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Liver Fatty Acid Binding Protein: Is it an early diagnostic and prognostic marker in liver damage?

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ABSTRACT

Objective: The majority of the liver function tests are not specific to the liver. The histological liver damage begins before patients are diagnosed with cirrhosis and continue afterwards. Therefore, there is an increasing demand for early and specific markers that are correlated with liver damage. This study aims to investigate if serum and urinary liver fatty acid-binding protein (L-FABP) levels could be used as an early diagnostic marker of liver cirrhosis.

Material and Methods: This cross-sectional study included 30 patients with compensated liver cirrhosis, 27 patients with decompensated liver cirrhosis, and 30 healthy controls. The patients and healthy controls were tested for serum and urinary L-FABP levels.

Results: The serum and urinary L-FABP levels were higher in patients with cirrhosis than the healthy controls (both $p<0.001$). The cut-off value of serum and urinary L-FABP was computed as 721.78 ng/ml and 621.25 ng/ml, respectively. The sensitivity of serum and urinary L-FABP to detect cirrhosis at this cut-off was 99.8% and 98.9%. The specificity, positive predictive value, and negative predictive value of serum and urinary L-FABP at these cut-off levels were 100%. There was no difference in terms of serum and urinary L-FABP between compensated and decompensated cirrhosis patients. Accordingly, no correlation was determined between serum/urinary L-FABP levels and cirrhosis complications.

Conclusion: L-FABP increases in serum and urine in response to hepatocyte damage that can result in liver fibrosis. We demonstrated that patients with liver cirrhosis had high L-FABP levels. L-FABP may be used as a predictive non-invasive marker of cirrhosis as it can be detected before the clinical symptoms of liver damage.

Keywords: biomarker, cirrhosis, FABP1, L-FABP, liver fatty acid-binding protein

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INTRODUCTION

Chronic liver disease (CLD) is a global health problem that affects more than 800 million people worldwide (1). The most common etiologies of CLD are hepatitis C virus (HCV), hepatitis B virus (HBV), non-alcoholic fatty liver disease (NAFLD) and alcohol consumption. Regardless of etiological factors, the prevalence of liver cirrhosis in the general population was found to be 0.27% (2). However, considering that a significant proportion of patients are asymptomatic and are only diagnosed with cirrhosis as premortem, it is estimated that the prevalence is higher than it is expected (3). Liver cirrhosis can cause high morbidity and mortality both by its complications as well as hepatocellular carcinoma. Although liver biopsy is still the gold standard method for the diagnosis of cirrhosis, it has some disadvantages because it is an invasive method. Further, false-negative results could be possible in the early stages of cirrhosis. In this regard, researches for inexpensive, safe, specific, and repeatable non-invasive disease markers are proceeding. APRI (AST-Platelet Ratio Index), FIB 4 (Age, AST, platelet count, and ALT), Fibroindex (platelet count, AST, and GGT) are some of the clinically accepted biochemical panels for fibrosis assessment.

In addition to these indirect indicators; hyaluronic acid (HA), tissue inhibitor of metalloproteinase -1 (TIMP -1), amino-terminal of serum procollagen Ⅲ peptide (PIIINP), and a bacterial enzyme as known chondrex (YKL-40) have also been found to reflect extracellular matrix turnover and are directly involved in fibrogenesis. However, all these markers also reflect inflammation and fibrosis in other organs that is why they are not specific to the liver. Besides, they are correlated with advanced fibrosis, but not with early-stage fibrosis (**4**).

Fatty acid-binding proteins (FABPs) are small cytoplasmic proteins that can bind many hydrophobic ligands such as fatty acids and cannot be detected in the serum as they do not possess a secretory signal physiologically. Some FABPs can be used as a diagnostic marker of tissue damage for many organs, including the liver (**5**). Liver FABP (L-FABP) is mainly expressed in the liver and is predominantly considered for liver damage. It comprises 2-5% of the cytosolic proteins in the liver tissue and is involved in the uptake, transport, oxidation, lipid synthesis, storage of fatty acids and the regulation of nuclear receptors (**6**). The L-FABP levels in hepatocytes are altered in response to physiological and pharmacological changes. It increases in parallel to the free oxygen radicals in the cell microenvironment and mediates systemic inflammation by increasing interleukin-6 and interleukin-1α release **(7, 8**). L-FABP can be considered as an early marker for hepatocellular damage while it is released into the circulation quickly due to being small proteins. In the present study, we aimed to investigate whether serum and urinary L-FABP levels could be used as a predictive non-invasive marker of liver cirrhosis and its complications.

MATERIAL and METHODS

Study population and biochemical assessments

This cross-sectional study included 57 patients with a diagnosis of cirrhosis in a hepatology department in a tertiary university hospital between October 2017 – April 2018 and healthy controls. Three groups were defined as follows: compensated cirrhosis (CC) (n=30), decompensated cirrhosis (DC) (n=27), and healthy controls (HC) (n=30). HC consisted of healthy volunteers working in the hospital without comorbid diseases. Patients with radiological (nodular appearance of the liver surface, parenchymal thickening, caudate lobe enlargement, portal vein diameter >13 mm) and endoscopic (varices, portal gastropathy) findings of cirrhosis were considered CC. Patients with ascites, hepatic encephalopathy (HE) or variceal hemorrhage were considered DC and these signs were indicated as a present or not. The exclusion criteria of the study were defined as malignancies, active systemic infections, acute cerebrovascular diseases, chronic kidney disease, psychiatric diseases, and nephrotoxic and sedative medication use. Hepatocellular carcinoma (HCC) was ruled out by radiological evaluation in cirrhotic patients. Demographic variables were recorded for all groups, and Child Turcotte-Pugh (CTP) classification and Model for End-Stage liver disease (MELD) score were calculated for patients with cirrhosis.

All patients and healthy controls were tested for complete blood count parameters, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total bilirubin, international normalized ratio (INR), creatinine, serum, and urinary L-FABP levels (ELISA kit; Sun Red, 201-12-2160, China, Shanghai).

Statistical analysis

Statistical data were analyzed using SPSS v.23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviations for continuous variables. Variables were tested for normality using the Kolmogorov-Smirnov test. The Mann-Whitney U test and Kruskal -Wallis H were used to compare nonparametric variables and the chi-squared test was used to compare categorical variables. While investigating the associations between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. When a significant cut-off value was observed, the sensitivity, specificity, positive and negative predictive values were presented. A p-value ⩽ of 0.05 was considered statistically significant.

Approval received from the local university ethics committee with the numbers 2017-09/07.

RESULTS

The mean age of the patients and healthy controls included in the study were 67.70 ± 11.32 and 59.67 ± 11.77 years. The mean age of patients with DC was 65.78±11.63 years, and they were older than CC patients and healthy controls. However, there was no statistical difference in age between the groups (p=0.144). The number of men in the study was 48 (55.2%). The male gender ratio in patients with decompensated cirrhosis was 77.8%, and it was found to be significantly higher than other groups (p=0.013). The etiologies of cirrhosis were HBV (n=19), HCV (n=11) and nonalcoholic fatty liver disease (NAFLD) (n=27). The distribution of DC patients according to CTP classification was found as CTP-B (59.3%), CTP-C (40.7%). Hepatic encephalopathy, ascites and variceal hemorrhage were found in 11 (40.7%), 17 (63%) and 7 (25.9%) patients with DC, respectively. Meld Score was calculated as 10.87± 3.80 and 16.89 ±6.41 for CC and DC patients, respectively. The clinical characteristics of the study groups are presented in Table 1.

Mean serum L-FABP were determined as 1273.42± 349.72, 1349.83 ± 321.44, 355.83±32.52 ng/ ml for CC, DC, and healthy controls, respectively (p<0.001). Mean urinary L-FABP were determined as 1450.92± 336.53, 1480.71 ± 178.74, 445.78±24.53 ng/ ml for CC, DC, and healthy controls, respectively (p<0.001). There was no difference between CC and DC cirrhosis in terms of serum and urinary L-FABP levels (p=0.212, p=0.898) (Table 2).

The cut-off value for serum L-FABP was determined as 721.78 ng/ml. For this value, serum L-FABP had a sensitivity of 99.8% and a positive predictive value of 100%. The specificity and the negative predictive value at the stated cut-off value were found as 100%. The cut-off value for urinary L-FABP was determined as 621.25 ng/ml. For this value, urinary L-FABP had a sensitivity of 98.9% and a positive predictive value of 100%.

The specificity and the negative predictive value at the stated cut-off value were found as 100% (Table 3).

Serum and urinary L-FABP levels were statistically shown to have a positive correlation with AST, GGT, INR, total bilirubin, and a negative correlation with haemoglobin, thrombocyte and leukocyte count, and albumin (all p<0.05). Urinary L-FABP but not serum L-FABP positively correlated with creatinine levels. There were no correlations between the MELD score and both serum and urinary L-FABP levels (Table 4).

Serum and urinary L-FABP levels did not differ statistically in terms of cirrhosis etiology. Serum L-FABP was determined as 1490.47±369.09, 1246.36±279.90, and 1208.12±286.71 in patients with cirrhosis with HBV, HCV, NAFLD, respectively (p=0.060). Urinary L-FABP was determined as 1516.99±307.13, 1460.11±291.55, and 1430.48±223.91 in patients with cirrhosis with HBV, HCV, NAFLD, respectively (p=0.681). Besides, there were no correlations between serum/ urinary L- FABP levels and the presence of HE, ascites, and varices (all p>0.05).

Table 1. Clinical characteristics of the study population

	CC (n=30)	DC (n=27)	HC (n=30)	P
Age (years) ±SD	63.73 ± 11.4	65.78 ± 11.63	59.67 ± 11.77	0.144
Sex, male, n (%)	15 (50)	21 (77.8)	12 (40)	0.013
Etiology, n (%)				
HBV	11 (36.7)	8 (29.6)		
HCV	7 (23.3)	4 (14.8)		
NAFLD	12 (40)	15 (55.6)		
CTP grade, n (%)				
A	30(100)			
B		16(59.3)		
C		11(40.7)		
Cirrhosis Complications, n (%)				
Hepatic encephalopathy		11(40.7)		
Ascites		17 (63)		
Variceal hemorrhage		7 (25.9)		
Meld Score ±SD	10.87 ± 3.80	16.89 ± 6.41		

CC, Compensated cirrhosis; CTP, Child Turcott Pugh; DC, Decompensated cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HC, Healthy controls; MELD, Model for End-Stage liver disease; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation

Table 2. Laboratory tests of the study population

Parameters (mean±SD)	CC	DC	HC	p*
Wbc (10^3/mm^3)	3791.00±1225.26	3594.44±1275.49	7681.20±1975.96	0.000
Hb (g/dl)	11.96±2.72	10.13±2.28	15.69±1.14	0.000
Plt (10^3/mm^3)m	115.87±45.39	115.19±60.07	266.63±65.59	0.000
AST (U/L)	38.83±31.20	46.67±26.81	20.63±9.80	0.000
ALT (U/L)	29.23±38.68	29.89±19.76	20.90±10.05	0.304
GGT(IU/L)	99.03±140.13	81.15±45.63	36.67±21.12	0.000
T.Bil (mg/dL)	1.13±1.42	3.76±4.44	0.69±0.31	0.001
Albumin (g/L)	3.58±0.64	2.89±0.58	4.15±0.55	0.000
INR	1.26±0.22	1.56±0.42	1.02±0.05	0.000
Cre (mg/dL)	1.06±0.98	1.34±0.89	0.92±0.14	0.633
Urinary L-FABP (ng/ml)	1450.92±326.53	1480.71±178.74	445.78±24.53	0.000
Serum L-FABP (ng/ml)	1273.42±349.72	1349.83±321.44	355.83±32.52	0.000

***: the difference between patients and healthy participants,** AST, aspartate aminotransferase; ALT, alanine aminotransferase; CC, Compensated cirrhosis; Cre, creatinine; DC, Decompensated cirrhosis; GGT, gamma-glutamyl transferase; Hb, Hemoglobin; INR, international normalized ratio; L-FABP, liver fatty acid-binding protein; MELD, Model for End-Stage liver disease Plt, Thrombocyte; SD, standard deviation; T.Bil: Total bilirubin; Wbc: Leukocyte

Table 3. Cut-off values of serum and urinary L-FABP

L-FABP (ng/ml)	Cut -off	Sensitivity	Specificity	PPV	NPV	Accuracy
Urinary	621.25	98.9%	100%	100%	100%	98.9%
Serum	721.78	99.8%	100%	100%	100%	99.8%

L-FABP, liver fatty acid-binding protein; NPV, negative predictive value; PPV: positive predictive value

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Table 4. Correlation of serum and urinary L-FABP levels with other laboratory tests

	L-FABP (ng/ml)			
	Urinary		Serum	
	r	*p*	*r*	*p*
WBC (10^3/mm^3)	-0.608	**<0.001**	-0.612	**<0.001**
Hb (g/dl)	-0.599	**<0.001**	-0.585	**<0.001**
Plt (10^3/mm^3)	-0.627	**<0.001**	-0.581	**<0.001**
AST (U/L)	0.348	**<0.001**	0.349	**<0.001**
ALT (U/L)	0.065	0.548	0.113	0.296
GGT (IU/L)	0.284	**<0.001**	0.366	**<0.001**
T.Bil (mg/dL)	0.344	**<0.001**	0.248	**<0.001**
Albumin (g/L)	-0.433	**<0.001**	-0.466	**<0.001**
INR	0.570	**<0.001**	0.501	**<0.001**
Cre (mg/dl)	0.114	**<0.001**	0.136	**0.208**
Meld Score	0.030	0.822	-0.039	0.772
Urinary L-FABP (ng/ml)	1.000	-	0.754	**<0.001**
Serum L-FABP (ng/ml)	0.754	**<0.001**	1.000	-

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cre, creatinine; GGT, gamma-glutamyl transferase; Hb, Hemoglobin; INR, international normalized ratio; L-FABP, liver fatty acid-binding protein; Plt, Thrombocyte; T.Bil: Total bilirubin; WBC: Leukocyte

DISCUSSION

L-FABP is an intracellular carrier protein that is synthesized in hepatocytes, and to some degree, in proximal tubule epithelial cells (**9**). Recently, urinary L-FABP is thought to be a useful clinical marker of acute kidney damage in the early period and it could play a role in the prediction of chronic kidney damage and the monitoring of the progression (**10, 11**). Similarly, cellular L-FABP levels are altered due to the changes in cellular lipid metabolism homeostasis in liver diseases such as cirrhosis, hepatitis, iron and copper accumulation, porphyria, and hepatocellular carcinoma (**12**). Besides chronic liver diseases, L-FABP levels were found to be high in acute liver injury that develops secondary to alcohol- or drug-induced toxicity (**13**). In acute hepatocellular damage induced by acetaminophen toxicity, serum L-FABP levels were shown to be negatively correlated with the survey (**14**). Further, L-FABP could be detected in the plasma earlier than alpha glutathione S-transferase (α-GST) and ALT, and that it was more sensitive in detecting hepatocellular damage due to rejection (**15**). Accordingly, its levels were shown to be a novel marker of early parenchymal damage following liver transplantation (**16**). However, there is a limited number of studies in the literature regarding the cut-off levels of L-FABP in acute or chronic liver disease.

In the present study, we found significantly higher serum and urinary L-FABP levels in patients with cirrhosis compared to the healthy control group ($p<0.001$). We determined the cut-off values as 721.78 ng/ml and 621.25 ng/ml for serum and urinary L-FABP, respectively. (Serum AUC= 0.998 and urinary AUC= 0.989). A study that compared patients with acute hepatitis, HE, and CC to healthy controls indicated lower cut-off values for both serum and urinary L-FABP (serum AUC= 0.985 and urinary AUC=1.000) (**17**). We think that these different cut-off levels with similar accuracy may be related to the heterogeneity of the patient groups and the higher number of cirrhosis patients in our study. In some of the heterogeneous validation studies investigating serum biomarkers for detection of cirrhosis; a significant correlation with advanced fibrosis was observed (AUC of HA=0.91, TIMP-1=0.92, PIIINP=0.88, and YKL-40=0.79) (**18-21**).

Although the importance of L-FABP in the pathogenesis of fibrosis is not clear yet, we think that it may be an encouraging marker for the presence of cirrhosis due to its high accuracy rates.

We determined higher serum and urinary L-FABP levels in NAFLD cirrhosis when compared with the healthy controls, although these levels were lower than those in patients with cirrhosis with viral hepatitis. L-FABP bears a critical effect on the ligand-dependent transactivation of peroxisome proliferator-activated receptor α (PPARα) which regulates the transcription of multiple genes involved in the lipid metabolism included in NAFLD pathogenesis (**22, 23**). Since the correlation between FABP levels and fibrosis/inflammation was shown in patients with non-alcoholic steatohepatitis, L-FABP has been introduced to be used as a non-invasive marker (**24**).

We also determined positive correlations between L-FABP (serum/urinary) and AST, GGT, total bilirubin and INR, a negative correlation with albumin. In the present study, creatinine levels were in the normal range and likely higher in patients with CC and DC, respectively. Additionally, there was a weak positive correlation between creatinine and urinary L-FABP but not serum L-FABP. A study conducted on patients who presented to the emergency service for any reason and showed normal serum creatinine levels at presentation showed that urinary L-FABP levels were predictive of acute kidney damage (**25**). Meanwhile, the significantly lower serum L-FABP levels seen in hemodialysis patients with the end-stage renal disease compared to healthy controls are thought to be linked to the decrease in the production of L-FABP in the liver due to severe renal failure (**8**). On the other hand, L-FABP levels were found to have no predictive value for the development of hepatorenal syndrome in decompensated cirrhosis patients (**26**).

In our study, there was no difference between CC and DC in terms of serum and urinary L-FABP. Also, there were no correlations between L-FABP levels and CTP stages, MELD score, and presence of cirrhosis complications such as HE,

ascites, and variceal hemorrhage. However, the present study included only two patients with hepatic coma, thirteen patients with tense ascites, and seven patients with variceal hemorrhage. Accordingly, we cannot completely suggest that L-FABP does not reflect the prognosis of liver cirrhosis due to low patient numbers.

Our study has some limitations. First, all patients had clinical cirrhosis and the liver biopsy was not performed. Second, the patient population is small to evaluate the prognostic importance of L-FABP levels. Third, it is a cross-sectional study that sequential measurements are not warranted.

CONCLUSIONS

In conclusion, L-FABP increases in serum and urine in response to the altered membrane permeability following hepatocyte damage that can result in liver fibrosis. L-FABP may be used as a predictive non-invasive marker of cirrhosis as it can be detected before the clinical symptoms of liver damage. However, L-FABP was not found to be related to the complications of cirrhosis. Further studies must be conducted to determine exact cut-off values and allow L-FABP to be recognized as a specific liver function test in the coming years.

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