The Urinary Level of Liver-type Fatty Acid Binding Protein in Children with Febrile UTI

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Keywords. fatty acid binding protein, L-FABP, pyelonephritis, scar formation, urinary tract infection

Introduction. We assessed the urinary level of L-FABP in patients with APN and compared between patients with scar versus normal kidneys.
Methods. We enrolled children aged 2 months to 12 years old with APN. The urine concentration of L-FABP and L-FABP/Cr were measured. Patients divided into three groups; patients with scarring APN as group 1, patients with non-scarring APN as group 2, and controls.
Results. 79 children (aged 57.4 ± 40.5 months, (87.5%) female) enrolled in the study. Group 1 was composed of 19 (16 female) cases, group two 35 (32 female) cases, and group three 26 (2 female) healthy controls. There was no significant difference in absolute urinary level of L-FABP between APN groups and controls. Group 1 patients had a significantly higher concentration than group 2 ($P < .05$). The UL-FABP /Cr was significantly higher in group 1, than groups 2 and 3 [(0.28 ± 0.39 pg/mg, 0.08 ± 0.08 pg/mg, and 0.10 ± 0.09 pg/mg; respectively), ($P < .05$, $P < .05$)]. The difference between group 2 and 3 was not significant ($P > .05$). The sensitivity and specificity of UL-FABP /Cr ratio in prediction of scar was 50% to 72% and 44% to 56%, respectively.
Conclusion. The urinary ratio of L-FABP to creatinine is not a useful tool for diagnosis of APN or VUR but could be helpful in prediction of long-term potency to renal parenchymal scar formation.

IJKD 2020;14:191-7
www.ijkd.org

Original Paper

INTRODUCTION

APN (acute pyelonephritis) is a common health problem among children.[1,2] The febrile urinary tract infection (UTI) is dangerous and more important diagnosis.[3] The importance of APN is its tendency to develop permanent renal damage and scar formation.[4] Kidney scar is complicated by some long term problems such as raised blood pressure, ESRD, and pregnancy renal complications.[5,6] This means that early diagnosis and proper management of APN is an important policy both for ideal management of infection and lowering chance of later morbidities.[3] APN is diagnosed by clinical and laboratory findings. Fever, dysuria, urine odor, frequent urine excretion, flank pain, and lower abdominal pain are common clinical manifestations. Microscopic analysis and culture of urine is the usual way for a definite diagnosis.[7] There is no need to perform any radiologic study in typical cases, but in atypical cases, with doubtful items in history such as past consumption of antibiotic before sampling and in cases with potential kidney damage, we need to use imaging such as DMSA renal scan.[7] DMSA scanning is the most sensitive clinical tool for the diagnosis of APN and persistent renal injury (scar). There is no clinical finding to

reveal scar subjectively.[8,9]

DMSA detects cortical uptake diminution in the acute phase of APN that can resolve spontaneously or lead to scar formation in the next 4 to 6 months. Therefore the diagnosis of scar needs to apply an ionizing imaging tool and taking 4 to 6 months.[8] Some other ways for diagnosis of UTI and scar formation are suggested recently with no delay or ionizing exposure such as Doppler study or urinary and blood biomarkers.[10-12]

Fatty acid-binding proteins (FABPs) are known as intracellular lipid chaperones, that regulate lipid trafficking and responses in cells. FABPs can reversibly bind to saturated and unsaturated long-chain fatty acids (FAs) with high affinity and broad selectivity. At least nine different isoforms have been identified some of them are expressed in macrophages and dendritic cells. In these cells, FABPs participate in the induction of inflammatory responses and differentiation from monocytes to macrophages.[13] L-FABP is one type of the proteins that expressed in kidney, hepatocyte, and intestine.[14] The role of L-FABP in some physiologic and pathologic renal conditions was studied recently. Acute kidney injury (AKI) is the most attractive field of such studies. The role of L-FABP in assessing and diagnosing AKI in patients undergoing cardiac surgery or ICU patients was explained.[15-18] There are few studies regarding the relation between L-FABP and infectious renal diseases.[19-21] We assessed the urinary level of L-FABP in patients with APN and compared with patients having scars versus normal kidneys.

MATERIALS AND METHODS

This prospective cohort study was approved by the Ethical Research Committee at Mazandaran University of Medical Sciences and performed at Avicenna Hospital in the department of Pediatric Nephrology, Sari, Northern Iran; between May 2015 and Oct 2017. All parents or relatives provided signed written informed consent before enrollment of their children in this study. We enrolled all children between 2 months to 12 years old with a clinical diagnosis of acute pyelonephritis (APN). The diagnosis of APN was suggested with a history of fever with or without urinary symptoms, flank pain, suprapubic pain or tenderness and confirmed by positive urine analysis or culture. A urine sample was obtained with catheter or suprapubic catheterization in younger children or infants and by midstream method in older patients with appropriate cooperation for sampling. The urine analysis defined as APN if pyuria (WBC count > 5-10 /HPF), bacteriuria, positive nitrite, or leukocyte esterase were seen. Positive urine culture made the confirmation of diagnosis; which was more than 50000 colony count for midstream, more than 10^3 for the catheter and any number for the suprapubic method.

Children with a history of APN, renal failure, evidence of scar on first DMSA scan and those who did not participate in follow up excluded from the study.

Follow-up of APN patients in our center performed based on local policy. We performed DMSA and kidney and urinary tract sonography for all patients. Voiding cystoureterography (VCUG) was done for patients with second episode of APN, those with abnormal DMSA or ultrasonography and children with severe and atypical APN to detect vesicoureteral reflux (VUR). The DMSA scan was performed using a tomographic gamma camera (Siemens DH E-CAM) with a low-energy high-resolution collimator. Inflammation was defined as an attenuation in uptake in some or all portions of the kidney with intact layout contour. Scarring defined as any break in kidney contour, or any volume loss.

Ultrasonography study (US) with a Siemens G-50 scanner and 2–5 MHz curved-array transducer was performed. For the diagnosis of VUR, conventional voiding cystoureterography (VCUG) was performed for male cases and radionuclide cystography (RNC) for female. The severity of VUR classified as either mild (equal to grade 1 or 2 on VCUG), moderate (equal to grade 3 on VCUG), or severe (equal to grade 4 or 5 on VCUG).

We treated patients with an appropriate antibiotic frequently third-generation cephalosporin or aminoglycosides based on our local epidemiological data and bacterial sensitivity patterns.

The urine sample for measuring L-FABP was given within the first hours of admission. All urine samples were subjected to centrifugation and then stored at -20 °C for future assessment. The urinary creatinine levels measured in the same sample.

The levels of L-type of fatty acid binding protein (L-FABP) were quantitatively determined in urine samples by a two-step sandwich method

of enzyme immunoassay kit (CMIC Holdings Co., Tokyo, Japan) according to manufacturer's9 recommendations. Briefly, L-FABP standards and urine samples were pretreated with pretreatment solution, and adding into L-FABP antibody coated micro-titer plate filled with assay buffer. After proper incubation, the second anti-POD conjugate was added to make L-FABP antigen be sandwiched between immobilized primary antibody and conjugated antibody. The colorimetric signal produced with the substrate in proportion to the amount of bounded L-FABP was detected with an ELISA reader (Biotek ELX800, USA) at 492 nm and background wave length 630 nm. Urinary L-FABP concentrations were interpolated from the five parameters logistic standard curve and expressed in ng/mL. The sensitivity of the assay was 3 ng/ml and the CV value was no more than 10%. All samples were blindly analyzed to clinical status to avoid any bias. All samples were run in duplicate with the appropriate standards.

Patients divided into three groups. Patients with a history of APN that had evidence of scarring on the second DMSA scan comprised group 1. Patients with a history of APN that had normal first DMSA scan in the acute phase and those with abnormal inflammatory DMSA findings on the first radioisotope scan but who had normal findings on the later scan were also enrolled in group 2. We consider a group of healthy children with normal prenatal renal sonography that had normal urine analysis and culture as a control group. The control group cases were selected from children who came to our hospital for routine childhood care.

The continuous variables showed non-normal distributions (an assessment with Kolmogorov-Smirnov test) and expressed as mean (standard deviation). We used the Mann-Whitney U test to compare numerical data regarding the partial distribution in two groups, and we used the Kruskal-Wallis test for comparisons among multiple groups. The best cut-off values for urine L-FABP and urine LFABP/Cr ratio determined by receiver operating characteristic (ROC) analysis and of area under the curve (AUC) calculations. Categorical variables were analyzed with a $\chi 2$ test and shown as number (percentages). A P value of $< .05$ was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL), except for the cut points estimation and accuracy of that points, which was analyzed using the R programming environment (optimal cut point's package).

RESULTS

Seventy-nine children were enrolled in our study. The mean patient age was 57.4 ± 40.5 months, 70 (87.5%) were female. The patients were located in three groups. Group one composed of 19 (16 female), group two 35 (32 female) and group three 26 (22 female). Study demographics and other patient characteristics summarized in Table 1. No significant differences in sex and age were observed between groups ($P > .05$, $P > .05$; respectively). VCUG was performed for 38 children from 53 patients with APN. 17 patients (45%) had VUR, and the frequency of VUR was 72% (13 of 18 VCUGs performed) for group 1, and 20% (4 of 20) for group 2. The severity of VUR in both groups is presented in Table 1. As expected the frequency of VUR was significantly higher in group 1 than group 2($P < .05$).

Biomarker Measurement

The mean levels of urinary L-FABP and the urinary ratio of L-FABP to Cr are presented in

Table 1. Baseline Data of 80 Children in 3 Groups

	Group			*P*
	1 (APN with Scar) (n = 19)	2 (APN Without Scar) (n = 35)	3 (Control) (n = 26)	
Age, mo (mean ± SD)	61 ± 38	60 ± 47	40 ± 15	> .05
Sex, F/M	16 / 3	32 / 3	22 / 4	> .05
VUR, n (%)	13 (72)	4 (20)	-	< .05
VUR severity, n (%)				
No reflux	5 (28)	16 (80)	-	< .05
Mild	4 (22)	2 (10)	-	
Moderate	4 (22)	1 (5)	-	
Sever	5 (28)	1 (5)	-	

Table 2. As shown in Table 2, there are no significant differences in absolute urinary levels of L-FABP between groups except for group 1 versus 2 ($P < .05$). The ratio of L-FABP to Cr level was significantly different between the three groups. This ratio was higher in group 1 than groups 2 and 3 and these differences were statistically significant ($P < .05$, $P < .05$; respectively), but the difference between group 2 and 3 was not statistically significant ($P > .05$).

We additionally assessed the level of the biomarker in 17 patients with VUR and 21 with normal cystography. Mean ratio of L-FABP to creatinine (Cr) was not different between children with VUR and those with normal VCUG (26 ± 39 vs. 8 ± 9 µg/g, $P > .05$).

ROC Analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of urinary L-FABP to creatinine ratio (L-FABP / Cr) was calculated from ROC curves (Figure), for comparisons of group 1 and group 2 or 3 to assess the role of test in diagnosis of scar. The cut-off values presented in each case (Table 3). As shown in Table 3, the optimal cut-off value of L-FABP / Cr ratio for diagnosis of APN with scar (group 1 vs. group 2) was 42 µg/g (AUC = 0.616, 95% CI: 0.45 to 0.78). The optimal cut-off value of L-FABP /Cr ratio for diagnosis of APN with the scar from healthy children was 60.2 µng/g (AUC = 0.575, 95% CI: 0.39 to 0.76).

We measured the cut-off values with the highest (100%) sensitivity and specificity. In our patients the U L-FABP /Cr ratio more than 20.8 µg/g. Cr and 36.8 µg/g. Cr had a sensitivity and specificity of 100%, respectively.

DISCUSSION

Febrile UTI is a serious childhood infection both for acute morbidity and late sequels on kidney structure. We analyzed the role of the urinary level of L-FABP in the acute diagnosis of APN and anticipation of scar formation. We showed that the absolute urinary level of L-FABP is similar between patients with APN and healthy children. In our study, the urinary ratio of L-FABP to Cr was significantly higher in scarring pyelonephritis than those with APN and no scar on DMSA and healthy children. The L-FABP assessed in some other diseases especially cardiovascular diseases and acute kidney injury.[16] Nakamura in a study on 30 patients with microscopic hematuria suggested that the urinary L-FABP level can be used to discriminate between IgA nephropathy and thin basement membrane nephropathy.[22] Mou measured uL-FABP in 123 patients with newly diagnosed chronic glomerulonephritis, and 28 healthy subjects. The patients were in follow-up for at least 5 years. uL-FABP in the patients with CGN was greater than in the healthy subjects.[17] Ivanisevic in a case-control study of children undergoing Cardiopulmonary bypass (CPB) suggested that urinary L-FABP can be used to diagnose AKI earlier than a rise in serum creatinine in children undergoing CPB.[16]

The study focused on two diagnosing way, first; diagnosis of APN and second; anticipating and diagnosis of later scar formation. We found no

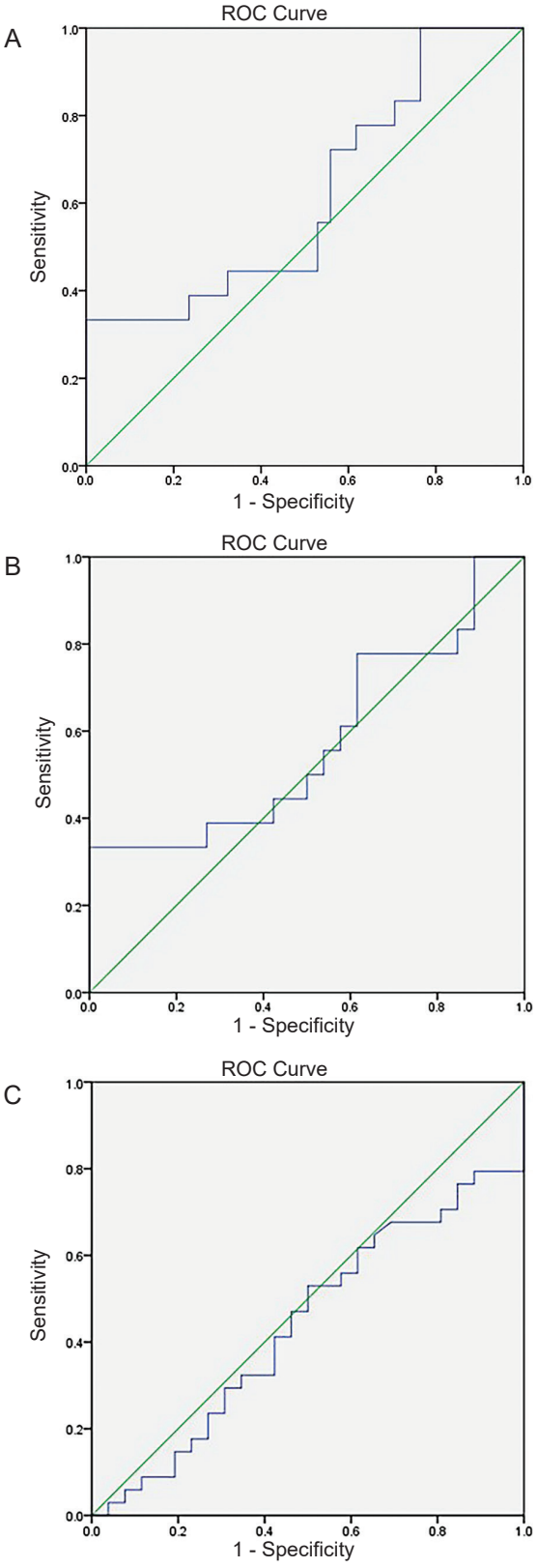
Table 2. Urine Concentration of L-FABP and U L-FABP /Cr Ratio in 3 Groups of Children

	Group			*P*	Statistically Significant Between-group
	1 (APN With Scar) (n = 19)	2 (APN Without Scar) (n = 35)	3 (Control) (n = 26)		
Urine L-FABP, pg/mL	6.82 ± 7.97	2.49 ± 2.58	4.20 ± 5.06	< .05	1 vs. 2
Urine L-FABP /Cr, µg/g	280 ± 390	80 ± 81	95 ± 90	< .05	1 vs. 2 1 vs. 3
Urine Cr, mg/dL	37 ± 27	37 ± 23	51 ± 32	> .05	-

Table 3. The Cut-off Value of Urinary L-FABP to Creatinine Ratio for Comparison of 3 Groups of Children

Groups Were Compared	Cut-off Value, µg/g	SEN	SPE	PPV	NPV	Cut-off With 100% Sensitivity	Cut-off With 100% Specificity
Group 1 VS 2	42	72.2	44.1	41	75	20.8	364.3
Group 2 VS 3	53.4	50	53	45	58	13	353.9
Group 1 VS 3	60.2	50	56	62	43	19.2	368

SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value.



It shows the roc curve of urine L-FABP to creatinine for distinguishing: A) group 1 (APN and scar) vs. group 2 (Controls), B) group 1 (APN without the scar) vs. group 3, and C) groups 2 vs. group 3.

useful relation for the first purpose but showed that the biomarker is a helpful tool to anticipating later scar formation. The first role of biomarkers in the diagnosis of UTI and scar was studied recently. Krzemień found that on average, both sNGAL and uNGAL levels were significantly higher in febrile UTI, compared to non-febrile UTI and controls.[23] Abedi compared the urinary concentration of matrix metalloproteinase (MMP9) and tissue inhibitor of metalloproteinase (TIMP1) in children with APN and scar with children with APN and normal DMSA scan. Urinary levels of MMP9 and TIMP1 were significantly higher in group 1 than in group 2 and with a (sensitivity 62% to 75%, specificity 55% to 71%, PPV 41% to 48%, NPV 82% to 84%).[24] Rafiei assessed the urinary and serum levels of IL-32 in 57 pediatric patients with acute pyelonephritis (APN) with and without renal scarring and 29 healthy children. He found that there were no significant differences in the serum and absolute urinary levels of IL-32 between groups, but the urinary IL-32 / creatinine ratio was significantly higher in children with pyelonephritis than controls.[25]

In our study, the urinary ratio of L-FABP /Cr was significantly higher in patients with scar than those without scar but the children with non-scarring APN had similar levels with healthy children.

The urinary level of L-FABP was studied by some others. Parmaksız and coworkers assessed patients with primary VUR into five groups, patients with VUR with or without renal parenchymal scarring (RPS); patients with resolved VUR with or without RPS; and the healthy reference group. They found that median uL-FABP /Cr is significantly higher in patients with RPS than in the reference group.[20] In this study similar to ours the urinary levels of the biomarker are higher in children with RPS. An important difference is the role of infection. In our study, all cases were selected from APN patients, and infection was the baseline item for all population of study except for controls.

Kiato studied 49 infants who underwent renal scintigraphy for febrile urinary tract infections and measured urinary L-FABP in patients with and without renal scarring. Conversely, he found that the urinary L-FABP/Cr levels are not significantly different between the groups ($P > .05$).[21] Benzer studied Fifty-six patients with vesicoureteral reflux in two groups as with or without renal parenchymal scarring and 51 healthy controls. Urinary L-FABP

and L-FABP /Cr levels were significantly higher in the whole patient group than in the controls ($P < .05$, $P < .05$).[19] In this study uL-FABP and uL-FABP /creatinine levels of the VUR patients were found as increased regardless of the reflux degree. Otherwise, the mean of uL-FABP and the median of uL-FABP /creatinine levels were found to be higher in patients with VUR who had no RPS than in the controls. In the study, absolute values of uL-FABP were thought to be more relevant than the adjusted values of that marker, for why uL-FABP and u-creatinine were inversely correlated. In our study, the corrected urine value of the biomarker to creatinine was significantly different between scarring patient and those without a scar and healthy children. The absolute value of UL-FABP was different between patients with APN with RPS and APN without scar, but both groups had similar value with healthy children. The difference in absolute value between two pyelonephritic groups is not certainly significant, because of daily variations in the urinary excretion of substances. The most important benefit of the assay could be the prediction value of long-term scar formation in the acute phase of APN. The diagnosis of APN usually is made easily on the basis of clinical manifestation and urine analysis and culture. We frequently need no other laboratory or imaging study to confirm the diagnosis. But the potency of scar formation in the acute phase is not clear, and need to perform renal scan 6 months later. The ability of this biomarker to anticipate scar is a helpful and promising item. We report two cut-off value with 100% sensitivity and 100% specificity.

Vesicoureteral reflux was another variable that was assessed. In our study, there was no difference in urinary L-FABP and L-FABP /Cr between refluxing and non-refluxing children. Parmaksız reported that the uL-FABP/Cr is significantly higher in children with current or resolved VUR than healthy children.[20] Benzer showed that UL-FABP /Cr levels are significantly higher in the whole patient group (VUR with RPS and VUR without RPS) than in the controls.[19] The reason for different data of our study and two others are not clear. The severity of VUR was not the reason, 33% of our refluxing units in our study, but 7% to 16% in other studies had severe grades of VUR. The small number of VUR cases says that it needs to perform larger studies to answer this question.

CONCLUSION

Our study revealed that serum and absolute urinary level of L-FABP is not a helpful tool to diagnosing APN or VUR but may have some benefit for the prediction of scar formation. The urinary ratio of L-FABP to creatinine is not a useful tool for diagnosis of APN or VUR but is helpful in anticipating long term potency to renal parenchymal scar formation.

ACKNOWLEDGEMENTS

We thank our hospital and research center staffs and patients and their parents. This work was supported by a grant from Mazandaran University of Medical Sciences.

DISCLOSURE STATEMENT

The authors declare that they have no conflict of interest

FUNDING

This work was supported by grants from Mazandaran University of Medical Sciences.

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Received November 2019
Revised January 2020
Accepted March 2020