Urinary Liver Type Fatty Acid Binding Protein Is Negatively Associated With Estimated Glomerular Filtration Rate in Renal Transplant Recipients With Graft Loss

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ABSTRACT

Background. Liver type fatty acid binding protein (L-FABP) is abundant not only in the liver but also in the kidney and is excreted in urine. Its primary function is to facilitate intracellular long chain fatty acid transport and it might also act as an endogenous antioxidant molecular. The purpose of this study was to investigate whether plasma or urinary L-FABP levels were associated with graft function in renal transplant recipients.

Patients and methods. Sixty-seven renal transplant recipients with a mean age of 48.8 years were recruited. The mean duration of renal transplantation was 4131 days. Recipients were divided into 2 groups based on their estimated glomerular filtration rate (eGFR) values: moderate graft function (eGFR $\geq$60 mL/min/1.73 m^2) and low graft function (eGFR $<$60 mL/min/1.73 m^2). Fasting plasma and urinary L-FABP levels were measured.

Results. There was no significant difference in plasma L-FABP level between the 2 groups, although recipients in the low graft function group had significantly lower urinary L-FABP level when compared with recipients in the moderate graft function group. Plasma and urinary L-FABP levels were not associated with eGFR in the 67 recipients; however, urinary L-FABP level ($\beta = -1.24$, $P = .037$) and level adjusted by urinary creatinine ($\beta = -0.75$, $P = .046$) were significantly negatively associated with eGFR in recipients with low graft function after adjusting for potential confounders.

Conclusion. Increased urinary L-FABP level seems to be a significant indicator of decreased graft function in renal transplant recipients with loss of graft function.

SHORT-TERM renal graft survival has been significantly improved by advances in potent immunosuppressive agents in recent decades; however, the long-term survival of renal transplant (RTx) recipients remains a considerable challenge. Increased oxidative stress, decreased antioxidant capacities, or comorbidities may cause the loss of graft function in patients who have received an RTx. In addition to the well-known oxidative stress indicators (ie, malondialdehyde, lipid peroxidation, F2-isoprostanes, protein carbonyls, advanced oxidation protein products, 8-oxo-7,8-dihydro-2′-deoxyguanosine) that have been shown to be related to renal function [1], urinary liver type fatty acid binding protein (L-FABP) is also considered to be an endogenous antioxidant and prognosis marker for patients with various kidney diseases [2–5].

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Table 1. Demographic and Clinical Characteristics of Renal Transplant Recipients

Characteristics	Low Graft Function (n = 31)	Moderate Graft Function (n = 36)
eGFR (mL/min/1.73 m^2)	42.02 ± 2.12	77.90 ± 2.54*
Age (y)	49.77 ± 2.35	47.92 ± 1.77
Sex (male; female)	16; 15	21; 15
Body mass index (kg/m^2)	24.12 ± 0.80	23.92 ± 0.75
Transplantation duration (d)	5375.70 ± 1359.13	3064.74 ± 283.71
Blood pressure (mm Hg)		
Systolic	136.06 ± 3.18	130.39 ± 2.15
Diastolic	81.61 ± 1.94	82.36 ± 1.44
Serum albumin (g/dL)	4.41 ± 0.14	4.29 ± 0.05
Serum hemoglobin (g/dL)	12.53 ± 0.32	13.79 ± 0.32*
Serum creatinine (mg/dL)	1.66 ± 0.11	1.00 ± 0.03*
Blood urea nitrogen (mg/dL)	27.19 ± 2.56	17.06 ± 0.83*
Lipid profiles		
Triglycerides (mg/dL)	143.94 ± 11.92	132.36 ± 10.79
Total cholesterol (mg/dL)	204.42 ± 8.59	183.66 ± 6.02*
LDL (mg/dL)	122.31 ± 7.69	105.94 ± 4.54
Urine		
Creatinine (mg/dL)	87.56 ± 6.67	90.81 ± 5.63
Total protein (mg/dL)	52.95 ± 14.00	29.72 ± 9.53*
Total protein-to-creatinine ratio	0.76 ± 0.24	0.32 ± 0.10*

Values are means ± standard error of mean.
Abbreviations: eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein cholesterol.
*Value is significantly different from the other group ($P < .05$).

L-FABP is a small protein mainly present in the liver but it is also abundant in renal proximal tubules. It has a high affinity and capacity to bind the products of fatty acid peroxidation and causes their excretion into the urine. Because renal tubular defects would increase L-FABP excretion into urine [2,6,7], studies have mainly focused on the association of urinary L-FABP concentration with renal function. Urinary L-FABP has been shown to reflect the progression of renal function and thus has been considered a new clinical biomarker for predicting the progression of various kidney diseases [2,5–8]. However, the utility of urinary L-FABP might be limited in patients with delayed graft function [4] as well as in a clinical setting because urinary samples may not always be available from RTx recipients with loss of graft function. Although blood samples might be more readily obtainable than urine samples, it is still unclear whether serum L-FABP level would be a superior indicator of renal function compared with urinary L-FABP or oxidative stress indicators. Thus, in the present study we investigated whether plasma or urinary L-FABP levels were associated with graft function in RTx recipients.

PATIENTS AND METHODS

This investigation employed a cross-sectional study design. Patients aged between 20 and 80 years, had RTx and were recruited from the outpatient clinic of the Division of Nephrology, Taichung Veterans General Hospital, Taichung, Taiwan. Most patients were treated with a maintenance dose of triple therapy. Patients were excluded if they were clinically unstable, pregnant, lactating, or suffered from liver disease, chronic inflammatory disease, cancer, or alcoholism. Patients were assigned to 2 groups based on their graft function: moderate graft function (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2) group or low graft function (eGFR <60 mL/min/1.73 m^2) group. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital. Informed consent was obtained from each subject prior to entering the study.

Patients' demography, anthropometry, and medical history data were recorded. Fasting blood and first-voided morning spot urinary samples were collected at an appointed day. Serum or plasma was separated within 30 minutes after blood was collected and immediately measured or then frozen (−80°C) until analysis. Hematological (albumin, hemoglobin, creatinine, blood urea nitrogen, total cholesterol, low-density lipoprotein cholesterol [LDL], and triglyceride), urinary entities (creatinine, total protein), plasma and urinary L-FABP, indicators of oxidative stress (malondialdehyde [MDA], oxidized-LDL), and antioxidant capacities (trolox equivalent antioxidant capacity [TEAC]) were measured. Plasma L-FABP (Cusabio, CBS-E13455h, China), urinary L-FABP (Z-007 ELISA kit, R&D Systems, Inc., Minneapolis, MN, United States), and plasma oxidized-LDL (Mercodia AB, Sylveniusgatan 8A, SE-754 50 Uppsala, Sweden) were measured by using the respective commercial kits. Plasma MDA concentration was determined by thiobarbituric acid reactive substances as an indicator of oxidative stress [9]. Plasma TEAC was measured according to a 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate) radical cation-based colorimetric and automated direct method [10].

All data analyses were performed using the SAS statistical software package (version 9.3; Statistical Analysis System Institute Inc, Cary, NC, United States). A Shapiro-Wilk test was performed to test the normal distribution. Differences in patients' anthropometric measurements and biochemical values were compared to determine significant differences between groups and were analyzed by Student t test or Mann-Whitney rank sum test. For categorical response variables, differences between groups were assessed by the χ^2 or Fisher exact test. Multiple linear regression with eGFR level as the dependent variable was used to evaluate the association of