ENDOTHELIN 1-21 SERUM LEVEL IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract: *Background: Endothelin plays a role in the pathology and severity of pulmonary hypertension which affects liver cirrhosis patients, but its importance in the context of other physiopathological modifications is not yet well defined.Objective: The assessment of the relationship between Endothelin 1-21 serum level and the presence and severity of pulmonary hypertension in patients with liver cirrhosis. Materials and methods: Between January 2007 and December 2008, 37 patients with liver cirrhosis (25 men), with an average age of 58.54 ± 9.01 years, diagnosed at Medicala III Clinic from Cluj-Napoca by liver enzymes, immunologic and viral markers, abdominal ultrasound, superior digestive endoscopy and/or liver biopsy, and a control group of 14 healthy subjects (4 men), with an average age of 59 ± 9.85 years were included in the study. The etiology of liver cirrhosis was hepatitis C for 29.73 % of the patients (11p) and alcohol for 45.94% (17p). Sixty seven percent of the patients were part of Child-Pugh class A (25p). The evaluation of pulmonary hypertension (PAH) was done using clinical examination, electrocardiogram and Doppler transthoracic echocardiography, performed in the Cardiology-Rehabilitation Clinic from Cluj-Napoca. A single parameter was assessed using Doppler transthoracic echocardiography – the systolic pressure in the pulmonary artery (PAPSs). PAPs value ≥ 30 mmHg was considered suggestive for the diagnosis of PAH. According to PAPs value, the patients were divided into 3 groups of pulmonary hypertension, as follows: mild PAH = 30 – 44 mmHg (14 patients); average PAH = 45 – 70 mmHg (12 patients); severe PAH > 70 mmHg (0 patients). Eleven patients did not have PAH (PAPs < 30 mmHg). The serum level of 1-21 endothelin (ET1-21) was measured for the all the patients in the cirrhosis and the control group, using the ELISA method (NV: 0.02 fmol/ml). For the statistical analysis, the t-Student test, χ^2 test and the Pearson correlation test were used. Results: In the liver cirrhosis group, the average values of ET1-21 were significantly higher than those in the healthy subjects group (1.90 ± 0.96 fmol/ml vs. 0.9 ± 0.07 fmol/ml, p<0.0001). The average serum values of ET1-21 were higher for the patients with liver cirrhosis and PAPs> 45 mmHg compared with those without pulmonary hypertension (2.02 ± 0.85 fmol/ml vs 1.92 ± 1.32 fmol/ml, p=0.41), but the difference was statistically significant (2.02 ± 0.85 fmol/ml vs 0.9±0.07 fmol/ml, p=0.0004) when compared to the values for the healthy subjects. In what concerns the severity of liver cirhhosis, the distribution of ET1-21 values was as follows: Child-Pugh class A 1.87 ± 0.87 fmol/ml, Child – Pugh class B 1.74 ± 0.26 fmol/ml, Child – Pugh class C 2.35 ± 1.89 fmol/ml. Conclusion: ET1-21 serum levels were significantly higher in patients with liver cirrhosis, the highest values being recorded in women. ET1-21 serum level was significantly higher in patients with liver cirrhosis and PAH compared to healthy subjects, supporting the role of the endothelin in the pathogenesis of PAH.*

Cuvinte cheie: *ciroză hepatică, hipertensiune arterială pulmonară, ecocardiografie transtoracică Doppler, ET1-21*

Rezumat: *Endotelina este incriminata in patogeneza si severitatea hipertensiunii pulmonare aparute la bolnavii cu ciroza hepatica, dar importanta sa in contextul altor modificari fiziopatologice nu este inca clar definita. Obiective: Studiul nivelului seric al endotelinei 1-21 in relatie cu prezenta si severitatea hipertensiunii pulmonare la bolnavii cu ciroza hepatica. Material şi metodă: În perioada ianuarie 2007 – decembrie 2008 s-au luat în studiu 37 pacienţi cu ciroză hepatică (25 bărbaţi), cu vârsta medie de 58,54±9,01 ani, diagnosticaţi la Clinica Medicală III Cluj - Napoca prin probe hepatice, imunologice, markeri virali, ecografie abdominală, endoscopie digestivă superioară şi/sau puncţie biopsie hepatică, şi un lot de 14 subiecţi sănătoşi (4 bărbaţi), cu vârsta medie 59±9.85 ani (martori). 29,73 % din pacienţii cu ciroză hepatică au avut etiologie virală C (11 p), 45,94 % etiologie etanolică (17 p). 67,56% din pacienţi au fost în clasa Child - Pugh A (25 p). Evaluarea hipertensiunii pulmonare (HAP) s-a făcut prin examen clinic, electrocardiografie, ecocardiografie transtoracică Doppler în Clinica de Cardiologie-Recuperare, Cluj-Napoca. Ecocardiografic s-a evaluat un singur parametru - presiunea sistolică în artera pulmonară (PAPs). Valoarea PAPs ≥ 30 mmHg a fost considerată sugestivă pentru diagnosticul de HAP. În funcţie de valoarea PAPs pacienţii au fost împărţiţi în trei grupe de hipertensiune pulmonară, după cum urmează: HAP uşoară = 30 – 44 mmHg (14 pacienţi); HAP medie = 45 – 70 mmHg (12 pacienţi); HAP severă > 70 mmHg (0 pacienţi).11 pacienţi nu au avut HAP (PAPs<30 mmHg). La toţi pacienţii şi subiecţii martori s-a determinat endotelina 1-21 serică (ET1-21),*

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utilizând metoda ELISA (VN: 0,02 fmol/ml). Pentru analiza statistică s-a folosit testul t-Student, testul χ^2 şi testul de corelaţie Pearson. Rezultate: La pacienţii cu ciroză hepatică valorile medii ale ET1-21 au fost semnificativ crescute faţă de cele ale lotului martor (1,90±0.96 fmol/ml vs 0,9±0,07 fmol/ml, p<0,0001). Valorile serice medii ale ET1-21 au fost mai mari în cazul pacienţilor cirotici cu PAPs > 45 mmHg faţă de cei fără hipertensiune pulmonară (2,02±0,85 fmol/ml vs 1,92±1,32 fmol/ml, p=0,41), dar comparativ cu subiectii sanatosi diferenta a fost semnificativa statistic (2,02±0,85 fmol/ml vs 0,9±0,07 fmol/ml, p=0,0004). În ceea ce priveşte severitatea cirozei hepatice, distribuţia valorilor ET-1-21 a fost următoarea: clasa Child-Pugh A 1,87±0,87 fmol/ml, clasa Child – Pugh B 1,74±0,26 fmol/ml, clasa Child – Pugh C 2,35±1,89 fmol/ml. Concluzie: Nivelele serice ale ET1-21 au fost semnificativ crescute la pacientii cu ciroza hepatica, valorile cele mai crescute inregistrandu-se la sexul feminin. De asemenea nivelul seric al ET1-21 a fost semnificativ mai mare la cei cu ciroza hepatica si HAP fata de subiectii sanatosi sustinand astfel rolul si interventia endotelinei in patogeneza HAP.

INTRODUCTION

Portopulmonary hypertension (PPH) is one of the complications described in liver cirrhosis patients, its pathology being insufficiently elucidated. Several studies showed that in liver cirrhosis, endothelin 1 (ET1) levels were increased, both by an augmented synthesis and by a reduced clearance (1,2,3), offering the premises for PAH development, and in the meantime, that ET1 levels are higher in patients with PPH, supporting its implication in the pathogenesis of PAH.

ET1 is the strongest vasoconstrictor in the endothelin family, having 3 isopeptides: ET1, ET2, ET3. Their precursor is represented by pre-pro-endothelin (pre-pro-ET1 – 203 aminoacids), which, under the action of certain endopeptidases, is transformed in big endothelin (big ET – 38 aminoacids), an inactive compound. Under the action of the endothelin conversion enzyme, big ET is transformed in ET1-21 (21 aminoacids), the mature form of endothelin. There are 2 types of endothelin receptors, ETA and ETB, which mediate the biological actions if ET1-21, more importantly vasoconstriction and cellular proliferation.

The purpose of this study was to evaluate ET1-21 serum level, the most powerful natural vasoconstrictor known to date, in relationship with the presence and the severity of PAH (echocardiographically determined) in patients with liver cirrhosis, due to the fact that this aspect was little studied in Romania.

MATERIAL AND METHOD

Between January 2007 and December 2008, 37 patients (25 men), with an average age of 58.54 ± 9.01 years, diagnosed at Medicala III Clinic from Cluj-Napoca with liver cirrhosis by clinical evaluation, liver enzymes – ALT, AST, γ-GT, alkaline phosphatase, total and direct bilirubin, protrombine time, total protein and albumin level; abdominal ultrasound, superior digestive endoscopy and/or liver biopsy. The etiology of liver cirrhosis was determined using viral markers: HbsAg, Anti HCV Ab, and immunological markers: ANA, AMA, SMA anti LKM. The severity of liver cirrhosis was evaluated using the Child-Pugh classification (Child class A = 5-6 points, Child Class B = 7-9 points, Child class C = 10-15 points).

A group of 14 healthy subjects (4 men) with an average age of 59 ± 9.85 years (47-73 years old) were also included in the study. Other possible causes of PAH were excluded from the study.

The evaluation of pulmonary hypertension was done using the clinical exam, electrocardiography, chest X-Ray, transthoracic echocardiography and Doppler ultrasound. The echocardiographic examinations were performed in the Cardiology-Rehabilitation Clinic from Cluj-Napoca, using an Esaote MyLab 50X Vision system, with a 3.5 MHz frequency transducer. For the diagnosis of pulmonary hypertension, the systolic pressure in the pulmonary artery (PAPs) was measured, quantifying the maximum velocity of the tricuspid regurgitation (VRT) in continuous Doppler mode, from the right ventricular inflow tract (RVIT) - modified parasternal long axis, parasternal short axis at the base of the great vessels, apical 4 chambers and subcostal incidences. The trans-tricuspid pressure gradient was calculated using Bernoulli's simplified equation, to which the right atrial pressure (PAD) was added, evaluated by the inspiratory collapse of the inferior vena cava from the subcostal view. PAPs value ≥ 30 mmHg was considered suggestive for the presence of PAH. According to PAPs value, the patients were divided into 3 groups of pulmonary hypertension, as follows: mild PAH = 30 – 44 mmHg (14 patients); average PAH = 45 – 70 mmHg (12 patients); severe PAH > 70 mmHg (0 patients). Eleven patients did not have PAH (PAPs < 30 mmHg). The serum level of 1-21 endothelin (ET1-21) was measured for the all the patients in the cirrhosis and the control group, using the ELISA method (NV: 0.02 fmol/ml). With the patients in a fasting state, 5 ml of blood was drawn, and after blood coagulation, the serum was separated by centrifugation at 3000G for 10 minutes. The serum was conserved at a temperature of -20°C.

In what concerns the etiology of liver cirrhosis, in 45.94% of the patients (17p) alcohol was incriminated and in 29.73% (11p) hepatitis C. Other causes were as follow: 2.7% (1p) hepatitis B, 8.1% (3p: viral B + alcohol - 2p, viral C + alcohol – 1p) mixed etiology, 2.7% (1p) primitive biliary cirrhosis (CBP), 2.7% (1p) autoimmune, 2.7% (1p) Wilson's disease and 5.4% (2p) cryptogenic origin. Hepatitis C virus-associated liver cirrhosis was more common in women (58.33% = 7p), while alcohol-associated liver cirrhoses was more common in men (64%=16p).

According to the severity of liver cirrhosis, evaluated by the Child-Pugh class, 67.56% of patients were in Child-Pugh class A (25p), 18.92% in Child-Pugh class B (7p) and 13.52p in Child-Pugh class C (6p).

For the statistical analysis, the t-Student test, χ^2 test and the Pearson correlation test were used. Data is presented as average ± standard deviation for continuous variables and percentage (%) for categorical variables.

RESULTS

ET1-21 serum level was significantly higher in the liver cirrhosis group compared to the healthy subjects group (1.90 ± 0.96 fmol/ml vs. 0.9 ± 0.07 fmol/ml, p<0.0001) (figure 1).

ET1-21 serum levels were also significantly higher in women with liver cirrhosis compared to men with liver cirrhoses. (2.5 ± 1.47 fmol/ml vs 1.6 ± 0.36 fmol/ml, p=0.03) (figure 2)

In patients with liver cirrhosis, a statistically significant inverse variation relationship between ET1-21 serum level and age was obtained (r=-0.02, p=0.0002) (figure 3).

The statistical analysis of the ET1-21 serum level according to the etiology of the liver cirrhosis did not show significant differences, but the highest ET1-21 serum levels

were obtained in the patients with primitive biliary cirrhosis and autoimmune cirrhosis (2.32 ± 0.79 fmol/ml).

In what concerns the severity of the liver disease, the patients with liver cirrhosis in Child-Pugh class A had an average ET1-21 serum level of 1,87±0,87 fmol/ml, those in Child – Pugh class B 1.74 ± 0.26 fmol/ml, and those in Child – Pugh class C 2.35 ± 1.89 fmol/ml, but these results were not statistically significant (p>0.05).

Figure no. 1. Comparison of ET1-21 serum levels in patients with liver cirrhosis vs. healthy subjects

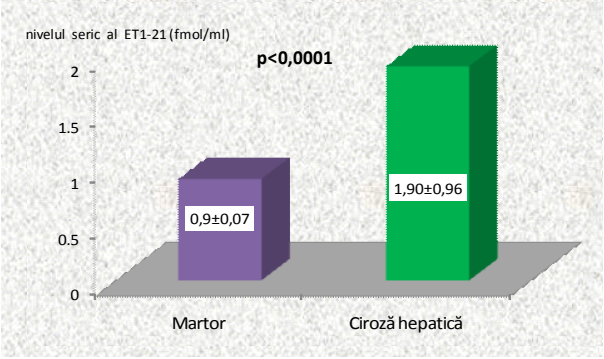


Figure no. 2. ET1-21 serum level sex distribution in patients with liver cirrhosis

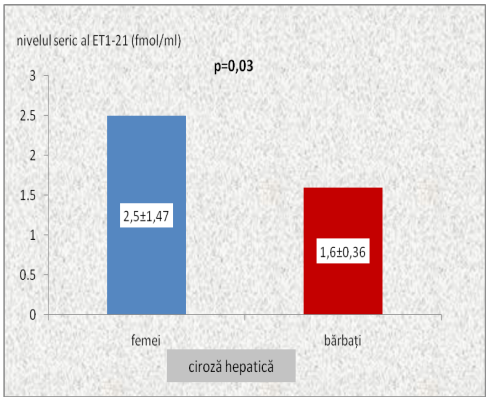
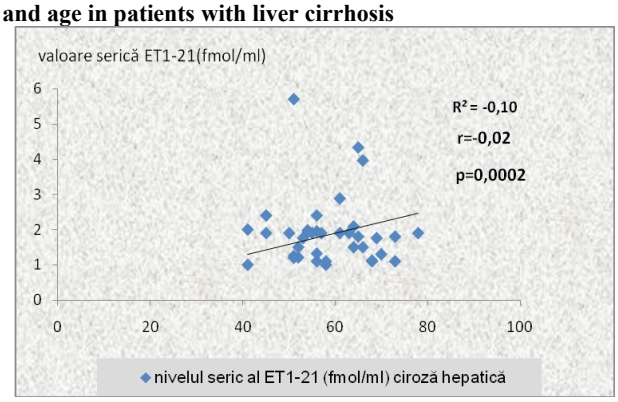


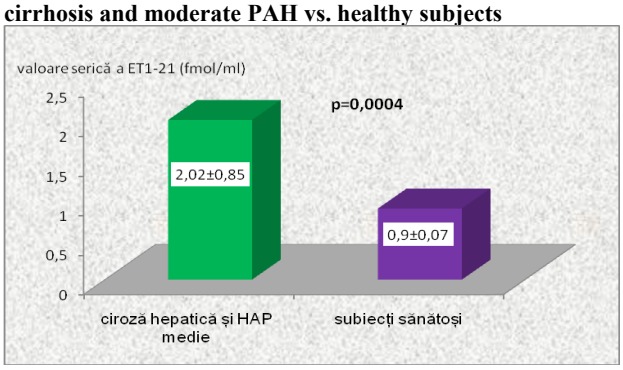
Figure no. 3. The relationship between ET1-21 serum level and age in patients with liver cirrhosis



According to the presence and the severity of PAH, higher serum values of ET1-21 were obtained in patients with moderate PAH compared to patients without PAH (2.02 ± 0.85 fmol/ml vs 1.92 ± 1.32 fmol/ml, p=0.41), with no statistical significance, but the difference was statistically significant when these data were compared to the healthy subjects group (2.02 ± 0.85 fmol/ml vs 0.9 ± 0.07 fmol/ml, p=0.0004) (figure 4).

From the 37 patients enroled in the study, 32.43% had echocardiographically diagnosed ascites (12p). These patients had a higher average ET1-21 serum level compared to those without ascites, but the data had no statistic significance (1.98 ± 1.21 fmol/ml vs. 1.86 ± 0.84 fmol/ml, p=0.38).

Figure no. 4. ET1-21 serum values in patients with liver cirrhosis and moderate PAH vs. healthy subjects



DISCUSSION

ET1 is a vasoactive peptide derived from the endothelia that plays a key role in the modulation of the vasomotor tone in healthy individuals, but with multiple other important roles in pathology, such as the stimulation of cell growth and fibrogenesis (8,9). In the last decade, a great intereset was accorded to the role of ET1 in the pathogenesis of liver cirrhoses. In patients with liver cirrhoses, the serum level of ET1 is increased, espiecially in those patients with advanced liver disease (1,2,3), and apparently the level increases with the severity of the liver function alteration, evaluated by the Child-Pugh score (3,10).

The patients usually have a hyperdinamic circulation, characterised by low arterial blood pressure, high cardiac output and low peripheral vascular resistance (11,12,13). Therefore, it has been suggested that in advanced liver cirrhoses, the peripheral arterial vasodilation with secondary neurohumoral activation represents the major stimulus for the synthesis of ET1 (14). But it has also been proved that the administration of isotonic saline solutions or iv albumine, which determines a rise in plasma volume, reduces the activity of plasma renin and aldosterone while the level of ET1 does not change, which contradicts the theory according to which arterial vasodilation influences the synthesis of ET1 (15).

The hepato-splanchnic circulation represents the major source for the increased secretion of ET1 (3,16,17,18). While in healthy subjects the most part of ET1 is synthetised at the level of vasculat endothelia, in the cirrhotic liver ET1 is produced by the activated hepatic stellate cells (18). Pinzani and co. demonstrated that mRNA ET1 and the expression of the protein in the liver are increased (17).

Experimental studies have showed that the endothelin contributes to the modulation of the intrahepatic vascular tone in cirrhosis. Also, it was showed that the alterated response to ET1 can contribute to the modifications in the systemic and mesenteric circulation (19). Despite the elevated circulating level of ET, of vasopressin, of the activation of the renin-angiotensin system and of the central nervous system, the systemic and mesenteric vascular tone are decreased in patients with advanced liver disease, the degree of activation of vasoconstrictor response being higher in those in which vasodilation is predominant (20). Therefore, it is sugested that the vascular response to these endogenous vasoconstrictors is altered.

For patients with liver cirrhosis who have associated pulmonary hypertension, the studies have showed that the endothelines system is overexpressed (21,22), and ET1 is

substantially involved in the pulmonary vasomotor tonus changes and in the pulmonary vascular remodeling. The precise sequence of events is less well understood. Initially, the increased levels of ET1 in the pulmonary circulation, resulted form the hepato-splanchnic circulation and from the local synthesis due to parietal stress, induce pulmonary vasocontriction and proliferation of smooth muscle cells. Subsequently, the vascular stretching resulted from the elevated pressure in the pulmonary artery determines supplementary structural adaptative responses, which leads to vascular obliteration (23).

But because only a little proportion of the patients with liver cirrhosis develop pulmonary hypertension, this suggests the involvement of aditional factors and/or genetic factors in this condition. This concept also explains why only a part of the patients with liver cirrhosis develop moderate PAH, while others develop a rapid progression of the disease (23).

In the present study the serum ET1 levels were two times higher in the patients with liver cirrhosis compared to healthy individuals, the difference being statistically significant, which allows us to say that ET1-21 is a marker of liver cirrhosis. We also observed that in the patients with liver cirrhosis, the serum levels of ET1-21 are influenced by sex (significantly higher serum levels for women, p=0.03) and by age (with an inverse variation existing between age and ET1-21 levels). The data from the existing literature are contradictory in this aspect.

The etiology does not seem to influence the serum level of ET1-21, although the hghest values of ET1-21 were seen in patients with primitive biliary cirrhosis, autoimmune cirrhosis and PAH, but which were not statistically significant. These results would suggest that women are more predisposed to developing PAH, because they have elevated serum levels of ET1-21, and are in concordance with the results published by Kawut and co., who found women to be at a greater risk of developing PAH and autoimmune hepatitis (24).

Even though in the present study the differences between the patients with liver cirrhosis without PAH who had an elevated serum level of ET1-21 and the patients who had already developed PAH were not statistically significant, the difference between the patients with PAH and healthy subjects strongly indicate the endothelin's role and implication in the pathogenesis of PAH. These results can probably be explained by the absence of patients with severe PAH in the present study and by the small number of patients included. It is also known that in patients with PAH, 40% of ET1-21 is eliminated by the lungs via ET-B receptors, which explains the short half-life and the reduced serum level and, on the other hand, that the level of ET1-21 is sensible to physiological and pathological fators such as clino- and orthostatism, venous stasis, systemic atrerial hypertension. In the patients with mild PAH the serum level of the endothelin were lower than in those without PAH, which suggests the contribution of the hyperdynamic circulation and the elevated plasma volume in this stage of the disease.

It is also known that the patients with liver cirrhosis with refractory ascites (defined by ascites which does not responde to maximal diuretic treatment: 160 mg of Furosemide + 400 mg of Spironolactone daily, for two weeks) have elevated plasma ET1 levels, because these patients have a more pronunced hyperdinamic circulation (25). In our study, only 32.43% of the patients with liver cirrhosis had ascites. And even though the patients with ascites had higher ET1-21 levels compared to those without ascites, the statistical analysis did not show significant differences (p=0.38). The patients in the present study had small/medium quantity ascites, easily influenced by diuretic treatment, and, on the other hand, there was no patient with liver cirrhosis and refractory ascites. These results can also be influenced by the fact that the analysis of the relationship between the high levels of ET1-21 and ascites was performed on a small number of cases and that it ws not quantitatively evaluated. In the present study we did not evaluate the relationship between the presence of ascites, diuretic treatment and ET1-21 serum level.

Limits of the study: The absence of severe PAH; the small number of Child-Pugh class C cases; the low number of patients with ascites (no cases of refractory ascites); The PAH was not confirmed by catheterisation; the imposibility of long-term follow-up.

In conclusion, ET1-21 serum levels are significantly higher in patients with liver cirrhosis, the highest values being recorded in women. ET1-21 serum level is significanlty higher in patients with liver cirrhosis and PAH compared to healthy individuals, supporting the role of endothelin in the pathogenesis of PAH.

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