ORIGINAL ARTICLE

Diagnostic value of plasma asymmetric and symmetric dimethylarginine levels in liver transplant recipients

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KEY WORDS

asymmetric dimethylarginine, liver cirrhosis, liver failure, liver transplantation, symmetric dimethylarginine

ABSTRACT

INTRODUCTION Nitric oxide is an important factor in the pathogenesis of liver cirrhosis. Its synthesis depends on the availability of L-arginine and is inhibited by asymmetric dimethylarginine (ADMA). Symmetric dimethylarginine (SDMA) seems to be a good marker of multiorgan failure, especially renal failure.

OBJECTIVES The aim of the present study was to evaluate the diagnostic significance of dimethylarginines in patients after liver transplantation.

PATIENTS AND METHODS The study included 30 cadaver liver donors and 30 recipients with liver cirrhosis. The following parameters were estimated in donors and in liver recipients before and at days 1 and 3 after transplantation: serum alanine transaminase (ALT), aspartate transaminase (AST), and γ-glutamyltranspeptidase (GGT) activity, international normalized ratio (INR), concentrations of bilirubin, albumin, creatinine, electrolytes, ADMA, SDMA, and L-arginine.

RESULTS Before transplantation cirrhotic patients showed higher bilirubin concentrations, higher ALT and GGT activity, and lower sodium and albumin levels compared with donors. At day 3 after transplantation, we observed a significant increase in ALT, AST, creatinine, sodium, ADMA, SDMA, and L-arginine, and a decrease in bilirubin levels. A significant positive correlation between SDMA and creatinine was found in donors ($P < 0.001$), recipients before transplantation ($P < 0.0005$), and at days 1 ($P < 0.004$) and 2 after transplantation ($P < 0.0005$). A significant positive correlation was also observed before transplantation between ADMA and bilirubin concentrations ($P = 0.0264$), ADMA and albumin concentrations at day 1 after transplantation ($P = 0.02$), while a negative correlation was observed between ADMA and INR before transplantation ($P = 0.008$) and at day 3 after transplantation ($P = 0.03$) in recipients.

CONCLUSIONS An increase in dimethylarginine levels after liver transplantation seems to be due not only to the dysfunction of the transplanted liver, but also to impaired kidney function caused by the surgery itself and/or the use of a nephrotoxic calcineurin inhibitor – tacrolimus. A significant correlation between serum creatinine and SDMA concentrations both in liver donors and recipients suggests that SDMA renal clearance may have diagnostic value to evaluate the glomerular filtration rate in these patients.

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INTRODUCTION Since 1983, liver transplantation has been recognized as a legitimate treatment for end-stage liver failure.[1] Immediately after liver transplantation, the patient requires intensive care, i.e., treatment of respiratory, circulatory, and renal dysfunction and monitoring of graft function. Indirect graft function biomarkers include assessment of the serum activity of alanine (ALT) and aspartate (AST) transaminases, γ-glutamyltranspeptidase (GGT), and alkaline phosphatase, serum concentrations of bilirubin, protein, and electrolytes, coagulation parameters, and clinical symptoms of liver dysfunction (jaundice, ascites, and encephalopathy).[2] Asymmetric dimethylarginine (ADMA) is an inhibitor of nitric oxide (NO) synthase (NOS).[3] Three

types of endogenous methylated arginines are known, including ADMA, symmetric dimethylarginine (SDMA), and N-monomethylarginine (NMA). NMA is a weaker NOS inhibitor than ADMA, and its plasma levels are 10-fold lower.[4]

Plasma SDMA and ADMA levels are almost equal,[5] but SDMA does not influence the synthesis of NO.[6] Normal plasma levels of ADMA, SDMA and L-arginine are 0.36–1.17 μmol/l,[7] 0.46–0.54 μmol/l,[8] and 40–100 μmol/l, respectively.[9]

ADMA deteriorates vascular flow, enhances atherosclerosis, and inhibits angiogenesis.[10] Elevated ADMA levels are observed in patients with kidney impairment,[4] arterial hypertension, hypercholesterolemia, diabetes mellitus, ischemic heart disease, pregnancy-induced hypertension,[8] atherosclerosis,[10] heart failure,[11] primary pulmonary hypertension,[12] arteriosclerosis obliterans,[13] portal hypertension,[14] hypopituitarism,[15] subarachnoid hemorrhage,[16] and systemic inflammatory response syndrome.[17]

In some clinical entities, such as Alzheimer's disease, septic shock, and neoplastic angiogenesis, NO seems to be a pathogenetic factor. Thus, ADMA appears to be beneficial in the therapy of these pathological conditions.[18] The synthesis of ADMA is dependent on L-arginine methylation and on protein transformation rate.[9] More than 90% of ADMA and NMA is decomposed by hepatic dimethylarginine dimethylaminohydrolase (DDAH).[19] Methylarginines bind to proteins and therefore are poorly eliminated by hemodialysis. Contrary to ADMA, SDMA is excreted into urine and is easily eliminated by hemodialysis, but is not metabolized by DDAH.[5]

Because reperfusion of the transplanted liver is a factor potentially injuring vascular endothelium (the main site of NOS activity), an alteration in the relationship between NO, ADMA, and L-arginine may be expected. These observations have provided the pathophysiological background of the current study, which aimed to answer the following questions: Do patients with end-stage liver failure have different levels of ADMA, SDMA, and L-arginine from liver donors? Is estimation of ADMA, SDMA, and L-arginine of diagnostic value in patients after liver transplantation?

TABLE 1 Causes of liver failure in recipients

Cause of liver failure	Number of patients
alcohol-induced liver cirrhosis	9
liver cirrhosis associated with HCV infection	7
liver cirrhosis associated with HCC and HCV infection	4
primary biliary cirrhosis	3
autoimmune hepatitis	2
cryptogenic liver cirrhosis	2
liver cirrhosis associated with HBV infections	1
liver cirrhosis associated with HCC and HBV infection	1
primary sclerosing cholangitis	1

Abbreviations: HBV – hepatitis B virus, HCC – hepatocellular carcinoma, HCV – hepatitis C virus

PATIENTS AND METHODS We studied 30 cadaver organ donors (14 women, 16 men; mean age, 37.5 years; range, 16–63 years) and 30 liver recipients (10 women, 20 men; mean age, 49.6 years; range, 31–62 years) who underwent liver transplantation between 6 May 2008 and 8 November 2009, in the Department of General, Vascular and Transplant Surgery in Katowice, Medical University of Silesia, Poland. The study was approved by the local Bioethics Committee. Patients characteristics are shown in TABLE 1.

Among recipients, 1 died at day 1 and 2 others at day 3 after transplantation. Thus, day 1 and day 3 data were assessed for 29 and 27 patients, respectively.

Only 1 recipient suffered from diabetes. Creatinine levels of donors and recipients are shown in FIGURE 1.

In recipients, 3 blood samples were taken: before surgery (day 0) and at days 1 and 3 after liver transplantation. L-arginine, ADMA, and SDMA levels were measured in EDTA plasma. We also estimated (by routine methods) plasma activity of ALT, AST, and GGT and the levels of albumin, bilirubin, creatinine, electrolytes, and coagulation parameters (international normalized ratio – INR). In donors, a blood sample was taken before organ donation and the levels of the above parameters were also assessed.

ADMA, SDMA, and L-arginine levels were measured by high-performance liquid chromatography with fluorescent detection.[7,20,21] The measurements were performed in the Laboratory of the Department of Internal and Occupational Diseases and Arterial Hypertension of the Medical University of Wroclaw, Wrocław, Poland.

The results were presented as mean values and standard deviations. The data were then compared between the following groups: donors, recipients at day 0, day 1, and day 3 after transplantation. The results were analyzed using PC SSTAT v. 4.0 – Pearson correlation coefficient *r* statistics. Statistical significance was set at a *P* value less than 0.05.

RESULTS The mean values and standard deviation are shown in TABLE 2 and significant correlations in TABLE 3.

Mean ALT activity in recipients was slightly higher than in donors. ALT activity over 50 IU/l was observed only in 8 donors and in 15 recipients (50%) (TABLE 2). In recipients, the baseline ALT activity was significantly lower than at days 1 and 3 after transplantation. Mean AST activity did not differ significantly between donors and recipients, although it was 60% higher in recipients than in donors (TABLE 2). AST activity increased significantly at days 1 and 3 after transplantation compared with the baseline values. AST activity at day 3 was significantly lower than at day 1, but it did not achieve normal levels (<50 IU/l) in any of the recipients.

Mean baseline GGT activity in recipients was higher than in donors (*P* = nonsignificant). Unlike ALT and AST activity, the baseline GGT activity dropped significantly at day 1 and increased significantly at day 3 after transplantation.

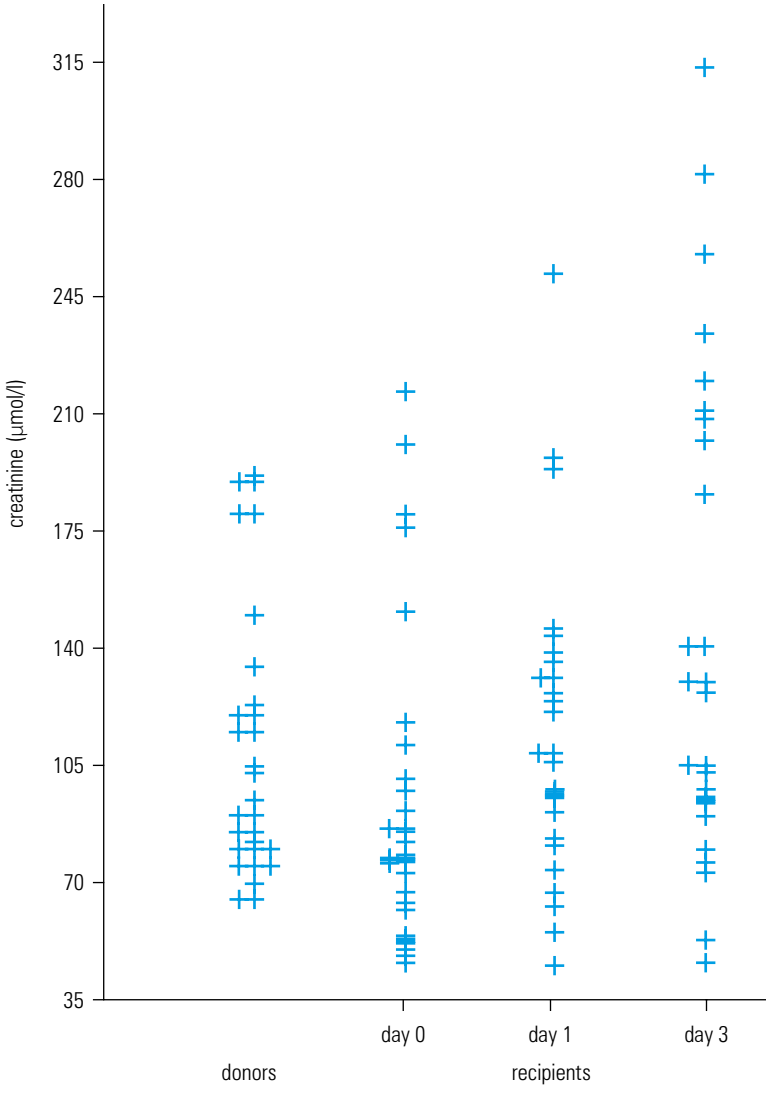

FIGURE 1 Serum creatinine levels in donors and in recipients before transplantation (day 0) and at days 1 and 3 after transplantation

The albumin level in recipients was slightly lower than in donors. It decreased significantly at days 1 and 3 after transplantation.

Recipients at day 0 and donors had almost identical baseline INR values, which transiently increased at day 1 after transplantation and subsequently decreased to baseline values.

As expected, bilirubin levels in donors were normal. Recipients at day 0 had 8-fold higher bilirubin levels compared with donors. Bilirubinemia decreased significantly at days 1 and 3 after transplantation but did not achieve normal levels (TABLE 2).

Creatinine levels in recipients were nonsignificantly lower than in donors (TABLE 2, FIGURE 1). In one-third of the recipients and in 3 donors, creatinine levels were below 70 μmol/l. At day 1 after transplantation, a significant rise of creatinine levels was observed and was even higher at day 3.

Sodium levels in recipients were lower than in donors at all time points (TABLE 2). In 22 donors, sodium levels were above 145 mmol/l. In almost all recipients, plasma sodium levels normalized after transplantation.

ADMA levels in recipients before transplantation were not significantly different from those in donors. At day 3, ADMA levels in recipients were significantly higher compared with the baseline values and those at day 1 (TABLE 2, FIGURE 2).

Baseline SDMA levels were similar in donors and recipients. In recipients at day 3, SDMA levels were significantly higher than before transplantation (TABLE 2, FIGURE 2).

The ADMA/SDMA ratio in liver recipients at baseline was not significantly higher than that in donors, showing a tendency to decrease at day 1 after transplantation and showing similar values to those in donors at day 3 (TABLE 2).

Changes in SDMA (ΔSDMA) and creatinine (Δcreatinine) levels in recipients between days 0 and 1 and days 1 and 3, respectively, increased nonsignificantly. There were no changes in the ΔSDMA / Δcreatinine ratio (TABLE 2).

Recipients showed higher baseline L-arginine levels than donors (nonsignificant). L-arginine levels increased significantly at day 3 after transplantation and were twice as high as in donors. L-arginine levels at day 3 were significantly higher than before transplantation (TABLE 2).

Correlations In donors, a significant negative correlation between SDMA levels and INR and a significant positive correlation between SDMA and creatinine levels were observed. In recipients, a strong correlation between SDMA and creatinine levels, a significant positive correlation between ADMA and bilirubin levels, and a significant negative correlation between ADMA concentration and INR were observed before transplantation (TABLE 3).

In recipients at day 1, a significant negative correlation was observed in recipients between SDMA levels and the activity of ALT, AST, and GGT as well as the level of albumin. In contrast, positive correlations were reported between creatinine and SDMA concentration, L-arginine levels, and INR and between ADMA and albumin levels.

In recipients at day 3, similarly to day 1, a significant negative correlation was observed between SDMA levels and AST activity, between SDMA levels and GGT activity, and between ADMA levels and INR. Finally, a significant positive correlation was found between SDMA and creatinine levels.

In summary, liver recipients before transplantation showed a slightly higher GGT activity, higher bilirubin concentration, and lower sodium levels.

After liver transplantation, we observed a significant increase in the activity of ALT and AST as well as in the plasma levels of creatinine, ADMA, SDMA, and L-arginine. Morover, we observed a significant decrease in bilirubinemia.

DISCUSSION

The present study revealed that liver recipients have slightly elevated ALT and GGT activity, higher INR values, elevated bilirubin levels, and significantly lower sodium levels than donors. These results may prove the presence of hepatocyte injury and deteriorated

TABLE 2 Liver function parameters in donors and in recipients before transplantation (day 0) and at days 1 and 3 after transplantation

	Donors	Recipients		
		day 0	day 1	day 3
ALT, IU/l	41 ±51	51 ±32	790 ±837[c]	695 ±1107[d,e]
AST, IU/l	53 ±44[b]	82 ±50	1357 ±2068[c]	432 ±644[d]
GGT, IU/l	41 ±37	112 ±110	57 ±37[c]	97 ±51[d]
albumin, g/dl	3.5 ±0.8	2.9 ±0.7	2.3 ±0.4[c]	2.5 ±0.4[d,e]
INR	1.23 ±0.21[a]	1.34 ±0.31	1.43 ± 0.28	1.31 ±0.4[d]
bilirubin, µmol/l	10 ±5	87 ±125	73 ±68[c]	55 ±56[d,e]
creatinine, µmol/l	110 ±40[b]	94 ±46	116 ±44[c]	144 ±73[d,e]
sodium, µmol/l	152 ±12	135 ±4	143 ±3[c]	139 ±4[d]
ADMA, µmol/l	0.484 ±0.273	0.589 ±0.168	0.552 ±0.262[c]	0.854 ±0.274[d,e]
SDMA, µmol/l	0.395 ±0.238	0.42 ±0.268	0.522 ±0.265[c]	0.804 ±0.501[d,e]
ADMA/SDMA	1.649 ±1.615	1.829 ±0.775	1.22 ±0.626	1.534 ±0.847
ΔSDMA	–	–	0.134 ±0.393	0.205 ±0.623
Δcreatinine	–	–	17.33 ±43.42	23.17 ±58.72
L-arginine, µmol/l	35.93 ±23.29	57.66 ±20.73	51.07 ±32.56	81.25 ±35.57[e]

Data presented as mean ± standard deviation; for significant differences, the Pearson correlation coefficient was used

a significant differences between donors and recipients at day 0
b significant differences between donors and recipients at day 1
c significant differences between recipients at days 0 and 1
d significant differences between recipients at days 1 and 3
e significant differences between recipients at days 0 and 3

Abbreviations: ADMA – asymmetric dimethylarginine, ALT – alanine transaminase, AST – aspartate transaminase, GGT – γ-glutamyltranspeptidase, INR – international normalized ratio, SDMA – symmetric dimethylarginine

TABLE 3 Significant correlations between asymmetric dimethylarginine, symmetric dimethylarginine, L-arginine, and other liver function parameters in donors and in recipients before transplantation (day 0) and at days 1 and 3 after transplantation

		ADMA		SDMA		L-arginine	
		r	*P*	*r*	*P*	*r*	*P*
donors	INR			–0.4036	0.0295		
	creatinine			0.8155	<0.001		
recipients day 0	INR	–0.4901	0.0081				
	bilirubin	0.4117	0.0264				
	creatinine			0.6690	<0.0005		
recipients day 1	ALT			–0.3793	0.0445		
	AST			–0.4108	0.0295		
	GGT			–0.4347	0.0423		
	albumin	0.377	0.02	–0.382	0.02		
	INR					0.4157	0.028
	creatinine			0.5698	0.0047		
recipients day 3	AST			–0.4138	0.0314		
	GGT			–0.5085	0.0081		
	INR	–0.4124	0.032				
	creatinine			0.8152	<0.0005		

Nonsignificant correlations were omitted.

Abbreviations: see TABLE 2

metabolism of porphyrins. Cirrhotic patients had similar ADMA, SDMA, and L-arginine levels as donors. Only SDMA levels showed a significant negative correlation with the activity of the studied enzymes.

Correlation results may suggest that the pathways of ADMA and SDMA synthesis are partially

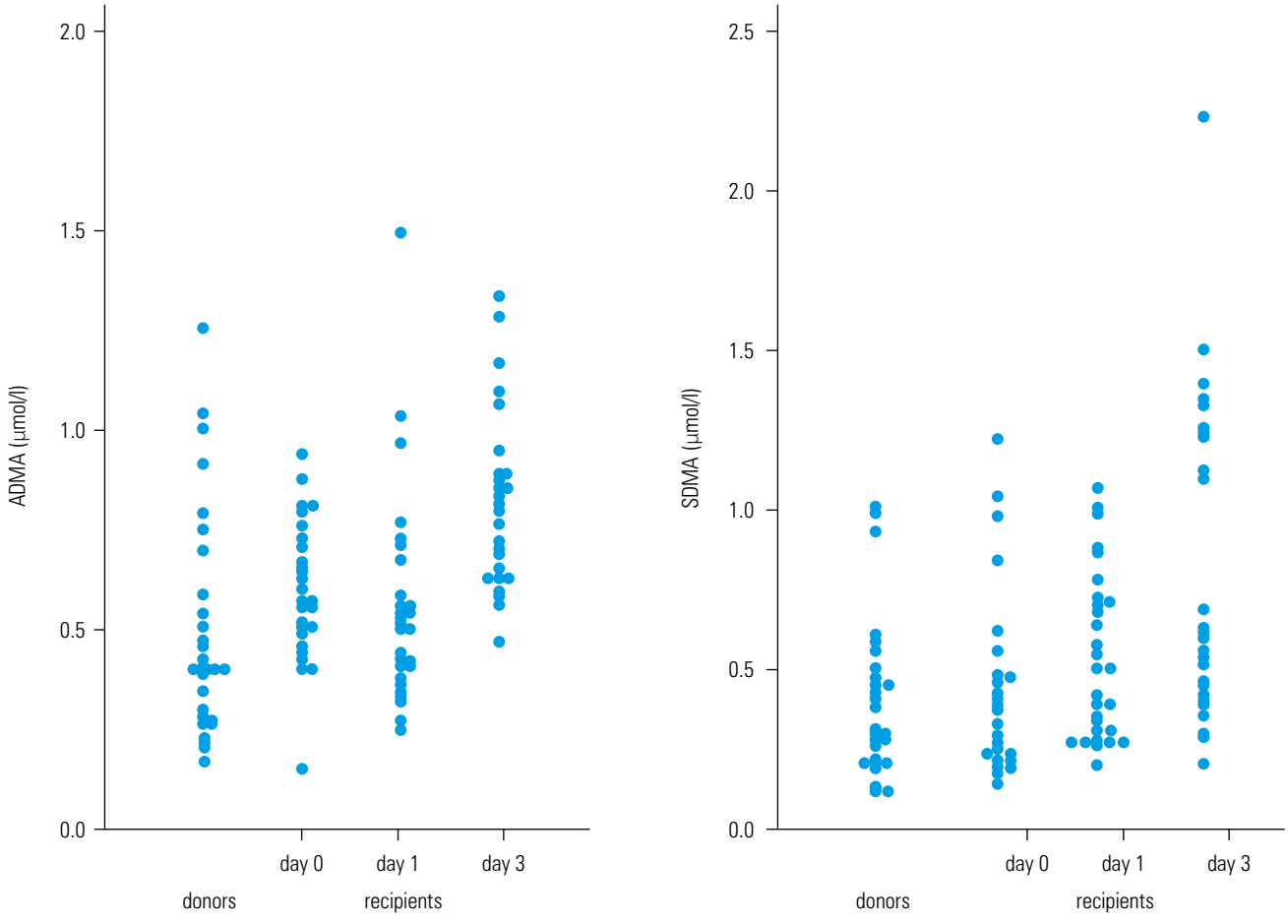

FIGURE 2 Serum asymmetric and symmetric dimethylarginine levels in donors and in recipients before transplantation (day 0) and at days 1 and 3 after transplantation
Abbreviations: see TABLE 2

linked pathogenically with other markers of liver injury. This hypothesis is supported by a strong negative correlation between ADMA concentrations and INR before transplantation and at day 3 after transplantation as well as a positive correlation between ADMA and bilirubin levels at day 1 after transplantation (TABLE 3).

We observed a significant rise in the activity of ALT and AST as well as in the levels of ADMA, SDMA, and L-arginine after liver transplantation. SDMA levels showed a negative correlation with ALT and AST activities. A significant increase in the activity of ALT and AST after transplantation may be due to reperfusion stress, administration of tacrolimus, graft ischemia during transplantation, or other causes.[3,22] An increase in ADMA and SDMA levels may be due to some compensatory mechanism, which prevents NOS from producing NO. In liver cirrhosis, a significant dilatation of arteries is common, caused by intensive NO synthesis.[22] The rise of ADMA levels after transplantation may prevent hemodynamic perturbations caused by inadequate NO production.

The study has several limitations. First, liver failure in recipients had different etiological factors. Second, the number of patients was small; therefore, it was not possible to study the effect of liver failure and its etiology on dimethylarginine levels.

Due to the risk of hepatorenal syndrome,[23-25] estimation of the glomerular filtration rate (GFR) after liver transplantation is mandatory in this patient group. GFR is typically calculated using the Cockroft-Gault or Modification of Diet in Renal Disease formulas,[26] based on serum creatinine levels. The diagnostic value of such GFR evaluation in cirrhotic patients with hepatorenal syndrome is controversial.[27-30,31] False high GFR values may be caused by: 1) high bilirubin levels, which make falsely underestimated creatinine levels; 2) liver failure, which deteriorates the conversion of creatine to creatinine; 3) muscle atrophy and dietary restriction in meat consumption in cirrhotic patients, leading to smaller creatinine production; and 4) high creatinine excretion via renal tubules in patients with hepatorenal syndrome.[26]

As shown in this study, a significant increase in creatinine levels in recipients after transplantation may be caused by impaired renal clearance of ADMA, SDMA, and L-arginine. It should be stressed that the formulas based on creatinine levels are not ideal measurements of the GFR in these patients.[26-30]

Our study provides interesting results on a positive correlation between SDMA and creatinine levels. SDMA, unlike ADMA, is excreted almost exclusively with urine. Therefore, SDMA may be a useful biomarker of the GFR in patients with end-stage liver failure.[32] A significant negative correlation between SDMA levels and the activity of ALT, AST, and GGT in liver recipients after transplantation is another interesting finding that requires further investigation. So far, SDMA

has been considered to be an inactive metabolite compared with ADMA. Our results suggest that this cannot by unanimously confirmed. If dimethylarginines were the markers of hepatic damage, a positive rather than a negative correlation between SDMA and the activity of the above enzymes should be expected. As reported by Paninsic and Lebowitz,[33] almost 80% of liver recipients showed symptoms of renal failure 48 hours after transplantation. Renal failure may be even more frequent when using the novel biomarkers of kidney injury (cystatin, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, interleukin 1, and others).[33]

Conclusions Patients with liver cirrhosis before transplantation have similar serum levels of ADMA, SDMA, and L-arginine as cadaver liver donors, and these parameters increase significantly after liver transplantation. The absence of significant correlations between ADMA levels and liver function indices (such as AST, ALT, GGT, natremia) may suggest that its diagnostic significance is different from that of other liver function markers in cirrhotic patients. The presence of a significant correlation between creatinine and SDMA levels both in donors and recipients suggests that the renal clearance rate of SDMA may have diagnostic value in the estimation of GFR in these patients. An increase in the levels of dimethylarginines after liver transplantation may be caused not only by graft's functional impairment but also by renal injury induced by the surgical procedure itself and/or by the use of nephrotoxic immunosuppressant drugs.

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ARTYKUŁ ORYGINALNY

Znaczenie diagnostyczne stężeń osoczowych asymetrycznej i symetrycznej dimetylargininy u biorców przeszczepionej wątroby

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asymetryczna dimetylarginina, marskość wątroby, niewydolność wątroby, przeszczepianie wątroby, symetryczna dimetylarginina

STRESZCZENIE

WPROWADZENIE W patogenezie marskości wątroby ważną rolę odgrywa tlenek azotu. Jego wytwarzanie jest zależne od dostępności L-argininy, a hamowane przez asymetryczną dimetylargininę (ADMA). Symetryczna dimetylarginina (SDMA) wydaje się dobrym wskaźnikiem niewydolności wielonarządowej, w szczególności niewydolności nerek.

CELE Niniejsza praca miała na celu ustalenie znaczenia diagnostycznego dimetylowanych arginin u chorych po transplantacji wątroby.

PACJENCI I METODY Badaniom poddano 30 zmarłych dawców wątroby i 30 biorców z marskością wątroby. U dawców przed eksplantacją wątroby, a u biorców przed transpalnatcją oraz w 1. i 3. dobie po niej oznaczano w surowicy: aktywność transaminazy alaninowej (ALT), transaminazy asparaginianowej (AST) oraz γ-glutamylotranspeptydazy (GGT), stężenie albuminy, międzynarodowy współczynnik znormalizowany (*international normalized ratio* – INR), stężenie bilirubiny, kreatyniny, elektrolitów, ADMA, SDMA i L-argininy.

WYNIKI Chorzy z marskością wątroby przed transplantacją różnili się od dawców zwiększonym stężeniem bilirubiny, wyższą aktywnością ALT i GTP oraz niższym stężeniem sodu i albuminy. W 3. dniu po przeszczepieniu zanotowano wzrost aktywności ALT, AST, kreatyniny, sodu, ADMA, SDMA i L-argininy, oraz zmniejszenie stężenia bilirubiny. Stwierdzono znamienną dodatnią korelację między stężeniami SDMA i kreatyniny u dawców ($p < 0{,}001$), biorców przed przeszczepieniem ($p < 0{,}0005$), w 1. ($p < 0{,}004$), i 3. dobie po przeszczepieniu ($p < 0{,}0005$). Stwierdzono również znamienną dodatnią korelację między stężeniami ADMA i bilirubiny przed przeszczepieniem ($p = 0{,}0264$), ADMA i albuminy w 1. dniu po przeszczepieniu ($p = 0{,}02$), natomiast znamienną ujemną korelację między stężeniem ADMA i INR przed przeszczepieniem ($p < 0{,}008$) i w 3. dniu po przeszczepieniu ($p < 0{,}03$) u biorców.

WNIOSKI Zwiększenie stężeń dimetylarginin po przeszczepieniu wątroby wydaje się być spowodowane nie tylko dysfunkcją przeszczepionej wątroby, ale również upośledzoną funkcją nerek spowodowaną samym zabiegiem operacyjnym i/lub stosowaniem inhibitora kalcyneuryny – takrolimusu, wykazującego działanie nefrotoksyczne. Stwierdzona w pracy znamienna korelacja między kreatyninemią a stężeniem SDMA w surowicy zarówno u dawców jak i u biorców wątroby sugeruje, że klirens nerkowy SDMA może być wykorzystany do oznaczania współczynnika przesączania kłębuszkowego u tych chorych.

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