RENAL IMPAIRMENT IN LIVER FAILURE – PATHOPHYSIOLOGICAL, CLINICAL AND IMAGISTIC ASPECTS

DEPRECIEREA FUNCȚIEI RENALE ÎN AFECTAREA – ASPECTE PATOFIZIOLOGICE, CLINCIE ȘI DE TRATAMENT

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Rezumat

În lucrare sunt descrise aspectele actuale ale depistării precoce a insuficienței renale la pacienții cu ciroză hepatică. Mecanismele care influențează apariția complicațiilor renale la pacienții cu ciroză hepatică rămân incerte, cu influențe nefavorabile în evoluția bolii hepatice. Sunt necesari noi markeri biologici pentru diagnosticarea leziunilor tubulare la pacienții cu ciroză hepatică. În mai multe studii este demonstrată utilitatea aprecierii precoce a enzimelor urinare pentru pronosticul severității și evoluției clinice a insuficienței renale la pacienții cu ciroză hepatică. La mai mulți pacienți cu ciroză hepatică a fost documentată prezența vasoconstricției renale în baza creșterii indicelui de rezistență(IR) . Afectarea funcției renale s-a produs la circa 55% pacienți cu IR crescut și la 6% pacienți cu IR normal. Sindromul hepatorenal s-a dezvoltat la 26% pacienți cu IR crecsut și la 1% pacienți cu IR normal.

Summary

Actual aspects in early detection of renal impairment in liver cirrhosis. The mechanisms that influence renal complications in patients with liver cirrhosis remain incompletely understood, causing unfavorable prognosis of liver disease. Recently, novel biomarkers for diagnosing tubular damage in patients with liver cirrhosis and HRS are in quest. Several studies have demonstrated the utility of early measurement of urinary enzymes for predicting the severity and clinical outcomes of renal impairment in liver cirrhosis. Renal vasoconstriction has been documented in several groups of cirrhotic patients on the base of increased resistive index (RI). Renal dysfunction developed in 55% of patients with an elevated RI at baseline, including 6% of patients with a normal RI. HRS developed in 26% of patients with elevated baseline RI and in 1% of patients with normal baseline RI.

Introduction

The kidney has a numerous group of enzymes located primarily in the nephron. Low concentrations of enzymes are normally found in urine as a result of pinocytosis in epithelial cells of the proximal tubules. Increased cell membrane permeability causes excessive amount of enzymes in urine, which in turn determines the extent and location of damage in the glomerular and tubular segments of the nephron. Although in human urine were detected around 50 enzymes, several of them are used for diagnostic purposes. Urinary lysosomal hydrolytic enzyme- N-acetyl-β-glicosaminidaza (NAG) is released by lysosomes from the cytoplasm of epithelial cells in the renal proximal convoluted tubules. Gamma-glutamyltransferase, (GTP), alkaline phosphatase (ALF) are released by lysosomes from the cytoplasm of epithelial cells in the renal proximal tubule, too, and demonstrates a high activity in certain clinical states, being eliminated in tubular fluid. Alpha-glucosidase (AGL) is another enzyme is localized in the cytoplasm of epithelial cells of the brush border membrane of renal proximal tubule cells and its excessive secretion in urine was reported. Similarly, increased number of cytoplasmic enzymes - lactate dehydrogenase and glutamate dehydrogenase, synthesized in mitochondria determine renal tubular epithelial cell cytolysis. The presence of high molecular weight enzyme – pseudocholinesterase (PCE) in urine (it is absent in the urine of healthy subjects) indicates a decrease in selectivity and increased permeability of the glomerular basement membrane of the kydney. Undoubtedly, an excessive amount of enzymes in urine is determined by impaired renal cell membranes and an intense enzymatic activity in certain clinical states. Multiple studies relate to the determination of urinary enzymes, especially NAG as an indicator of early renal tubular injury in hypertensive patients, in diabetic nephropathy, chronic pyelonephritis, as markers of nephrotoxic drugs, etc. Determination of urinary enzymes in patients with liver cirrhosis as a diagnostic tool in the control of renal impairment was studied over the years. Gatta A., Amodio P et al. observed an increased activity of enzyme GTP, alpha-glucosidase and beta-2-microglobulin from tubular cells in 93 patients with liver cirrhosis, particularly in those with a significant reduction of GFR. Solis-Herruzo J. et al. assessed the importance of urinary enzymes as markers of early renal impact in 32 patients with LC, 12 of them with HRS, concluding that high values of GTP, alkaline phosphatase, beta-galactosidase suggest that they have a high risk of developing renal complications and have a low life expectancy. Amakasu H. et al. studied enzyme activity of N-acetyl-beta-glucosaminidase in patients with liver cirrhosis. The enzyme output of 32 patients was compared and urinary NAG values were higher in patients with liver cirrhosis Child-Pugh class C than in patients with Child-Pugh class A and class B, especially in 8 patients with ARI. In 1994 the further studies of Bruno C. et al. suggested that the highest average enzymuria occured in decompensated cirrhosis as compared with the control group ($p < 0.01$).

Some urinary enzymes (NAG, lysozyme) considered to be sufficiently sensitive and reliable markers of renal tubular damage were controlled in 20 patients with cirrhosis of the liver and in 20 healthy control subjects. The results, stated as mean +/- SD, showed a statistically very significant increase ($p < 0.01$)

of NAG and lysozyme in cirrhotics.

A number of imposing recent studies concluded that some urinary enzymes are sufficiently sensitive and reliable markers of renal damage in patients with LC. An impressive study that was carried out by Liang A et al. Assessed the activity of urinary NAG in 201 hospitalized patients with prerenal ARF genesis. The presence of elevated NAG in the early stages of the ARF, including 42% of patients with liver cirrhosis was established. Furthermore, this increase of NAG could be at least in part related with the severity of clinical condition. Based on these results, we concluded that in subjects with liver cirrhosis the urinary dosage of NAG and lysozyme is a bloodless method to show an early renal damage. Recently Lisowska-Myjak B has classified acute kidney injury markers into several groups: enzymes of tubular nephrotelium - FTA, GTP, alanine aminopeptidase, glutathione transferase isoenzyme, NAG, enzymes with small molecular weight- alpha-1-microglobulin, beta-2 microglobulin, neutrophil gelatinase-associated lipocalin (NGAL), cytokines and chemokine (growth-regulated protein alpha, IL-18) and renal tubular structural proteins- F-Actin, Na+/H+-exchanger izoform 3 protein. In summary, this results show, that the analysis of urinary enzyme patterns may be a helpful adjunct for differential diagnosis of ARI in liver cirrhosis.

Doppler ultrasound provides one of the most successful images of renal arteries, its sensitivity is 85% as compared with CT angiography of renal arteries (95%) and magnetic resonance angiography (90%). A high finesse diagnostic classification was possible due to duplex and color coding particular installation, which allowed a more accurate interpretation of ultrasound morphology. HRS occurred in 26% of those with an elevated resistive index, as compared with only 1% of those with normal values. In cirrhotic patients with renal failure, the resistive index correlates with the glomerular filtration rate, arterial pressure, plasma renin activity and free water clearance and has a sensitivity rate and specificity rate for the detection of renal failure of 71% and 80%, respectively. The RI may be regarded as a barometer of the intrarenal vascular tone and this is elevated in HRS due to increased vasoconstrictor activity.

The deviations of renal Doppler US parameters were also related in patients with liver cirrhosis, as well as deviations in serum urea and creatinine levels. The resistive index increases progressively from normal values in control patients (0.53) to higher values in cirrhotic patients with ascites, renal Doppler US parameters correlate with the severity and complications of liver cirrhosis.

Götzberger M. et al. performed Renal Duplex Doppler Ultrasonography in 81 cirrhotic patients and 75 healthy subjects. They found significantly higher values of RI in patients with ascites compared with those without ascites - RI (0.74 vs. 0.67, p <0.01) and those without ascites as compared with the control group (RI 0.67 vs. 0.62, p <0.01). As a result, in 48% of patients with decompensated liver cirrhosis and normal values of serum creatinine renal RI was increased more than 0.70. Fouad Y. study presented similar occurrence of high values of RI and pulsatility index (PI) in 60 patients with Child-Pugh class C, especially in patients with refractory ascites and 15 patients with HRS.

Methods and materials

In our study we evaluated 114 patients with liver cirrhosis (including 24 patients with HRS) according to the degree of liver disease. Enzyme activities were assayed in three hour morning samples after gel filtration of urine in 23 cirrhotic patients with HRS. Activities were related to time volume, and to urinary creatinine concentration. Abdominal ultrasound (US) and renal Doppler US, were made and interpreted by the same investigator according to standard protocol. Intrarenal arteries, segmental branch were evaluated by Color Doppler US. The mean values of the parameters for each kidney were obtained from the measurement of the waveforms of both, right and left renal areas. We evaluated the following intrarenal blood flow Doppler parameters (m/sec): RA peak systolic velocity (RA-PSV), RA minimal end diastolic velocity (RA-EDV), RA mean velocity (RA-MnV), RA resistance index (RA-RI = RA-PSV – RA-EDV/RA-PSV) and RA pulsatility index (RA-PI = RA-PSV – RA-EDV/RA-MnV). One single experienced operator was used.

Results and discussions

Patients with HRS type II had a significantly higher excretion of alkaline phosphatase and GTP ($p<0.05$) as compared with HRS type I and as compared with patients with Child-Pugh A score ($p<0,01$), ($p<0,001$). N-acetyl-beta-glucosaminidase, AGL , PCE enzyme activity ware significantly higher in type I and type II HRS as compared with with patients with Child-Pugh A score. ($p <0,01$) (Table.1).

Table 1

Urinary enzyme activity in patients with acute renal failure- HRS Type I and II

Values	HRS type I	HRS type II	Child –Pugh A cass	$p_{1,2}$	$p_{1,3}$	$p_{2,3}$
	$M_1 \pm m_1$	$M_2 \pm m_2$	$M_3 \pm m_3$			
Urinary FTA (nmol/s mmol creat)	1513,82±276,89	2640,22±489,44	307,21,0±21,41	**	***	***
Urinary γ-GTP (nmol/s mmol creat)	1264,52±88,17	1199,01±90,46	266,7 ± 29,87	**	****	****
Urinary NAG (pmol/s mmol creat)	11,74±1,85	15,27±1,35	1,15±0,20	*	****	****
Urinary PCE (nmol/s mmol creat)	7,66±1,36	5,76 ± 0,95	0,66±0,06	*	****	****
Urinary AGN (pmol/s mmol creat)	123,25±6,62	149,11± 16,37	36,94±2,71	*	****	****

Note: * p>0,05 ** p<0,05 *** p<0,01 **** p<0,001

We evaluated the following intrarenal blood flow Doppler parameters (m/sec): RA peak systolic velocity (RA-PSV), RA minimal end diastolic velocity (RA-EDV), RA mean velocity (RA-MnV), RA resistance index (RA-RI = RA-PSV – RA-EDV/RA-PSV), and RA pulsatility index (RA-PI = RA-PSV – RA-EDV/RA-MnV). All intrarenal blood flow Doppler parameters except right and left RA peak systolic velocity showed significant differences between Child-Pugh class A, B, and C. In addition, we also found a significant relationship between Child's score and right and left RA minimal end diastolic velocity, right and left RA resistance and RA pulsatility indices.

The deviations of renal Doppler US parameters were also related with the complications of liver cirrhosis, as well as serum urea and creatinine levels. Resistive index and pulsatility index

were significantly elevated in group of cirrhotics with Child -Pugh class B ($p < 0.05$) and Child -Pugh class C ($p < 0.001$) as compared with healthy subjects and Child-Pugh class A ($p < 0.001$), (Figure 11,12).

Our results show, renal Doppler US parameters correlate with the severity and complications of liver cirrhosis. The resistive index increases progressively from normal values in control patients (0.63) to higher values in non-ascitic cirrhotic patients (0.72) and those with ascites. Compared with those with Child--Pugh class A, values of RI are also higher in Child--Pugh class B and C cirrhotic patients. Therefore, abnormal values may help identify high-risk patients.

In our study all intrarenal blood flow Doppler parameters except RA peak systolic velocity show a significant association with the severity of liver cirrhosis, evaluated by Child's scores. Most of these parameters also correlate with the presence of esophageal varices and ascites, as well as with the severity of liver cirrhosis.

Conclusions

In summary, these results show, that the analysis of urinary enzyme patterns may be a helpful adjunct for differential diagnosis of different types of ARI in liver cirrhosis.

Renal Doppler US parameters correlate with the severity and complications of liver cirrhosis. Doppler US of renal artery as a part of follow up of these patients because of dynamic deviations of renal Doppler US parameters during the evolution of liver cirrhosis. The RI may be regarded as a barometer of the intrarenal vascular tone and this is elevated in decompensated liver cirrhosis and HRS due to increased vasoconstrictor activity.

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