Postprint: Application Value of Urinary Liver-type Fatty Acid-Binding Protein in Traumatic Brain Injury

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Abstract

Objective To investigate the value of urinary liver-type fatty acid-binding protein (L-FABP) in early assessment of disease severity and prediction of acute kidney injury (AKI) occurrence in patients with traumatic brain injury, thereby providing a basis for clinical treatment. Methods Sixty-five patients with traumatic brain injury of varying severity were enrolled and divided into 4 groups according to their Glasgow Coma Scale (GCS) scores. Blood and urine specimens were collected at 2, 6, 12, 24, 48, and 72 hours post-injury. Serum creatinine (SCr) levels were measured using a biochemical analyzer, and urinary L-FABP levels were detected by enzyme-linked immunosorbent assay (ELISA). Fifteen healthy adults served as controls. The correlations between blood SCr and urinary L-FABP levels with GCS scores at admission and AKI occurrence were analyzed. Results Blood SCr and urinary L-FABP levels in experimental groups B, C, and D were significantly elevated compared with the control group ($P<0.05$). As GCS scores decreased (severity increased), blood SCr and urinary L-FABP levels gradually increased, demonstrating a negative correlation ($P<0.05$). The elevation of urinary L-FABP was more pronounced than that of blood SCr. The incidence of AKI was approximately 21.54%. The peak elevation of urinary L-FABP in AKI patients occurred at 6 hours post-injury, whereas the peak elevation of SCr occurred at 24-48 hours post-injury, indicating that urinary L-FABP elevation preceded SCr elevation by a significant margin. Conclusion Urinary L-FABP measurement can serve as an important novel biomarker for early prediction of traumatic brain injury severity and AKI occurrence, holding significant clinical application value.

Full Text

Preamble

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Abstract

Objective: To investigate the value of urinary liver-type fatty acid-binding protein (L-FABP) in early assessment of traumatic brain injury severity and prediction of acute kidney injury (AKI) occurrence, providing evidence for clinical treatment.

Methods: Sixty-five patients with traumatic brain injury of varying severity were collected and divided into four groups based on Glasgow Coma Scale (GCS) scores. Blood and urine specimens were collected at 2, 6, 12, 24, 48, and 72 hours post-injury. Serum creatinine (SCr) levels were measured using a biochemical analyzer, and urinary L-FABP levels were detected by enzyme-linked immunosorbent assay (ELISA), with 15 healthy adults serving as controls. The correlations among SCr, urinary L-FABP, GCS scores at admission, and AKI occurrence were analyzed.

Results: Experimental groups B, C, and D showed significantly elevated SCr and urinary L-FABP levels compared with the control group ($P<0.05$). As GCS scores decreased (indicating increased severity), SCr and urinary L-FABP levels gradually increased, demonstrating a negative correlation ($P<0.05$). The increase in urinary L-FABP was more pronounced than that in SCr. The AKI incidence was approximately 21.54%. In AKI patients, urinary L-FABP peaked at 6 hours post-injury, while SCr peaked at 24–48 hours, indicating that urinary L-FABP elevation occurred significantly earlier than SCr elevation.

Conclusion: Urinary L-FABP determination can serve as an important novel biomarker for early assessment of traumatic brain injury severity and prediction of AKI occurrence, holding significant clinical application value.

Keywords: traumatic brain injury; urinary liver-type fatty acid-binding protein; acute kidney injury; SCr; GCS score

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Acute traumatic brain injury carries high clinical mortality and morbidity rates, with its incidence showing a marked increasing trend that seriously threatens patients' lives and health. Cranial trauma stress can lead to functional impairment in multiple body systems. In recent years, the incidence of acute kidney

injury (AKI) following severe trauma has reached up to 50%, with high mortality rates [1], particularly in intensive care unit (ICU) settings where the fatality rate ranges from 37% to 76.19% and prognosis is poor [2-3]. Trauma-induced acute kidney injury has gradually attracted clinical attention, and improper management can result in long-term severe renal function damage. Early diagnosis is the prerequisite and key to management. Employing accurate evaluation systems to timely assess conditions and detect AKI is crucial for prognosis and treatment. Commonly used indicators for judging early renal function changes include neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), Na+/H+ exchanger-3 (NHE-3), recombinant human cysteine-rich protein-61 (Cyr61), N-acetyl- -D-glucosaminidase (NAG), fetuin-A, and others [4-5].

The GCS score is widely applied in clinical classification and severity assessment of traumatic brain injury, serving as an indicator for evaluating injury conditions and prognosis. However, the score can be influenced by various factors such as sedatives, muscle relaxants, physician experience, observation conditions, and unstable vital signs. In recent years, numerous studies have investigated the use of biochemical indicators for injury assessment and prediction, such as central nervous system damage markers including S-100 , NSE, and Tau. These indicators have difficulty achieving satisfactory sensitivity and specificity simultaneously, and current practice often employs GCS scoring combined with multiple biomarkers for joint detection and judgment.

Liver-type fatty acid-binding protein (L-FABP) is an intracellular molecular protein belonging to the fatty acid-binding protein (FABPs) family. L-FABP is primarily expressed in the liver and also in renal proximal tubules, participating in various metabolic pathways including intracellular uptake, transport, and oxidation of free fatty acids. It is a key regulatory factor for maintaining free fatty acid homeostasis in the cytoplasm [6]. Whether changes in human homeostasis caused by traumatic brain injury can be reflected through urinary L-FABP expression has been rarely studied. This study focuses on investigating the application value of early urinary L-FABP detection for assessing injury severity and predicting AKI occurrence, providing reference for clinical treatment.

Methods

1.1 General Data

Sixty-five patients with traumatic brain injury of varying GCS scores admitted to the Neurosurgery Department of Third Xiangya Hospital of Central South University between May 2014 and October 2015 were randomly selected. None of the patients underwent craniotomy within 3 days post-injury. The cohort included 38 males and 27 females, with a mean age of 45.5±8.6 years. Patients were divided into four groups based on GCS scores [7-10]: mild traumatic brain injury group A (GCS 13-15, n=15), moderate group B (GCS 9-12, n=20), severe group C (GCS 6-8, n=15), and severe group D (GCS 3-5, n=15). Fifteen healthy

volunteers from the same period served as normal controls. All participants were excluded if they had a history of hepatic or renal insufficiency or other underlying metabolic diseases. Both experimental and control groups provided venous blood and clean midstream urine specimens at 2, 6, 12, 24, 48, and 72 hours post-injury. AKI was diagnosed according to clinical practice guidelines: absolute increase in serum creatinine 26.5 mol/L (or increase of 0.3 mg/dL) within 48 hours [11].

1.2 Specimen Collection and Reagents

Clean urine samples (20 mL) and peripheral venous blood (4 mL) were collected from healthy volunteers and traumatic brain injury patients after onset. Samples were centrifuged and supernatants were stored in a refrigerator for testing. Urinary L-FABP was detected using enzyme-linked immunosorbent assay (ELISA) with kits purchased from R&D Systems (USA). Serum SCr detection was performed in the hospital biochemistry laboratory using reagents from Roche (USA) and Hitachi biochemical analysis instruments for automated testing.

1.3 Statistical Analysis

SPSS 16.0 statistical software was used for data analysis. Measurement data were expressed as mean±standard deviation. Comparison among multiple groups was performed using one-way ANOVA, and intergroup differences were compared using LSD-T test. $P<0.05$ was considered statistically significant.

Results

2.1 Serum SCr Results

As shown in Table 1 , serum SCr levels in experimental group A showed no significant increase compared with the normal control group ($P>0.05$). Group B showed elevated SCr, while groups C and D demonstrated more pronounced elevation compared with controls ($P<0.05$). Differences in SCr levels among experimental groups were statistically significant ($P<0.05$). As GCS scores decreased, serum SCr levels gradually increased, showing a negative correlation ($P<0.05$, Figure 1 [Figure 1: see original paper]), indicating that more severe conditions were associated with more prominent creatinine elevation and higher incidence of acute kidney injury.

2.2 Urinary L-FABP Results

Urinary L-FABP levels in experimental group A showed no significant increase compared with controls ($P>0.05$, Table 1). Group B showed elevated urinary L-FABP, while groups C and D demonstrated more pronounced elevation ($P<0.05$). Differences in urinary L-FABP levels among experimental groups

were statistically significant (P<0.05). As patients' GCS scores decreased (severity increased), urinary L-FABP levels gradually increased, showing a negative correlation (P<0.05, Figure 2 [Figure 2: see original paper]).

2.3 AKI Occurrence

Based on SCr detection results and AKI diagnostic criteria, 5 patients in group C and 9 patients in group D developed AKI, with an incidence of approximately 21.54%. No AKI was observed in mild and moderate traumatic brain injury groups A and B. The incidence of AKI in severe traumatic brain injury patients was significantly higher than in mild and moderate cases. Among the 14 AKI patients, 1 case occurred at 6 hours post-injury, 5 cases at 12 hours, and 8 cases at 24 hours.

2.4 Comparison of Serum SCr and Urinary L-FABP Level Changes

Serum SCr elevation generally occurred after 12 hours post-injury, with the peak concentrated at 24–48 hours. AKI diagnosis based on SCr was most frequent at 24 hours (Figure 3 [Figure 3: see original paper]). Urinary L-FABP levels began to increase as early as 2 hours, peaked at 6 hours, and gradually decreased after 24 hours (Figure 4 [Figure 4: see original paper]). Urinary L-FABP elevation showed positive correlation with SCr elevation, but occurred significantly earlier. When comparing urinary L-FABP levels between AKI and non-AKI patients in groups C and D, AKI patients showed significantly higher values (11.02±1.54 g/mL vs. 8.63±0.85 g/mL, P<0.05).

Discussion

Acute traumatic brain injury is a critical condition with high morbidity and mortality, ranking second among all traumatic injuries but first in terms of disability and fatality rates [12-13]. Early assessment of injury severity is the prerequisite for achieving favorable outcomes, and accurate evaluation to detect AKI is crucial for treatment and prognosis. Previous studies have found that serum heart-type fatty acid-binding protein (H-FABP) holds certain reference value for early diagnosis and prognosis prediction in acute brain injury patients [14].

This study employed a single biomarker—urinary L-FABP—to assess traumatic brain injury severity. We found that urinary L-FABP levels in groups B, C, and D were significantly elevated compared with controls, while mild traumatic brain injury group A showed minimal increase. As patients' GCS scores decreased (injury severity increased), urinary L-FABP levels gradually increased, demonstrating a negative correlation (P<0.05), suggesting that urinary L-FABP can be used to assess traumatic brain injury severity. These findings further confirm the close relationship between urinary L-FABP levels and multiple functional impairments caused by traumatic brain injury. This may be related to L-FABP's roles in binding and transporting long-chain fatty acids, participating

in intracellular signal transduction, exerting antioxidant effects, and regulating cell growth and proliferation following brain injury. During severe conditions, the body requires secretion of more L-FABP to maintain homeostasis [15-17]. Additionally, we observed that urinary L-FABP levels began to increase at 2 hours post-injury, peaked at 6 hours, and gradually decreased after 24 hours. More severe injuries showed earlier elevation, more prominent increases, and later declines—though our study duration was insufficient to determine the exact timeline accurately. Therefore, urinary L-FABP can predict traumatic brain injury severity at an earlier stage, consistent with other domestic and international findings [16-18].

Clinically, serum creatinine and urine output are commonly used as AKI diagnostic criteria. However, these indicators are influenced by numerous factors, and by the time significant changes appear, renal function is already severely impaired and may be irreversible, reducing their sensitivity and specificity for early AKI diagnosis. This study detected serum SCr and found that more severe conditions were associated with more prominent SCr elevation, with group B showing increased SCr compared with controls ($P<0.05$) and groups C and D showing even more pronounced increases. Concurrent urinary L-FABP level changes were consistent with SCr changes, suggesting that urinary L-FABP can predict renal damage occurrence. However, urinary L-FABP elevation occurred earlier than SCr elevation, demonstrating that urinary L-FABP can indicate renal impairment more promptly and serves as a superior potential biomarker for diagnosing kidney injury. Comparison between AKI and non-AKI patients in groups C and D revealed that AKI patients showed significantly higher urinary L-FABP levels, indicating that urinary L-FABP changes are more sensitive. This is primarily because traumatic brain injury causes damage to vital organs including the heart and kidneys, which is controlled by multiple systems including the diencephalic regulatory center and hypothalamic-pituitary-adrenal axis, leading to increased renin-angiotensin and thromboplastin levels and resulting in neurogenic renal impairment. L-FABP protein expression is upregulated at damaged sites, facilitating renal tubular repair and causing markedly elevated urinary L-FABP levels—findings consistent with other researchers both domestically and internationally [17-20]. Studies have also found that early urinary L-FABP levels after renal ischemia are closely related to ischemia duration, peritubular capillary blood flow, and hospital stay. In mouse ischemia-reperfusion models, urinary L-FABP levels increased significantly after reperfusion, much earlier than serum creatinine elevation [19,21], which we will gradually confirm in future studies.

Since L-FABP is abundantly expressed in the liver, urinary L-FABP content is affected by blood levels, and its detection specificity and sensitivity are somewhat limited. This study found that urinary L-FABP can serve as a sensitive early biological marker for assessing traumatic brain injury severity and predicting post-traumatic AKI. However, our sample size was limited, and we could not determine the specific cutoff value for urinary L-FABP when AKI occurs. We believe that increasing research in this area will provide valuable assistance

to clinical practice.

References

[1] Kitchlu A, Adhikari N, Burns KA, et al. Outcomes of sustained low efficiency dialysis versus continuous renal replacement therapy in critically ill adults with acute kidney injury: a cohort study[J]. BMC Nephrol, 2015, 16(1): 127.

[2] Gomes E, Antunes R, Dias C, et al. Acute kidney injury in severe acute kidney injury in preterm infants[J]. Pediatr Res, 2016, 64(2):

[3] Li C, Wang H, Yin M, et al. The differences in the epidemiology and predictors of death between candidemia acquired in intensive care units and other hospital settings[J]. Intern Med, 2015, 54(23):

[4] Hanna M, Brophy P, Joshi M, et al. Early urinary biomarkers of trauma assessed by RIFLE criteria: a common feature without implications on mortality[J]. Scand J Trauma Resusc Emerg Med, 2010, 18: 1.

[5] Ho J, Tangri N, Komenda P, et al. Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis[J]. Am J Kidney Dis, 2015, 66(6): 993-1005.

[6] Xu Y, Xie Y, Shao X, et al. L-FABP: A novel biomarker of kidney disease[J]. Clin Chim Acta, 2015, 20(445): 85-90.

[7] Li G, Xu R, Ke Y, et al. Clinical observation of changes in coagulation routine and D-dimer during acute phase of craniocerebral injury[J]. J South Med Univ, 2008, 28(5): 758-60.

[8] Hossein N, Tahmineh A. Correlation between Glasgow Coma Scale and brain computed tomography-scan findings in head trauma patients[J]. Asian J Neurosurg, 2016, 11(1): 46-9.

[9] Foreman BP, Caesar RR, Parks J, et al. Usefulness of the abbreviated injury score and the injury severity score in comparison to the Glasgow Coma Scale in predicting outcome after traumatic brain injury[J]. J Trauma, 2007, 62(4): 946-50.

[10] Hu Y, Sun H, Yuan YQ, et al. Acute bilateral mass-occupying lesions in non-penetrating traumatic brain injury: a retrospective study[J]. BMC Surg, 2015, 15(1): 6-11.

[11] Kellum JA. Diagnostic criteria for acute kidney injury: present and future[J]. Crit Care Clin, 2015, 31(4): 621.

[12] Kawoos U, Mccarron RM, Auker CR, et al. Advances in intracranial pressure monitoring and its significance in managing traumatic brain injury[J]. Int J Mol Sci, 2015, 16(12): 28979-97.

[13] Pfeifer R, Teuben M, Andruszkow H, et al. Mortality patterns in patients with multiple trauma: a systematic review of autopsy studies[J]. PLoS One,

2016, 11(2): 1-9.

[14] Walder B, Robin X, Rebetez MM, et al. The prognostic significance of the serum biomarker Heart-Fatty acidic binding protein in comparison with S100b in severe traumatic brain injury[J]. J Neurotrauma, 2013, 30(19): 1631-7.

[15] Mcintosh AL, Atshaves BP, Landrock D, et al. Liver fatty acid binding protein Gene-Ablation exacerbates weight gain in High-Fat fed female mice[J]. Lipids, 2013, 48(5): 435-48.

[16] Huang H, Mcintosh AL, Martin GG, et al. Structural and functional interaction of fatty acids with human liver fatty acid-binding protein (L-FABP) T94A variant[J]. FEBS J, 2014, 281(9): 2266-83.

[17] Fujita D, Takahashi M, Doi K, et al. Response of urinary liver-type fatty acid-binding protein to contrast media administration has a potential to predict one-year renal outcome in patients with ischemic heart disease[J]. Heart Vessels, 2015, 30(3): 296-303.

[18] Ferguson M, Vaidya VS, Waikar SS, et al. Urinary liver-type fatty acid-binding protein predicts adverse outcome in acute kidney injury[J]. Kidney Int, 2010, 77(8): 708-14.

[19] Przybylowski P, Koc-Zorawska E, Malyszko JS, et al. Liver Fatty-Acid-Binding protein in heart and kidney allograft recipients in relation to kidney function[J]. Transplant Proc, 2011, 43(8): 3064-7.

[20] Kamijo-Ikemori A, Sugaya T, Ichikawa DA, et al. Urinary liver type fatty acid binding protein in diabetic nephropathy[J]. Clin Chim Acta, 2013, 424(424): 104-8.

[21] Hisamichi M, Kamijo-Ikemori A, Sugaya T, et al. Increase in urinary markers during the acute phase reflects the degree of chronic tubulointerstitial injury after ischemia-reperfusion renal injury[J]. Biomarkers, 2016, Mar 30: 1-9. [Epub ahead of print].

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Note: Figure translations are in progress. See original paper for figures.