conjugate was prepared: a solution liquefying the conjugate was added to the conjugate concentrate in volume which was brought in the instructions. A working substrate mixture was prepared: a substrate buffer was added to tetramethylbenzidine in the volume, which was brought in the instructions.

Standards, control solutions and samples were laid in the volume, which were brought to the microplate in the instructions. With extirpation, the luges were shaken, the top was closed with a tape and incubated at 37°C for 60 Minutes in a thermostat. After incubation, the tape was taken and washed 4-5 times with a washing solution. The filter was gutted with strip and luges on paper.

A 50-100 MCL stop-reagent was inserted into the microplate at the volume, which was brought to the instructions, and an optical density was measured within 15 minutes at 450 nm using a 2-Wave Spectrometer, and a reference-filter at 540-550 nm.

3. Results and Discussion

In chronic diffuse liver diseases of viral etiology, the progression of the disease is observed due to endothelial dysfunction and hemodynamic disturbances in the liver, and because of this, chronic hepatitis turns into liver cirrhosis. Endothelin-1 (ET-1), adhesion molecule (sICAM-1), Willebrand factor (vWf) were examined as laboratory markers of endothelial dysfunction. A change in these indicators causes an imbalance in the blood coagulation process, damage to the endothelium of blood vessels, various rashes on the skin, and progression of the disease. [6]. The results of examination of endothelial dysfunction in chronic diffuse liver diseases with HCV etiology are presented in Table 1.

As shown in Table 1, markers of endothelial dysfunction increased in chronic diffuse liver diseases, and the amount of Endothelin-1 was 2.7 ± 0.2 pg/ml* in group 1, 2.9 ± 0.2 pg in group 2 /ml*, increased to 4.4 ± 0.4 pg/ml*** in group 3 and 4.5 ± 0.4 pg/ml *** in group 4. The amount of Endothelin-1 in the control group was 2.2 ± 0.1 pg/ml.

At the same time, the study of the Willebrand factor in chronic diffuse liver diseases showed that its amount also increased. Willebrand factor was $90 \pm 8\%$ in the control group, $134 \pm 11\%$ in group 1**, $136 \pm 12\%$ in group 2**, $161 \pm 13\%$ in group 3*** and $164 \pm 12\%$ in group 4. increased to ***.

Table 1. Laboratory markers of endothelial dysfunction in chronic hepatitis and liver cirrhosis of HCV etiology

Groups	Willebrand factor, %	Endothelin-1, pg/ml	sICAM-1, ng/ml
Control group, n=20	90 ± 8	2,2 ± 0,1	5,6 ± 0,4
1 group, n=20	134 ± 11**	2,7 ± 0,2*	8,1 ± 0,6**
2 group, n=30	136 ± 12**	2,9 ± 0,2*	8,3 ± 0,7**
3-group, n=20	161 ± 13***	4,4 ± 0,4***	15,1 ± 0,14***
4-group, n=30	164 ± 12***	4,5 ± 0,4***	15,8 ± 0,13***

Note: * - reliable compared to control group indicators (* - p < 0,05, ** - p < 0,01, *** - p < 0,001).

Table 2. Laboratory markers of endothelial dysfunction in chronic hepatitis with HCV etiology

Groups	Willebrand factor, %	Endothelin-1,pg/ml	sICAM-1, ng/ml
Nazorat guruhi, n=20	90 ± 8	2,2 ± 0,1	5,6 ± 0,4
Group 2, n=30 Before treatment	136 ± 12**	2,9 ± 0,2*	8,3 ± 0,7**
Group 2, n=30 1 month AVT	116 ± 9*	2,6 ± 0,2	7,1 ± 0,6*
Group 2, n=30 3 month AVT	102 ± 8^	2,1 ± 0,2^	6,4 ± 0,5^

Note: * - reliable compared to the control group indicators (* - p < 0,05, ** - p < 0,01, *** - p < 0,001).

^ is reliable compared to the indicator before treatment (^ - p < 0,05, ^^ - p < 0,01, ^^ - p < 0,001).

Table 3. Laboratory markers of endothelial dysfunction in liver cirrhosis with HCV etiology

Groups	Willebrand factor, %	Endothelin-1,pg/ml	sICAM-1, ng/ml
Control group, n=20	90 ± 11	2,2 ± 0,3	5,6 ± 0,4
Group 4, n=30 Before treatment	164 ± 12***	4,5 ± 0,4***	15,8 ± 0,13***
Group 4, n=30 1 month AVT	159 ± 16***	3,7 ± 0,4**	13,5 ± 0,12***
Group 4, n=30 3 months AVT	132 ± 10***^	3,3 ± 0,3*^	10,2 ± 0,14***^

note: * - the difference is reliable compared to the indicators of the control group (*-p<0.05; **-p<0.01;

*** - p<0.001) ^ - reliable compared to the pre-treatment indicator (^ - p < 0,05, ^^ - p < 0,01, ^^ - p < 0,001).

The study of the laboratory marker sICAM-1 showed that in group 1 sICAM-1 was 8.1 ± 0.6 pg/ml**, while in group 2 it was 8.3 ± 0.7 pg/ml**, it was found that it increased sharply to 15.1 ± 0.14 pg/ml*** in group 3 and 15.8 ± 0.13 pg/ml*** in group 4.

In conclusion, this study showed that Willebrand factor, which is a marker of vascular endothelium dysfunction, increases by 44-46% in HCV etiology chronic hepatitis, 69-74% in HCV etiology liver cirrhosis, Endothelin-1 1,2-1,3 times in HCV etiology sg, HCV etiology 2 times increase in liver cirrhosis, sICAM-1 1.4-1.5 times increase in HCV etiology liver cirrhosis, 2.7-2.8 times increase in HCV etiology liver cirrhosis.

In chronic hepatitis of HCV etiology, vWF decreased against the background of AVT: before treatment, vWF was 136 ± 12%**, after 1 month of AVT it became 116 ± 9%*, and after 3 months of AVT it became 102 ± 8%^ (Table 2). ET-1 also improved on the background of AVT in chronic hepatitis of HCV etiology: ET-1 was 2.9 ± 0.2 pg/ml* before treatment, 2.6 ± 0.2 pg/ml after 1 month of AVT, 3 months from AVT and then it was 2.1 ± 0.2^. sICAM also decreased on the background of AVT in chronic hepatitis of HCV

etiology: 8.3 ± 0.7 ng/ml* before treatment, 7.1 ± 0.6 ng/ml* after 1 month of AVT, and 6, after 3 months of AVT. It was 4 ± 0.5 ng/ml.

In liver cirrhosis with HCV etiology, endothelial dysfunction markers also improved on the background of AVT: vWf 164 ± 12%*** before treatment, 159 ± 16%*** after 1 month of AVT, and 132 ± 10% after 3 months of AVT***^ was (Table 3).

Table 3 shows that ET-1 improved on the background of AVT in liver cirrhosis of HCV etiology: ET-1 before treatment was 4.5 ± 0.4 pg/ml***, and after 1 month of AVT it was 3.7 ± 0.4 pg/ml**, and after 3 months of AVT it was 3.3 ± 0.3 pg/ml*^.

sICAM also decreased on the background of AVT in liver cirrhosis of HCV etiology: 15.8 ± 0.13 ng/ml*** before treatment, 13.5 ± 0.12 ng/ml*** 1 month after AVT, 3 months And after AVT it was 10.2 ± 0.14 ng/ml***^.

Willebrand factor, Endothelin-1, sICAM-1, which are considered markers of vascular endothelium dysfunction, improved against the background of AVT in chronic hepatitis and liver cirrhosis of HCV etiology. From the above data, it became clear that there is dysfunction of the endothelium in chronic liver diseases of HCV etiology, which was especially

strongly manifested in liver cirrhosis of HCV etiology and improved against the background of AVT.

4. Conclusions

This study highlights the significant role of endothelial dysfunction in the progression of chronic liver diseases, particularly those of HCV etiology. Increased levels of endothelial dysfunction markers such as Willebrand factor, Endothelin-1, and sICAM-1 underscore the heightened risk of thrombotic and inflammatory responses, especially in advanced liver cirrhosis. These markers reflect a disrupted balance between pro-coagulant and anticoagulant factors, leading to vascular complications that exacerbate liver damage. The findings demonstrate that antiviral therapy (AVT) positively influences endothelial function, reducing the levels of these markers and suggesting an improved vascular environment. Given these outcomes, endothelial dysfunction should be regarded as a key therapeutic target for managing and potentially mitigating the progression of chronic liver disease. Future studies should continue exploring targeted therapies that address endothelial health to enhance the prognosis for patients with HCV-related liver diseases.

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