Published in final edited form as:

J Pediatr Urol. 2019 February ; 15(1): 44.e1–44.e7. doi:10.1016/j.jpuro.2018.10.007.

Elevated urinary LCN2 and MCP1 protein levels in children with congenital ureteropelvic junction obstruction

Liang Yu^a, Ling Zhou^b, Qifeng Li^a, Shuixue Li^b, Xinhui Luo^a, Chiyuan Zhang^c, Bo Wu^c, James D Brooks^{c,*}, and He Sun^{a,*}

^aXinjiang Institute of Pediatrics, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

^bDepartment of Pediatric Surgery, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

^cDepartment of Urology, Stanford University School of Medicine, Stanford, CA, USA

Summary

Introduction—In children with congenital ureteropelvic junction obstruction (UPJO), urinary biomarkers could assist in the diagnosis of renal damage or kidneys at risk for damage. Urinary levels of interleukin-6 (IL6), neutrophil gelatinase-associated lipocalin (LCN2), Monocyte Chemoattractant Protein 1 (MCP1) and transforming growth factor- β 1 (TGFB1) proteins have been correlated with renal damage in several contexts. We tested whether they might be useful non-invasive biomarkers of obstructive nephropathy due to unilateral and bilateral congenital UPJO.

Patients and methods—We performed a cohort study at People's Hospital of Xinjiang Uygur Autonomous Region in China. Bladder urine samples from 17 UPJO patients were obtained prior to surgical intervention and from 17 healthy age-matched controls. Levels of IL6, LCN2, MCP1 and TGFB1 were determined by ELISA and normalized to urinary creatinine levels.

Results—Levels of urinary LCN2, MCP1 and IL6 were significantly elevated in the urine from individuals with UPJO compared to controls ($p = 0.0003$, $p = 0.0003$ and $p = 0.0073$, respectively). Children with bilateral UPJO ($n=5$) showed significantly higher levels of IL6, LCN2 and MCP1 protein in their urine compared to controls or those with unilateral UPJO ($n=12$) ($p = 0.007$, $p < 0.0001$ and $p = 0.0002$, respectively). Combining LCN2 and MCP1 slightly improved biomarker performance.

*Co-corresponding authors, James D Brooks, Department of Urology, Stanford University School of Medicine, Stanford, CA 94305, USA, Tel.: +1 650 498 4464; fax: +1 650 723 4200 jdbrooks@stanford.edu, He Sun, People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Institute of Pediatrics, Urumqi 830001, China, hesun@xjrmmy.com.

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Ethical approval

The local hospital ethical committee approved the study.

Conflict of interest

None.

Discussion—Urinary biomarkers could be used in obstructed patients to monitor for renal damage and might find particular utility on patients with bilateral UPJO. Monitoring urinary biomarkers and imaging features in untreated patients could provide insights into the natural history of renal damage due to obstruction and will be necessary to test their performance characteristics as biomarkers.

Conclusions—Urinary levels of LCN2 and MCP1 protein are promising biomarkers monitoring children with UPJO, particularly in those with bilateral disease.

Graphical Abstract

Summary Fig Ratio of urinary biomarker concentrations to urinary creatinine levels in patients with unilateral and bilateral UPJO.

Keywords

Urinary biomarker; UPJO; renal damage; MCP1; LCN2

Introduction

Ureteropelvic junction obstruction (UPJO) is the major cause of renal injury and chronic renal insufficiency in children and is a common cause of hydronephrosis in newborns [1]. While many cases of hydronephrosis resolve spontaneously, some require surgical repair[2]. The decision to intervene is usually made on the basis of worsening hydronephrosis or fractional loss of renal function based on functional scans such as MAG3. Urinary biomarkers could assist in earlier and more reliable determination of obstructive nephropathy or renal units at risk, guiding therapeutic decisions and monitoring treatment efficacy.

Several urinary biomarkers have been evaluated in children with UPJO, including TGFB1 [3, 4], MCP1 [5, 6], and LCN2 [5, 7]. Transcript levels of IL6 have been found to be elevated in mouse models of urinary obstruction[8, 9]. However, the performance of these urinary biomarkers has been inconsistent between studies and it remains unclear whether this variation is due to biomarker performance, the degree of obstruction, the amount of renal damage, or whether the disease is unilateral or bilateral [5, 7]. To better understand the performance of these candidate urinary biomarkers of renal damage in the context of UPJO and obstructive nephropathy, we measured protein levels of IL6, LCN2, MCP1 and TGFB1 in unilateral and bilateral UPJO patients. By performing analysis of all 4 of the markers simultaneously, we could compare their relative performance as biomarkers of obstructive nephropathy.

Patients and methods

Patient enrollment

This study included children who were seen at the Department of Pediatric Urology, People's Hospital of Xinjiang Uygur Autonomous Region, China. After obtaining institutional review board approval and parental consent, 17 patients (male=14, female=3, median age=84 months) with both unilateral and bilateral UPJO were recruited to the study (Table 1). We also collected urine from 17 age- and sex- matched healthy controls with normal renal function from a general pediatric clinic (male=16, female=1, median age=78 months). Patients with UPJO that met criteria for surgery described previously [10, 11] underwent dismembered pyeloplasty for correction of their obstruction and urine samples were collected as detailed below. One patient with mild hydronephrosis did not undergo surgery. Surgical intervention was recommended based on ultrasound imaging, clinical symptoms, loss of renal function based on decreased GFR estimated on ^{99m}Tc -DTPA(Diethylenetriaminepentaacetic Acid) renal dynamic imaging (children <2 years old, 60-80 ml/min; children with >2 years old, 80-120 ml/min) [12] and/or MAG3 renography demonstrating ureteropelvic junction obstruction, with prolonged T1/2 drainage profiles (>15 min) or equivocal drainage with decreased ipsilateral renal function.

Urine sample collection and analysis

Urine samples were obtained intraoperatively from the bladders of both UPJO patients by catheterization immediately after the induction of anesthesia. Control urine samples and 1 case with mild hydronephrosis were collected from voided samples. Urine specimens were centrifuged and stored within 4 h of collection at -80°C until further analysis. Quantitative urine protein analysis was performed using commercially available human IL6, LCN2, MCP1 and TGFB1 sandwich enzyme-linked immunosorbent assay (ELISA) kits (RayBiotech, GA). Each specimen was analyzed in duplicate, and the concentration of the patient samples was determined by using standard curve analysis on generating a four-parameter logistic curve-fit. Urinary creatinine levels were used to normalize protein levels for each of the markers analyzed.

Statistical analysis

Data analysis was performed using Prism Statistics software (GraphPad software 7.03, La Jolla, CA). Statistical analysis was performed using the Kruskal-Wallis test, ANOVA, Wilcoxon rank sum test and receiver operating characteristic (ROC) curve analysis. The data are presented as median values unless specified otherwise. The differences were considered statistically significant if $p < 0.05$ for two-sided tests.

Results

We tested whether the candidate protein biomarkers of renal damage LCN2, MCP1, IL6 and TBFB1 were increased in children undergoing surgery for obstructive uropathy compared to age- and sex-matched controls. Creatinine-normalized urinary levels of LCN2, MCP1 and IL6 proteins were higher in patients with UPJO compared to control subjects (Fig. 1A, 1B and 1C). For TGFB1, no significant differences in urinary protein levels were observed between obstructed and control subjects (Fig. 1D).

Performance of urinary biomarkers of obstruction could be compromised by dilution with urine from the contralateral normal kidney. We tested whether the performance of the urinary biomarkers improved in patients with bilateral UPJO. Compared to normal controls, creatinine-normalized urinary protein levels of IL6, LCN2 and MCP1 were increased significantly in patients with bilateral UPJO (Fig. 2). Likewise, patients with bilateral obstruction showed higher levels of IL6, LCN2 and MCP1 compared to those with unilateral obstruction. Analysis of controls, unilateral and bilateral obstructed patients by ANOVA showed that LCN2 had the best performance characteristics ($X^2(2) = 19.2$, $P < 0.0001$), with little or no overlap of LCN2 protein levels in the bilateral UPJO patients compared to the non-obstructed controls. MCP1 also showed excellent discrimination ($X^2(2) = 17.3$, $P = 0.0002$) while IL6 showed modest discrimination ($X^2(2) = 9.9$, $P = 0.007$). TGFB1 did not discriminate normal from unilateral or bilateral obstruction ($P = 0.85$).

We used Receiver Operating Characteristic (ROC) analysis to evaluate the performance of these biomarkers in our total patient dataset. The calculated Area Under the Curve (AUC) for IL6 was modest at 0.78 (Fig. 3A). The AUC for LCN2 levels for identifying individuals with UPJO was 0.90, with 88% sensitivity and 76% specificity (Fig. 3B). The AUC for MCP1 was 0.89, with 88% sensitivity, and 88% specificity (Fig. 3C). TGFB1 showed very poor performance characteristics in our cohort with a calculated AUC of 0.56 (Fig. 3D). When LCN2 with MCP1 were combined the AUC improved to 0.93 (Fig. 3E). When IL6 was added to LCN2 and MCP1, AUC did not improve (Fig. 3F, AUC: 0.92).

Discussion

Bladder urinary levels of LCN2, MCP1 and IL6 were significantly elevated in patients undergoing surgery for UPJO, suggesting that they could serve as biomarkers of renal damage in patients with UPJO. The performance of these biomarkers was modest in patients with unilateral obstruction, and TGFB1 urinary levels did not distinguish UPJO patients from healthy controls. The excellent performance of LCN2 suggests it should be investigated as a biomarker for monitoring patients with bilateral UPJO.

The urine is a logical source of biomarkers indicative of renal damage that could be used for clinical decision-making, and many candidate markers of renal damage have been identified [13]. Using animal model systems, investigators have identified urinary biomarkers of damage in renal ischemia/reperfusion injury, obstruction, toxins, glomerular disease and interstitial nephritis. Several of these biomarkers, including the 4 investigated in the current study, have been shown to correlate with renal damage in human urine and have undergone large-scale clinical validation. In adult patients with CRF, neutrophil gelatinase-associated lipocalin (NGAL or LCN2), kidney injury molecule -1 (KIM-1), N-acetyl- β -D-glucosaminidase (NAG) and liver fatty acid binding protein (L-FABP) have been shown to correlate strongly with future progression to renal failure and dialysis on univariate analysis [14]. However, none of the biomarkers provided prognostication that was independent of currently used measures of renal failure: urinary protein/creatinine ratio and estimated Glomerular Filtration Rate (eGFR). In other words, the biomarkers fail to predict the clinical course of patients with moderate CKD (G3, median eGFR=44), regardless of cause. Similar findings have been noted in other large-scale validation studies [15-17].

Despite these disappointing results, urinary biomarkers could find utility in obstructive nephropathy, where renal function is relatively normal (i.e. normal eGFR and no proteinuria) and where intervention is recommended for those renal units in the early phases of damage or are at high risk for damage. For example, LCN2 has been shown to be elevated in patients presenting to the emergency room with acute obstruction [18]. In cases with chronic obstruction, such as UPJO, several groups have reported LCN2, KIM-1, MCP1, TGFB1, IL6 and others as candidate markers of damage in renal obstruction [3, 5, 19, 20]. However, in other reports these biomarkers have failed [7, 21]. Even when considering positive studies, biomarker performance, singly and in combination, has been remarkably inconsistent, dampening enthusiasm for development of biomarkers that can guide surgical decision-making in patients with obstruction. Reflecting these inconsistencies, biomarker levels were elevated in our single case with mild hydronephrosis, while a few cases with severe dilation had much lower levels.

There are many possible causes for the variable performance of biomarkers of renal damage in the context of obstructive nephropathy. In nearly all cases, obstructive nephropathies are due to partial obstruction, including patients with UPJO, extrinsic compression of the ureter from a malignancy, or a ureteral stone. In patients followed longitudinally for partial obstruction, decrements in renal function appear to occur discontinuously or episodically, where a stable ultrasound can suddenly worsen, or a renal scan show a significant loss of renal function [22]. Clinically, these episodic elevations can manifest as Dietl's crisis. Therefore, it is possible that loss of renal function from partial obstruction occurs during episodic elevations of pelvic and renal pressure, such as during a period of diuresis. In that case, urinary biomarkers might be quiescent at most times and only elevated during periods of exacerbations. Biomarkers might also show inconsistent results because most cases of obstruction are unilateral, and the decreased GFR in the affected kidney as well as the obstruction itself would decrease the amount of any biomarker reaching the bladder, particularly since increased filtration in the opposite kidney would overwhelm any biomarker signal. It is possible that the optimal biomarkers have not been identified, since obstruction could result in secretion of unique proteins (e.g due to physical stretching of the

tubules). Finally, biomolecules other than protein (transcripts, microRNAs) could show better performance characteristics, particularly since nucleotides can be detected with greater sensitivity [9].

It is possible that urinary biomarkers will be best used in discrete clinical situations. Although the LCN2 does not aid in predicting progression of CRF in adults with renal insufficiency, it might be better used in subsets of patients such as children and neonates with bilateral UPJO [19]. A significant portion of neonates with bilateral obstruction can be managed conservatively and will show spontaneous improvement, and with close monitoring it does not appear that any of them get significant renal damage [23]. Urinary biomarkers such as LCN2 or MCP1 should be tested in bilateral obstruction in patients who are monitored to see if they provide independent prediction of progression.

Our study has several shortcomings. Our study size was relatively small, heterogeneous and based at a single institution, leading to possible biases in patient characteristics that affected biomarker performance. All patients in the obstructed group underwent surgery for documented significant obstruction. Four of our patients had a history of febrile urinary tract infections and it is possible that infection could elevate urinary biomarker levels. However, all patients had been treated prior to surgery and confirmed to be non-infected in a pre-operative urine culture. Whether the biomarkers could be used to select patients for surgery was not tested, and future studies need to include relevant controls, namely, patients with hydronephrosis that resolves spontaneously and does not require surgery. Only by comparing longitudinally collected urine samples from patients who progress to those that do not progress can we test whether these biomarkers can provide information independent of currently used clinical tools used for decision-making.

Conclusions

We find that LCN2 and MCP1 are elevated in children with UPJO, while TGFB1 are not. LCN2 and MCP1 appear to perform significantly better in bilateral UPJO and it is possible that these biomarkers could have their greatest utility in this population. Further studies are necessary to test whether longitudinal monitoring urinary biomarkers can help select patients of surgical correction of obstruction. In addition, other urinary biomarkers, such as RNA and DNA should be tested and compared to protein biomarkers.

Acknowledgments

Funding

This project was supported by the Research Fund from People's Hospital of Xinjiang Uygur Autonomous Region in China to L.Z. and R01DK101736 to J.D.B.

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Figure 1.

Ratio of urinary biomarker concentrations to urinary creatinine levels in UPJO patients and controls. (A) IL6, (B) LCN2, (C) MCP1 and (D) TGFB1. Horizontal bar indicates median.

Figure 2. Ratio of urinary biomarker concentrations to urinary creatinine levels in patients with unilateral and bilateral UPJO. (A) IL6, (B) LCN2, (C) MCP1 and (D) TGFB1. Horizontal bar indicates median.

Figure 3. Receiver Operating Characteristic (ROC) curves of creatinine-normalized urinary biomarkers in patients with UPJO. (A) IL6. (B) LCN2. (C) MCP1. (D) TGFB1. (E) LCN2+MCP1. (F) LCN2+MCP1+IL6. AUC: Area Under the Curve.

Table 1.

Summary of clinical characteristics of UPJO patients

Case #	Gender	Age (months)	Type of Hydronephrosis	Grade/Laterality*	Operative indication	Clinical Symptoms	99mTc-DTPA GFR (ml/min)
1	M	11	Unilateral	Moderate/Left	APD>20mm with caliceal dilation	N/A	N/A
2	M	25	Unilateral	Mild/Left	No surgery	Febrile UTI	L:50.77; R:43.25
3	M	96	Bilateral	Severe/Left, Mild/Right	APD>30mm	Flank/abdominal pain	L:9.91; R:85.82
4	M	23	Bilateral	Moderate/Left, Moderate/Right	APD>20mm with caliceal dilation	N/A	L:14.25; R:13.86
5	F	192	Bilateral	Moderate/Left, Mild/Right	APD>20mm with caliceal dilation	Flank/abdominal pain	N/A
6	M	132	Unilateral	Moderate/Left	Decreasing renal function	Febrile UTI	L:95.69; R:83.87
7	M	72	Unilateral	Severe/Left	APD>30mm	Flank/abdominal pain	L:39.06; R:53.81
8	M	24	Unilateral	Moderate/Left	APD>20mm with calyceal dilation	Flank/abdominal pain	L:67.78; R:77.60
9	M	156	Unilateral	Severe/Right	APD>30mm	N/A	L:49.47; R:26.83
10	M	108	Bilateral	Severe/Left, Mild/Right	APD>30mm	Flank/abdominal pain	L:17.76; R:58.88
11	F	15	Unilateral	Moderate/Right	APD>20mm with calyceal dilation	Febrile UTI	L:52.94; R:34.19
12	M	108	Unilateral	Severe/Left	APD>30mm	Hematuria	L:41.84; R:54.12
13	M	132	Unilateral	Moderate/Left	APD>20mm with caliceal dilation	Hematuria	L:40.42; R:53.79
14	M	24	Unilateral	Severe/Right	APD>30mm	None	L:110.58; R:6.11
15	M	108	Bilateral	Severe/Left, Moderate/Right	APD>30mm	Flank/abdominal pain	L:12.52; R:8.24
16	M	84	Unilateral	Moderate/Right	APD>30mm	Flank/abdominal pain	L:52.75; R:60.21
17	F	17	Unilateral	Moderate/Left	APD>20mm with caliceal dilation	Febrile UTI	L:67.45; R:88.85

* Mild: SUFU Grade 0-1, Moderate: Grade 2-3, Severe: Grade 4

N/A: Not available