

# Liver Type Fatty Acid Binding Protein (L-FABP): A Marker of Contrast Induced -Acute Kidney Injury

Vijayasimha M, M.Sc, M.Phil  
Dept of Biochemistry, Micropath Med.Center, Gurgaon, India  
Email: mvsimha@yahoo.co.uk

Saroj Kumar Das Majumdar, MD  
Department of Radiotherapy, All India Institute of Medical Sciences, Bhubaneswar, Odisha

P VV Satyanarayana, Ph.D  
Dept of Biochemistry, Micropath Med.Center, Gurgaon, India

Ashok Yadav M.Sc  
Dept. of Biochemistry, Micropath Medical Center, Gurgaon-122051, Haryana

## Abstract

**Background:** Urinary Liver type fatty acid binding protein (L-FABP) is an early biomarker for renal damage. A few studies have been published analyzing the potential use of urinary Liver type fatty acid binding protein (L-FABP) as a biomarker for acute kidney injury. However no study has been done related to Acute Kidney Injury associated with contrast administration.

**Aim:** To search for new markers to identify Acute Kidney Injury (AKI) associated with contrast administration earlier than serum creatinine.

**Material and Methods:** We studied 100 consecutive patients with normal serum creatinine undergoing angiographic procedure. We assessed urinary liver type fatty acid binding protein (L-FABP) levels at basal, 2h, 4h, 12h, 24 h and 48 hours after the angiographic procedure. Serum creatinine was measured at basal, 24h and 48 hours after the procedure.

**Results:** There was a significant rise in urinary L-FABP levels at 12 hours after the angiographic procedure. The presence of contrast induced nephropathy associated with acute Kidney Injury was 9%.

**Conclusion:** The present study highlighted the importance of urinary L-FABP in detecting Acute Kidney Injury associated with contrast administration earlier than Serum creatinine.

**Keywords:** Liver type fatty acid binding protein (L-FABP). Glomerular Filtration Rate (GFR), Contrast induced acute kidney injury (CI-AKI).

## INTRODUCTION

Renal Failure is a silent epidemic of the 21st century. Its occurrence is universal; not confined to the developed countries. The numbers afflicted with Renal failure are going to rise sharply because of the rising incidence of diabetes mellitus and hypertension. Glomerular filtration rate is routinely assessed by measuring the serum markers such as urea nitrogen and serum creatinine. Although these markers are widely used to assess renal function, they do not perform optimally in certain clinical settings. Radio-contrast administration is one of the important reasons for Acute Kidney Injury. Acute Kidney Injury is an independent risk factor for mortality in adult and children<sup>(1-3)</sup> even with a small increase in serum creatinine<sup>(4-5)</sup>. Radiological procedures requiring intravascular administration of iodinated contrast media are becoming a common source of an iatrogenic disease known as contrast induced nephropathy (CIN).<sup>6</sup> Acute Kidney Injury is defined as an acute impairment of the renal function manifested by an absolute increase in the serum creatinine level of at least 0.5 mg/dl or by a relative increase of at least 25% from the baseline level<sup>7</sup>. Now a days Cardiologists are being asked more frequently to perform angiography in increasing number of patients, in which contrast induced nephropathy (CIN) is a potentially serious complication.<sup>8</sup> Contrast-induced nephropathy (CIN) is at present the third leading cause of hospital-acquired acute kidney injury (AKI).<sup>9</sup> Increased serum creatinine values typically occur 3-5 days after contrast administration and return to baseline levels within 1-3 weeks<sup>8</sup>; when patients are discharged from the hospital. Unfortunately, serum creatinine is an unreliable indicator during acute changes in the kidney function<sup>10</sup>. A marked reduction in the glomerular filtration rate (GFR) can be present before it is reflected in a rise in serum creatinine levels. All these reasons contribute to significant delay in the diagnosis of acute Kidney Injury associated with contrast administration. More over the renal function may not return to baseline, leading to an increased risk of chronic Kidney Injury.<sup>4</sup> Therefore new markers that help to identify Acute Kidney Injury earlier than serum creatinine are required for timely treatment.

Urinary liver-type fatty acid binding protein (L-FABP) is a fatty acid binding protein having a molecular weight of approximately 14 kDa, with its distribution confined to the proximal tubular cells of the human kidney<sup>11</sup>. In

healthy human kidney L-FABP is reportedly found in the cytoplasm of the proximal tubular cells and is rapidly released into the tubular lumen in response to ischaemia or oxidative stress<sup>12-14</sup>

One report suggests that the increase in L-FABP level reaches a maximum within 24h after contrast medium exposure and that L-FABP level could be an indicator of CI-AKI<sup>15</sup>. However, whether L-FABP level acts an indicator of CI-AKI in patients undergoing angiography remains unknown. Hence we conducted this study to determine whether urinary L-FABP level acts as an indicator of the CI-AKI and to examine the changes in urinary L-FABP levels in patients undergoing angiography.

Table1: Basal clinical characteristics of patients undergoing angiography.

Parameter	Value
Age in years	45.8 ±9.0
Systolic BP, mmHg	134.5±27.0
Diastolic BP, mmHg	81.5±19.0
Heamoglobin, g/dl	13.5±2.0
HbA1c %	5.0±2.5
Serum creatinine, mg/dl	1.2±0.18
eGFR byMDRD equation, ml/min	80.2±21.0
Cholesterol, mg/dl	165±41
HDL, mg/dl	45±9
Fasting Blood Sugar, mg/dl	116±39

## MATERIALS AND METHODS

The study was performed in one hundred consecutive patients undergoing angiographic procedure. The study was approved by the Ethics Committee of Micropath Medical Center, Gurgaon, Haryana. Written informed consent was obtained from each patient before enrolment. All consecutive adult patients undergoing coronary angiographic procedure from January, 2010 to October, 2013 were included. Clinical characteristics of all patients from whom urine was evaluated for L-FABP are reported in Table No.1. Patients with diabetic mellitus comprised 36 of 20 male and 16 females. Patients with non-diabetic mellitus comprised 64 of 40 male and 24 females. Among diabetic patients, 11 were treated with insulin and the rest with oral hypoglycemic drugs.

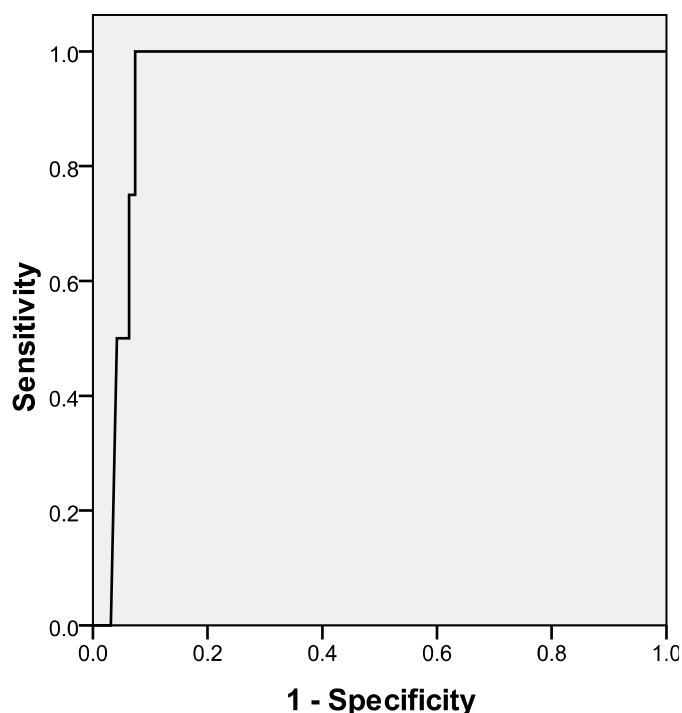
All subjects were discharged home from the angiography area after 8 hours of their procedure with advice to give specimen at scheduled time and encouraged to drink about 1.5 liters of water at least for the first 24 hours. The coronary angiography was performed by a consultant doctor in a standard manner using femoral artery. We excluded patients with pre-existing chronic kidney disease, serum creatinine greater than 1.5 mg/dl in males and 1.3 mg/dl in females. None of the subjects investigated had received nephrotoxic drugs at least 2 weeks before and during the study period. Before the procedure, all of the participating patients were given their urine and blood specimens for investigations such as cholesterol, High Density Lipoprotein, (HDL), Triglycerides, Hemoglobin, HbA1C and Fasting Blood Sugar (FBS). Blood pressure (BP) also studied on admission. Each patient was given low-osmolar contrast (iodizanol or iopromide) medium. Specific protocols and medications for contrast induced nephropathy prevention were not used in this study, but patients were persistently encouraged to drink plenty of fluids and oral fluid intake was maximally encouraged.

Blood samples were collected for serum creatinine and other screening evaluation before (at basal level). Thereafter urine samples were collected at 2 hours, 4 hours, 8 hours, 12 hours and 24 hours after the angiographic procedure. Urinary Samples were kept for 30 minutes at room temperature then supernatant was stored at -80 deg C. Serum creatinine was assessed before ( at basal level), and 24h and 48 hours after the procedure using Jaffe method. L-FABP was evaluated using a commercially available enzyme-linked immunosorbent assay from Hycult Biotech, Frontstraat 2a, The Netherlands. L-FABP test was performed according to manufactures instruction. For the choice of optimal cut-off, receiver operating characteristic (ROC) curve were constructed and the Youden index was calculated<sup>16</sup>. The Youden index is defined as follows: (sensitivity+specificity)-1. The best cut-off is the highest Youden index. The commercial statistical software package SPSS17.0 (SPSS, Inc, Chicago, IL, USA) was utilized. Results are evaluated with 95% confidence intervals. The significance level was < 0.05.

## RESULTS

Demographic data, clinical and biochemical criteria of the studied groups are presented in Table 1. The present study revealed an increase in Urinary L-FABP, at 2hours, 4hours, 8 hour , 12hours, and 24 hours after coronary angiography procedure (Table 2). Urinary L-FABP levels were increased at 4hours, 8 hours, 24 hours and 48 hours but highest levels were noted at 12 hours after the procedure. There was a mild increase in serum creatinine at 24h and milder at 48 hours after the angiographic procedure, but there was no significant increase in eGFR during 48 hours of the procedure (Table 2).

### ROC Curve



Diagonal segments are produced by ties.

Fig.1. Receiver operative characteristics (ROC) showing curve against serum creatinine 48 hours vs 12 hours urinary L-FABP and contrast induced acute kidney injury defined as a serum creatinine increase >0.3 mg/dl at 48 hours. Using a cutoff value of 25.0 pg/ml, sensitivity, specificity and area under the receiver operating characteristic (ROC) curve for prediction of Acute Kidney Injury were excellent for urinary L-FABP at 12 h (85%, 83% and 0.95 respectively).

There is no statistically significant differences in the levels of L-FABP between the diabetes and non-diabetes were noted in this study.

Table: 2 Changes in urinary L-FABP, serum creatinine levels, eGFR and blood pressure (BP) in patients undergoing angiography.

Name of the parameter	Before angiography	After 2 hrs	After 4 hrs	After 12 hrs	After 24 hrs	After 48 hrs
Urinary L-FABP (pg/ml)	4.3±1.42	5.75±0.78*	26.6±22.6**	38.3±26.7*	34.8±25.4	19.35±11.5
Serum Creatinine, mg/dl	1.2±0.18	ND	ND	ND	1.27±0.32	1.24±0.31
eGFR by MDRD equation, ml/min	80.21±21.00	ND	ND	ND	79.9±25.35	80.31±25.40
Cystolic BP, mmHg	138.45±30.15	129.5±32.2	ND	ND	135.55±25.65	136.75±24.15
Diastolic BP, mmHg	80.5±23.1	80.6±21.0	ND	ND	81.8±15.45	81.65±13.55

ND: Not determined. Data given are mean values ± SD or median values (minimum-maximum) \*p<0.05 vs baseline; \*\*p<0.001 vs baseline.

Using the Youden index, the best cutoff value for urinary L-FABP to predict acute Kidney Injury was: 25.0pg/ml.

### DISCUSSION

This clinical study of patients with normal serum creatinine who underwent angiographic procedure with contrast administration revealed 9% of contrast induced acute kidney injury. The diagnosis of contrast induced

acute kidney injury is a challenging clinical problem. Several studies have been published reporting the presence of elevated levels of urinary L-FABP in postcardiopulmonary bypass surgery patients<sup>17</sup>. Urinary L-FABP in the AKI patients measured 4 hours after the surgery was significantly higher than that in the non-AKI patients, where as serum creatinine started to increase after 24-48 hours in the AKI patients. Receiver operating characteristics (ROC) curve analysis for post-CBP AKI diagnosis revealed the area under the ROC curve of urinary L-FABP (4 hours after surgery ) was 0.810, which is an acceptable level for the single predictive biomarker. Univariate logistic regression analysis showed that both bypass time and urinary L-FABP were significantly independent risk indicators for AKI. Liver-type fatty acid binding protein is a carrier protein having a molecular weight of 14 kDa and is involved in the transport of fatty acid to mitochondria or peroxisomes<sup>11</sup>. Where they are metabolized via beta-oxidation. L-FABP plays a key role in fatty acids metabolism in the proximal tubules of the kidney. Free fatty acids are easily transformed to non-oxidized fatty acids, and this transformation escalates not only with proteinuria but also with other stresses, including ischaemia and the presence of toxins<sup>13</sup>. The most commonly used definition of CI-AKI in clinical trials is a rise in serum creatinine levels of 0.5 mg/dl or a 25% increase from the baseline value, assessed on day 2 after administration of contrast medium<sup>18</sup>. Recently, on the basis of the finding that even a slight elevation of serum creatinine level is associated with a poor outcome<sup>19</sup>. The Acute Kidney Injury Network (AKIN) issued a new definition for CI-AKI, which is a rise in serum creatinine levels of greater than 0.3 mg/dl with oliguria. This new definition may provide a new standard to follow<sup>20</sup>. The present study with the latest definition of CI-AKI, revealed 9% of CI-AKI.

## SUMMARY

The present study highlighted the importance of urinary L-FABP levels in detecting Acute Kidney Injury associated with contrast administration earlier than Serum creatinine. Persistently increased urinary L-FABP levels may suggest renotubular damage in this population. Limitation of this study is that we could have missed patients who developed acute Kidney Injury after 48 hours of the procedure. In summary, this is the first study to test the efficiency of new bio-markers in this setup revealing advantages of urinary L-FABP. The population studied is not representative of the global group of patients with AKI associated with Contrast administration. Our findings may have important implications for the clinical management of patients undergoing angiographic procedure. Further studies in patients undergoing radio-contrast administration are required to assess the usefulness of L-FABP as a biomarker for early diagnosis.

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