Journal of Pediatric Urology (2016) 12, 120.e1–120.e7

Proximal tubule proteins are significantly elevated in bladder urine of patients with ureteropelvic junction obstruction and may represent novel biomarkers: A pilot study

Claire Gerber [a], Miriam Harel [a,b], Miranda L. Lynch [c], Katherine W. Herbst [b], Fernando A. Ferrer [a,b], Linda H. Shapiro [a,b]

[a]Center for Vascular Biology, University of Connecticut Health Center, Farmington, CT, USA

[b]Division of Urology, Department of Surgery, Connecticut Children's Medical Center, Hartford, CT, USA

[c]Center for Quantitative Medicine and Department of Community Medicine and Health Care, University of Connecticut Health Center, Farmington, CT, USA

Correspondence to: L.H. Shapiro, Center for Vascular Biology, UConn Health, 263 Farmington Avenue, Farmington, CT 06030–3501, USA

Correspondence to: F.A. Ferrer, Department of Urology, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT, USA

fferrer@connecticutchildrens.org (F.A. Ferrer)
lshapiro@uchc.edu (L.H. Shapiro)

Keywords
Ureteral obstruction; Urinary bladder; Proximal tubules; Biological markers

Received 13 March 2015
Accepted 5 October 2015
Available online 28 November 2015

Summary

Purpose
Ureteropelvic junction obstruction (UPJO) is the major cause of hydronephrosis in children and may lead to renal injury and early renal dysfunction. However, diagnosis of the degree of obstruction and severity of renal injury relies on invasive and often inconclusive renal scans. Biomarkers from voided urine that detect early renal injury are highly desirable because of their noninvasive collection and their potential to assist in earlier and more reliable diagnosis of the severity of obstruction. Early in response to UPJO, increased intrarenal pressure directly impacts the proximal tubule brush border. We hypothesize that single-pass, apically expressed proximal tubule brush border proteins will be shed into the urine early and rapidly and will be reliable noninvasive urinary biomarkers, providing the tools for a more reliable stratification of UPJO patients.

Materials and methods
We performed a prospective cohort study at Connecticut Children's Medical Center. Bladder urine samples from 12 UPJO patients were obtained prior to surgical intervention. Control urine samples were collected from healthy pediatric patients presenting with primary nocturnal enuresis. We determined levels of NGAL, KIM-1 (previously identified biomarkers), CD10, CD13, and CD26 (potentially novel biomarkers) by ELISA in control and experimental urine samples. Urinary creatinine levels were used to normalize the urinary protein levels measured by ELISA.

Results
Each of the proximal tubule proteins outperformed the previously published biomarkers. No differences in urinary NGAL and KIM-1 levels were observed between control and obstructed patients ($p = 0.932$ and $p = 0.799$, respectively). However, levels of CD10, CD13, and CD26 were significantly higher in the voided urine of obstructed individuals when compared with controls ($p = 0.002$, $p = 0.024$, and $p = 0.007$, respectively) (Figure).

Conclusions
Targeted identification of reliable, noninvasive biomarkers of renal injury is critical to aid in diagnosing patients at risk, guiding therapeutic decisions and monitoring treatment efficacy. Proximal tubule brush border proteins are reliably detected in the urine of obstructed patients and may be more effective at predicting UPJO.

http://dx.doi.org/10.1016/j.jpurol.2015.10.008

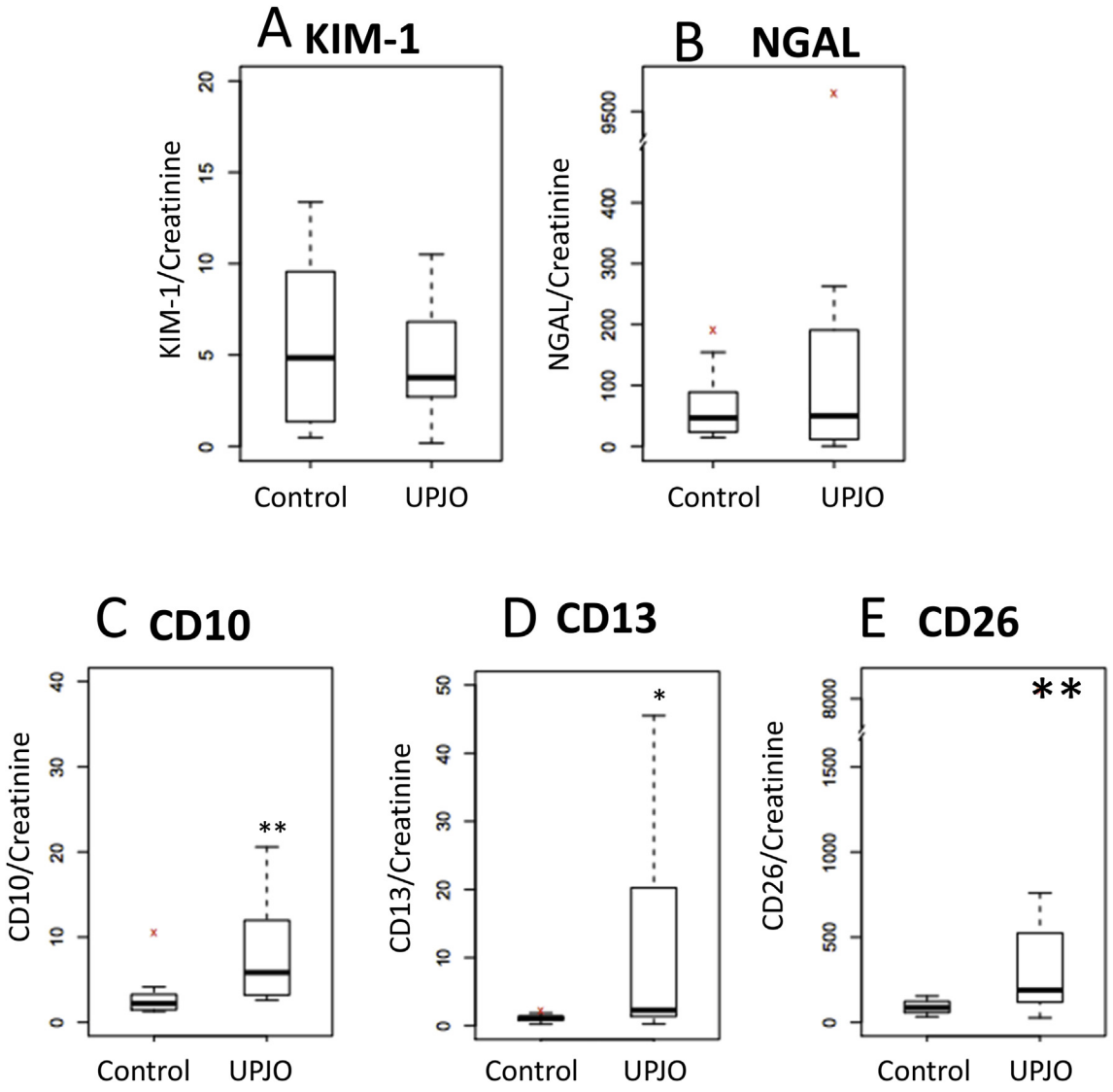

Figure Box plot of known biomarkers (KIM-1 (A) and NGAL (B)) compared with novel proximal tubule biomarkers (CD10 (C), CD13 (D) and CD26 (E)). Data expressed in relative units.*$p < 0.05$; **$p < 0.01$.

Introduction

Obstructive nephropathy is the underlying cause of end-stage renal disease (ESRD) in most pediatric patients. With an estimated prevalence of 1 in 500 births, ureteropelvic junction obstruction (UPJO) is the major cause of hydronephrosis and may lead to renal injury and early renal dysfunction [1]. With the advent of widespread antenatal ultrasonography, many cases of UPJO are identified prenatally in asymptomatic patients. The indications for surgical intervention have become controversial, with some advocating initial observation with serial imaging techniques and surgical intervention reserved for patients with decreasing ipsilateral renal function and/or worsening drainage [2]. Although this strategy may minimize overtreatment in children who may prove to have benign, self-limited hydronephrosis, other patients may suffer ongoing renal damage during this period of nonoperative management.

Mechanisms to assess the severity of damage caused by obstruction are decisively lacking and primarily rely on serum creatinine, which remains unchanged until 50% of nephron volume is lost [3,4]. Alternatively, differential renal function is determined by nuclear scans such as radiolabeled mercapto-acetyl-triglycine (MAG3) that measure the rate of kidney drainage ($t_{1/2}$) and differential function. Generally, the diagnosis of obstruction on MAG3 renography is based on a $t_{1/2}$ greater than 20 min or poor differential renal function, while a $t_{1/2}$ under 10 min is consistent with unobstructed drainage. Cases with a $t_{1/2}$ between 10 and 20 min are considered equivocal, which may be difficult to interpret clinically [5]. Furthermore, nuclear renography is costly, may require sedation in younger children, and often requires repeat evaluation to assess progression of obstruction or deterioration in renal function.

Targeted identification of reliable urinary biomarkers would be invaluable for diagnosing patients at risk for renal damage, guiding therapeutic decisions, and potentially