Journal of Pediatric Urology (2018) xx, 1.e1–1.e7

Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction

L. Yu [a], L. Zhou [b], Q. Li [a], S. Li [b], X. Luo [a], C. Zhang [c], B. Wu [c], J.D. Brooks [c,*], H. Sun [a,**]

[a]Xinjiang Institute of Pediatrics, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

[b]Department of Pediatric Surgery, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

[c]Department of Urology, Stanford University School of Medicine, Stanford, CA, USA

* Corresponding author. Department of Urology, Stanford University School of Medicine, Stanford, CA 94305, USA. Tel.: +1 650 498 4464; fax: +1 650 723 4200.

** Corresponding author. People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Institute of Pediatrics, Urumqi, 830001, China.
jdbrooks@stanford.edu (J.D. Brooks)
hesun@xjrmyy.com (H. Sun)

Keywords
Urinary biomarker; UPJO; Renal damage; MCP1; LCN2

Received 8 May 2018
Accepted 5 October 2018
Available online xxx

Summary

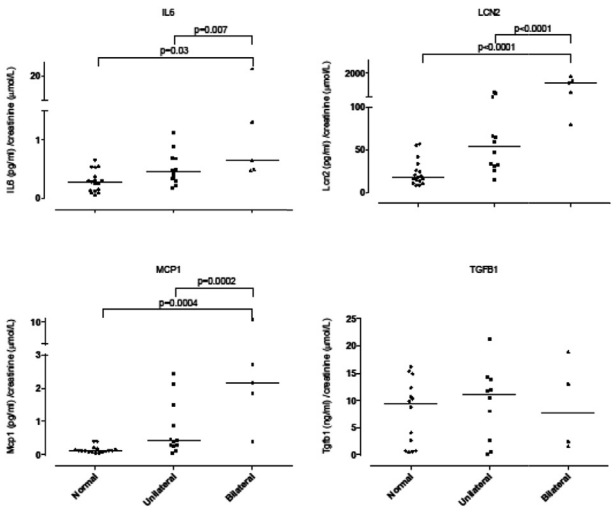
Introduction
In children with congenital ureteropelvic junction obstruction (UPJO), urinary biomarkers could assist in the diagnosis of renal damage or kidneys at risk for damage. Urinary levels of interleukin-6 (IL6), neutrophil gelatinase–associated lipocalin (LCN2), monocyte chemoattractant protein-1 (MCP1), and transforming growth factor-β1 (TGFB1) proteins have been correlated with renal damage in several contexts. Whether they might be useful non-invasive biomarkers of obstructive nephropathy due to unilateral and bilateral congenital UPJO was tested.

Patients and methods
A cohort study was performed at People's Hospital of Xinjiang Uygur Autonomous Region in China. Bladder urine samples from 17 patients with UPJO were obtained before surgical intervention and from 17 healthy age-matched controls. Levels of IL6, LCN2, MCP1, and TGFB1 were determined by enzyme-linked immunosorbent assay 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 with 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 with 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.

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.



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

https://doi.org/10.1016/j.jpurol.2018.10.007

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 transforming growth factor-β1 (TGFB1) [3,4], monocyte chemoattractant protein-1 (MCP1) [5,6], and lipocalin-2 (LCN2) [5,7]. Transcript levels of interleukin-6 (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, protein levels of IL6, LCN2, MCP1, and TGFB1 in patients with unilateral and bilateral UPJO were measured. By performing analysis of all four of the markers simultaneously, their relative performance as biomarkers of obstructive nephropathy could be compared.

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). 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) was collected. Patients with UPJO who met the criteria for surgery described previously [10,11] underwent dismembered pyeloplasty for correction of their obstruction, and urine samples were collected as detailed in the following section. 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 glomerular filtration rate (GFR) estimated on 99mTc-diethylenetriaminepentaacetic acid renal dynamic imaging (children aged <2 years, 60–80 ml/min; children aged >2 years, 80–120 ml/min) [12], and/or MAG3 renography demonstrating UPJO, 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 one 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 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, analysis of variance (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

Whether the candidate protein biomarkers, LCN2, MCP1, IL6, and TBFB1, of renal damage were increased in children undergoing surgery for obstructive uropathy compared with age- and sex-matched controls was tested. Creatinine-normalized urinary levels of LCN2, MCP1, and IL6 proteins were higher in patients with UPJO compared with control subjects (Fig. 1A, B and C). 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. Whether the performance of the urinary biomarkers improved in patients with bilateral UPJO was tested. Compared with normal controls, creatinine-normalized urinary protein levels of IL6, LCN2, and MCP1 were increased significantly in patients with bilateral UPJO (Fig. 2). Similarly, patients with bilateral obstruction showed higher levels of IL6, LCN2, and MCP1 compared with those with unilateral obstruction. Analysis of controls and patients with unilateral and bilateral obstruction 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 patients with bilateral UPJO compared with 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 ($P = 0.85$).

ROC analysis was used to evaluate the performance of these biomarkers in the total patient data set. The

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007

Table 1 Summary of clinical characteristics of patients with UPJO.

Case#	Gender	Age (months)	Type of hydronephrosis	Grade/ laterality[a]	Operative indication	Clinical symptoms	99mTc-DTPA GFR (ml/min)
1	M	11	Unilateral	Moderate/left	APD>20 mm with calyceal 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>30 mm	Flank/abdominal pain	L:9.91; R:85.82
4	M	23	Bilateral	Moderate/left, moderate/right	APD>20 mm with calyceal dilation	N/A	L:14.25; R:13.86
5	F	192	Bilateral	Moderate/left, mild/right	APD>20 mm with calyceal 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>30 mm	Flank/abdominal pain	L:39.06; R:53.81
8	M	24	Unilateral	Moderate/left	APD>20 mm with calyceal dilation	Flank/abdominal pain	L:67.78; R:77.60
9	M	156	Unilateral	Severe/right	APD>30 mm	N/A	L:49.47; R:26.83
10	M	108	Bilateral	Severe/left, mild/right	APD>30 mm	Flank/abdominal pain	L:17.76; R:58.88
11	F	15	Unilateral	Moderate/right	APD>20 mm with calyceal dilation	Febrile UTI	L:52.94; R:34.19
12	M	108	Unilateral	Severe/left	APD>30 mm	Hematuria	L:41.84; R:54.12
13	M	132	Unilateral	Moderate/left	APD>20 mm with calyceal dilation	Hematuria	L:40.42; R:53.79
14	M	24	Unilateral	Severe/right	APD>30 mm	None	L:110.58; R:6.11
15	M	108	Bilateral	Severe/left, moderate/right	APD>30 mm	Flank/abdominal pain	L:12.52; R:8.24
16	M	84	Unilateral	Moderate/right	APD>30 mm	Flank/abdominal pain	L:52.75; R:60.21
17	F	17	Unilateral	Moderate/left	APD>20 mm with calyceal dilation	Febrile UTI	L:67.45; R:88.85

UPJO, ureteropelvic junction obstruction; APD, anterior-posterior diameter; UTI, urinary tract infection; DTPA, diethylene-triaminepentaacetic acid; GFR, glomerular filtration rate; N/A, not available.

[a] Mild: Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction grade 0—1; moderate: grade 2—3; severe: grade 4.

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 the cohort with a calculated AUC of 0.56 (Fig. 3D). When LCN2 and 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 patients with UPJO from healthy controls. The excellent

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007

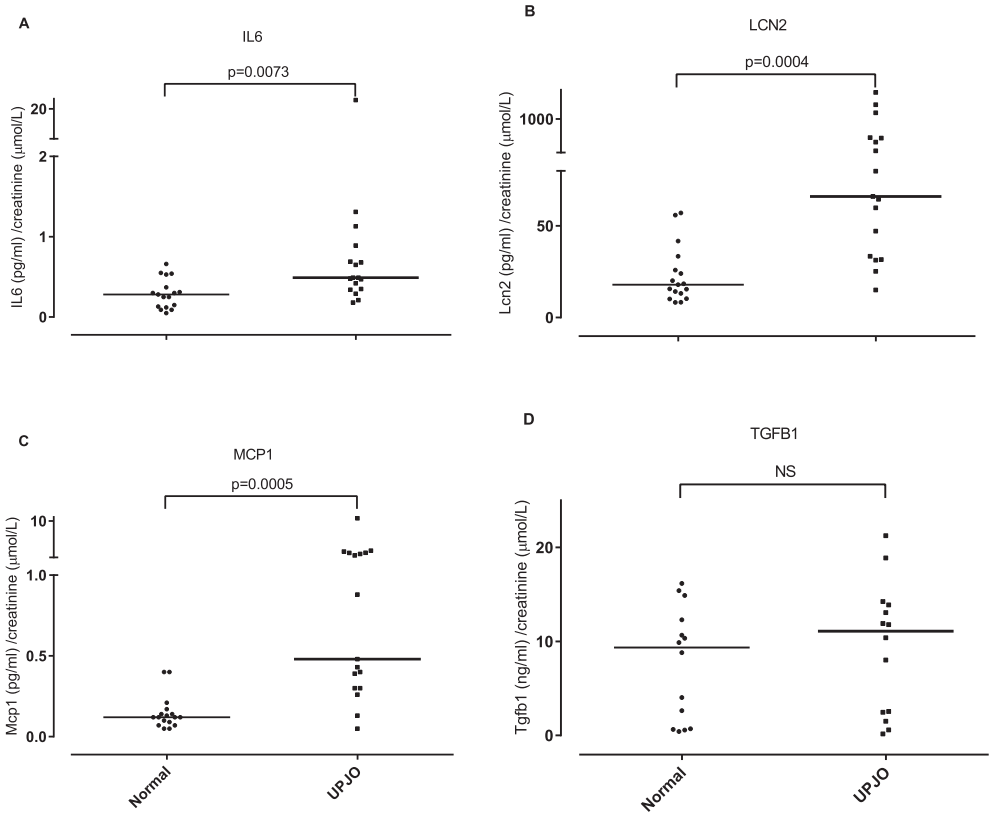


Fig. 1 Ratio of urinary biomarker concentrations to urinary creatinine levels in patients with UPJO and controls. (A) IL6, (B) LCN2, (C) MCP1, and (D) TGFB1. Horizontal bar indicates the median. UPJO, ureteropelvic junction obstruction; IL6, interleukin-6; LCN2, lipocalin-2; MCP1, monocyte chemoattractant protein-1; TGFB1, transforming growth factor-β1.

performance of LCN2 suggests that 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 four investigated in the present study, have been shown to correlate with renal damage in human urine and have undergone large-scale clinical validation. In adult patients with chronic renal failure, neutrophil gelatinase—associated LCN (LCN2), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase, and liver fatty acid binding protein 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 GFR (eGFR). In other words, the biomarkers fail to predict the clinical course of patients with moderate chronic kidney disease (G3, median eGFR = 44), regardless of the 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 the 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 up 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 shows a significant loss of renal

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007

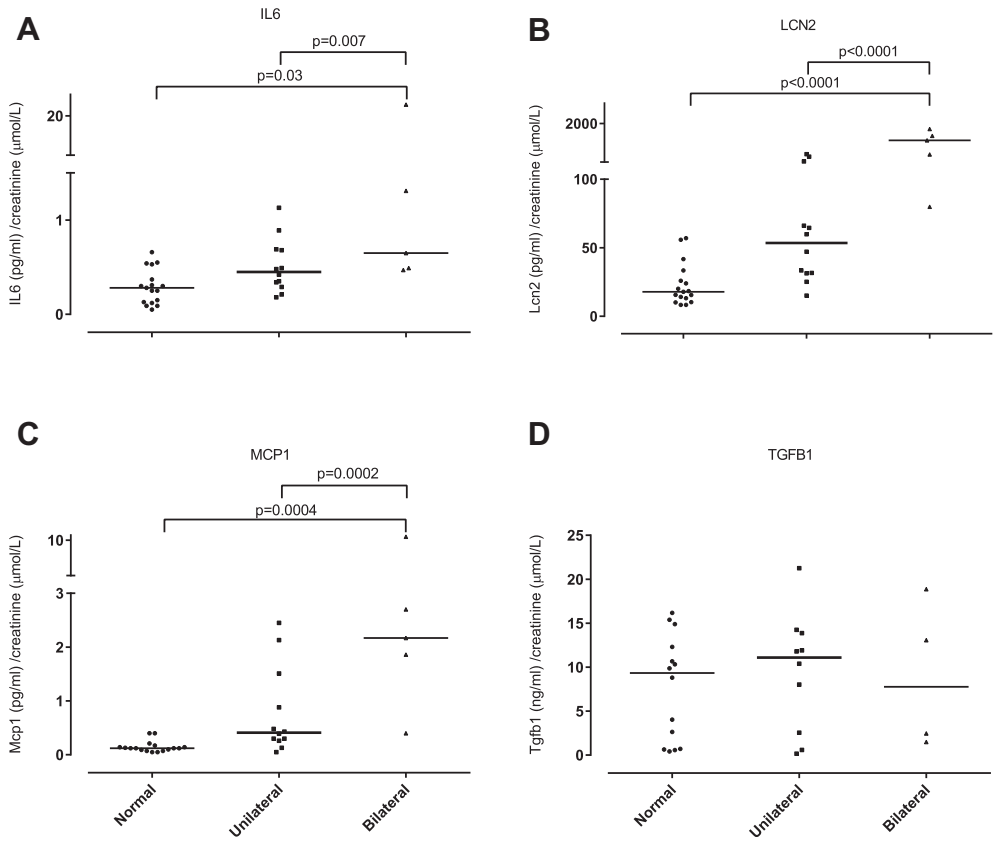


Fig. 2 Ratio of urinary biomarker concentrations to urinary creatinine levels in patients with unilateral and bilateral UPJO. (A) IL6, (B) LCN2, (C) MCP1, and (D) TGFB1. Horizontal bar indicates the median. UPJO, ureteropelvic junction obstruction; IL6, interleukin-6; LCN2, lipocalin-2; MCP1, monocyte chemoattractant protein-1; TGFB1, transforming growth factor-β1.

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 and the obstruction itself would decrease the amount of any biomarker reaching the bladder, particularly because increased filtration in the opposite kidney would overwhelm any biomarker signal. It is possible that the optimal biomarkers have not been identified because obstruction could result in secretion of unique proteins (e.g. owing to physical stretching of the tubules). Finally, biomolecules other than protein (transcripts and microRNAs) could show better performance characteristics, particularly because 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.

The study has several shortcomings. The 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 the 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 before 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 with those who do not progress can it be tested whether these biomarkers provide information independent of currently used clinical decision-making tools.

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007

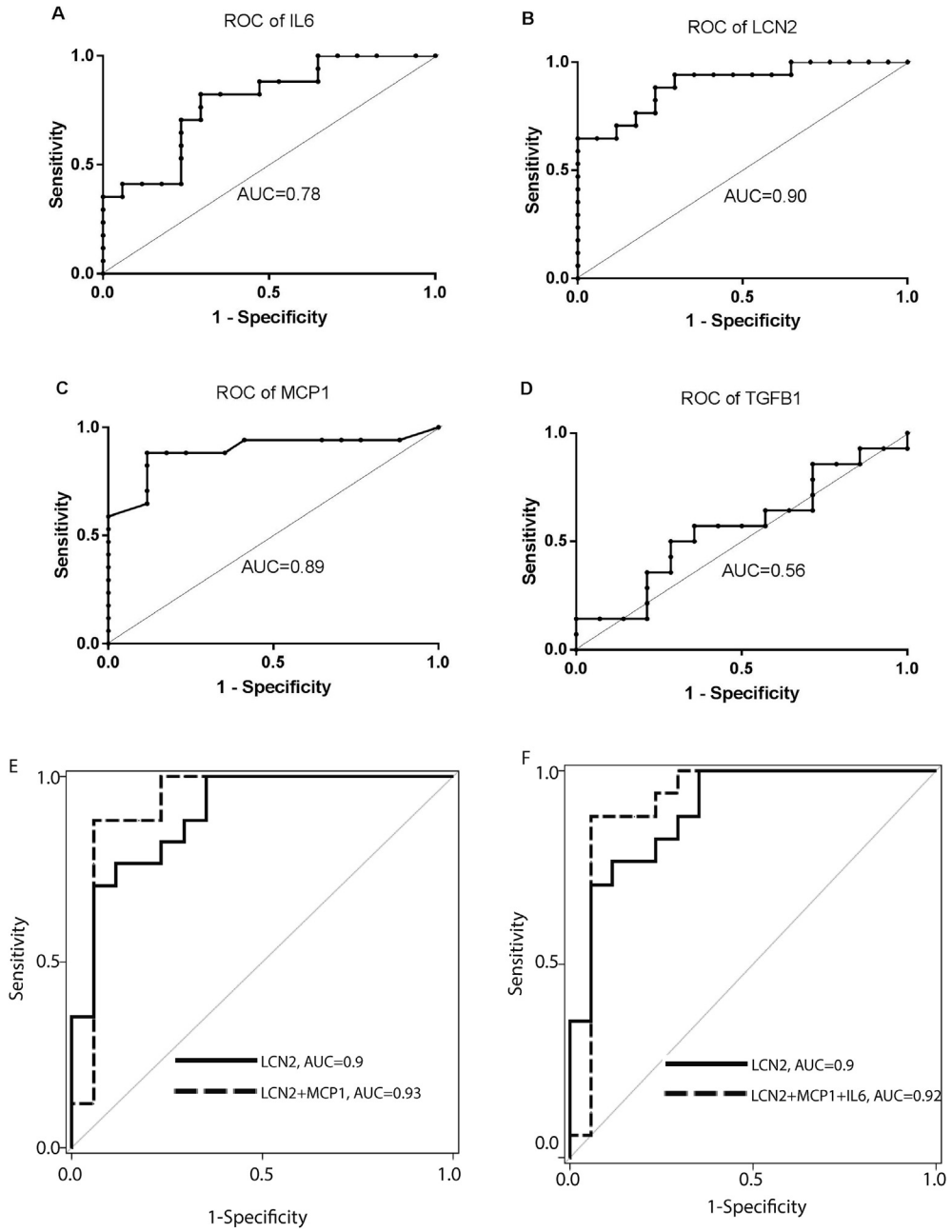


Fig. 3 Receiver operating characteristic (ROC) curves of creatinine-normalized urinary biomarkers in patients with UPJO, (A) IL6, (B) LCN2, (C) MCP1, (D) TGFB1, (E) LCN2+MCP1, and (F) LCN2+MCP1+IL6. AUC, area under the curve; UPJO, ureteropelvic junction obstruction; IL6, interleukin-6; LCN2, lipocalin-2; MCP1, monocyte chemoattractant protein-1; TGFB1, transforming growth factor-β1.

Conclusions

It was found that LCN2, IL-6 and MCP1 levels are elevated in children with UPJO, while TGFB1 level is 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 with protein biomarkers.

Author statements

Ethical approval

The local hospital ethical committee approved the study.

Funding

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

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007

Competing interests

None declared.

References

[1] Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol 2012; 27:363—73. https://doi.org/10.1007/s00467-011-1939-1.
[2] Koff SA, Campbell K. Nonoperative management of unilateral neonatal hydronephrosis. J Urol 1992;148:525—31.
[3] Merrikhi A, Bahraminia E. Association of urinary transforming growth factor-beta1 with the ureteropelvic junction obstruction. Adv Biomed Res 2014;3:123. https://doi.org/10.4103/2277-9175.133196.
[4] Sager C, Lopez JC, Duran V, Burek C, Perazzo E. Transforming growth factor-beta1 in congenital ureteropelvic junction obstruction: diagnosis and follow-up. Int Braz J Urol 2009;35: 315—23. discussion 23-5.
[5] Karakus S, Oktar T, Kucukgergin C, Kalelioglu I, Seckin S, Atar A, et al. Urinary IP-10, MCP-1, NGAL, cystatin-C, and KIM-1 levels in prenatally diagnosed unilateral hydronephrosis: the search for an ideal biomarker. Urology 2016;87:185—92. https://doi.org/10.1016/j.urology.2015.09.007.
[6] Madsen MG, Norregaard R, Palmfeldt J, Olsen LH, Frokiaer J, Jorgensen TM. Epidermal growth factor and monocyte chemotactic peptide-1: potential biomarkers of urinary tract obstruction in children with hydronephrosis. J Pediatr Urol 2013;9:838—45. https://doi.org/10.1016/j.jpurol.2012.11.011.
[7] Gerber C, Harel M, Lynch ML, Herbst KW, Ferrer FA, Shapiro LH. Proximal tubule proteins are significantly elevated in bladder urine of patients with ureteropelvic junction obstruction and may represent novel biomarkers: a pilot study. J Pediatr Urol 2016;12. https://doi.org/10.1016/j.jpurol.2015.10.008. 120 e1-7.
[8] Wu B, Brooks JD. Gene expression changes induced by unilateral ureteral obstruction in mice. J Urol 2012;188:1033—41. https://doi.org/10.1016/j.juro.2012.05.004.
[9] Wu B, Gong X, Kennedy WA, Brooks JD. Identification of transcripts associated with renal damage due to ureteral obstruction as candidate urinary biomarkers. Am J Physiol Renal Physiol 2018;315:F16—26. https://doi.org/10.1152/ajprenal.00382.2017.
[10] Liu D, Zhou H, Ma L, Zhou X, Cao H, Tao T, et al. Comparison of laparoscopic approaches for dismembered pyeloplasty in children with ureteropelvic junction obstruction: critical analysis of 11-year experiences in a single surgeon. Urology 2017;101:50—5. https://doi.org/10.1016/j.urology.2016.10.007.
[11] Dos Santos J, Parekh RS, Piscione TD, Hassouna T, Figueroa V, Gonima P, et al. A new grading system for the management of antenatal hydronephrosis. Clin J Am Soc Nephrol 2015;10: 1783—90. https://doi.org/10.2215/CJN.12861214.
[12] Gates GF. Glomerular filtration rate: estimation from fractional renal accumulation of 99mTc-DTPA (stannous). AJR Am J Roentgenol 1982;138:565—70. https://doi.org/10.2214/ajr.138.3.565.
[13] Lucarelli G, Mancini V, Galleggiante V, Rutigliano M, Vavallo A, Battaglia M, et al. Emerging urinary markers of renal injury in obstructive nephropathy. BioMed Res Int 2014:303298. https://doi.org/10.1155/2014/303298. 2014.
[14] Hsu CY, Xie D, Waikar SS, Bonventre JV, Zhang X, Sabbisetti V, et al. Urine biomarkers of tubular injury do not improve on the clinical model predicting chronic kidney disease progression. Kidney Int 2017;91:196—203. https://doi.org/10.1016/j.kint.2016.09.003.
[15] Fufaa GD, Weil EJ, Nelson RG, Hanson RL, Bonventre JV, Sabbisetti V, et al. Association of urinary KIM-1, L-FABP, NAG and NGAL with incident end-stage renal disease and mortality in American Indians with type 2 diabetes mellitus. Diabetologia 2015;58:188—98. https://doi.org/10.1007/s00125-014-3389-3.
[16] Lin HY, Hwang DY, Lee SC, Kuo HT, Kuo MC, Chang JM, et al. Urinary neutrophil gelatinase-associated lipocalin and clinical outcomes in chronic kidney disease patients. Clin Chem Lab Med 2015;53:73—83. https://doi.org/10.1515/cclm-2014-0647.
[17] Foster MC, Coresh J, Bonventre JV, Sabbisetti VS, Waikar SS, Mifflin TE, et al. Urinary biomarkers and risk of ESRD in the atherosclerosis risk in communities study. Clin J Am Soc Nephrol 2015;10:1956—63. https://doi.org/10.2215/CJN.02590315.
[18] Nickolas TL, Schmidt-Ott KM, Canetta P, Forster C, Singer E, Sise M, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. J Am Coll Cardiol 2012;59:246—55. https://doi.org/10.1016/j.jacc.2011.10.854.
[19] Sise ME, Forster C, Singer E, Sola-Del Valle D, Hahn B, Schmidt-Ott KM, et al. Urine neutrophil gelatinase-associated lipocalin identifies unilateral and bilateral urinary tract obstruction. Nephrol Dial Transplant 2011;26:4132—5. https://doi.org/10.1093/ndt/gfr569.
[20] Ruiz-Deya G, Sikka SC, Thomas R, Abdel-Mageed AB. Potential role for the nuclear transcription factor NF-kappa B in the pathogenesis of ureteropelvic junction obstruction. J Endourol 2002;16:611—5. https://doi.org/10.1089/089277902320913323.
[21] Olvera-Posada D, Dayarathna T, Dion M, Alenezi H, Sener A, Denstedt JD, et al. KIM-1 is a potential urinary biomarker of obstruction: results from a prospective cohort study. J Endourol 2017;31:111—8. https://doi.org/10.1089/end.2016.0215.
[22] Tsai JD, Huang FY, Lin CC, Tsai TC, Lee HC, Sheu JC, et al. Intermittent hydronephrosis secondary to ureteropelvic junction obstruction: clinical and imaging features. Pediatrics 2006;117:139—46. https://doi.org/10.1542/peds.2005-0583.
[23] Onen A, Jayanthi VR, Koff SA. Long-term followup of prenatally detected severe bilateral newborn hydronephrosis initially managed nonoperatively. J Urol 2002;168:1118—20. https://doi.org/10.1097/01.ju.0000024449.19337.8d.

Please cite this article in press as: Yu L, et al., Elevated urinary lipocalin-2, interleukin-6 and monocyte chemoattractant protein-1 levels in children with congenital ureteropelvic junction obstruction, Journal of Pediatric Urology (2018), https://doi.org/10.1016/j.jpurol.2018.10.007