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ENDOTHELIUM DYSFUNCTION IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract

Aim: To assess endothelial dysfunction in patients with liver cirrhosis.
Material and methods: The study involved 95 patients with alcoholic liver cirrhosis. The data were subjected to analysis of variance involving the calculation of arithmetic mean value and variance (M±m), estimating the values validity according to Student's t-test and measuring Pearson correlation coefficient for binary variables.
Results: The brachial artery diameter was 0.4±0.02 mm narrower, with its blood velocity flow being 25.8±3.4 cm/s slower in the mean, in the patients with liver cirrhosis with signs of hepatic encephalopathy as compared to the control group. The maximum EDV values were recorded in the patients in Group I (7.5±1.9 %), while Group III patients displayed the lowest EDV value (5.6±1.9 %). The LC patients were found to exhibit a significant increase in the concentration of ET-1 up to 1.14±0.07 fmol/ml as opposed to 0.34±0.05 fmol/ml in the control group ($p<0.01$), an increase in the level of VWF by 139.4±24,8 % as compared to the control group ($p<0.01$) and D-dimer by a factor of 6.8.
Conclusions: The patients with liver cirrhosis were found to have endothelial damage, namely the dysfunction of the vasoregulating activity of vascular wall against the background of portal hypertension. Changes in the vasoactive BAS values are indicative of the damage to the vascular endothelium in LC patients with signs of HE. A steady and gradual increase or decrease in the levels of ET-1, VWF, AT III, and D-dimer may suggest the progressive character of ED in the LC patients.

Key words

liver cirrhosis,
endothelial dysfunction,
portal hypertension

INTRODUCTION

At present, vascular endothelium (ETH) and its functional status are attracting increasing scholars' attention. According to the present-day knowledge, ETH is an active endocrine organ that is dispersed throughout all the tissues, is the largest human body's organ and is capable of the continuous production of biologically active substances (BAS) rather than a simple semi-permeable membrane that lines the inside of blood vessels [1-3, 24].

There is scarce research on the issue, although its importance is apparent. The study into the particular aspects of the participation of vasodilatory (VD), angioprotective and vasoconstrictive (VC) agents may enable the objective assessment of the role these substances play in the physiological control of many system processes and analysis of their pathogenic role in the development of portal hypertension (PH) and its complications in patients with liver cirrhosis (LC) [4, 5]. Internal hepatic hemodynamic disorders affect LC pathogenesis and its progression, which may be attributed to the injury of endothelial lining of sinusoidal capillaries and endothelium dysfunction (ED). ED is primarily understood as an imbalance in the production of vasodilatory angioprotective, prothrombotic and proliferative agents [3, 6, 21-26].

THE AIM

The research paper aims to assess the endothelium dysfunction in patients with liver cirrhosis.

MATERIAL AND METHODS

The study involved 95 patients with LC who were admitted to the anesthesiology and intensive care unit, the surgery unit or the gastroenterological unit of A. Novak Transcarpathian Regional Clinical Hospital (Uzhhorod) during the period from 2018 to 2020. The study group comprised only the patients with alcohol-related liver cirrhosis. The exclusion criteria for the study were virus-related LC, primary biliary cirrhosis, liver cancer and Budd-Chiari syndrome.

The participants' ages ranged from 28 to 65 years, the mean age being 42.1 ± 6.8 years. The control group included 15 apparently healthy individuals aged 26-59 years, the mean age being 42.2 ± 3.4 years. The group was composed of 9 males (60.0 %) and 6 females (40.0 %). The patients with LC were allocated to the respective severity class of the disease according to the Child-Pugh classification. Group I (class A by Child-Pugh – well-compensated disease) included 18 (18.95 %) patients, Group II (class B – moderate disease with significant compromise) included 25 (26.3 %) patients, and Group III (class C – decompensated disease) was

composed of 52 (54.7 %) patients. The groups were homogenous with respect to the severity class of liver cirrhosis. The effects of gender and age on LC treatment outcomes were not taken into account. The presence of concurrent conditions and changes in other systems were assessed consistently in each group depending on the liver cirrhosis severity class.

In order to perform the clinical assessment of the endothelium function the standard technique developed by D. Celermajer was used. The endothelium-dependent vasodilation (EDV) of the brachial artery (BA) was studied using D. Celermajer method - the brachial artery was examined 3-10 cm above the crook of the arm. The examination was performed by scanning in the two-dimensional display mode while simultaneously recording an electrocardiogram (ECG); the arterial diameter was measured in the diastolic phase in the B-scan mode; the flow velocity changes were measured in the Doppler mode before and after the reactive hyperemia test. A 10% and over 10% increase in the BA diameter within 60-90 seconds in the presence of reactive hyperemia was considered to be a normal response. A lesser degree of the magnitude of dilation or vasoconstriction was evaluated as a pathological response. Ultrasound duplex scanning of the brachial artery was performed with an HDI-1500 device (USA) using a pulse-wave Doppler sensor 2.5 MHz and 5-10 MHz "Zonarae" (USA).

Within 15 minutes after the artery resumed its natural diameter the patient took 0,5 mg of nitroglycerin sublingually. In this procedure, nitroglycerin was used as an endothelium-independent (EIV) stimulus that causes the relaxation of peripheral vessels. The measurements were taken consecutively after 2 and 5 min following the nitroglycerin administration. It is generally accepted that the normal response of the brachial artery is its 10% and over 10% dilation in comparison with its original diameter in the presence of reactive hyperemia. A lesser degree of the magnitude of dilation or vasoconstriction was evaluated as a pathological response. Endothelium dysfunction was detected to be significantly less when the vessel dilated in response to reactive hyperemeia than when nitrates were administered.

The data collected at the patients' examination were analysed and processed using the software STATISTICA (StatSoft Inc, USA). The obtained results were subjected to the analysis of variance that involved calculating arithmetic mean value and variance (M±m), estimating the validity of values according to Student's t-test and measuring Pearson correlation coefficient for binary variables to find the relationships between the values obtained.

RESULTS

During the dopplerographic examination, the patients with LC with signs of hepatic encephalopathy (HE) exhibited a significant decrease in the BA diameter as compared to the control group. Hyperergic response to occlusion, i.e. the enlargement of the BA diameter, was also evaluated (Table 1).

The BA diameter was 0,4±0,02 mm narrower in the patients with LC with HE signs as compared to the control group at the beginning of the study. The patients with LC also exhibited less pronounced enlargement of the BA diameter in the 30th and the 60th second of the examination as compared to the control group.

The patients with LC showed the following results in the increase in the BA diameter in the 30th second of the examination: BA increased in the mean only by 0.57±0.02 mm as opposed to 0.98±0.01 mm in the control group. The same results for this value were registered in the 60th second of the examination, namely: BA in the LC patients increased in the mean only by 0.13±0.01 mm as opposed to 0.49±0.03 mm in the control group. The blood velocity flow in the BA was also in the mean 25.8±3.4 cm/s slower in the LC patients than in the control group. The groups of the patients with LC exhibited the same results when these values were measured (Table 2).

At the beginning of the study, among all the examined LC patients with HE, Group I patients exhibited the maximum BA diameter whose value was 4.11±0.12 mm as compared to 3.84±0.07 mm (the minimum value) displayed by Group II patients, $p<0.05$. Group I patients were also found to display the largest increase in the BA in the 30th second of the examination (4.86±0.04 mm), while the minimum enlargement of the BA diameter was recorded in Group III patients (4.41±0.08 mm), $p<0.05$. The same tendency was displayed in the 60th second of the examination. In particular, the maximum value was recorded in Group I patients (4.52±0.06 mm), whereas the minimum value was shown by Group III patients (3.99±0.17 mm), $p<0.05$. The blood flow velocity in the BA was also13.7±2.7 cm/s higher in Group I patients with LC than in Group III patients.

The changes experienced by the LC patients described above are indicative of the paradoxical vasoconstrictor response which is one of the manifestations of the endothelium dysfunction in this patient population.

The analysis of the results of the instrumental examination, namely the evaluation of endothelium-dependent vasodilation (EDV), is indicative of the presence of endothelium dysfunction in LC patients

with HE signs, which was exhibited by the decrease in this value as compared to the same value in the control group (8.2±0.2 % as opposed to 13.9±1.1% respectively).

Within 15 minutes after the artery resumed its natural diameter, the patients took 0,5 mg nitroglycerin sublingually, which acted as an endothelium-independent stimulus. The measurements were repeated 2 and 5 minutes after the patients taking nitroglycerin. When evaluating endothelium-independent vasodilation (EIV) in the LC patients, the respective value was found to decrease as compared to the control group (in the mean by 10.3±1.0%).

Hence, according to the results of the reactive hyperemia technique applied to evaluate EDV and EIV, the LC patients with HE signs exhibited pronounced signs of the endothelium dysfunction.

The further analysis of the findings showed that there was a dependence between the LC patients' functional classes by the Child-Pugh classification and EDV and EIV values (Table III).

The findings of the study indicate that there is a dependence between the ED values in the LC patients and the liver injury grade by Child-Pugh. The analysis of the ED value dynamics in the presence of the progression of hepatic impairment indicated the presence of stage-related changes, in particular, Class A patients with LC exhibited higher EDV and EIV values than LC patients belonging to Classes B and C.

The maximum EDV values were recorded in the LC patients in Group I (7.5±1.9%), while the LC patients belonging to Group III displayed the lowest EDV value (5.6±1.9%).

The analysis of EIV values yielded the same results as the EDV evaluation, in particular, the presence of the maximum values in Group I patients (16.2±4.4%) and minimum values in Group III patients (10.7±4.1%).

The performed examinations are indicative of the pronounced changes in ED in patients with LC at the subcompensation and decompensation stages. The specified regularity may be caused by the fact that the progression of liver damages affects the steady balance between the components of the vascular control. This fact is indicative of the involvement of the liver in the synthesis and deactivation of BAS with vasoactive properties. The ED pronouncement depends on the functional capacity of the liver. Conversely, ED promotes the faster progression of the complications in the presence of LC.

The further analysis of the data obtained in the study showed that there was a correlational dependence between EDV and EIV values and functioning hepatocyte mass according to the results of 13C methacetin breath test (13C-MBT). In all the cases, the comparison of functioning hepatocyte mass (FHM) with EDV and EIV values was indicative of the correlation. The correlation was found to be more pronounced between Class C patients with LC and the EDV values ($r=0,79$, $p<0,01$). According to the results of the analysis, the most pronounced correlation between FHM and EIV was recorded in Group II and Group III ($r= 0.97$; $p<0.01$ and $r= 0.90$; $p<0.01$ respectively).

All these changes are indicative of the lack of the functional capacity of the vessel wall in LC patients in the presence of the progression of the signs of portal hypertension. Hence, it has been proven that there are signs of the endothelium injury, in particular the impairment of the vasoregulating activity of the vessel wall in LC patients with portal hypertension.

The findings presented show that patients with LC at the subcompensation and decompensation stages of the disease (classes B and C by Child-Pugh) exhibit the most pronounced ED values. In addition, the findings suggest there is a dependence between functioning hepatocyte mass and the EDV and EIV values with the EDV and EIV values displaying the tendency to reduce when the number of hepatocytes decreases.

The endothelium has been found to regulate the vascular tone through the release of the vasoactive factors by means of which it modulates the contraction activity of smooth muscle cells.

The LC patients exhibited a significant increase in the concentration of ET-1 up to 1.14±0.07 fmol/ml as opposed to 0.34±0.05 fmol/ml in the control group ($p<0.01$), an increase in the level of VWF by 139.4±24.8% as compared to the control group ($p<0.01$) and D-dimer by a factor of 6.8. Additionally, the LC patients displayed a significant decrease in AT III by 32.0±0.2% as compared to the values recorded in the control group $p<0.05$ (Tables 3).

Table 4 shows the ED laboratory markers recorded in the patients with LC by the groups.

The analysis of the ED laboratory values depending on the severity class of LC by Child-Pugh yielded the same results as the evaluation of EDV and EIV according to Celermajer method. Class A patients with LC (Group I) exhibited the least pronounced changes in the levels of Et-1, VWF, AT III and D-dimer, while the maximum deviations from the normal values were recorded at the subcompensation and decompensation stages of the liver cirrhosis (Group II and Group III).

The concentration of vasoactive BAS in the blood serum increases due to disorders of their deactivation in the cirrhotically altered liver. The more pronounced liver injury is, the higher the values for ET-1, VWF

are, etc. The level of ET-1 and VWF strongly correlates with the severity of the liver injury depending on FHM in all the cases. When determining the correlations between AT III and the severity of cirrhosis in the examined patients, the dependence was found only in FHM class B ($r = 0.43$; $p < 0.05$), and in the analysis of D-dimer - only between FHM in patients of classes B and C ($r = 0.37$; $p < 0.05$ and $r = 0.50$; $p < 0.05$, respectively).

DISCUSSION

According to Poredos et al, normal endothelial function is achieved by maintaining the balance between vasodilation and vasoconstriction [5].

One of the endothelial key functions is balanced secretion of regulating substances that ensure the integrated manner of the operation of the cardiovascular system. These substances play a pivotal role in a human body by regulating the vascular tone (the secretion of vasoactive mediators), maintaining the anatomic structure of blood vessels (the synthesis and inhibition of proliferation factors), maintaining normal haemostasis (the synthesis and inhibition of fibrinolytic factors and platelet aggregation) and contributing to local inflammatory processes (the production of pro-inflammatory and anti-inflammatory agents) [12-16].

The findings of the present study are in line with the results reported by Volosovets et al. researchers such as Deng et al., Pasarin at al., Davies et al., etc. More specifically, long-term exposure to harmful factors (hypoxia, intoxication, inflammation, hemodynamic abnormalities, etc.) results in the gradual exhaustion and distortion of the compensatory dilating mechanism of the endothelium [17]. When this occurs, vasoconstriction and dilation are the most prevailing types of response of endothelial cells to usual stimuli [18-23, 25, 27].

The nature of the relationships between the function of the endothelium and surrounding tissues remains poorly studied. Endothelial dysfunction is currently viewed as an imbalance between mediators that ensure the optimal performance of all endothelium-dependent processes under normal conditions [12, 14, 17-21].

Endothelial dysfunction has proven to have a pathogenetic effect in a range of the most common diseases and pathological conditions, however, its role in chronic liver diseases is understudied. According to Bulatov at al. [13], the treatment of liver cirrhosis must involve lowering target levels of the values of liver function performance as well as the recovery of the functions of the endothelium, which is also reflected in the present study.

CONCLUSIUONS

1. Endothelial damage was found to be present in Group III LC patients, in particular, the patients were found to have disorder of the vasoregulating activity of the vascular wall against the background of portal hypertension, which is characterised by the correlation relationship between the reduction in FHM and EDV ($r=0,79$; $p<0.01$).
2. Changes in the values of the vasoactive BAS are indicative of the damage to the vascular endothelium in LC patients with signs of HE. A steady and gradual increase or decrease in the levels of ET-1, VWF, AT III, and D-dimer may suggest the progressive character of ED in the LC patients and can be used to predict the progression of the signs of hepatic encephalopathy.

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CONFLICT OF INTEREST

The Author declares no conflict of interest

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