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Intestinal fatty acid–binding protein levels in patients with chronic renal failure

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ARTICLE INFO

Article history:
Received 8 February 2018
Received in revised form
30 March 2018
Accepted 24 April 2018
Available online xxx

Keywords:
Biomarker
Critically ill patients
Enterocyte
Glomerular filtration rate
Intestinal ischemia
Renal insufficiency

ABSTRACT

Background: Intestinal fatty acid–binding protein (I-FABP), a biomarker of enterocyte injury, has been reported to be a diagnostic marker of intestinal ischemia and a prognostic marker in critically ill patients. However, the kinetics of I-FABP in renal failure patients is unknown. We sought to identify I-FABP levels in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) on hemodialysis (HD) and to identify the manner in which the I-FABP levels change.

Materials and methods: Adult patients who were admitted for elective cardiac surgery with either normal renal function (NRF), CKD, or ESKD on HD were enrolled. Serum I-FABP levels in NRF and CKD patients and in ESKD patients before and after HD were determined.

Results: A total of 124 patients were evaluated: 47 NRF, 53 CKD, and 24 ESKD. The I-FABP levels of the CKD patients and pre-HD ESKD patients were significantly higher than those of the NRF patients ($P = 0.018$ and $P < 0.001$, respectively). I-FABP levels were significantly negatively correlated with the estimated glomerular filtration rate in NRF and CKD patients (Spearman's $\rho = -0.313$, $P = 0.002$). In addition, I-FABP levels in ESKD patients were significantly lower after HD than those before HD ($P < 0.001$).

Conclusions: I-FABP levels in CKD and pre-HD ESKD patients were significantly higher than those in NRF patients. In addition, I-FABP was significantly eliminated by HD in patients with ESKD. Clinicians and researchers should consider this aspect of I-FABP when using it as a diagnostic and prognostic marker in patients with renal insufficiency.

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https://doi.org/10.1016/j.jss.2018.04.057

Introduction

Intestinal fatty acid–binding protein (I-FABP) is a low–molecular weight (14-15 kDa) cytosolic, water-soluble protein specifically expressed by enterocytes from the duodenum to the ileum.[1] I-FABP is rapidly released into systemic circulation on enterocyte injury and is thus reported as a useful biomarker for diagnosing acute intestinal ischemia, including nonocclusive mesenteric ischemia (NOMI),[2,3] and necrotizing enterocolitis.[4] Recently, it was reported that an elevated I-FABP level was associated with states of shock and 28-day mortality in general ICU patients.[5] Relevant studies have been conducted to investigate I-FABP levels, related factors, and the clinical course of critically ill patients, including septic shock,[6,7] trauma,[8] cardiac arrest,[9] acute heart failure,[10] and cardiovascular surgery with cardiopulmonary bypass.[11]

I-FABP is thought to be rapidly cleared by the kidneys (half-time of approximately 11 min) similar to other members of the FABP multigene family.[12,13] I-FABP levels in patients with renal insufficiency are predicted to be elevated, although it can be removed by renal replacement therapy. However, these aspects of I-FABP are not fully elucidated. It is important to study I-FABP levels in renal failure patients, as most patients suffering from critical illnesses also suffer from renal problems,[14] and these problems likely alter I-FABP levels. Therefore, clinicians and researchers who use I-FABP as a diagnostic and prognostic marker should be aware of the typical concentration and kinetics of I-FABP in patients with renal problems.

The purpose of this pilot study was to elucidate the association between the I-FABP level and renal function in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) undergoing hemodialysis (HD) and to determine whether I-FABP is eliminated by HD in patients with ESKD.

Materials and methods

Study design and oversight

We conducted a single-center, prospective, preliminary, observational study in a dialysis unit and operation room at Nagasaki University Hospital from July 2014 to March 2017. The study was approved by the Institutional Review Board of Nagasaki University Hospital (No.14032491), and written informed consent was obtained from the patients.

Study population

Adult (≥18 y of age) patients with normal renal function (NRF), CKD, and ESKD undergoing conventional HD, who were admitted to our hospital for elective cardiac surgery, were randomly enrolled. Exclusion criteria were as follows: history of small intestine resection or recent abdominal complication, recent admission to the hospital for acute cardiac failure, cardiogenic pulmonary edema, and renal failure.

Data collection

Data on age, sex, body mass index, admitting diagnosis, comorbidities, and left ventricular ejection fraction were collected for all patients at baseline.

Blood samples for I-FABP in NRF and CKD patients were collected at the time of anesthetic induction for the elective cardiac surgery. The blood samples were taken through the arterial line. Estimated glomerular filtration rates (eGFRs) of patients with NRF and CKD were calculated using serum creatinine (Cr) measured at admission. eGFR was used as a measure of renal function and was calculated using the following equation for Japanese patients: eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ (if female × 0.739).[15]

Blood samples for I-FABP and Cr for ESKD patients on HD were collected just before (pre) and just after (post) conventional HD, and before the elective cardiac surgery. The blood samples were taken through the arterial line of their vascular access. The HD protocols were as follows: 150-320 mL/min blood flow, 500 mL/min dialyzate, and 4 h of treatment. Blood flow, amount of water removal, and the dialyzers were decided by the attending physician in the dialysis unit. Dialysis time, the amount of water removal, and dialysis vintage of the patients were collected.

Serum Cr was measured by enzymatic methods using a commercial kit (Mizuho Medy CO, Ltd Saga, Japan) at Nagasaki University Hospital.

Serum I-FABP measurement

Samples for I-FABP analysis were separated by a centrifugal separator and the serum was frozen at −20°C until assayed. All measurements were performed in a blinded fashion at a laboratory (DS Pharma Biomedical Co, Ltd Osaka, Japan) according to manufacturer's instructions, using an enzyme-linked immunosorbent assay highly specific for human I-FABP (DS Pharma Biomedical Co, Ltd Osaka, Japan).[16]

Statistical analysis

Baseline characteristics were compared among NRF patients, CKD patients, and ESKD patients on HD. For this pilot study, NRF was defined as eGFR ≥60 mL/min/1.73 m^2; CKD was defined as eGFR <60 mL/min/1.73 m^2;[17] and ESKD patients on HD were those who needed maintenance HD for ESKD. We could not subdivide the patient groups because of the small number of participants. Categorical variables are presented as frequencies and percentages, and quantitative variables as medians and interquartile ranges (IQRs). Differences between groups were assessed using the Kruskal–Wallis test and Fisher's exact test.

I-FABP levels of CKD patients and pre- and post-HD ESKD patients were compared with the levels for NRF patients using Wilcoxon's rank-sum test. The correlation of I-FABP levels and eGFRs in patients with NRF and CKD was evaluated using Spearman's rank correlation coefficient, ρ. The association of I-FABP levels and Cr levels before and after HD in ESKD patients was calculated by repeated measures ANOVA.

All tests were two sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using SAS version 9.4 (SAS institute Inc, Cary, NC) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Over a period of 2 y 9 mo, 282 patients with NRF, CKD, or ESKD on HD were assessed for eligibility. Among them, 47 patients with NRF, 53 with CKD, and 24 with ESKD on HD—that is, 124 patients in total—were randomly selected for study inclusion. There were no patients who met the exclusion criteria. Patient characteristics are presented in Table 1. The median eGFRs of the patients with NRF, CKD, and ESKD pre-HD were 71.8 (66.5-78.7) mL/min/1.73 m^2, 45.9 (37.4-53.2) mL/min/1.73 m^2, and 4.7 (4.0-5.3) mL/min/1.73 m^2, respectively. Patients with ESKD on HD had a median dialysis vintage (length of time on HD) of 70.5 (37.4-151.6) mo. Baseline characteristics were similar across the three groups except for age and some comorbidities.

I-FABP levels of NRF, CKD, and ESKD on HD patients

The results of the univariate analysis for I-FABP level of NRF, CKD, and ESKD on HD patients are shown in Figure 1. As compared with the I-FABP level of NRF patients (median, 2.6 [IQR: 1.7-3.9] ng/mL), the median I-FABP levels for CKD patients (3.4 [1.9-6.0] ng/mL, $P = 0.018$) and ESKD pre-HD patients (5.1 [2.8-8.3] ng/mL, $P < 0.001$) were significantly higher. In addition, the median I-FABP level for ESKD patients was lowered to the level in NRF patients (2.8 [1.2-4.3] ng/mL, $P = 0.88$) after HD. Previous studies applying the same measuring method determined that the mean I-FABP level in healthy adults was 1.1 ± 0.9 (range: 0.1-5.5) ng/mL.[16]

Correlation between I-FABP level and eGFR in patients with NRF and CKD

The correlation between I-FABP levels and eGFRs in patients with NRF and CKD is shown in Figure 2. The I-FABP levels were significantly negatively correlated with eGFRs, but the correlation coefficient was low (Spearman's $\rho = -0.313$, $P = 0.002$).

Elimination of I-FABP by HD

The increase in I-FABP seen in pre-HD ESKD patients was lost after HD treatment (Fig. 3). The post-HD levels were significantly lower compared with the pre-HD levels (5.1 [2.8-8.3] ng/mL *versus* 2.8 [1.2-4.3] ng/mL, $P < 0.001$), as were the Cr levels (9.34 [7.88-10.33] mg/dL *versus* 3.34 [2.82-3.98] mg/dL, $P < 0.001$) (Fig. 3). The post-HD eGFR value was significantly higher than the pre-HD value (4.7 [4.0-5.3] mL/min/1.73 m^2 *versus* 13.2 [12.0-15.3] mL/min/1.73 m^2, $P < 0.001$). The median HD treatment time was 246 (236-248) min, and the median total amount of water removed was 1925 (1375-2738) mL. There were no patients who complained of abdominal symptoms or developed shock before or during HD treatment.

Discussion

In this pilot study, we demonstrated that serum I-FABP levels in patients with CKD and ESKD on HD were significantly

Table 1 – Summary of baseline characteristics.

Characteristics	NRF ($n = 47$)	CKD ($n = 53$)	ESKD pre-HD ($n = 24$)	P value*
Age (y)	61 (52-72)	76 (71-79)	70 (64-75)	<0.001†
Male sex, *n* (%)	26 (55.3)	27 (50.9)	14 (58.3)	0.819
Body mass index (kg/m^2)	23.2 (19.8-24.9)	21.7 (19.6-25.4)	20.6 (19.4-22.9)	0.130
Admitting diagnosis				
Valve disease, *n* (%)	41 (87.2)	52 (98.1)	22 (91.7)	0.072
Coronary artery disease, *n* (%)	6 (12.8)	2 (3.8)	3 (12.5)	0.187
Other, *n* (%)	3 (6.4)	1 (1.9)	1 (4.2)	0.512
Comorbidity				
Hypertension, *n* (%)	19 (40.4)	32 (60.4)	12 (50.0)	0.133
Chronic heart failure, *n* (%)	19 (40.4)	38 (71.7)	11 (45.8)	0.004†
COPD, *n* (%)	4 (8.5)	2 (3.8)	1 (4.2)	0.603
Diabetes mellitus, *n* (%)	10 (21.3)	15 (28.3)	12 (50.0)	0.048†
Liver disease, *n* (%)	2 (4.3)	6 (11.3)	3 (12.5)	0.350
Ejection fraction (%)	64 (54-71)	64 (50-70)	63 (50-71)	0.942
Creatinine (mg/dL)	0.74 (0.63-0.85)	1.06 (0.86-1.30)	9.34 (7.88-10.33)	<0.001†
eGFR (mL/min/1.73 m^2)	71.8 (66.5-78.7)	45.9 (37.4-53.2)	4.7 (4.0-5.3)	<0.001†

Data are presented as the median (interquartile range) or *n* (%).
COPD, chronic obstructive pulmonary disease.
* *P* values were determined by Kruskal–Wallis test or Fisher's exact test.
† Statistically significant: $P < 0.05$.

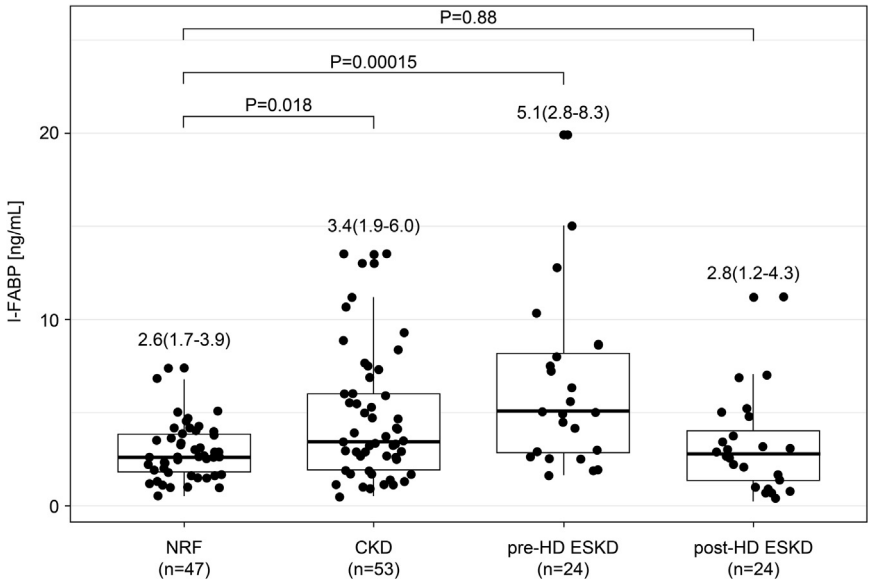

Fig. 1 – I-FABP levels for patients with NRF, CKD, and ESKD on HD. As compared with the I-FABP level of NRF patients, the I-FABP levels for CKD patients and ESKD pre-HD patients were significantly higher. In addition, the I-FABP level was lowered to the level of NRF patients for ESKD patients after HD. I-FABP levels are presented as the median (interquartile range).

elevated as compared to the values in patients with NRF. In addition, the increase in the I-FABP levels of patients with ESKD was decreased significantly by conventional HD to nearly the level in patients with NRF.

Acute mesenteric ischemia is one of the major causes of death among ICU patients.[18] However, diagnosis of acute mesenteric ischemia in ICU patients, especially NOMI, is often difficult because of its nonspecific physical and laboratory findings.[19] Recently, I-FABP has been reported as a new, reliable marker of acute intestinal ischemia, including NOMI.[2] It is well known that renal failure and HD are the major risk factors for NOMI.[20,21] However, the influence of renal function on the level

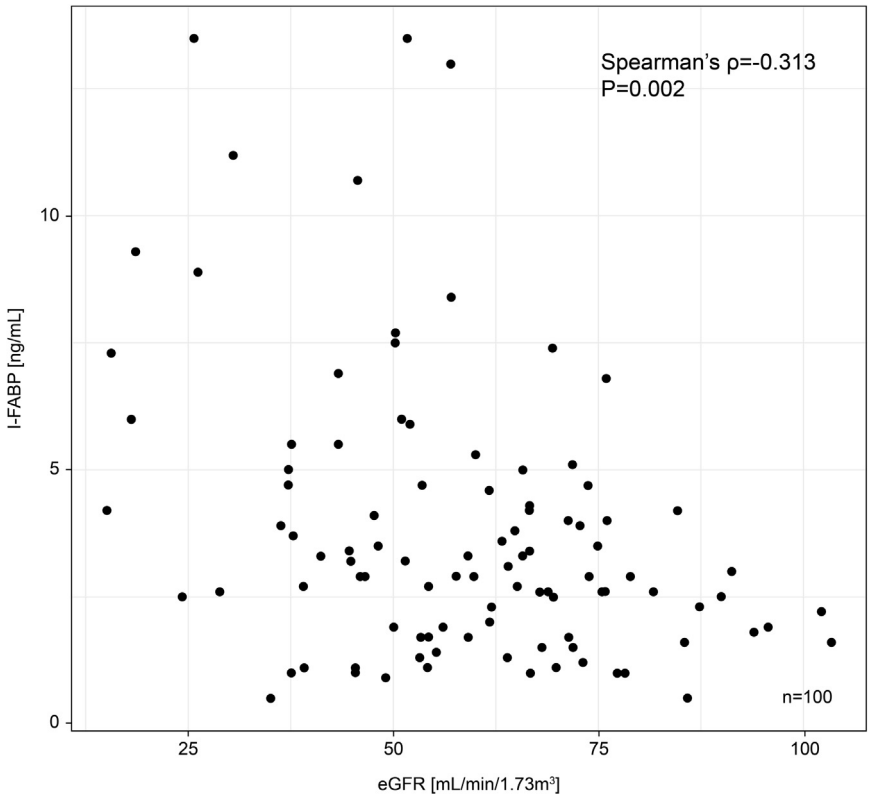

Fig. 2 – Correlation between I-FABP levels and eGFRs in patients with NRF and CKD. I-FABP level was significantly negatively correlated with eGFR, but the correlation coefficient was low.

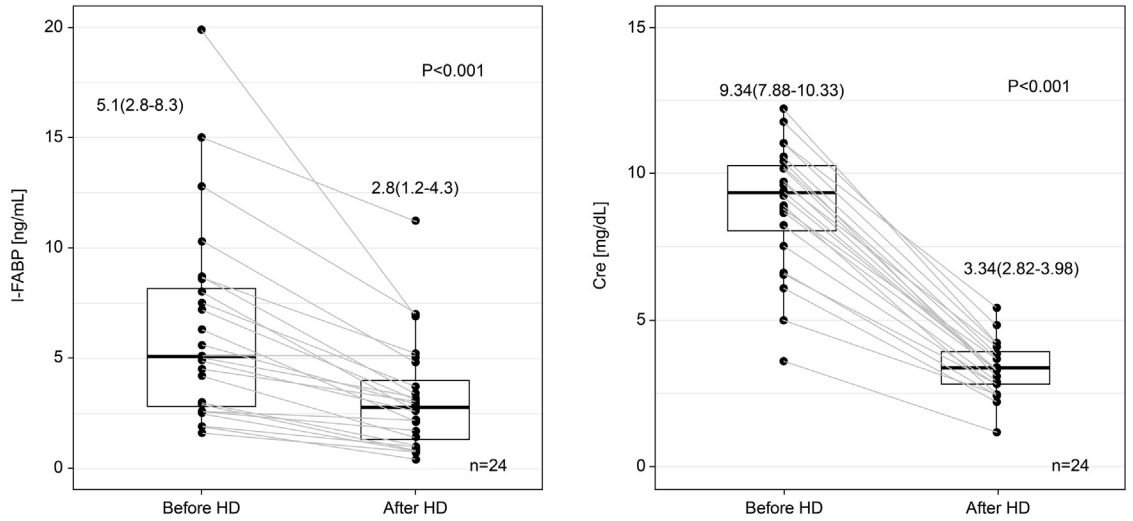

Fig. 3 – Elimination of I-FABP by HD in ESKD patients. I-FABP levels were significantly lowered by HD treatment compared with pre-HD, as were the levels of Cr. I-FABP and Cr levels are presented as the median (interquartile range).

of I-FABP has not been elucidated in the studies that investigated the diagnostic utility of I-FABP.[2,22,23] Therefore, the difference between the normal I-FABP levels and the cutoff point for diagnosis of intestinal ischemia between patients with NRF, CKD, and ESKD on HD has never been reported. In addition, the reports that investigated I-FABP as a prognostic marker of outcome and subsequent undesirable events in critically ill patients often did not take into account the influence of renal function on I-FABP levels in patients with a critical illness,[5] sepsis or septic shock,[6,7,24,25] trauma,[8,26] cardiac arrest,[9,27] or cardiovascular surgery with cardiopulmonary bypass,[11,28,29] despite the evidence that renal failure is often seen in patients with critical illnesses.[14,30] In a recent study that reported the association between I-FABP levels and adverse clinical outcomes in patients with acute decompensated heart failure, the impact of I-FABP on the outcome was neutral after adjusting for cofounders, including renal function.[10] Decreased clearance of I-FABP in patients with renal insufficiency was described as a limitation in some research articles.[5,6]

In this study, the median I-FABP levels in CKD and pre-HD ESKD patients were 3.4 (1.9-6.0) ng/mL and 5.1 (2.8-8.3) ng/mL, respectively. Previous studies applying the same measuring method determined the cutoff point for diagnosing vascular intestinal ischemia was 9.1 ng/mL.[2] Six of 53 patients (11.3%) with CKD and four of 24 patients (16.7%) with ESKD pre-HD had values that exceeded the cutoff point despite the absence of signs suspicious for intestinal ischemia. In addition, as I-FABP was eliminated significantly by conventional HD in patients with ESKD, interpretation of I-FABP levels must be carried out carefully. Our results suggest that the normal value for I-FABP in patients with CKD and those with ESKD on HD seems to be obviously high compared with patients with NRF, and the increase in I-FABP seen in ESKD patients is lost after HD. Therefore, when using I-FABP as a diagnostic biomarker of intestinal ischemia in a clinical setting, there is a possibility that renal insufficiency may lead to false-positive result in CKD and pre-HD ESKD patients and false-negative results in post-HD ESKD patients. Clinicians should be aware of this aspect of I-FABP when using it as a diagnostic as well as a prognostic marker in patients with renal insufficiency and research should be conducted based on this aspect of I-FABP. There is no specific biomarker that indicates enterocyte injury. Hence, it would be worthwhile to investigate the normal value and cutoff point of I-FABP for diagnosis of intestinal ischemia and prognosis of clinical outcome in patients with renal insufficiency in further studies with a large cohort.

This study has potential limitations. First, it was conducted in a single center with a small population, and the lack of previous research precluded a formal power calculation. In addition, all participants had cardiac problems, and the chronic heart failure rate was significantly higher in patients with CKD. Acute decompensated heart failure is reported as one of the potential causes of high I-FABP levels.[10] Indeed, the I-FABP levels of NRF patients (median, 2.6 [IQR: 1.7-3.9] ng/mL) seem to be higher than the previously reported value in healthy adults (mean, 1.1 ± 0.9 [range: 0.1-5.5] ng/mL).[16] There have been no investigations on the I-FABP levels in patients with chronic heart failure. However, there is a possibility that I-FABP levels in this study were affected by the hemodynamic parameters of the patients. In addition, age and a history of diabetes mellitus affect renal function and, as a result, might elevate I-FABP levels. This needs to be investigated further in a much larger cohort and in more detail. Second, eGFR was used as a measure of renal function in this study. GFR measured using the clearance of inulin should be used to collect accurate data, but the method is not applicable in daily practice. eGFR was calculated using the equation for Japanese patients, and this equation has been reported to provide reasonably accurate eGFR assessments and to be suitable for use in clinical practice and epidemiologic studies.[15]

Conclusions

This is the first organized study to evaluate the difference in I-FABP levels between patients with NRF, CKD, and ESKD on HD and to investigate the clearance of I-FABP by HD. Serum I-FABP levels in patients with CKD and pre-HD ESKD

patients were significantly higher than those in patients with NRF. Furthermore, post-HD I-FABP levels for patients with ESKD were significantly decreased, nearly to the level in patients with NRF. Clinicians and researchers should take into consideration this aspect of I-FABP when using it as a diagnostic and prognostic marker in patients with renal insufficiency. In addition, the normal value and cutoff point for I-FABP as a diagnostic and prognostic marker in these patients should be elucidated by further studies in a much larger heterogeneous cohort.

Acknowledgment

The authors would like to thank Editage (www.editage.jp) for English language editing.

Authors' contributions: K.O. and M.S. conceptualized, planned all experiments, collected and analyzed the data, and wrote the article. H.F. and T.H. conceptualized, planned all experiments, and analyzed the data. S.S. performed all the statistical analyses. T.I., H.M., T.M., M.N., and K.E. contributed to conception, data collection, and analysis. All authors were involved in the drafting or critical revision of the article and approved the final submitted version.

Disclosure

This work was supported in part by Japan Society for the Promotion of Science KAKENHI grants (16K10942 to MS). The remaining authors do not have any conflicts of interest. As this was a collaborative study with DS Pharma Biomedical, there is no conflict of interest with the company.

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