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Urinary excretion of liver-type fatty acid-binding protein reflects the severity of sepsis

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Abstract

Sepsis due to microbial invasion often causes multiple organ failure (MOF), including acute kidney injury (AKI), with high mortality rates in serious cases. Hence, there is an urgent need for diagnostic biomarkers that can be used to rapidly, accurately, and easily detect sepsis to identify the condition early and guide the selection of appropriate treatment. Liver-type fatty acid-binding protein (L-FABP), which localizes in renal proximal tubules, is excreted into the urine in response to oxidative stress-induced tubular injury. Because of this mechanism, L-FABP has been reported to be a useful urinary biomarker not only for renal disease but also for the severity of sepsis. Based on this concept, we developed a new L-FABP point-of-care (POC) assay kit that can be used to rapidly measure human L-FABP in the urine to further improve the usefulness of this biomarker in clinical settings. In this review, we describe the molecular mechanisms of L-FABP, its clinical usefulness, and the performance of the POC assay kit.

Keywords: L-FABP, POC, Sepsis, AKI, Oxidative stress, Biomarker

Background

Sepsis is a severe inflammatory response to microbial invasion of the bloodstream and causes multiple organ failure (MOF), including acute kidney injury (AKI). Serious cases of sepsis have a high mortality rate. The initial definition of sepsis was proposed in 1991 [1] and then revised in 2001 [2] and 2016 [3] by the sepsis definition task-force. The most recent definition emphasized the severity of organ failure, although previous definitions mainly focused on inflammation. Sepsis was defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" in the most recent revision [3]. Moreover, Systemic Inflammatory Response Syndrome (SIRS) criteria were excluded, and a new clinical score for multiple organ failure was proposed, named the quick sepsis-related organ failure assessment (qSOFA) criteria, which comprise the following: a high respiratory rate (≥22/min), altered mentation, and low systolic blood pressure (≤100 mmHg). With the qSOFA criteria, a blood test is not necessary, and the scoring is very simple and intuitive compared with the SIRS criteria. Thus, all medical staff can identify patients with infections who are likely to have a poor outcome by using the qSOFA at the bedside, and the patients can receive appropriate treatment at an early stage.

Therefore, diagnostic biomarkers that can be used to rapidly detect sepsis and MOF and predict its progression are needed. These biomarkers could guide early decisions regarding the appropriate treatment for sepsis. To date, more than 170 biomarkers for sepsis have been evaluated [4]. Among these biomarkers, C-reactive protein (CRP) and procalcitonin (PCT) are reported that these have been most widely used, but these biomarkers require broader validation before they can be incorporated into the clinical criteria describing sepsis [3]. Hence, there is an urgent need for diagnostic biomarkers that can be used to rapidly, accurately, and easily detect the severity of sepsis to identify the condition early and guide the selection of appropriate treatment.

Liver-type fatty acid-binding protein (L-FABP), which localizes in renal proximal tubules, is excreted into the urine during the response to tubular injury in renal disease [5]. L-FABP has been shown to be a useful urinary biomarker for the diagnosis of renal disease in the following clinical conditions: diabetic nephropathy [6–9], anemia [10], acute kidney injury (AKI) [11–16], pediatric

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AKI [17], contrast medium-induced nephropathy [18, 19], IgA nephropathy [20], human immunodeficiency virus (HIV)-associated nephropathy [21, 22], and reduced graft function in renal transplantation [23, 24]. Numerous AKI cohort studies have reported increased urinary levels of L-FABP in patients with septic shock-induced AKI [25–28]. In this review, we describe the molecular mechanisms of L-FABP in response to ischemic and oxidative stress, the clinical usefulness of urinary L-FABP for sepsis, and a new method for detecting L-FABP using a POC assay kit.

Molecular characteristics of L-FABP

Fatty acid-binding proteins (FABPs) are members of the intracellular lipid-binding protein family and are expressed as 14–15 kDa proteins; they reversibly bind to hydrophobic ligands such as fatty acids and function as intracellular transporters [29]. To date, nine human FABPs have been identified: L-FABP (or FABP1), intestinal FABP (I-FABP or FABP2), heart FABP (H-FABP or FABP3), adipocyte FABP (A-FABP or FABP4), epidermal FABP (E-FABP or FABP5), ileal FABP (Il-FABP or FABP6), brain FABP (B-FABP or FABP7), myelin FABP (M-FABP or FABP8), and testis FABP (T-FABP, FABP9). The structure of L-FABP includes ten stranded β-barrel structures that form interior hydrophobic ligand binding pockets and two α-helixes as cap domains [30] (Fig. 1). The *l-fabp* gene has binding domains for the following transcriptional factors: hypoxia inducible factor (HIF-1α and HIF-2α), caudal-related homeobox (CDX), CCAAT/enhancer-binding protein (C/EBP), forkhead box A (FOXA), GATA, hepatocyte nuclear factor (HNF-1 and HNF-4), and peroxisome proliferator-activated receptor (PPAR), which are related to cell proliferation, cell differentiation, and lipid metabolism [31–33]. Hence, it was concluded that L-FABP transports free fatty acids to organelles such as the mitochondria and lysosomes for β-oxidation for use in these cellular processes [34].

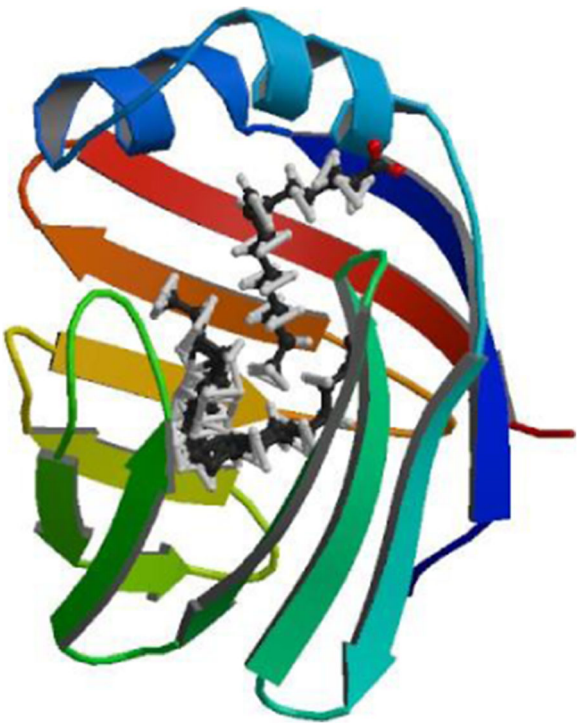

Fig. 1 Structure model of L-FABP (PDBID:2LKK). Two molecules of oleic acid are bound to L-FABP in the *inner pocket*

Ischemic and oxidative stress induces the excretion of L-FABP into the urine

Hypoxic regulation induces *l-fabp* gene expression by HIF-1α and HIF-2α [33]. To evaluate the response of L-FABP to hypoxic stress, the gene expression of *l-fabp* was measured in the LLC-PK1 porcine cell line, which was derived from proximal tubules, after the cells were cultured in hypoxic conditions using an anaerobic chamber. The results indicated that the expression level of *l-fabp* was increased by hypoxic stress (Fig. 2), demonstrating that L-FABP was a hypoxic-induced protein in proximal tubular cells [35].

It was also reported that L-FABP was excreted into the urine following ischemic stress in vivo. Yamamoto T. and colleagues studied the association of peritubular capillary blood flow with the urinary excretion of L-FABP during reperfusion after living donor kidney transplantation [36]. They found that urinary L-FABP was inversely correlated with peritubular capillary blood flow (Fig. 3). This finding indicates that L-FABP is excreted into the proximal tubular lumen in response to ischemic and oxidative stress [36].

Antioxidative effect of L-FABP

The findings regarding the response of L-FABP to ischemic and oxidative stress led to the hypothesis that L-FABP itself has an antioxidative role. Hence, the association of reactive oxygen species (ROS) generation with *l-fabp* gene expression was evaluated, and it was found that L-FABP itself has an antioxidative property that is independent of the activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) [37, 38]. The antioxidative capacity was also demonstrated using an animal model in which the human *l-fabp* gene was expressed in the proximal tubules of transgenic mice (Tg-mice) [39]. Administration of aristolochic acid [40] and aldosterone [41], which induced ROS generation, promoted tubular injury and the urinary excretion of L-FABP. However, the oxidative markers Nε-hexanoyl lysine (HEL) and 2-thiobarbituric acid reactive substances (TBARS) were lower in the Tg-mice than in the wild type controls, indicating that the

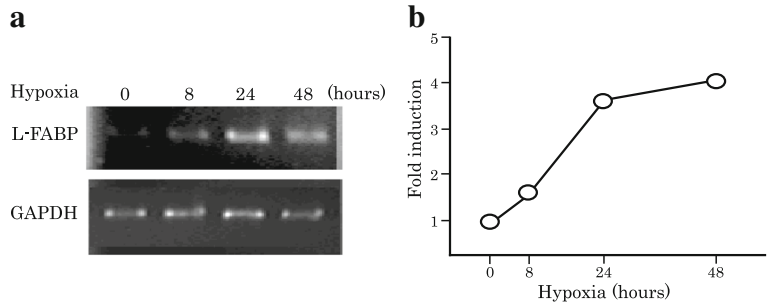

Fig. 2 Expression of the *l-fabp* gene following hypoxic stress. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene. The results of the RT-PCR analysis are shown in (**a**), and the quantified the expression levels are shown in (**b**) [35]

tubulointerstitial injury caused by ischemic and oxidative stress was attenuated by the antioxidative effect of L-FABP. The kidney contains a large amount of fatty acids, which can easily form lipid peroxides (LOOH), through peroxidation. Because L-FABP has high selectivity for fatty acids possessing long alkyl chains or carbon double bonds, or fatty acid peroxides [42–44] (Table 1), suggesting that L-FABP might protect the kidney by removing LOOH from the proximal tubules as shown in Fig. 4.

Urinary L-FABP reflects the severity of sepsis

As mentioned above, L-FABP has an antioxidant capacity and is excreted into the urine in response to ischemic and oxidative stress. It has also been reported that endotoxin-induced oxidative stress in sepsis induces AKI in patients [45], suggesting that L-FABP would be excreted into the urine in these cases. Indeed, it was shown that the urinary L-FABP level was higher in patients with sepsis than in healthy controls [25, 26] (Table 2). It was noted that urinary L-FABP levels differed significantly among patients with septic shock, severe sepsis, or AKI and healthy subjects (as well as patients with an infectious disease or a non-infectious disease). An endotoxin removal cartridge (Toraymyxin) composed of a polymyxin B-immobilized fiber (PMX-F) was developed to apply to patients with endotoxemia or suspected gram-negative infection [46]. Our group also showed that PMX-F hemoperfusion decreased the plasma endotoxin level, urinary L-FABP level, and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) level [25, 47]. Doi K et al. were also reported that in patients treated with PMX, the urinary L-FABP and blood endotoxin levels decreased in survivors but not in non-survivors [48].These reports suggested that the urinary L-FABP level might reflect the severity of the oxidative state in patients with sepsis and have value as an indicator of whether the treatment is successful.

Predicting poor outcomes

Several studies have reported the clinical significance of urinary L-FABP as a predictor of and risk factor for poor outcomes. Urinary L-FABP can predict the onset of AKI after cardiac surgery [13, 49, 50], pediatric cardiopulmonary bypass [17], stem cell transplantation [12], and endovascular and open-abdominal aortic aneurysm repair [16] as well as in intensive care unit populations [15]. Additionally, L-FABP can also predict the progression to end-stage renal disease (ESRD), the onset of cardiovascular disease (CVD), or death for patients with AKI [14, 51], type 2 diabetes [8, 52], or chronic kidney

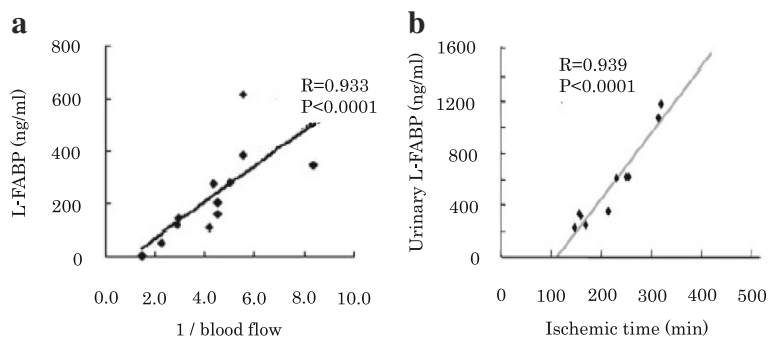

Fig. 3 Correlation between ischemic stress and urinary L-FABP. **a** Correlation between peritubular capillary blood flow and urinary L-FABP. **b** Correlation between ischemic time and urinary L-FABP. *R* indicates correlation coefficient [36]

Table 1 Affinity of fatty acids for L-FABP

Fatty acids		K_d (μM)	Refs.
Palmitic acid	16:0	4.02	[42]
Oleic acid	18:1, n-9	0.89	
Arachidonic acid	20:4, n-6	0.44	
Eicosapentaenoic acid	20:5, n-3	0.2	[43]
Docosapentaenoic acid	22:5, n-3	0.067	
Docosahexaenoic acid	22:6, n-3	0.14	
Tetracosapentaenoic acid	24:5, n-3	0.066	
Tetracosahexaenic acid	24:6, n-3	0.18	
Arachidonic acid	20:4, n-6	0.11	
Adrenic acid	22:4, n-6	0.11	
Tetracosatetraenoic acid	24:4, n-6	0.054	
Tetracosapentaenoic acid	24:5, n-6	0.007	
Oleic acid	18:1, n-9	1.2	[44]
Arachidonic acid	20:4, n-6	1.7	
15-Hydroperoxy-5, 8, 11, 13-eicosatetraenoic acid (15-HPETE)		0.076	
5-Hydroxy-6, 8, 11, 14-eicosatetraenoic acid (5-HETE)		0.175	
15-Hydroxy-5, 8, 11, 13-eicosatetraenoic acid (15-HETE)		1.8	

disease (CKD) [53] or those who have undergone cardiac catheterization [54, 55] or renal transplantation [56, 57]. Clinical prospective observation studies to predict mortality in sepsis using urinary L-FABP have been conducted with both adult patients and pediatric patients (Table 3) [27, 28]. A significant difference in the urinary L-FABP level in the first urine sample was observed between survivors and non-survivors in each study. In the ROC curve analysis, the area under the curve (AUC) values were 0.993 (95% CI, 0.956–0.999) for adult patients and 0.647 (95% CI, 0.500–0.795) for pediatric patients. Further improvement would be required before using L-FABP as a predictor of mortality in pediatric patients with sepsis, but it might be useful for adult patients because the AUC-ROC of urinary L-FABP was significantly higher than the acute physiology and chronic health evaluation (APACHE) II score (0.927) and sepsis-related organ failure assessment (SOFA) score (0.813) (Fig. 5) [27].

Animal models of sepsis

Animal models that mimic human sepsis have been developed, and their usefulness was reviewed by Doi K. et al. [58]. The diagnostic value of urinary L-FABP for sepsis has been evaluated in animal models of sepsis [27]. In this study, sepsis was induced by cecal ligation puncture (CLP) or intratracheal lipopolysaccharide (LPS) injection, causing mild tubular damage with vacuolization, an increase in bronchoalveolar lavage fluid protein, and leukocyte infiltration in the interstitial space of the

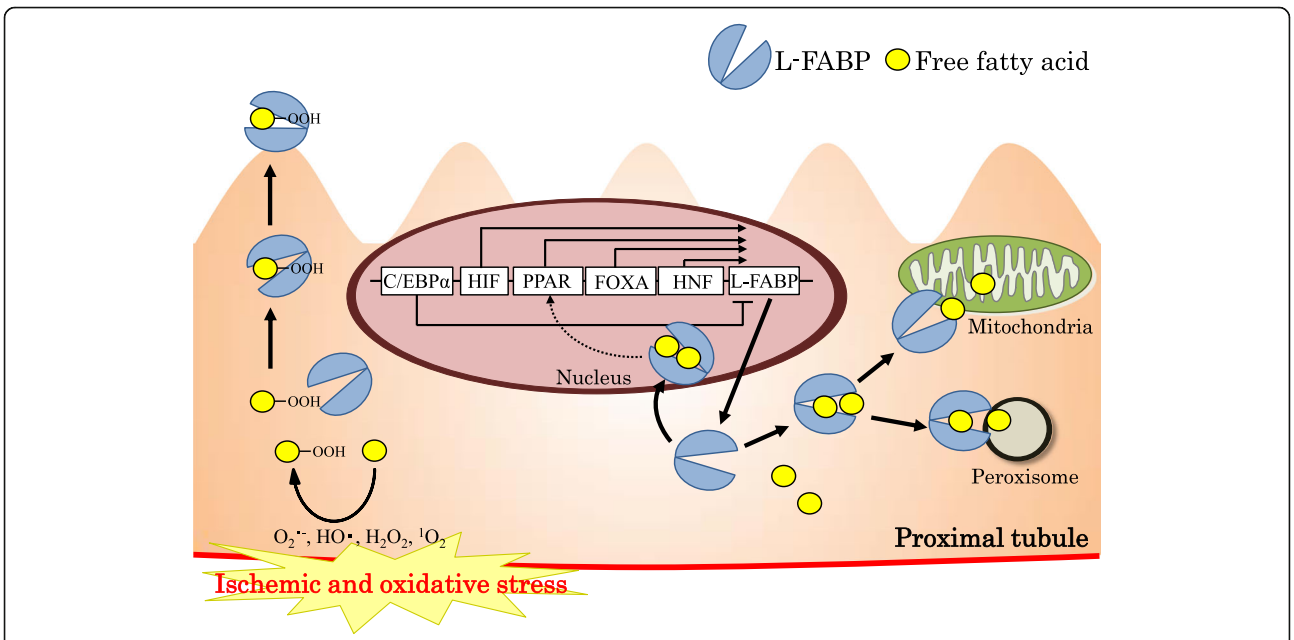

Fig. 4 Schematic model for the urinary excretion of L-FABP. In the kidney, fatty acids are transferred into proximal tubules together with albumin. Free fatty acids bind to L-FABP and are relocated to the mitochondria, peroxisome, or nucleus. If lipid peroxidation products accumulate in the proximal tubules, L-FABP binds to those cytotoxic lipids and is excreted into the urine

Table 2 Urinary L-FABP levels in patients with sepsis

	Number	Urinary L-FABP concentration	Refs.
Septic shock			
PMX-F treatment	40	1860 ± 1260 μg/g Cr	[25]
Nom-PMX-F treatment	10	1740 ± 1140 μg/g Cr	
Severe sepsis	20	248 ± 100 μg/g Cr*	
AKI	20	120 ± 84 μg/g Cr*†	
Healthy subjects	30	4.2 ± 2.4 μg/g Cr*†	
Sepsis (severe sepsis/septic shock)	25	2054 ± 8839 ng/ml	[26]
SIRS	13	598 ± 1939 ng/ml	
Infectious disease	20	33 ± 57 ng/ml	
Non-infectious disease	22	9.0 ± 10.4 ng/ml	

Values are presented as the mean ± SD
*$P < 0.001$ vs. septic shock; †$P < 0.01$ vs. severe sepsis
Cr indicates creatinine

lung. Urinary L-FABP was higher in the severe group than in the less severe group and sham-operated animals, suggesting it can indicate the severity of sepsis.

These reports indicate that urinary L-FABP might not only detect the severity of sepsis but also predict poor outcomes. Although, to date, there have been several reports on diagnosing sepsis using urinary L-FABP, additional studies are required to elucidate the usefulness of urinary L-FABP within the context of the new definition of sepsis.

POC assay kit for urinary L-FABP

In many studies, L-FABP was measured using the enzyme-linked immunosorbent assay (ELISA) method. However, this assay requires several hours, specialized equipment, and highly trained personnel to obtain reliable results. If L-FABP is to be used to diagnose sepsis, the method must be rapid, accurate, and easy to perform at the bedside. Therefore, we developed the L-FABP POC assay kit, which can rapidly measure human L-FABP in the urine.

Clinical significance of the POC assay for urinary L-FABP

The principles of the POC assay kit are shown as Fig. 6. The POC assay kit utilizes an immuno-chromatography method, and the result is obtained within 15 min. The POC assay and ELISA (CMIC HOLDINGS Co., Ltd., Tokyo, Japan) were performed on urine samples from two groups of patients: 35 patients who were admitted to the intensive care unit (ICU) at Shinmatsudo Central General Hospital (Chiba, Japan) as critically ill patients with sepsis (186 points) and 80 patients who were outpatients with CKD at St. Marianna University School of Medicine Hospital (Kanagawa, Japan) (106 points). When the ELISA and POC assay results were compared, the result of POC assay was assessed using three-score method, score 1; <12.5 ng/ml, score 2; ≥12.5 ng/ml and <100 ng/ml, or score 3; ≥ 100 ng/ml (Fig. 7). It is important to measure the higher range near 100 ng/ml for ICU patients because it was suggested that upper levels of urinary L-FABP than 100 μg/g Cr may be specific to septic shock [25]. Additionally, it is also important to measure the range near 12.5 ng/ml for CKD patients because it was reported that levels of urinary L-FABP above the

Table 3 Urinary L-FABP levels in patients with sepsis

	Number	Urinary L-FABP concentration			Refs.
Septic shock					
Non-survivors	68	4366 ± 192 μg/g Cr*			[27]
Survivors	77	483 ± 71 μg/g Cr			
Pediatric sepsis		First urine	Day 1	Day 2	
Non-survivors	22	715 ng/ml** (61.4–2470)	370 ng/ml (67.0–2047)	580 ng/ml† (38.8–2053)	[28]
Survivors	83	107 ng/ml (35.1–303)	152 ng/ml (40.1–627)	68.2 ng/ml (21.6–231)	

Urine samples were obtained at the time of admission to the ICU except as otherwise noted. Values are presented as the mean ± SEM [27] or median (interquartile range) [28]
*$P < 0.05$ vs. survivors; **$P = 0.034$ vs. survivors; †$P = 0.016$ vs. survivors
Cr indicates creatinine

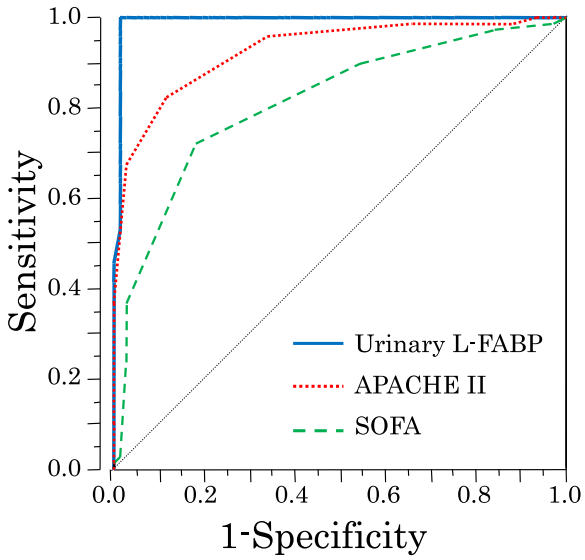

Fig. 5 Mortality prediction using urinary L-FABP, APACHE II, and SOFA. Receiver operation characteristic curve analysis for the prediction of mortality was performed using patients with septic shock with AKI ($n = 145$, mortality rate = 47%) [27]

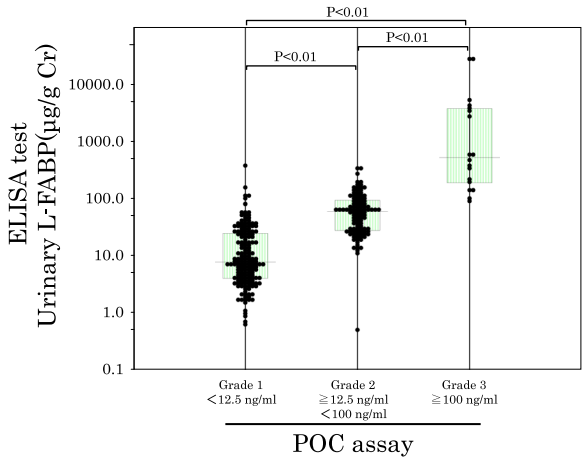

Fig. 7 Correlation between the ratio of urinary L-FABP to urinary creatinine and POC assay results. Urine samples from 35 patients who were admitted to the ICU (186 points) and from 80 patients who were outpatients with CKD (106 points) were measured with the ELISA test and POC assay. The test lines obtained with the POC assay were assessed using three-score method. The L-FABP/creatinine levels from the ELISA were log transformed, and the median and quartile values are presented with the score obtained with the POC assay. Statistical analysis was performed with the Mann-Whitney *U* test

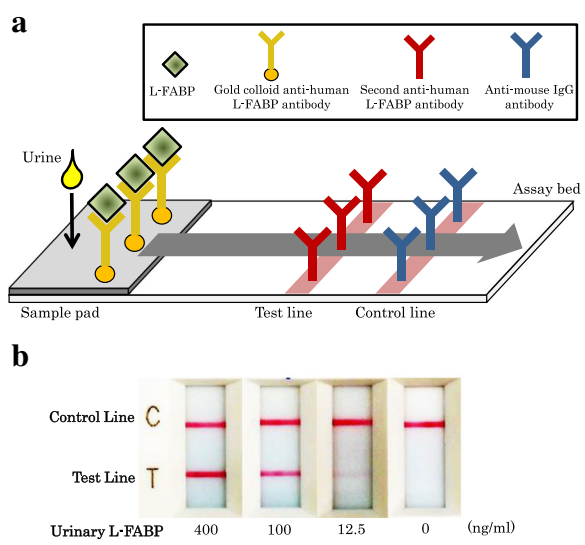

Fig. 6 L-FABP POC assay kit. **a** Schematic representation of the immuno-chromatographic assay. When the urine samples are applied to the sample pad, L-FABP proteins in the sample react with a gold colloid anti-human L-FABP mouse monoclonal antibody. The antigen-antibody complexes move in the assay bed by capillary action to a second anti-human L-FABP mouse monoclonal antibody situated on the test line, and the conjugate is visualized with a *red line*. **b** *Color chart* of the POC assay kit for quantitative measurements. The test line (T) and control line (C) were visualized within 15 min after applying the urine samples

upper limit of the reference value (8.4 μg/g Cr [6]) are a risk factor for the progression to ESRD, the onset of cardiovascular disease CVD, and death [53]. When we reanalyzed reference value to L-FABP concentration, the reference value which converted to L-FABP concentration was 10.1 ng/ml. Therefore, the assessment of the upper level of 12.5 ng/ml in POC assay indicated that urinary L-FABP/creatinine level was at least the upper level of 8.4 μg/g Cr.

The correlation between the ratio of urinary L-FABP to urinary creatinine and POC assay results and the accuracy of the L-FABP POC assay for diagnosis of the patients with sepsis or CKD was evaluated for clinical use. The ratio of urinary L-FABP to urinary creatinine for the ICU patients and the outpatients were determined and compared with the POC assay results. The results showed multi-group comparisons revealed significant differences in the L-FABP/creatinine levels between the results of the POC assay (Fig. 7). Additionally, it was found that the specificity (true negative ratio) and sensitivity (true positive ratio) to assess the reference value (8.4 μg/g Cr) were 99% (87/88) and 61% (125/204), respectively. Recently, Asada T. and colleagues reported that concentration of urinary L-FABP above the upper limit of the reference value (100 ng/ml) were defined as a risk factor of AKI in ICU patients [59]. This report supports the validity of the higher cutoff value of L-FABP (100 ng/ml) for diagnosis of AKI. Further evaluation is necessary to confirm the cutoff values of L-

FABP. Moreover, Sato R. and colleagues reported that urinary L-FABP levels in ICU patients including those with sepsis were also measured using the POC assay [26]. They found a positive correlation between serum creatinine levels and POC assay score, suggesting that the L-FABP POC assay might be alternative method for assessing creatinine levels, which are widely used. These results indicate the potential of the POC assay for use in diagnosing sepsis-induced AKI and CKD in patients rapidly.

Clinical evaluation of POC assay for urinary L-FABP in PMX intervention

Clinical evaluation of the L-FABP POC assay kit was performed in PMX intervention.

The POC assay and ELISA (CMIC HOLDINGS Co., Ltd., Tokyo, Japan) were performed on urine samples from three patients who were admitted to the ICU at Shinmatsudo Central General Hospital (Chiba, Japan) as critically ill patient with sepsis. The lactate level which was described as the new criteria of sepsis in third international consensus definition for sepsis and septic shock (sepsis-3) was also evaluated at pre- and post-PMX intervention by the blood gas analyzer. In the result, the patient who is 84-year-old man had septic shock with transverse colon cancer after surgery suture failure. The lactate (mg/dl) and urinary L-FABP/creatinine (μg/g Cr) were decreased after PMX intervention. Moreover, the patient who is 93-year-old woman had septic shock with iliopsoas abscess. Similarly, the lactate and urinary L-FABP/creatinine were decreased after PMX intervention. The results of POC assay were assessed as score 3; ≥100 ng/ml at pre-1st PMX intervention and as score 1; <12.5 ng/ml at post-2nd PMX intervention in the patients (Fig. 8a, b). Urinary creatinine excretion was 78.6 and 112.7 mg/dl in pre-PMX and 117.3 and 220.1 mg/dl in post-PMX in two patients. These patients discharged from the hospital. In contrast, the patient who is a 75-year-old woman has septic shock with acute obstructive suppurative cholangitis. In the patient after PMX intervention, the lactate was decreased slightly, whereas the urinary L-FABP was increased. Also, the result of POC assay was assessed as score 2; ≥ 12.5 and <100 ng/ml at pre-PMX intervention, and as score 3; ≥100 ng/ml at post-PMX intervention (Fig. 8c). Urinary creatinine excretion was 78.6 mg/dl in pre-PMX and 19.1 mg/dl in post-PMX. The patient died after 3 days of PMX intervention. In this case, serum lactate and urinary L-FABP levels were sustained abnormal level in each point. In this sense, neither lactate value nor urine L-FABP value decreased by PMX intervention. Furthermore, another group developed a new algorithm by combining urinary

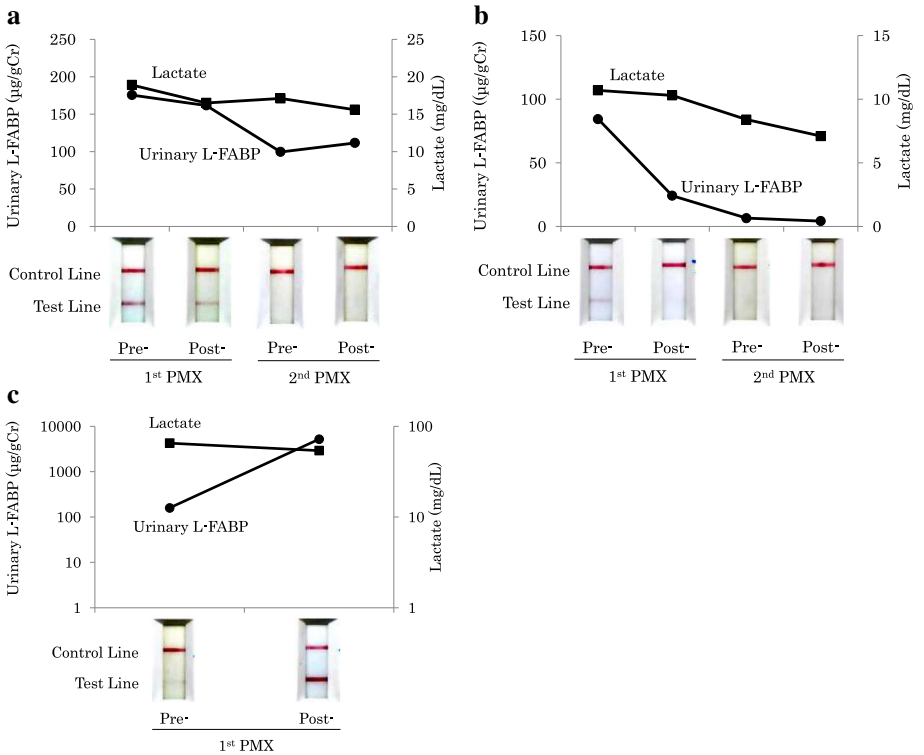

Fig. 8 Correlation between the ratio of urinary L-FABP to urinary creatinine, POC assay results and lactate levels in PMX-treated patients. Urine samples from three patients who were admitted to the ICU were measured with the ELISA test and POC assay. The test lines obtained with the POC assay kit were scored using three-score method. Lactate levels measured by the blood gas analyzer. Two patients had discharged from the hospital (**a**, **b**). Another patient died after 3 days of PMX intervention (**c**)

NGAL and L-FABP with stratification by the APACHE II score, presence of sepsis and blood lactate levels to improve their AKI predictive performance [59]. From this report, it is also considered that there are cases in which it is difficult to make a prognostic prediction only by changes in urine L-FABP in a high concentration range. As a whole, when the score of POC assay for urinary L-FABP and lactate level were decreased in the patients after PMX intervention, the patient tended to improve the condition. On the other hand, when the score of POC assay and lactate were sustained high level in the patient even after PMX intervention, the patient tended to deteriorate the condition. Therefore, these results suggested that POC assay for urinary L-FABP may be useful to evaluate therapeutic efficacy of PMX intervention in sepsis patient.

Conclusions

In conclusion, endotoxin induces oxidative stress and the excretion of L-FABP into the urine in patients with sepsis-induced AKI. If urinary L-FABP can be measured in these patients, it is possible to diagnose the severity of sepsis. However, to date, there is little evidence for the clinical usefulness of urinary L-FABP for sepsis. Further studies are required to elucidate the reliability of diagnostic methods using urinary L-FABP and to determine the cutoff values for predicting poor outcomes. The L-FABP POC assay kit is expected to be useful for its rapidness and simplicity. Our study was performed at a single center. Our findings should be confirmed in a large multicenter trial. Future studies need to be conducted.

Abbreviations

A-FABP/FABP4: Adipocyte-type fatty acid-binding protein; AKI: Acute kidney injury; APACHE: Acute physiology and chronic health evaluation; AUC: Area under the curve; B-FABP/FABP7: Brain-type fatty acid binding protein; CAT: Catalase; CDX: Caudal-related homeobox; C/EBP: CCAAT/enhancer-binding protein; CKD: Chronic kidney disease; CLP: Cecal ligation puncture; Cr: Creatinine; CRP: C-reactive protein; CVD: Cardiovascular disease; E-FABP/FABP5: Epidermal-type fatty acid-binding protein; ELISA: Enzyme-linked immunosorbent assay; ESRD: End-stage renal disease; FABPs: Fatty acid-binding proteins; FOXA: Forkhead box A; GPx: Glutathione peroxidase; HEL: Nε-hexanoyl lysine; HIF: Hypoxia inducible factor; HIV: Human immunodeficiency virus; H-FABP/FABP3: Heart-type fatty acid-binding protein; HNF: Hepatocyte nuclear factor; ICU: Intensive care unit; I-FABP/FABP2: Intestinal-type fatty acid-binding protein; Il-FABP/FABP6: Ileal-type fatty acid binding protein; L-FABP/FABP1: Liver-type fatty acid-binding protein; LOOH: Lipid peroxides; M-FABP/FABP8: Myelin-type fatty acid-binding protein; MOF: Multiple organ failure; 8-OHdG: 8-Hydroxy-2′-deoxyguanosine; PCT: Procalcitonin; PPAR: Peroxisome proliferator-activated receptor; POC: Point-of-care; PMX-F: Polymyxin B-immobilized fiber; qSOFA: Quick sepsis-related organ failure assessment; ROC: Receiver operatorating characteristic; ROS: Reactive oxygen species; SIRS: Systemic inflammatory response syndrome; SOD: Superoxide dismutase; SOFA: Sepsis-related organ failure assessment; TBARS: 2-Thiobarbituric acid reactive substances; T-FABP/FABP9: Testis-type fatty acid-binding protein; Tg-mice: Transgenic mice

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Authors' contributions

ES, AK-I, TS, KK, TN, and YS contributed to the study design. AO, TO, AK-I, and ES performed the data collection. ES, TO, and TS participated in the data analysis. ES, AK-I, TO, TS, and TN interpreted the data. ES and TO carried out the literature search and generation of figures. ES and TO wrote the manuscript. All authors gave their final approval of the submitted version.

Competing interests

T. Sugaya is the Director and Senior scientist, and T. Oikawa and A. Okuda are the scientist of CMIC HOLDINGS Co., Ltd., the company that produced the ELISA and POC assay for L-FABP analysis.
None of the other authors have competing interest or financial disclosures of any relevance to the present study.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Our study received approval from the ethic examination of the ethics committee of St. Marianna University School of Medicine on November 11, 2014 (accept no. 2856). We obtained written informed consent from the subjects and registered them as study subjects.

Publisher's Note

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