

**Unilateral Ureteral Obstruction (UO) and Renal Studies literatures**Ma Hongbao<sup>1</sup>, Margaret Ma<sup>2</sup>, Yang Yan<sup>1</sup><sup>1</sup> Brookdale University Hospital and Medical Center, Brooklyn, New York 11212, USA; <sup>2</sup> Cambridge, MA 02138, USA. [ma8080@gmail.com](mailto:ma8080@gmail.com)

**Abstract:** Renal fibrosis is the hallmark of progressive renal disease of virtually any etiology. Unilateral ureteral obstruction (UO) is a experimental model of renal injury. The UO model of in the rodent generates progressive renal fibrosis. The surgically created UO can be experimentally manipulated with respect to timing, severity, and duration, while reversal of the obstruction permits the study of recovery. Symptoms and signs of obstruction are often mild, occurring over long periods of time and requiring a high index of suspicion for diagnosis. Early recognition and treatment are the keys to preventing renal loss.

[Ma H, Young M, Yang Y. **Unilateral Ureteral Obstruction (UO) and Renal Studies literatures.** *N Y Sci J* 2015;8(12):76-101]. (ISSN: 1554-0200). <http://www.sciencepub.net/newyork>. 10. doi:[10.7537/marsnys081215.10](https://doi.org/10.7537/marsnys081215.10).

**Key words:** unilateral ureteral obstruction (UO); life; renal

**Introduction**

Renal fibrosis is the hallmark of progressive renal disease of virtually any etiology. Unilateral ureteral obstruction (UO) is a experimental model of renal injury. The UO model of in the rodent generates progressive renal fibrosis. The surgically created UO can be experimentally manipulated with respect to timing, severity, and duration, while reversal of the obstruction permits the study of recovery. Symptoms and signs of obstruction are often mild, occurring over long periods of time and requiring a high index of suspicion for diagnosis. Early recognition and treatment are the keys to preventing renal loss. Most chronic kidney disease in children results from congenital or inherited disorders, which can be studied in mouse models.

The following introduces recent reports as references in the related studies.

Acikgoz, Y., B. Can, et al. "The effect of simvastatin and erythropoietin on renal fibrosis in rats with unilateral ureteral obstruction." *Ren Fail.* 2014 Mar;36(2):252-7. doi: [10.3109/0886022X.2013.836936](https://doi.org/10.3109/0886022X.2013.836936). Epub 2013 Oct 2.

Prevention of fibrosis is a very important therapeutic strategy in the treatment of obstructive nephropathy (ON). The aim of this study is to show and compare the actions of Simvastatin (Simv) and Erythropoietin (Epo) in renal expression of nuclear factor kappa B (NFkappaB), transforming growth factor-beta (TGF-beta), basic fibroblast growth factor (bFGF), platelet-derived growth factor B (PDGF-B), fibronectin and development of interstitial fibrosis in rats with unilateral ureteral obstruction (UO). A total of 48 Sprague-Dawley rats were allocated to 4 groups of sham, Epo, Simv and control. Unilateral ureteral ligation was performed on all rats except the Sham group. For interstitial fibrosis Masson's trichrome stain

and for the expression of TGF-beta, PDGF-B, bFGF, NFkappaB and fibronectin, immunohistochemical methods were used. In the Epo and Simv groups, expression of TGF-beta and fibronectin and staining with Masson's trichrome were less compared to the control group. In addition, fibronectin expression in the Epo group was less than the Simv group. Unlike the Simv group, NFkappaB and bFGF expression in the Epo group were less when compared to the control group. Consequently, it was seen that both Epo and Simv prevented fibrosis in ON. Epo was superior in this effect by suppressing the expressions of NFkappaB and bFGF more effectively than Simv. Based on this finding, Epo might be a better agent than Simv in the prevention of fibrosis in ON.

Atar, A., T. Oktar, et al. "The roles of serum and urinary carbohydrate antigen 19-9 in the management of patients with antenatal hydronephrosis." *J Pediatr Urol.* 2015 Mar 13. pii: S1477-5131(15)00075-3. doi: [10.1016/j.jpuro.2014.12.012](https://doi.org/10.1016/j.jpuro.2014.12.012).

**INTRODUCTION:** Serum carbohydrate antigen (CA) 19-9 has been clinically applied as a valuable tumor marker for pancreatic and gastrointestinal carcinoma. CA 19-9 is expressed in normal excretory epithelium tissues. Increased CA 19-9 has also been observed in uroepithelial tumors as well as in nonmalignant conditions including hydronephrosis secondary to ureteral stones. **OBJECTIVE:** The purpose of this article is to evaluate the role of urinary CA 19-9 as a non-invasive biomarker in the postnatal differentiation of obstructive and non-obstructive hydronephrosis in patients with unilateral antenatal hydronephrosis. **STUDY DESIGN:** Infants with isolated renal pelvic dilatation, defined as the presence of anteroposterior pelvic diameter (APPD) equal to or greater than 7 mm based on antenatal ultrasound after 28 weeks'

gestation, underwent systematic investigation for uropathies and were prospectively followed up. The pyeloplasty group consisted of 17 patients with ureteropelvic junction (UPJ) obstruction who had undergone pyeloplasty. The non-obstructive dilatation (NOD) group consisted of 17 patients with non-obstructive hydronephrosis, and the control group consisted of 21 healthy children. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used to measure the urinary and serum CA 19-9 levels. In both hydronephrosis groups (pyeloplasty and non-obstructive dilatation), the correlations between urinary and serum CA 19-9 levels with the anteroposterior pelvic diameter measured at the third trimester and the postnatal initial evaluation and differential renal function were investigated. RESULTS: The initial median urinary CA 19-9 levels were significantly greater in children who underwent pyeloplasty than in both the non-obstructive hydronephrosis (143 +/- 38 vs. 68 +/- 23, respectively;  $p = 0.007$ ) and the healthy control groups (143 +/- 38 vs. 13 +/- 3, respectively;  $p = 0.001$ ) (Figure). Three months after surgery, the urinary CA 19-9 levels had decreased significantly according to the preoperative levels in the pyeloplasty group (143 +/- 38 vs. 55 +/- 16,  $p = 0.039$ ). In both the pyeloplasty and NOD groups, there was a correlation of urinary CA 19-9 levels with differential renal function and a correlation of serum CA 19-9 levels with the initial anteroposterior pelvic diameter. Receiver operator characteristic (ROC) analysis revealed a better diagnostic profile for the urinary CA 19-9 level than for the serum CA 19-9 level in terms of identifying obstruction in the hydronephrosis groups (areas under the curve = 0.8 and 0.7, respectively). The best cut-off value of for urinary CA 19-9 was 85.5U/mL with 76% sensitivity, 85% specificity. The negative predictive value was 80%. DISCUSSION: The results suggest that voided urine CA 19-9 levels seems to be a more useful marker than serum CA 19-9 in obstructive dilatation. An appropriate decrease in urinary CA 19-9 levels after pyeloplasty may be used as a predictor of surgical outcome. In addition, the results have a number of important diagnostic implications that should be further validated in a larger study population. CONCLUSIONS: Based on these results, we suggest that a high urinary CA 19-9 level is a non-invasive clinically applicable marker for differentiating between obstruction and non-obstructive dilatation.

Azam, A., h. Arfan ul, et al. "Role of renal arterial resistive index (RI) in obstructive uropathy." *J Pak Med Assoc.* 2013 Dec;63(12):1511-5.

OBJECTIVE: To determine the diagnostic accuracy of renal arterial resistive index on doppler

ultrasound in patients with acute renal colic to diagnose obstructive uropathy taking non-enhanced helical computed tomography as the gold standard. METHODS: The descriptive study, conducted at the Radiology Department of Pakistan Naval Ship Shifa Hospital, Karachi, from October 10, 2010 to July 17, 2011, comprised 160 patients referred from the Emergency Department with complaint of unilateral renal colic. Ultrasound was carried out. Subsequently, computed tomography scan of kidney, ureter and bladder was performed. Data was collected on prescribed proforma and analysed using SPSS 19. RESULTS: By taking the resistive index value of  $> 0.70$  as a discriminatory level for obstruction, the overall sensitivity of the index was 76.23% and specificity was 88.13%. The positive predictive values of the index in patients with obstructive uropathy was 91.6%, and negative predictive value was calculated to be 68.42%. The diagnostic accuracy of the test was 80%. CONCLUSION: Duplex Doppler ultrasound can detect acute renal obstruction with sensitivity of approximately 77%. However, ultrasound is an operator-dependent examination, and the results are much affected by patient body habitus.

Chevalier, R. L., M. S. Forbes, et al. "Responses of proximal tubular cells to injury in congenital renal disease: fight or flight." *Pediatr Nephrol.* 2014 Apr;29(4):537-41. doi: 10.1007/s00467-013-2590-9. Epub 2013 Aug 16.

Most chronic kidney disease in children results from congenital or inherited disorders, which can be studied in mouse models. Following 2 weeks of unilateral ureteral obstruction (UUO) in the adult mouse, nephron loss is due to proximal tubular mitochondrial injury and cell death. In neonatal mice, proximal tubular cell death is delayed beyond 2 weeks of complete UUO, and release of partial UUO allows remodeling of remaining nephrons. Progressive cyst expansion develops in polycystic kidney disease (PKD), a common inherited renal disorder. The polycystic kidney and fibrosis (pcy)-mutant mouse (which develops late-onset PKD) develops thinning of the glomerulotubular junction in parallel with growth of cysts in adulthood. Renal insufficiency in nephropathic cystinosis, a rare inherited renal disorder, results from progressive tubular cystine accumulation. In the Ctns knockout mouse (a model of cystinosis), proximal tubular cells become flattened, with loss of mitochondria and thickening of tubular basement membrane. In each model, persistent obstructive or metabolic stress leads ultimately to the formation of atubular glomeruli. The initial "fight" response (proximal tubular survival) switches to a "flight" response (proximal tubular cell death) with ongoing oxidative injury and mitochondrial damage. Therapies

should be directed at reducing proximal tubular mitochondrial oxidative injury to enhance repair and regeneration.

da Silva, A. F., K. Silva, et al. "Bone Marrow-Derived Mesenchymal Stem Cells and Their Conditioned Medium Attenuate Fibrosis in an Irreversible Model of Unilateral Ureteral Obstruction." *Cell Transplant.* 2015 Feb 18. doi: 10.3727/096368915X687534.

The therapeutic potential of mesenchymal stem cells (MSCs) and their conditioned medium (MSC-CM) has been extensively studied. MSCs can repair tissue, reduce local inflammation and modulate the immune response. Persistent renal tubular interstitial inflammation results in fibrosis and leads to chronic kidney disease (CKD). Unilateral ureteral obstruction (UO) is a very well-accepted renal fibrosis model. In this study, we evaluated factors influenced by the administration of MSCs or MSC-CM in the UO model. MSCs extracted from rat bone marrow were cultivated in vitro and characterized by flow cytometry and cellular differentiation. Eight groups of female rats were used in experiments (n=7, each), including SHAM, UO (Ureteral Unilateral Obstruction), UO+MSC (Obstruction + MSC) and UO+CM (Obstruction + MSC-CM) for 7 days of obstruction and SHAM, UO, UO+MSC and UO+CM for 14 days of obstruction. The MSCs or MSC-CM was administered via the abdominal vena cava after total ligation of the left ureter. After 7 or 14 days, rats were euthanized and serum and obstructed kidney samples were collected. MSCs or MSC-CM decreased the expression of molecules, such as Colla1,  $\alpha$ -SMA and TNF- $\alpha$ . We also observed reductions in the levels of caspase-3,  $\alpha$ -SMA and PCNA in treated animals by immunohistochemistry. Our results suggest that the intravenous administration of MSCs or MSC-CM improves fibrosis progression and factors involved in apoptosis, inflammation, cell proliferation and epithelial-mesenchymal transition in Wistar rats subjected to unilateral ureteral obstruction, indicating a potential tool for preventing CKD.

de Lima, M. L., R. Bertti, et al. "(99m) Tc-DTPA Study to Validate an Experimental Model of Ureteral Obstruction in Rabbits: Preliminary Results." *Adv Urol.* 2013;2013:929620. doi: 10.1155/2013/929620. Epub 2013 Dec 29.

**Objective.** To create a ureteral obstruction experimental model that can be proved through (99m)Tc-DTPA renal scintigraphy and histopathological studies, without causing total renal function loss. **Materials and Methods.** Ten New Zealand white rabbits were submitted to a surgical experiment to create a model of unilateral obstruction to urinary flow. Surgery procedure provided unilateral

ureteral obstruction (left kidney) to urinary flow and posteriorly was evaluated by (99m)Tc-DTPA renal scintigraphy and histopathological study. (99m)Tc-DTPA renal study was performed to detect and quantify signs of obstruction and to evaluate renal function. Statistical analysis was performed through the Student t-test with a significance level of  $P < 0.05$ . **Results.** Nine of the ten rabbits presented left renal unit obstruction and one nonobstructive on the (99m)Tc-DTPA and histopathological studies. All the right renal units, which were not submitted to surgical procedure, were nonobstructed by the studies. There was a general agreement between scintigraphy and histopathological results in both groups. **Conclusion.** The experimental model promoted the creation of ureteral obstruction in rabbits, confirmed by nuclear medicine scintigraphy and histopathology, and could be used in further studies to better understand urinary obstruction.

Denby, L., V. Ramdas, et al. "MicroRNA-214 antagonism protects against renal fibrosis." *J Am Soc Nephrol.* 2014 Jan;25(1):65-80. doi: 10.1681/ASN.2013010072. Epub 2013 Oct 24.

Renal tubulointerstitial fibrosis is the common end point of progressive renal disease. MicroRNA (miR)-214 and miR-21 are upregulated in models of renal injury, but the function of miR-214 in this setting and the effect of its manipulation remain unknown. We assessed the effect of inhibiting miR-214 in an animal model of renal fibrosis. In mice, genetic deletion of miR-214 significantly attenuated interstitial fibrosis induced by unilateral ureteral obstruction (UO). Treatment of wild-type mice with an anti-miR directed against miR-214 (anti-miR-214) before UO resulted in similar antifibrotic effects, and in vivo biodistribution studies demonstrated that anti-miR-214 accumulated at the highest levels in the kidney. Notably, in vivo inhibition of canonical TGF- $\beta$  signaling did not alter the regulation of endogenous miR-214 or miR-21. Whereas miR-21 antagonism blocked Smad 2/3 activation, miR-214 antagonism did not, suggesting that miR-214 induces antifibrotic effects independent of Smad 2/3. Furthermore, TGF- $\beta$  blockade combined with miR-214 deletion afforded additional renal protection. These phenotypic effects of miR-214 depletion were mediated through broad regulation of the transcriptional response to injury, as evidenced by microarray analysis. In human kidney tissue, miR-214 was detected in cells of the glomerulus and tubules as well as in infiltrating immune cells in diseased tissue. These studies demonstrate that miR-214 functions to promote fibrosis in renal injury independent of TGF- $\beta$  signaling in vivo and that antagonism of miR-214

may represent a novel antifibrotic treatment in the kidney.

Diez, E. R., L. B. Altamirano, et al. "Heart remodeling and ischemia-reperfusion arrhythmias linked to myocardial vitamin D receptors deficiency in obstructive nephropathy are reversed by paricalcitol." *J Cardiovasc Pharmacol Ther.* 2015 Mar;20(2):211-20. doi: 10.1177/1074248414538704. Epub 2014 Jun 12.

Cardiovascular disease is often associated with chronic kidney disease and vice versa; myocardial vitamin D receptors (VDRs) are among the probable links between the 2 disorders. The vitamin D receptor activator paricalcitol protects against some renal and cardiovascular complications. However, the structural and electrophysiological effects of myocardial vitamin D receptor modification and its impact on the response to ischemia-reperfusion are currently unknown. This work attempted to determine whether obstructive nephropathy induced myocardial changes (in rats) linked to vitamin D receptor deficiency and to ventricular arrhythmias in Langendorff-perfused hearts. Unilateral ureteral-obstructed and Sham-operated rats were treated with either paricalcitol (30 ng/kg/d intraperitoneal) or vehicle for 15 days. In 5 hearts from each group, we found that obstructed rats showed a reduction in VDRs and an increase in angiotensin II type 1 receptor expression (messenger RNA and protein), suffered fibrosis (determined by Masson trichrome stain) and myofibril reduction with an increase in mitochondrial size, and had dilated crests (determined by electron microscopy). These changes were reversed by paricalcitol. In 8 additional hearts per group, we found that obstructed rats showed a higher incidence of ventricular fibrillation during reperfusion (after 10 minutes of regional ischemia) than did those treated with paricalcitol. The action potential duration was prolonged throughout the experiment in paricalcitol-treated rats. We conclude that the reduction in myocardial vitamin D receptor expression in obstructed rats might be related to myocardial remodeling associated with an increase in arrhythmogenesis and that paricalcitol protects against these changes by restoring myocardial vitamin D receptor levels and prolonging action potentials.

Engel, D. R., T. A. Krause, et al. "CX3CR1 reduces kidney fibrosis by inhibiting local proliferation of profibrotic macrophages." *J Immunol.* 2015 Feb 15;194(4):1628-38. doi: 10.4049/jimmunol.1402149. Epub 2015 Jan 16.

A dense network of macrophages and dendritic cells (DC) expressing the chemokine receptor CX3CR1 populates most tissues. We recently reported that CX3CR1 regulates the abundance of

CD11c(+) DC in the kidney and thereby promotes renal inflammation in glomerulonephritis. Given that chronic inflammation usually causes fibrosis, we hypothesized that CX3CR1 deficiency should attenuate renal fibrosis. However, when we tested this hypothesis using the DC-independent murine fibrosis model of unilateral ureteral obstruction, kidney fibrosis was unexpectedly more severe, despite less intrarenal inflammation. Two-photon imaging and flow cytometry revealed in kidneys of CX3CR1-deficient mice more motile Ly6C/Gr-1(+) macrophages. Flow cytometry verified that renal macrophages were more abundant in the absence of CX3CR1 and produced more of the key profibrotic mediator, TGF-beta. Macrophages accumulated because of higher intrarenal proliferation, despite reduced monocyte recruitment and higher signs of apoptosis within the kidney. These findings support the theory that tissue macrophage numbers are regulated through local proliferation and identify CX3CR1 as a regulator of such proliferation. Thus, CX3CR1 inhibition should be avoided in DC-independent inflammatory diseases because it may promote fibrosis.

Forbes, M. S., B. A. Thornhill, et al. "Chronic unilateral ureteral obstruction in the neonatal mouse delays maturation of both kidneys and leads to late formation of atubular glomeruli." *Am J Physiol Renal Physiol.* 2013 Dec 15;305(12):F1736-46. doi: 10.1152/ajprenal.00152.2013. Epub 2013 Oct 9.

Unilateral ureteral obstruction (UO) in the adult mouse is the most widely used model of progressive renal disease: the proximal tubule is the nephron segment most severely affected and atubular glomeruli are formed after only 7 days of UO. To determine the proximal nephron response to UO in the maturing kidney, neonatal mice were examined 7 to 28 days following complete UO under general anesthesia. Proximal tubular mass and maturation were determined by staining with Lotus tetragalonus lectin. Superoxide was localized by nitroblue tetrazolium and collagen by Sirius red. Cell proliferation, cell death, PAX-2, megalin, alpha-smooth muscle actin (alpha-SMA), renin, and fibronectin were identified by immunohistochemistry. During the first 14 days of ipsilateral UO, despite oxidative stress (4-hydroxynonenal staining), glomerulotubular continuity was maintained and mitochondrial superoxide production persisted. However, from 14 to 28 days, papillary growth was impaired and proximal tubules collapsed with increased apoptosis, autophagy, mitochondrial loss, and formation of atubular glomeruli. Fibronectin, alpha-SMA, and collagen increased in the obstructed kidney. Oxidative stress was present also in the



contralateral kidney: renin was decreased, glomerulotubular maturation and papillary growth were delayed, followed by increased cortical and medullary growth. We conclude that neonatal UO initially delays renal maturation and results in oxidative stress in both kidneys. In contrast to the adult, proximal tubular injury in the neonatal obstructed kidney is delayed at 14 days, followed only later by the formation of atubular glomeruli. Antioxidant therapies directed at proximal tubular mitochondria during early renal maturation may slow progression of congenital obstructive nephropathy.

Friedman, A. A. and M. K. Hanna "Split-cuff nipple technique of ureteral reimplantation in children with thick-walled bladders due to posterior urethral valves." *Urology*. 2015 Jan;85(1):199-204. doi: [10.1016/j.urology.2014.09.023](https://doi.org/10.1016/j.urology.2014.09.023). Epub 2014 Nov 8.

**OBJECTIVE:** To describe a novel technique of ureteral reimplantation in patients with thick-walled bladders, which addresses the technical challenges and high failure rates seen in this population. **METHODS:** From 1997 to 2012, 45 megaureters were reimplanted in 26 children aged 2-11 years. Key surgical modifications included ureteral trough creation within the detrusor, formation of a distal ureteral split-cuff nipple, reliance on transureteroureterostomy (TUU) when the bladder would not support the reimplantation of 2 ureters, performance of psoas vesicopexy, and judicious utilization of ureteral stump augmentation in patients undergoing TUU. Follow-up ranged from 1 to 12 years. **RESULTS:** Seven patients underwent unilateral and 4 underwent bilateral ureteral reimplantation; TUU was performed in 15. Psoas vesicopexy was performed in 22 patients. Voiding cystourethrography showed no reflux in all children who underwent vesicopexy. Reflux resolved in 6 of 8 bilaterally reimplanted ureters; 2 of 8 had improved reflux that later resolved with Deflux injection. No ureters obstructed. Hydronephrosis improved in 32 of 45 renal units and remained stable in 13. Seven patients continue to develop bacteriuria. Five have developed renal failure. **CONCLUSION:** In our experience, a long ureteral trough combined with a split-cuff nipple technique for reimplanting megaureters into thick-walled bladders yields improved results over conventional submucosal tunneling, effectively eliminating or improving reflux and preventing obstruction. TUU and psoas vesicopexy proved useful adjuncts in creating adequate intravesical trough length. The risk for continued bacteriuria and renal failure due to limited renal reserve, however, remain notable in this group.

Galarreta, C. I., J. J. Grantham, et al. "Tubular obstruction leads to progressive proximal tubular

injury and atubular glomeruli in polycystic kidney disease." *Am J Pathol*. 2014 Jul;184(7):1957-66. doi: [10.1016/j.ajpath.2014.03.007](https://doi.org/10.1016/j.ajpath.2014.03.007). Epub 2014 May 9.

In polycystic kidney disease (PKD), renal parenchyma is destroyed by cysts, hypothesized to obstruct nephrons. A signature of unilateral ureteral obstruction, proximal tubular atrophy leads to formation of atubular glomeruli. To determine whether this process occurs in PKD, kidneys from pcy mice (moderately progressive PKD), kidneys from cpk mice (rapidly progressive PKD), and human autosomal dominant PKD were examined in early and late stages. Integrity of the glomerulotubular junction and proximal tubular mass were determined in sections stained with Lotus tetragonolobus lectin. Development of proximal tubular atrophy and atubular glomeruli was determined in serial sections of individual glomeruli. In pcy mice, most glomerulotubular junctions were normal at 20 weeks, but by 30 weeks, 56% were atrophic and 25% of glomeruli were atubular; glomerulotubular junction integrity decreased with increasing cyst area ( $r = 0.83$ ,  $P < 0.05$ ). In cpk mice, all glomerulotubular junctions were normal at 10 days, but by 19 days, 26% had become abnormal. In early-stage autosomal dominant PKD kidneys, 50% of glomeruli were atubular or attached to atrophic tubules; in advanced disease, 100% were abnormal. Thus, proximal tubular injury in cystic kidneys closely parallels that observed with ureteral obstruction. These findings support the hypothesis that, in renal cystic disorders, cyst-dependent obstruction of medullary and cortical tubules initiates a process culminating in widespread destruction of proximal convoluted tubules at the glomerulotubular junction.

Giannarini, G., T. M. Kessler, et al. "Functional multiparametric magnetic resonance imaging of the kidneys using blood oxygen level dependent and diffusion-weighted sequences." *J Urol*. 2014 Aug;192(2):434-9. doi: [10.1016/j.juro.2014.02.048](https://doi.org/10.1016/j.juro.2014.02.048). Epub 2014 Feb 25.

**PURPOSE:** Little data are available on noninvasive magnetic resonance imaging based assessment of renal function during upper urinary tract obstruction. We determined whether functional multiparametric kidney magnetic resonance imaging could monitor the treatment response in cases of acute unilateral upper urinary tract obstruction. **MATERIAL AND METHODS:** Between January 2008 and January 2010, 18 patients with acute unilateral upper urinary tract obstruction due to calculi were prospectively enrolled to undergo kidney magnetic resonance imaging with conventional, blood oxygen level dependent and diffusion-weighted sequences upon emergency hospital admission and after release of

obstruction. We assessed functional imaging parameters of obstructed and contralateral unobstructed kidneys derived from blood oxygen level dependent (apparent spin relaxation rate) and diffusion-weighted (total apparent diffusion coefficient, pure diffusion coefficient and perfusion fraction) sequences during acute upper urinary tract obstruction and after its release. RESULTS: During acute obstruction the apparent spin relaxation rate and perfusion fraction were lower in the cortex ( $p=0.020$  and  $0.031$ ) and medulla ( $p=0.012$  and  $0.190$ , respectively) of obstructed kidneys compared to contralateral unobstructed kidneys. After obstruction release the apparent spin relaxation rate and perfusion fraction increased in the cortex ( $p=0.016$  and  $0.004$ ) and medulla ( $p=0.071$  and  $0.044$ , respectively) of formerly obstructed kidneys to values similar to those in contralateral kidneys. Total apparent diffusion coefficient and pure diffusion coefficient values did not significantly differ between obstructed and contralateral unobstructed kidneys during or after obstruction. CONCLUSIONS: In our patients with acute unilateral upper urinary tract obstruction due to calculi functional kidney magnetic resonance imaging using blood oxygen level dependent and diffusion-weighted sequences enabled us to monitor pathophysiological changes in obstructed kidneys during obstruction and after its release.

Goel, A., P. Tiwari, et al. "Extragenitourinary retroperitoneal primary hydatid cyst: a rare cause of bilateral lower ureteric obstruction and unilateral limb edema." Saudi J Kidney Dis Transpl. 2013 Sep;24(5):991-4.

Hydatid cyst is an endemic disease in our country. Most commonly, it occurs in the liver and lungs. Bilateral hydronephrosis is one of the rare presentations of hydatid disease. Herein, we are reporting an unusual case of hydatid disease where the primary mode of presentation was external iliac vein compression with chronic renal failure because of bilateral ureteric involvement. The patient was treated with bilateral double-J stenting to improve the renal function and operated later for removal of hydatid cyst under albendazole drug treatment.

Grgic, I., A. M. Krautzberger, et al. "Translational profiles of medullary myofibroblasts during kidney fibrosis." J Am Soc Nephrol. 2014 Sep;25(9):1979-90. doi: 10.1681/ASN.2013101143. Epub 2014 Mar 20.

Myofibroblasts secrete matrix during chronic injury, and their ablation ameliorates fibrosis. Development of new biomarkers and therapies for CKD will be aided by a detailed analysis of myofibroblast gene expression during the early stages of fibrosis. However, dissociating myofibroblasts from

fibrotic kidney is challenging. We therefore adapted translational ribosome affinity purification (TRAP) to isolate and profile mRNA from myofibroblasts and their precursors during kidney fibrosis. We generated and characterized a transgenic mouse expressing an enhanced green fluorescent protein (eGFP)-tagged L10a ribosomal subunit protein under control of the collagen1alpha1 promoter. We developed a one-step procedure for isolation of polysomal RNA from collagen1alpha1-eGFP-L10a mice subject to unilateral ureteral obstruction and analyzed and validated the resulting transcriptional profiles. Pathway analysis revealed strong gene signatures for cell proliferation, migration, and shape change. Numerous novel genes and candidate biomarkers were upregulated during fibrosis, specifically in myofibroblasts, and we validated these results by quantitative PCR, in situ, and Western blot analysis. This study provides a comprehensive analysis of early myofibroblast gene expression during kidney fibrosis and introduces a new technique for cell-specific polysomal mRNA isolation in kidney injury models that is suited for RNA-sequencing technologies.

Honma, S., M. Shinohara, et al. "Effect of cyclooxygenase (COX)-2 inhibition on mouse renal interstitial fibrosis." Eur J Pharmacol. 2014 Oct 5;740:578-83. doi: 10.1016/j.ejphar.2014.06.027. Epub 2014 Jun 26.

Unilateral ureteral obstruction (UO) is a well-established model for the study of interstitial fibrosis in the kidney. In this study, we investigated the effects of a COX-2 inhibitor, meloxicam, on UO-induced renal interstitial fibrosis in mice. Serum creatinine, blood urea nitrogen and urinary glucose were significantly increased by UO. However, all of these changes were attenuated by meloxicam (1 mg/kg/day). Masson's trichrome staining showed that interstitial fibrosis was significantly increased by UO, but that meloxicam also significantly diminished the area of UO-induced fibrosis. Heat shock protein (HSP) 47 protein, a collagen-specific molecular chaperone essential for the biosynthesis of collagen molecules, and type IV collagen mRNA were increased in kidneys of UO mice. Meloxicam reduced the expression of both HSP47 protein and type IV collagen mRNA. The phosphorylation of extracellular regulated kinase (ERK) and c-jun-N-terminal kinase (JNK) was increased by UO, but these changes were inhibited by meloxicam. Collectively, these results suggest that COX-2 may be involved in the expression of HSP47 and type IV collagen through the phosphorylation of ERK and JNK, accelerating renal interstitial fibrosis.

Hsieh, L. T., M. V. Nastase, et al. "Soluble biglycan as a biomarker of inflammatory renal diseases." *Int J Biochem Cell Biol.* 2014 Sep;54:223-35. doi: [10.1016/j.biocel.2014.07.020](https://doi.org/10.1016/j.biocel.2014.07.020). Epub 2014 Aug 1.

Chronic renal inflammation is often associated with a progressive accumulation of various extracellular matrix constituents, including several members of the small leucine-rich proteoglycan (SLRP) gene family. It is becoming increasingly evident that the matrix-unbound SLRPs strongly regulate the progression of inflammation and fibrosis. Soluble SLRPs are generated either via partial proteolytic processing of collagenous matrices or by de novo synthesis evoked by stress or injury. Liberated SLRPs can then bind to and activate Toll-like receptors, thus modulating downstream inflammatory signaling. Preclinical animal models and human studies have recently identified soluble biglycan as a key initiator and regulator of various inflammatory renal diseases. Biglycan, generated by activated macrophages, can enter the circulation and its elevated levels in plasma and renal parenchyma correlate with unfavorable renal function and outcome. In this review, we will focus on the critical role of soluble biglycan in inflammatory signaling in various renal disorders. Moreover, we will provide new data implicating proinflammatory effects of soluble decorin in unilateral ureteral obstruction. Finally, we will critically evaluate the potential application of soluble biglycan vis-a-vis other SLRPs (decorin, lumican and fibromodulin) as a promising target and novel biomarker of inflammatory renal diseases.

Huart, A., J. Klein, et al. "Kinin B1 receptor antagonism is equally efficient as angiotensin receptor 1 antagonism in reducing renal fibrosis in experimental obstructive nephropathy, but is not additive." *Front Pharmacol.* 2015 Feb 2;6:8. doi: [10.3389/fphar.2015.00008](https://doi.org/10.3389/fphar.2015.00008). eCollection 2015.

**BACKGROUND:** Renal tubulointerstitial fibrosis is the pathological hallmark of chronic kidney disease (CKD). Currently, inhibitors of the renin-angiotensin system (RAS) remain the sole therapy in human displaying antifibrotic properties. Further antifibrotic molecules are needed. We have recently reported that the delayed blockade of the bradykinin B1 receptor (B1R) reduced the development of fibrosis in two animal models of renal fibrosis. The usefulness of new drugs also resides in outperforming the gold standards and eventually being additive or complementary to existing therapies. **METHODS:** In this study we compared the efficacy of a B1R antagonist (B1Ra) with that of an angiotensin type 1 receptor antagonist (AT1a) in the unilateral ureteral obstruction (UUO) model of renal fibrosis and determined whether bi-therapy presented higher

efficacy than any of the drugs alone. **RESULTS:** B1R antagonism was as efficient as the gold-standard AT1a treatment. However, bitherapy did not improve the antifibrotic effects at the protein level. We sought for the reason of the absence of this additive effect by studying the expression of a panel of genes involved in the fibrotic process. Interestingly, at the molecular level the different drugs targeted different players of fibrosis that, however, in this severe model did not result in improved reduction of fibrosis at the protein level. **CONCLUSIONS:** As the B1R is induced specifically in the diseased organ and thus potentially displays low side effects it might be an interesting alternative in cases of poor tolerability to RAS inhibitors.

Huuskens, B. M., A. F. Wise, et al. "Combination therapy of mesenchymal stem cells and serelaxin effectively attenuates renal fibrosis in obstructive nephropathy." *FASEB J.* 2015 Feb;29(2):540-53. doi: [10.1096/fj.14-254789](https://doi.org/10.1096/fj.14-254789). Epub 2014 Nov 13.

Chronic kidney disease (CKD) results from the development of fibrosis, ultimately leading to end-stage renal disease (ESRD). Although human bone marrow-derived mesenchymal stem cells (MSCs) can accelerate renal repair following acute injury, the establishment of fibrosis during CKD may affect their potential to influence regeneration capacity. Here we tested the novel combination of MSCs with the antifibrotic serelaxin to repair and protect the kidney 7 d post-unilateral ureteral obstruction (UUO), when fibrosis is established. Male C57BL6 mice were sham-operated or UUO-injured (n = 4-6) and received vehicle, MSCs (1 x 10<sup>6</sup>), serelaxin (0.5 mg/kg per d), or the combination of both. In vivo tracing studies with luciferin/enhanced green fluorescent protein (eGFP)-tagged MSCs showed specific localization in the obstructed kidney where they remained for 36 h. Combination therapy conferred significant protection from UUO-induced fibrosis, as indicated by hydroxyproline analysis (P < 0.001 vs. vehicle, P < 0.05 vs. MSC or serelaxin alone). This was accompanied by preserved structural architecture, decreased tubular epithelial injury (P < 0.01 vs. MSCs alone), macrophage infiltration, and myofibroblast localization in the kidney (both P < 0.01 vs. vehicle). Combination therapy also stimulated matrix metalloproteinase (MMP)-2 activity over either treatment alone (P < 0.05 vs. either treatment alone). These results suggest that the presence of an antifibrotic in conjunction with MSCs ameliorates established kidney fibrosis and augments tissue repair to a greater extent than either treatment alone.

Ikeda, Y., I. Ozono, et al. "Iron chelation by deferoxamine prevents renal interstitial fibrosis in

mice with unilateral ureteral obstruction." PLoS One. 2014 Feb 19;9(2):e89355. doi: [10.1371/journal.pone.0089355](https://doi.org/10.1371/journal.pone.0089355). eCollection 2014.

Renal fibrosis plays an important role in the onset and progression of chronic kidney diseases (CKD). Although several mechanisms underlying renal fibrosis and candidate drugs for its treatment have been identified, the effect of iron chelator on renal fibrosis remains unclear. In the present study, we examined the effect of an iron chelator, deferoxamine (DFO), on renal fibrosis in mice with surgically induced unilateral ureter obstruction (UUO). Mice were divided into 4 groups: UUO with vehicle, UUO with DFO, sham with vehicle, and sham with DFO. One week after surgery, augmented renal tubulointerstitial fibrosis and the expression of collagen I, III, and IV increased in mice with UUO; these changes were suppressed by DFO treatment. Similarly, UUO-induced macrophage infiltration of renal interstitial tubules was reduced in UUO mice treated with DFO. UUO-induced expression of inflammatory cytokines and extracellular matrix proteins was abrogated by DFO treatment. DFO inhibited the activation of the transforming growth factor-beta1 (TGF-beta1)-Smad3 pathway in UUO mice. UUO-induced NADPH oxidase activity and p22(phox) expression were attenuated by DFO. In the kidneys of UUO mice, divalent metal transporter 1, ferroportin, and ferritin expression was higher and transferrin receptor expression was lower than in sham-operated mice. Increased renal iron content was observed in UUO mice, which was reduced by DFO treatment. These results suggest that iron reduction by DFO prevents renal tubulointerstitial fibrosis by regulating TGF-beta-Smad signaling, oxidative stress, and inflammatory responses.

Inoue, T., A. Umezawa, et al. "The contribution of epithelial-mesenchymal transition to renal fibrosis differs among kidney disease models." Kidney Int. 2015 Jan;87(1):233-8. doi: [10.1038/ki.2014.235](https://doi.org/10.1038/ki.2014.235). Epub 2014 Jul 9.

The impact of the epithelial-mesenchymal transition (EMT) to the formation of renal fibrosis has been debated in several lineage-tracing studies, with conflicting findings. Such disparities may have arisen from varying experimental conditions such as different disease models, the mouse strain, and type of genetic alteration used. In order to determine the contribution of these factors to EMT, we generated four kidney disease models in several mouse strains genetically modified to express enhanced green fluorescence protein (EGFP) in cortical tubular epithelial cells under the control of the gamma-glutamyl transpeptidase promoter. Using this approach, the EMT was visible and quantifiable based on a count of

EGFP-positive interstitial cells in the fibrotic kidney sections of the four renal disease models found to be either EMT-prone or -resistant. The EMT-prone models consisted of unilateral ureteral obstruction and ischemic nephropathy in SJL mice. The EMT-resistant models consisted of ureteral obstruction in C57B/6 and F1(C57B/6 x SJL) mice, adriamycin nephrosis in 129 mice, and nephrotoxic serum nephritis in SJL mice. Analyses of these renal disease models suggest the emergence of EMT-derived fibroblasts arises in a disease-specific and strain-dependent manner. Thus, when considering molecular mechanisms and involvement of the EMT in renal fibrosis, it is important to take into account the experimental conditions, particularly the mouse strain and type of disease model.

Javali, T., A. Pathade, et al. "Laparoscopic extravesical detrusorraphy, a minimally invasive treatment option for vesicoureteral reflux: A single centre experience." J Pediatr Urol. 2015 Mar 5. pii: [S1477-5131\(15\)00042-X](https://doi.org/S1477-5131(15)00042-X). doi: [10.1016/j.jpuro.2015.01.007](https://doi.org/10.1016/j.jpuro.2015.01.007).

INTRODUCTION: Laparoscopy in pediatric patients offers more benefits than was earlier presumed and these widely reported benefits significantly outweigh any concerns regarding the technical difficulties. Laparoscopic correction of vesicoureteral reflux aims to duplicate the excellent results of open surgery while at the same time reducing perioperative morbidity and analgesic requirements, improving cosmesis and shortening hospital stay. OBJECTIVE: To share our experience of laparoscopic extravesical detrusorraphy, highlight our technical modification of intraoperative minimal "atraumatic" ureteric handling of the ureter, which we hypothesize may decrease ureteral complications, and report our results. STUDY DESIGN: This was a retrospective chart review of 76 toilet-trained children (98 refluxing units), in the age group of 3-16 years, with Grade I-IV reflux, who underwent laparoscopic detrusorraphy from June 2006 to January 2014. A ureteric catheter is inserted into the refluxing ureter and is tied to the Foleys to drain into a common bag. A three port technique is used. During ureteral dissection, a vascular sling in the form of a Rumel loop is used for atraumatic handling of the ureter. A detrusor tunnel is created with hook electrocautery. A stay suture is later passed through the abdominal wall and slings around the dissected ureter, which helps in holding the ureter approximated against the mucosal trough during detrusorraphy. Detrusor fibers are approximated with 5-0 Vicryl. No drain is placed and the Foley and ureteric catheter(s) are removed after 24 h. Intravenous ketorolac is given every 6 h for the first 24 h. Oral paracetamol is used for analgesia after the



first 24 h. Adequate bladder emptying is ensured by assessment of post void residual urine before discharge. Renal USG alone is performed 2 weeks post operatively and repeated after 3 months along with a VCUG (voiding cystourethrography). Success was defined as absence of reflux in the follow-up VCUG done at 3 months. RESULTS: Mean operative time was 102 +/- 26.5 min for unilateral detrusorraphy and 165 +/- 18 min for bilateral extravesical detrusorraphy. The mean duration of hospital stay was 1.5 +/- 1.7 days. There was one case of urinary retention that was managed with temporary recatheterization. There were no cases of ureteral ischemia, obstruction, hematuria or bladder spasms. Surgery was successful in 97.9% of the refluxing units (96/98). In two patients with grade IV reflux, there was downgrading to grade II on VCUG done at 3 months' follow-up. The reflux resolved at 8 and 14 months' follow-up, respectively. DISCUSSION: Our technique of atraumatic handling of the ureter, initially with the help of a vascular sling and later with the help of a stay suture passed percutaneously through the abdominal wall, resulted in no ureteric injuries. The postoperative morbidity of this procedure is low because the bladder is not opened, the ureter is not transected, no new UVJ is created and there is no need for placement of a drain. The risk of postoperative bowel adhesions is low as the ureter is dissected out through a narrow peritoneal window, which is again extraperitonealized at the end of the procedure (see figure). The postoperative complications of gross hematuria and bladder spasms, which may be especially encountered in patients undergoing laparoscopic Cohen's, were not seen in our case series. CONCLUSION: Laparoscopic extravesical detrusorraphy provides a minimally invasive treatment option for treatment of unilateral/bilateral grade I-IV vesicoureteral reflux. The postoperative morbidity is low and the success rate is favorable. Our technical modification of a "vascular sling" around the ureter facilitates atraumatic ureteric handling, which may reduce distal ureteral complications like ureteral ischemia and obstruction.

Kamata, M., K. Hosono, et al. "Role of cyclooxygenase-2 in the development of interstitial fibrosis in kidneys following unilateral ureteral obstruction in mice." *Biomed Pharmacother.* 2015 Mar;70:174-80. doi: 10.1016/j.biopha.2015.01.010. Epub 2015 Jan 15.

Unilateral ureteral obstruction (UUO) induced tubulointerstitial fibrosis in kidneys mimics the pathogenesis of chronic kidney diseases and is considered a suitable model for studying the mechanisms leading to fibrosis. To study the role of cyclooxygenase-2 (COX-2) in kidney fibrosis, we investigated whether a selective COX-2 inhibitor,

celecoxib, affected renal interstitial fibrosis during UUO in mice. To induce UUO, the left proximal ureter was ligated in male C57BL/6 mice. The mice were fed a diet with or without celecoxib from the day of UUO induction. Following UUO, the renal pelvis was observed to be dilated and the kidney cortex was significantly thinner than that of sham-operated mice. Immunofluorescent staining of type I, III, and IV collagen in UUO kidneys revealed that interstitial collagen deposition was significantly increased in the celecoxib-treated group. Expression of type I, III, and IV collagen in UUO kidneys was also significantly higher in the celecoxib-treated group than in the vehicle-treated group. In the celecoxib-treated group, mRNA levels of TGF-beta/FGF-2 were also significantly higher than those in the vehicle-treated group. The present study demonstrates that COX-2 plays a protective role against fibrosis in UUO kidneys and suggests that supplementation of COX-2 products, such as PG analogues, will be a good option for preventing interstitial fibrosis.

Kamihira, O., T. Hirabayashi, et al. "A new treatment for retroperitoneal fibrosis: initial experiences of using Septrafilm(R) to wrap the ureter." *BJU Int.* 2014 Oct;114(4):563-7. doi: 10.1111/bju.12701.

OBJECTIVE: To confirm the efficacy of using Septrafilm(R) (Genzyme Corp., Cambridge, MA, USA) for wrapping the ureter to treat the ureteric stenosis caused by retroperitoneal fibrosis (RPF). PATIENTS AND METHODS: Between August 2010 and September 2012, 11 ureters in eight patients with RPF (seven males and one female, mean age 65 years) were treated. The mean (range) length of the narrow segment of the ureter was 30 (10-90) mm. During surgery, after having been released from adhesive tissue, the stenotic segment of the ureter was wrapped with Septrafilm to isolate it from the surrounding tissue. A radiographic follow-up was performed every 6 months using computed tomography, i.v. pyelography and/or (99m) Tc-mercapto-acetylglycylglycyl-glycine ((99m) Tc-MAG3) renal scintigraphy. RESULTS: For the unilateral operations, the mean estimated blood loss was 39 mL, and the mean operating time was 154 min. All ureters were isolated from the fibrotic tissue and wrapped with Septrafilm successfully without major complications. During the mean follow-up period of 17 months, no ureteric restenoses were observed in the affected sides, but new stenosis occurred in the contralateral side of the ureter in one patient. CONCLUSIONS: Although the follow-up period is still limited, we believe that the use of Septrafilm has the potential to become an effective option in the treatment of ureteric stenosis caused by RPF, when the omentum cannot be used. To establish the relative advantages of using Septrafilm over

performing a standard omental wrap, further experimentation will be required to compare the two techniques.

Kanno, Y., E. Kawashita, et al. "alpha2AP mediated myofibroblast formation and the development of renal fibrosis in unilateral ureteral obstruction." *Sci Rep.* 2014 Aug 6;4:5967. doi: 10.1038/srep05967.

Renal fibrosis is the final common pathway of a wide variety of chronic kidney diseases. Myofibroblast formation via the differentiation of from tissue-resident fibroblasts and bone marrow-derived mesenchymal stem cells (MSCs), and epithelial-to-mesenchymal transition (EMT) is known to play a pivotal role in the development of renal fibrosis. However, the detailed mechanisms underlying this disorder remain unclear. We herein investigated the role of alpha 2-antiplasmin (alpha2AP) in myofibroblast formation and the development of renal fibrosis. We observed the development of renal fibrosis using unilateral ureteral obstruction (UUO). alpha2AP had accumulated in the UUO-induced obstructed kidneys and alpha2AP deficiency attenuated UUO-induced renal fibrosis in mice. The degree of myofibroblast formation in the obstructed kidneys of alpha2AP(-/-) mice was less than that in alpha2AP(+/+) mice. In vitro, alpha2AP induced myofibroblast formation in renal tubular epithelial cells (RTECs), renal fibroblasts, and bone marrow-derived mesenchymal stem cells (MSCs). alpha2AP also induced the production of TGF-beta, which is known to be a key regulator of myofibroblast formation and fibrosis. alpha2AP-induced the TGF-beta production was significantly reduced by SP600125, c-Jun N-terminal kinase (JNK) specific inhibitor. Our findings suggest that alpha2AP induces myofibroblast formation in the obstructed kidneys, and mediates the development of renal fibrosis.

Karadag, M. A., T. Aydin, et al. "Endometriosis presenting with right side hydronephrosis only: a case report." *J Med Case Rep.* 2014 Dec 11;8:420. doi: 10.1186/1752-1947-8-420.

**INTRODUCTION:** Endometriosis can be defined as the presence of endometrial glandular and stromal tissue outside the uterus. Affected sites of endometriosis can even be the urinary tract. Here, we present the case of a 30-year-old woman with right ureteral endometriosis. This case was important due to the unusual localization and no signs of the disease except for hydronephrosis. **CASE PRESENTATION:** A 30-year-old Caucasian woman with para 2 was admitted to our department for right side flank pain, dysuria and suprapubic pain. She had no complaints of vaginal discharge, bleeding or painful menstruation. Her menstrual cycles were

normal and lasting for three to four days. She did not have a history of any surgical interventions. A physical examination revealed a right side costovertebral angle and suprapubic tenderness. Laboratory test results including a complete blood count, serum biochemical analysis, urine analysis and urine culture were normal. Urinary ultrasonography showed right side hydronephrosis with renal cortical thinning. We suspected a right ureteral stone obstructing the ureter and a computed tomography scan was performed. The computed tomography scan revealed similar right side hydronephrosis with obstruction of the ureter. No signs of stone were observed on the scan. Retrograde pyelography and diagnostic ureterorenoscopy were performed and they showed a focal stricture with a length of approximately 3 cm at the distal ureteral part and secondary hydronephrosis. Open partial ureterectomy and ureteroneocystostomy with Boari flap were performed. The pathologic specimen of her ureter demonstrated intrinsic endometriosis of the right ureter with endometrial glandular cells and stromal tissue. **CONCLUSIONS:** Clinicians should suspect ureteral endometriosis in premenopausal women with unilateral or bilateral distal ureteral obstruction of uncertain cause. The main goals of the treatment should be preservation of renal function, relief of obstruction and prevention of recurrence.

Kitada, M. and D. Koya "Renal protective effects of resveratrol." *Oxid Med Cell Longev.* 2013;2013:568093. doi: 10.1155/2013/568093. Epub 2013 Nov 28.

Resveratrol (3,5,4'-trihydroxystilbene), a natural polyphenolic compound found in grapes and red wine, is reported to have beneficial effects on cardiovascular diseases, including renal diseases. These beneficial effects are thought to be due to this compound's antioxidative properties: resveratrol is known to be a robust scavenger of reactive oxygen species (ROS). In addition to scavenging ROS, resveratrol may have numerous protective effects against age-related disorders, including renal diseases, through the activation of SIRT1. SIRT1, an NAD(+)-dependent deacetylase, was identified as one of the molecules through which calorie restriction extends the lifespan or delays age-related diseases, and this protein may regulate multiple cellular functions, including apoptosis, mitochondrial biogenesis, inflammation, glucose/lipid metabolism, autophagy, and adaptations to cellular stress, through the deacetylation of target proteins. Previous reports have shown that resveratrol can ameliorate several types of renal injury, such as diabetic nephropathy, drug-induced injury, aldosterone-induced injury, ischemia-reperfusion injury, sepsis-related injury, and unilateral

ureteral obstruction, in animal models through its antioxidant effect or SIRT1 activation. Therefore, resveratrol may be a useful supplemental treatment for preventing renal injury.

Kocherov, S., I. Ulman, et al. "Multicenter survey of endoscopic treatment of vesicoureteral reflux using polyacrylate-polyalcohol bulking copolymer (Vantris)." *Urology*. 2014 Sep;84(3):689-93. doi: [10.1016/j.urology.2014.04.033](https://doi.org/10.1016/j.urology.2014.04.033).

**OBJECTIVE:** To evaluate an outcome of endoscopic correction of vesicoureteral reflux (VUR) using Vantris (Promedon, Cordoba, Argentina) in terms of its effectiveness and morbidity in a multicenter study. **MATERIALS AND METHODS:** From 2009 to 2013, 611 patients (210 boys and 401 girls) with a mean age of 3.56 years (range, 1 month-18 years) were treated at 7 centers worldwide endoscopically with Vantris injection. VUR was unilateral in 413 and bilateral in 198 patients comprising 809 renal refluxing units (RRUs). Of these, primary VUR was present in 674 RRUs (83.3%) and 135 (16.7%) were complex cases. Reflux was grades I-V in 24 (2.96%), 123 (15.2%), 451 (55.8%), 158 (19.5%), and 53 (6.6%) RRUs respectively. The follow-up continued from 6 to 54 months. **RESULTS:** Reflux resolved in 759 RRUs (93.8%) after first Vantris injection, in 26 (3.1%) after second, and in 6 (0.7%) after third injection, respectively. VUR improved to grade I after 1 or 2 injections in 5 ureters (0.6%), which needed no further treatment. Thirteen ureters (1.6%) failed endoscopic correction and required ureteral reimplantation. Vesicoureteral junction obstruction requiring ureteral reimplantation developed in 6 ureters (0.7%) and in 4 (0.5%) required stent insertion. Twenty-three patients (3.8%) suffered afebrile urinary tract infection. Seven (1.2%) developed febrile urinary tract infection. None of the studied patients demonstrated VUR recurrence on voiding cystourethrography. **CONCLUSION:** The results of this multicenter survey confirm that endoscopic subureteral Vantris injection is a simple, safe, and effective outpatient procedure for treating all grades of VUR.

Koike, K., S. Ueda, et al. "Protective role of JAK/STAT signaling against renal fibrosis in mice with unilateral ureteral obstruction." *Clin Immunol*. 2014 Jan;150(1):78-87. doi: [10.1016/j.clim.2013.11.003](https://doi.org/10.1016/j.clim.2013.11.003). Epub 2013 Nov 13.

Inflammation is involved in renal fibrosis, a final common pathway for kidney diseases. To clarify how JAK/STAT/SOCS system was involved in renal fibrosis, UUU was induced in BALB/c or SOCS3(+/-) mice in the presence or absence of JAK inhibitor-incorporated nanoparticle (pyridine6-PGLA). UUU

increased pSTAT3 and subsequently elevated SOCS3 levels in the obstructed kidneys. pSTAT3 levels were further increased in SOCS3(+/-) mice. UUU-induced renal fibrosis was markedly suppressed in SOCS3(+/-) mice, while it was aggravated by pre-treatment with pyridine6-PGLA. Although there were no differences in renal mRNA levels of TGF-beta and collagens between wild and SOCS3(+/-) mice, MMP-2 activity was enhanced in SOCS3(+/-) UUU mice. Activated MMP-2 was completely suppressed by pyridine6-PGLA-pre-treatment. TNF-alpha one of JAK/STAT activators, increased pSTAT3 levels and subsequently induced MMP-2 activation in proximal tubular cells. These results suggest that JAK/STAT3 signaling may play a role in repair process of renal fibrosis in UUU partly via MMP-2 activation.

Komada, T., F. Usui, et al. "ASC in renal collecting duct epithelial cells contributes to inflammation and injury after unilateral ureteral obstruction." *Am J Pathol*. 2014 May;184(5):1287-98. doi: [10.1016/j.ajpath.2014.01.014](https://doi.org/10.1016/j.ajpath.2014.01.014). Epub 2014 Mar 5.

Inflammation plays a crucial role in the pathophysiological characteristics of chronic kidney disease; however, the inflammatory mechanisms underlying the chronic kidney disease process remain unclear. Recent evidence indicates that sterile inflammation triggered by tissue injury is mediated through a multiprotein complex called the inflammasome. Therefore, we investigated the role of the inflammasome in the development of chronic kidney disease using a murine unilateral ureteral obstruction (UUO) model. Inflammasome-related molecules were up-regulated in the kidney after UUO. Apoptosis-associated speck-like protein containing a caspase recruitment domain deficiency significantly reduced inflammatory responses, such as inflammatory cell infiltration and cytokine expression, and improved subsequent renal injury and fibrosis. Furthermore, apoptosis-associated speck-like protein containing a caspase recruitment domain was specifically up-regulated in collecting duct (CD) epithelial cells of the UUO-treated kidney. In vitro experiments showed that extracellular adenosine triphosphate (ATP) induced inflammasome activation in CD epithelial cells through P2X7-potassium efflux and reactive oxygen species-dependent pathways. These results demonstrate the molecular basis for the inflammatory response in the process of chronic kidney disease and suggest the CD inflammasome as a potential therapeutic target for preventing chronic kidney disease progression.

Komiakov, B. K. and V. A. Ochelenko "[The results of intestinoplasty of ureters]." *Urologiia*. 2013 May-Jun;(3):5-9.

The article presents the immediate and long-term results of intestoplasty of extensive uretral obstructions. From 2001 to 2012, 47 patients underwent intestoplasty, and 3 patients--sigmoureteroplasty. 33 patients (66%) had unilateral lesions, and 17 (34%)--bilateral lesions. Postoperative complications occurred in 14% of cases. Early complications occurred in 6 (12%), late complications--in 1 (2%) patient. Complications requiring surgery occurred in 3 (6%) patients. The results of re-operations were successful. Deaths were not recorded. The observation period ranged from 3 months to 11 years. All patients achieved the restoration of urodynamics and normalization of kidney function. Intestoplasty in extensive uretral obstruction is the operation of choice, as it allows to restore the flow of urine from the kidney, improves its function, arrests the chronic pyelonephritis and rescues patients from permanent renal and ureteral fistulas.

Lam, W., A. Fernando, et al. "Is routine postoperative diuresis renography indicated in all adult patients after pyeloplasty for ureteropelvic junction obstruction?" *Urology*. 2015 Jan;85(1):246-51. doi: [10.1016/j.urology.2014.09.033](https://doi.org/10.1016/j.urology.2014.09.033).

**OBJECTIVE:** To determine if routine follow-up diuresis renography is indicated in all adult patients after pyeloplasty for ureteropelvic junction obstruction (UPJO). **METHODS:** A multicenter retrospective analysis was conducted in adults who underwent pyeloplasty for symptomatic UPJO between January 2002 and August 2012. Patients with unilateral UPJO demonstrated on diuresis renography, treated with pyeloplasty, and aged >18 years at time of surgery were included in the study. Patients with contralateral renal abnormalities, genitourinary anomalies, and those who declined renography during follow-up were excluded. All eligible patients underwent diuresis renography approximately 3 months postoperatively. Minimal follow-up was 12 months. Patients were divided into 2 groups: patients with persistent pain at 3 months after pyeloplasty and patients who became asymptomatic. Treatment failures in each cohort were identified. Comparisons were performed using the Fisher exact test. **RESULTS:** A total of 100 pyeloplasties were performed. Of them, 90 were eligible for the study. Mean age was 40 years. Mean follow-up was 21 months. Seventy-three patients (81.1%) became pain free after pyeloplasty. One patient (1.4%) had worsening of differential renal function despite unobstructed drainage on diuresis renogram. None of the patients in the asymptomatic cohort was identified to have unequivocal drainage obstruction on postoperative renogram. Seventeen patients (18.9%) remained symptomatic with pain at 3 months after pyeloplasty; 3 (17.6%) of those patients

with loin pain after pyeloplasty were confirmed to have persistent obstructed drainage postoperatively on diuresis renogram ( $P < .001$ ). All 3 patients required insertion of ureteric stents and/or revision surgery ( $P < .007$ ). **CONCLUSION:** In our series, adult patients who became pain free after unilateral pyeloplasty for UPJO did not have persistent obstruction of renal drainage on renography. Routine diuresis renogram to assess drainage and differential renal function in patients who become pain free after pyeloplasty for UPJO may not be necessary. If objective evidence of postoperative outcome is required, then a single renogram at 3 months is recommended.

Lavoz, C., M. Alique, et al. "Gremlin regulates renal inflammation via vascular endothelial growth factor receptor 2 pathway." *J Pathol*. 2015 Mar 23. doi: [10.1002/path.4537](https://doi.org/10.1002/path.4537).

Inflammation is a main feature of progressive kidney disease. Gremlin binds to bone morphogenetic proteins (BMPs), acting as an antagonist and regulating nephrogenesis and fibrosis among other processes. Gremlin also binds to vascular endothelial growth factor receptor-2 (VEGFR2) in endothelial cells to induce angiogenesis. In renal cells, Gremlin regulates proliferation and fibrosis, but there are no data about inflammatory-related events. We have investigated the direct effects of Gremlin in the kidney, evaluating whether VEGFR2 is a functional Gremlin receptor. Administration of recombinant Gremlin to murine kidneys induced rapid and sustained activation of VEGFR2 signalling, located in proximal tubular epithelial cells. Gremlin bound to VEGFR2 in these cells in vitro, activating this signalling pathway independently of its action as an antagonist of BMPs. In vivo, Gremlin caused early renal damage, characterized by activation of the nuclear factor-kappaB pathway linked to up-regulation of pro-inflammatory factors and infiltration of immune inflammatory cells. VEGFR2 blockade diminished Gremlin-induced renal inflammatory responses. The link between Gremlin/VEGFR2 and NF-kappaB/inflammation was confirmed in vitro. Gremlin overexpression was associated to VEGFR2 activation in human renal disease and in the unilateral ureteral obstruction experimental model, where VEGFR2 kinase inhibition diminished renal inflammation. Our data show that a Gremlin/VEGFR2 axis participates in renal inflammation and could be a novel target for kidney disease.

Lecru, L., C. Desterke, et al. "Cannabinoid receptor 1 is a major mediator of renal fibrosis." *Kidney Int*. 2015 Mar 11. doi: [10.1038/ki.2015.63](https://doi.org/10.1038/ki.2015.63).

Chronic kidney disease, secondary to renal fibrogenesis, is a burden on public health. There is a



need to explore new therapeutic pathways to reduce renal fibrogenesis. To study this, we used unilateral ureteral obstruction (UUO) in mice as an experimental model of renal fibrosis and microarray analysis to compare gene expression in fibrotic and normal kidneys. The cannabinoid receptor 1 (CB1) was among the most upregulated genes in mice, and the main endogenous CB1 ligand (2-arachidonoylglycerol) was significantly increased in the fibrotic kidney. Interestingly, CB1 expression was highly increased in kidney biopsies of patients with IgA nephropathy, diabetes, and acute interstitial nephritis. Both genetic and pharmacological knockout of CB1 induced a profound reduction in renal fibrosis during UUO. While CB2 is also involved in renal fibrogenesis, it did not potentiate the role of CB1. CB1 expression was significantly increased in myofibroblasts, the main effector cells in renal fibrogenesis, upon TGF-beta1 stimulation. The decrease in renal fibrosis during CB1 blockade could be explained by a direct action on myofibroblasts. CB1 blockade reduced collagen expression in vitro. Rimonabant, a selective CB1 endocannabinoid receptor antagonist, modulated the macrophage infiltrate responsible for renal fibrosis in UUO through a decrease in monocyte chemoattractant protein-1 synthesis. Thus, CB1 has a major role in the activation of myofibroblasts and may be a new target for treating chronic kidney disease. *Kidney International* advance online publication, 11 March 2015; doi:10.1038/ki.2015.63.

Lindquist, J. A. and P. R. Mertens "Myofibroblasts, regeneration or renal fibrosis--is there a decisive hint?" *Nephrol Dial Transplant*. 2013 Nov;28(11):2678-81. doi: 10.1093/ndt/gft247. Epub 2013 Aug 23.

Activated fibroblasts, denoted as myofibroblasts, express smooth muscle actin (SMA) and are considered key mediators of renal fibrosis. To identify and isolate these elusive cells, LeBleu et al. generated a new transgenic mouse model expressing a red fluorescent protein under the control of the alpha SMA promoter. Gene expression profiling from cultured myofibroblasts identified human epididymis protein 4 [HE4, also denoted whey acidic protein (WAP) four-disulphide core domain 2] as the most upregulated gene. Since the WAP domains are implicated in protease inhibition, the authors demonstrate the ability of recombinant HE4 to bind and inhibit a number of known proteases. To demonstrate an involvement of HE4 in disease pathology, the authors next showed that the neutralization of HE4 alleviates kidney fibrosis in murine disease models, i.e. 5/6 nephrectomy, unilateral ureteral obstruction and nephrotoxic serum-induced nephritis. Finally, they went on to verify the

enhanced expression of HE4 in human fibrosis-associated fibroblasts in comparison to normal fibroblasts as well as in serum samples of patients with chronic kidney diseases. Thus, they conclude that HE4 can serve as a biomarker as well as a therapeutic target for the treatment of renal fibrosis.

Lopes, R. I., F. T. Denes, et al. "Serum and Urinary Values of CA 19-9 and TGFss1 in a Rat Model of Partial or Complete Ureteral Obstruction." *Eur J Pediatr Surg*. 2015 Jan 5.

Introduction Abnormal levels of serum and urinary markers occur in the presence of renal damage associated to obstructive uropathy. Urinary and serum transforming growth factor beta 1 (TGFss1) and carbohydrate antigen (CA 19-9) have not yet been evaluated in an experimental model of obstructive uropathy. Material and Methods Rats were divided into seven groups: reference, sham operation, unilateral nephrectomy, complete unilateral ureteral obstruction, partial unilateral ureteral obstruction, partial bilateral ureteral obstruction, and unilateral nephrectomy with contralateral partial ureteral obstruction. Kidney and ureter morphometry, TGFss1 and CA 19-9 serum and urinary concentrations and CA 19-9 renal tissue expression were analyzed. Correlation of these markers to complete, partial obstruction, or unobstructed groups was performed. Results Pathological findings correlated positively with the degree of ureteral obstruction, but negatively with urinary CA 19-9 levels. Marked underexpression of CA 19-9 was observed in kidneys with complete ureteral obstruction. No statistically significant differences were found for urinary and serum TGFss1 and also for serum CA 19-9. Conclusion Urinary CA 19-9 correlated negatively with ureteral obstruction grade. Immunohistochemistry depicted CA 19-9 expression on epithelial tubular cells cytoplasm, suggesting renal origin. Serum and urinary TGFss1 did not show alterations in response to severity and length of urinary obstruction, which might be associated with less intense renal remodeling.

Ma, F. Y., G. H. Tesch, et al. "ASK1/p38 signaling in renal tubular epithelial cells promotes renal fibrosis in the mouse obstructed kidney." *Am J Physiol Renal Physiol*. 2014 Dec 1;307(11):F1263-73. doi: 10.1152/ajprenal.00211.2014. Epub 2014 Oct 8.

Stress-activated kinases p38 MAPK and JNK promote renal fibrosis; however, how the pathways by which these kinases are activated in kidney disease remain poorly defined. Apoptosis signal-regulating kinase 1 (ASK1/MAPKKK5) is a member of the MAPKKK family that can induce activation of p38 and JNK. The present study examined whether ASK1 induces p38/JNK activation and renal fibrosis in

unilateral ureteric obstruction (UUO) using wild-type (WT) and Ask1-deficient (Ask1(-/-)) mice. Basal p38 and JNK activation in WT kidneys was increased three- to fivefold in day 7 UUO mice in association with renal fibrosis. In contrast, there was no increase in p38 activation in Ask1(-/-) UUO mice, whereas JNK activation was only partially increased. The progressive increase in kidney collagen (hydroxyproline) content seen on days 7 and 12 of UUO in WT mice was significantly reduced in Ask1(-/-) UUO mice in association with reduced alpha-smooth muscle actin-positive myofibroblast accumulation. However, cultured WT and Ask1(-/-) renal fibroblasts showed equivalent proliferation and matrix production, indicating that ASK1 acts indirectly on fibroblasts. Tubular epithelial cells are the main site of p38 activation in the obstructed kidney. Angiotensin II and H(2)O(2), but not IL-1 or lipopolysaccharide, induced p38 activation and upregulation of transforming growth factor-beta(1), platelet-derived growth factor-B, and monocyte chemoattractant protein-1 production was suppressed in Ask1(-/-) tubular epithelial cells. In addition, macrophage accumulation was significantly inhibited in Ask1(-/-) UUO mice. In conclusion, ASK1 is an important upstream activator of p38 and JNK signaling in the obstructed kidney, and ASK1 is a potential therapeutic target in renal fibrosis.

Mael-Ainin, M., A. Abed, et al. "Inhibition of periostin expression protects against the development of renal inflammation and fibrosis." *J Am Soc Nephrol.* 2014 Aug;25(8):1724-36. doi: 10.1681/ASN.2013060664. Epub 2014 Feb 27.

Increased renal expression of periostin, a protein normally involved in embryonic and dental development, correlates with the decline of renal function in experimental models and patient biopsies. Because periostin has been reported to induce cell differentiation, we investigated whether it is also involved in the development of renal disease and whether blocking its abnormal expression improves renal function and/or structure. After unilateral ureteral obstruction in wild-type mice, we observed a progressive increase in the expression and synthesis of periostin in the obstructed kidney that associated with the progression of renal lesions. In contrast, mice lacking the periostin gene showed less injury-induced interstitial fibrosis and inflammation and were protected against structural alterations. This protection was associated with a preservation of the renal epithelial phenotype. In vitro, administration of TGF-beta to renal epithelial cells increased the expression of periostin several-fold, leading to subsequent loss of the epithelial phenotype. Furthermore, treatment of these cells with periostin increased the expression of

collagen I and stimulated the phosphorylation of FAK, p38, and ERK 42/44. In vivo delivery of antisense oligonucleotides to inhibit periostin expression protected animals from L-NAME-induced renal injury. These data strongly suggest that periostin mediates renal disease in response to TGF-beta and that blocking periostin may be a promising therapeutic strategy against the development of CKD.

Maeshima, A., K. Mishima, et al. "Follistatin, an activin antagonist, ameliorates renal interstitial fibrosis in a rat model of unilateral ureteral obstruction." *Biomed Res Int.* 2014;2014:376191. doi: 10.1155/2014/376191. Epub 2014 May 5.

Activin, a member of the TGF-beta superfamily, regulates cell growth and differentiation in various cell types. Activin A acts as a negative regulator of renal development as well as tubular regeneration after renal injury. However, it remains unknown whether activin A is involved in renal fibrosis. To clarify this issue, we utilized a rat model of unilateral ureteral obstruction (UUO). The expression of activin A was significantly increased in the UUO kidneys compared to that in contralateral kidneys. Activin A was detected in glomerular mesangial cells and interstitial fibroblasts in normal kidneys. In UUO kidneys, activin A was abundantly expressed by interstitial alpha-SMA-positive myofibroblasts. Administration of recombinant follistatin, an activin antagonist, reduced the fibrotic area in the UUO kidneys. The number of proliferating cells in the interstitium, but not in the tubules, was significantly lower in the follistatin-treated kidneys. Expression of alpha-SMA, deposition of type I collagen and fibronectin, and CD68-positive macrophage infiltration were significantly suppressed in the follistatin-treated kidneys. These data suggest that activin A produced by interstitial fibroblasts acts as a potent profibrotic factor during renal fibrosis. Blockade of activin A action may be a novel approach for the prevention of renal fibrosis progression.

Manson, S. R., J. B. Song, et al. "Cell Type Specific Changes in BMP-7 Expression Contribute to the Progression of Kidney Disease in Patients with Obstructive Uropathy." *J Urol.* 2015 Mar 23. pii: S0022-5347(14)04847-2. doi: 10.1016/j.juro.2014.10.117.

PURPOSE: Congenital urinary tract obstruction is a leading cause of renal maldevelopment and pediatric kidney disease. Nonetheless, few groups have examined its molecular pathogenesis in humans. We evaluated the role of BMP-7, a protein required for renal injury repair and nephrogenesis, in disease progression in patients with obstructive uropathy. MATERIALS AND METHODS: Whole kidney and

cell specific BMP-7 expression was examined in a murine model of unilateral ureteral obstruction and in patients with congenital ureteropelvic junction obstruction. Findings were correlated with molecular markers of renal injury and clinical parameters. RESULTS: Unilateral ureteral obstruction led to a dramatic decrease in BMP-7 expression in the proximal and distal tubules before the onset of significant loss of renal architecture and fibrosis, suggesting that this is a critical molecular event that drives early stage disease progression. Loss of BMP-7 expression then extended to the collecting ducts and glomeruli in end stage kidney disease. When translating these findings to patients with ureteropelvic junction obstruction, global loss of BMP-7 expression correlated with a decreased number of nephrons, loss of renal architecture, severe renal fibrosis and loss of kidney function. CONCLUSIONS: Given that BMP-7 has a critical role in renal injury repair and nephrogenesis, these findings show that cell specific changes in BMP-7 expression contribute to the onset of irreversible renal injury and impaired kidney development secondary to congenital urinary tract obstruction. Accordingly therapies that target these cell populations to restore BMP-7 activity may limit disease progression in patients with obstructive uropathy.

Moosavi, S. M., Z. Bagheri, et al. "Pre- or post-treatment with aminoguanidine attenuates a renal distal acidification defect induced by acute ureteral obstruction in rats." *Can J Physiol Pharmacol.* 2013 Nov;91(11):920-8. doi: 10.1139/cjpp-2013-0059. Epub 2013 Jun 20.

Acute unilateral ureteral obstruction (UUO) impairs distal nephron acid secretion and stimulates expression of inducible nitric oxide synthase (iNOS) in post-obstructed kidney (POK). This study investigated the influence of pre- or post-treatment with aminoguanidine as a selective iNOS inhibitor on UUO-induced renal functional disturbances. To induce acute UUO, the left ureter in rats was ligated and released after 24 h. Then, a 3 h clearance period followed by bicarbonate loading and thereafter a 30 min clearance period were allocated. Aminoguanidine was administered either prior to the UUO induction or after release of the obstruction in the different rat groups, while untreated and sham groups received normal saline. During the first clearance period, fractional bicarbonate excretion and urinary pH increased markedly in the POK of the untreated group compared with the left kidney of sham group, and a large drop in the difference between urine and blood pCO<sub>2</sub> (U-B pCO<sub>2</sub>) was observed after bicarbonate loading; all of these parameters were ameliorated in the pre-treated and post-treated groups. However, the

UUO-induced decreases in creatinine clearance, sodium reabsorption, urine osmolality, and free-water reabsorption in the POK were attenuated only in the post-treated group. Therefore, the in vivo application of a selective iNOS inhibitor partially improved the acute UUO-induced distal nephron acidification defect, while post-treatment but not pre-treatment with aminoguanidine ameliorated decrements of glomerular filtration, sodium reabsorption, and urine-concentrating ability.

Morizane, R., S. Fujii, et al. "miR-34c attenuates epithelial-mesenchymal transition and kidney fibrosis with ureteral obstruction." *Sci Rep.* 2014 Apr 3;4:4578. doi: 10.1038/srep04578.

micro RNAs (miRNAs) are small non-coding RNAs that act as posttranscriptional repressors by binding to the 3'-UTR of target mRNAs. On the other hand, mesenchymal-epithelial transition (EMT) and kidney fibrosis is a pathological process of chronic kidney disease (CKD), and its relationship to miRNAs is becoming recognized as a potential target for CKD therapies. To find new miRNAs involved in EMT, we examined miRNA expression in experimental models of EMT and renal epithelialization using microarray, and found that miR-34c attenuates EMT induced by TGF-beta in a mouse tubular cell line. To confirm the effects of miR-34c in vivo, we administered the precursor of miR-34c to mice with unilateral ureteral obstruction, and miR-34c decreased kidney fibrosis area and the expression of connective tissue growth factor, alpha-SMA, collagen type 1, collagen type 3 and fibronectin. In conclusion, our study showed miR-34c attenuates EMT and kidney fibrosis of mice with ureteral obstruction.

Neelisetty, S., C. Alford, et al. "Renal fibrosis is not reduced by blocking transforming growth factor-beta signaling in matrix-producing interstitial cells." *Kidney Int.* 2015 Mar 11. doi: 10.1038/ki.2015.51.

Transforming growth factor-beta (TGF-beta) strongly promotes renal tubulointerstitial fibrosis, but the cellular target that mediates its profibrotic actions has not been clearly identified. While in vitro data suggest that TGF-beta-induced matrix production is mediated by renal fibroblasts, the role of these cells in TGF-beta-dependent tubulointerstitial fibrosis following renal injury is not well defined. To address this, we deleted the TGF-beta type II receptor in matrix-producing interstitial cells using two different inducible Cre models: COL1A2-Cre with a mesenchymal enhancer element and tenascin-Cre that targets medullary interstitial cells, and either the mouse unilateral ureteral obstruction or the aristolochic acid renal injury model. Renal interstitial cells lacking the TGF-beta receptor had significantly

impaired collagen I production, but, unexpectedly, overall tissue fibrosis was unchanged in the conditional knockouts after renal injury. Thus, abrogating TGF-beta signaling in matrix-producing interstitial cells is not sufficient to reduce fibrosis after renal injury. *Kidney International* advance online publication, 11 March 2015; doi:10.1038/ki.2015.51.

Ordorica, R., L. R. Wiegand, et al. "Ureteral replacement and onlay repair with reconfigured intestinal segments." *J Urol.* 2014 May;191(5):1301-6. doi: 10.1016/j.juro.2013.11.027. Epub 2013 Nov 18.

**PURPOSE:** Ureteral loss represents a surgical challenge to provide low pressure drainage while avoiding urinary stasis and reflux. The ideal replacement should optimize drainage while minimizing absorption, allowing for ureteral repair of varied lengths and locations with maximal preservation of the urinary tract. We reviewed our experience with ureteral repair, focusing on the use of reconfigured intestine. We report what is to our knowledge the novel use of reconfigured intestine as an onlay flap on the preserved ureteral segment and as a circumferential interpositioned segment. **MATERIALS AND METHODS:** A total of 16 ureters were repaired in 4 men and 9 women using reconfigured ileum, colon or appendix. Mean patient age was 45 years (range 26 to 66). The etiology of the ureteral defect was iatrogenic in 8 patients, retroperitoneal fibrosis in 3, trauma in 3 and ureteritis cystica in 1. Mean defect length was 10 cm (range 5 to 20) in the 10 right and 6 left ureters, and the defect was proximal in 3, mid in 4, distal in 7 and panureteral in 2. Ureteral replacement was performed using a segment of ileum in 13 cases or colon in 1. The segment was detubularized and reconfigured according to the Yang-Monti principle and used as a complete retubularized interposed segment in 7 cases or as an onlay flap on the opened ureter without resection in 7. Also, 2 ureters were reconstructed with an incised appendiceal flap onlayed over the preserved ureteral plate. At a mean followup of 44 months (range 12 to 78) all patients underwent antegrade nephrostogram, followed by renal scan and upper tract imaging. **RESULTS:** All patients tolerated the procedure without initial bowel or urinary tract complications. In 1 patient who had received radiation a ureteral fistula developed to a blind Hartmann pouch at 9 months, requiring repair. Ultimately, cystectomy was done for irradiation cystitis (onlay group). Another patient with bilateral obstruction at presentation lost unilateral renal function during 5 years. Urinary drainage was achieved in all 14 remaining renal units with preservation of function, as shown on renal scan. Patients reported minor mucous production without renal colic or stone formation. **CONCLUSIONS:** Long

ureteral defects require tissue replacement when bladder flaps do not suffice. Ureteral replacement can be achieved by reconfigured intestinal segments, which are readily mobilized and secured as interposed segments or as an onlay flap on the preserved ureter. A relatively short segment can be used to repair a lengthy defect along any segment of ureter, also allowing for nonrefluxing reimplantation.

Ostergaard, M., M. Christensen, et al. "ROS dependence of cyclooxygenase-2 induction in rats subjected to unilateral ureteral obstruction." *Am J Physiol Renal Physiol.* 2014 Jan;306(2):F259-70. doi: 10.1152/ajprenal.00352.2013. Epub 2013 Nov 13.

Oxidative stress resulting from unilateral ureteral obstruction (UO) may be aggravated by increased production of ROS. Previous studies have demonstrated increased cyclooxygenase (COX)-2 expression in renal medullary interstitial cells (RMICs) in response to UO. We investigated, both in vivo and in vitro, the role of ROS in the induction of COX-2 in rats subjected to UO and in RMICs exposed to oxidative and mechanical stress. Rats subjected to 3-day UO were treated with two mechanistically distinct antioxidants, the NADPH oxidase inhibitor diphenyleneiodonium (DPI) and the complex I inhibitor rotenone (ROT), to interfere with ROS production. We found that UO-mediated induction of COX-2 in the inner medulla was attenuated by both antioxidants. In addition, DPI and ROT reduced tubular damage and oxidative stress after UO. Moreover, mechanical stretch induced COX-2 and oxidative stress in RMICs. Likewise, RMICs exposed to H<sub>2</sub>O<sub>2</sub> as an inducer of oxidative stress showed increased COX-2 expression and activity, both of which were reduced by DPI and ROT. Similarly, ROS production, which was increased after exposure of RMICs to H<sub>2</sub>O<sub>2</sub>, was also reduced by DPI and ROT. Furthermore, oxidative stress-induced phosphorylation of ERK1/2 and p38 was blocked by both antioxidants, and inhibition of ERK1/2 and p38 attenuated the induction of COX-2 in RMICs. Notably, COX-2 inhibitors further exacerbated the oxidative stress level in H<sub>2</sub>O<sub>2</sub>-exposed RMICs. We conclude that oxidative stress as a consequence of UO stimulates COX-2 expression through the activation of multiple MAPKs and that the induction of COX-2 may exert a cytoprotective function in RMICs.

Otunctemur, A., E. Ozbek, et al. "Pomegranate extract attenuates unilateral ureteral obstruction-induced renal damage by reducing oxidative stress." *Urol Ann.* 2015 Apr-Jun;7(2):166-71. doi: 10.4103/0974-7796.150488.

**AIMS:** Ureteral obstruction may cause permanent kidney damage at late period. We know that the pomegranate extract (PE) play a strong role on



removal of free oxygen radicals and prevention of oxidative stress. In the current study study, we evaluated the effect of PE on kidney damage after unilateral ureteral obstruction (UO). SETTINGS AND DESIGN: A total of 32 rats were divided into four groups. Group 1 was a control, Group 2 was a sham, Group 3 was rats with UO and Group 4 was rats with UO that were given PE (oral 100 mg/day). After 14 days, rats were killed and their kidneys were taken and blood analysis was performed. SUBJECTS AND METHODS: Tubular necrosis, mononuclear cell infiltration, and interstitial fibrosis scoring were determined histopathologically in a part of kidneys; nitric oxide (NO), malondialdehyde (MDA), and reduced glutathione (GSH) levels were determined in the other part of kidneys. STATISTICAL ANALYSIS USED: Statistical analyses were performed by the Chi-square test and one-way analysis of variance. RESULTS: There was no difference significantly for urea-creatinine levels between groups. Pathologically, there was serious tubular necrosis, mononuclear cell infiltration and fibrosis in Group 3, and there was significantly decreasing for tubular necrosis, mononuclear cell infiltration and fibrosis in Group 4 ( $P < 0.005$ ). Furthermore, there was significantly increasing for NO and MDA levels; decreasing for GSH levels in Group 3 compared the other groups ( $P < 0.005$ ). CONCLUSIONS: We think that the PE prevents kidney damage by decreasing oxidative stress in kidney.

Panda, S. S., M. Bajpai, et al. "Comparison of different morphological parameters with duration of obstruction created experimentally in unilateral upper ureters: an animal model." *Afr J Paediatr Surg.* 2014 Jan-Mar;11(1):15-7. doi: 10.4103/0189-6725.129204.

BACKGROUND: The objective of the following study is to determine and to compare the different morphological parameters with duration of obstruction created experimentally in unilateral upper ureters of rats. MATERIALS AND METHODS: Unilateral upper ureteric obstruction was created in 60 adult Wistar rats that were reversed after predetermined intervals. Rats were sacrificed and ipsilateral kidneys were subjected for analysis of morphological parameters such as renal height, cranio-caudal diameter, antero-posterior diameter, lateral diameter, volume of the pelvis and average cortical thickness: Renal height. RESULTS: Renal height and cranio-caudal diameter of renal pelvis after ipsilateral upper ureteric obstruction started rising as early as 7 days of creating obstruction and were affected earlier than antero-posterior and lateral diameter and also were reversed earlier than other parameters after reversal of obstruction. Renal cortical thickness and volume of the pelvis were affected after prolonged

obstruction ( $> 3$  weeks) and were the late parameters to be reversed after reversal of obstruction. CONCLUSIONS: Cranio-caudal diameter and renal height were the early morphological parameters to be affected and reversed after reversal of obstruction in experimentally created ipsilateral upper ureteric obstruction.

Park, J., S. Y. Lee, et al. "Glucosamine hydrochloride exerts a protective effect against unilateral ureteral obstruction-induced renal fibrosis by attenuating TGF-beta signaling." *J Mol Med (Berl).* 2013 Nov;91(11):1273-84. doi: 10.1007/s00109-013-1086-1. Epub 2013 Sep 27.

Renal fibrosis is a common consequence of unilateral ureteral obstruction, which provides a useful model to investigate the pathogenesis of obstructive nephropathy and progressive renal fibrosis. Transforming growth factor (TGF-beta1) has been recognized as a key mediator in renal fibrosis by stimulating matrix-producing fibrogenic cells and promoting extracellular matrix deposition. Therefore, considerable efforts have been made to regulate TGF-beta signaling for antifibrotic therapy. Here, we investigated the mode of action of glucosamine hydrochloride (GS-HCl) on TGF-beta1-induced renal fibrosis. In the obstructed kidneys and TGF-beta1-treated renal cells, GS-HCl significantly decreased renal expression of alpha-smooth muscle actin, collagen I, and fibronectin. By investigating the inhibitory mechanism of GS-HCl on renal fibrosis, we found that GS-HCl suppressed TGF-beta signaling by inhibiting N-linked glycosylation of the type II TGF-beta receptor (TbetaRII), leading to an inefficient trafficking of TbetaRII to the membrane surface. Defective N-glycosylation of TbetaRII further suppressed the TGF-beta1-binding to TbetaRII, thereby decreasing TGF-beta signaling. Notably, GS-HCl treatment significantly reduced TGF-beta1-induced up-regulation of Smad2/3 phosphorylation and transcriptional activity in vivo and in vitro. Taken together, GS-HCl-mediated regulation of TGF-beta signaling exerted an antifibrotic effect, thereby ameliorating renal fibrosis. Our study suggests that GS-HCl would be a promising agent for therapeutic intervention for preventing TGF-beta1-induced renal fibrosis in kidney diseases. KEY MESSAGE: Glucosamine-mediated attenuation of TGF-beta signaling ameliorates renal fibrosis in vivo TGF-beta1-induced fibrogenic action is reduced by glucosamine in vitro N-glycosylation of the type II TGF-beta receptor is suppressed by glucosamine Glucosamine-induced defective N-glycosylation of TbetaRII decreases TGF-beta signaling.

Prakoura, N., P. K. Politis, et al. "Epithelial calreticulin up-regulation promotes profibrotic responses and tubulointerstitial fibrosis development." *Am J Pathol.* 2013 Nov;183(5):1474-87. doi: [10.1016/j.ajpath.2013.07.014](https://doi.org/10.1016/j.ajpath.2013.07.014). Epub 2013 Sep 11.

Renal fibrosis is the common anatomical feature underlying the progression of chronic kidney disease, a leading cause of morbidity and mortality worldwide. In a previous study, we demonstrated that during development of renal fibrosis in a rat model of unilateral ureteric obstruction, calreticulin (CRT) is up-regulated in tubular epithelial cells (TECs). In the present study, we used *in vitro* and *in vivo* approaches to examine the role of CRT in TECs and its contribution to the progression of fibrosis. In cultured renal TECs, CRT overexpression induced acquisition of an altered, profibrotic cellular phenotype. Consistently, the opposite effects were observed for CRT knockdown. Subsequently, we confirmed that critical changes observed *in vitro* were also apparent in tubular cells *in vivo* in the animal model of unilateral ureteric obstruction. In agreement with these results, we demonstrate that substantial (50%) reduction in the expression of CRT reduced the development of tubulointerstitial fibrosis at a comparable level through regulation of inflammation, transcriptional activation, transforming growth factor beta1-associated effects, and apoptosis. In summary, our findings establish that CRT is critically involved in the molecular mechanisms that drive renal fibrosis progression and indicate that inhibition of CRT expression might be a therapeutic target for reduction of fibrosis and chronic kidney disease development.

Pulskens, W. P., L. M. Butter, et al. "Nlrp3 prevents early renal interstitial edema and vascular permeability in unilateral ureteral obstruction." *PLoS One.* 2014 Jan 15;9(1):e85775. doi: [10.1371/journal.pone.0085775](https://doi.org/10.1371/journal.pone.0085775). eCollection 2014.

Progressive renal disease is characterized by tubulo-interstitial injury with ongoing inflammation and fibrosis. The Nlrp3 inflammasome contributes to these pathophysiological processes through its canonical effects in cytokine maturation. Nlrp3 may additionally exert inflammasome-independent effects following tissue injury. Hence, in this study we investigated potential non-canonical effects of Nlrp3 following progressive renal injury by subjecting WT and Nlrp3-deficient (-/-) mice to unilateral ureter obstruction (UO). Our results revealed a progressive increase of renal Nlrp3 mRNA in WT mice following UO. The absence of Nlrp3 resulted in enhanced tubular injury and dilatation and an elevated expression of injury biomarker NGAL after UO. Moreover, interstitial edema was significantly elevated in Nlrp3<sup>-/-</sup> mice. This could be explained by increased

intratubular pressure and an enhanced tubular and vascular permeability. In accordance, renal vascular leakage was elevated in Nlrp3<sup>-/-</sup> mice that associated with reduced mRNA expression of intercellular junction components. The decreased epithelial barrier function in Nlrp3<sup>-/-</sup> mice was not associated with increased apoptosis and/or proliferation of renal epithelial cells. Nlrp3 deficiency did not affect renal fibrosis or inflammation. Together, our data reveal a novel non-canonical effect of Nlrp3 in preserving renal integrity and protection against early tubular injury and interstitial edema following progressive renal injury.

Radovic, N., G. Aralica, et al. "Effect of unilateral ureteral obstruction and anti-angiotensin II treatment on renal tubule cell apoptosis and interstitial fibrosis in rats." *Coll Antropol.* 2014 Jun;38(2):583-8.

Unilateral ureteral obstruction (UO) results in a number of pathophysiological and morphological changes in the renal parenchyma, including interstitial inflammation and fibrosis, apoptotic changes of tubular and interstitial cells. Recent studies have indicated an association between renin-angiotensin system and apoptotic alterations in the kidney after unilateral obstructive nephropathy. In this study, the effect of ACE inhibitors and AT1 receptor antagonists on tubular cell apoptosis and interstitial fibrosis in obstructive nephropathy after UO in rats was investigated. The study was conducted on Wistar rats with unilaterally ligated ureter and sham operated animals (control group). The rats with UO were treated with ACE inhibitor (cilazapril) or AT1 receptor antagonists (losartan) and control group was treated with H<sub>2</sub>O. Sham-operated animals were treated in the same way. Tubular and interstitial cell apoptosis was detected morphologically by hematoxylin and eosin (HE) staining and terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL). The area of interstitial fibrosis was determined using computer-assisted image processing after Gomory silver impregnation of paraffin sections. All experimental animal groups with unilateral ureter ligation showed a significantly increased number of apoptotic tubular and interstitial cells in the obstructed kidney compared with the contralateral, unobstructed kidney. Histomorphometric analysis of renal interstitial fibrotic changes in the groups of rats treated with losartan or water showed a statistically significant difference ( $p < 0.05$ ) between the operated and sham-operated animals. In conclusion, following UO there is a significantly increased number of apoptotic tubular cells and interstitial fibrosis in the ipsilateral kidney compared with the contralateral kidney. ACE inhibitors and AT1 receptor antagonists could not

decrease the extent of renal cells apoptosis and interstitial fibrosis after UUU.

Ramdas, V., M. McBride, et al. "Canonical transforming growth factor-beta signaling regulates disintegrin metalloprotease expression in experimental renal fibrosis via miR-29." *Am J Pathol.* 2013 Dec;183(6):1885-96. doi: [10.1016/j.ajpath.2013.08.027](https://doi.org/10.1016/j.ajpath.2013.08.027). Epub 2013 Oct 6.

Fibrosis pathophysiology is critically regulated by Smad 2- and Smad 3-mediated transforming growth factor-beta (TGF-beta) signaling. Disintegrin metalloproteases (Adam) can manipulate the signaling environment, however, the role and regulation of ADAMs in renal fibrosis remain unclear. TGF-beta stimulation of renal cells results in a significant up-regulation of Adams 10, 17, 12, and 19. The selective Smad2/3 inhibitor SB 525334 reversed these TGF-beta-induced changes. In vivo, using ureteral obstruction to model renal fibrosis, we observed increased Adams gene expression that was blocked by oral administration of SB 525334. Similar increases in Adam gene expression also occurred in preclinical models of hypertension-induced renal damage and glomerulonephritis. miRNAs are a recently discovered second level of regulation of gene expression. Analysis of 3' untranslated regions of Adam12 and Adam19 mRNAs showed multiple binding sites for miR-29a, miR-29b, and miR-29c. We show that miR-29 family expression is decreased after unilateral ureter obstruction and this significant decrease in miR-29 family expression was observed consistently in preclinical models of renal dysfunction and correlated with an increase in Adam12 and Adam19 expression. Exogenous overexpression of the miR-29 family blocked TGF-beta-mediated up-regulation of Adam12 and Adam19 gene expression. This study shows that Adams are involved in renal fibrosis and are regulated by canonical TGF-beta signaling and miR-29. Therefore, both Adams and the miR-29 family represent therapeutic targets for renal fibrosis.

Rampanelli, E., K. Rouschop, et al. "CD44v3-v10 reduces the profibrotic effects of TGF-beta1 and attenuates tubular injury in the early stage of chronic obstructive nephropathy." *Am J Physiol Renal Physiol.* 2013 Nov 15;305(10):F1445-54. doi: [10.1152/ajprenal.00340.2013](https://doi.org/10.1152/ajprenal.00340.2013). Epub 2013 Sep 11.

CD44 family members are cell surface glycoproteins, which are expressed on tubular epithelial cells (TEC) solely upon kidney injury and are involved in renal fibrosis development. Renal interstitial fibrosis is the final manifestation of chronic kidney diseases and is regulated by a complex network of cytokines, including the profibrotic factor

transforming growth factor-beta1 (TGF-beta1) and the two antifibrotic cytokines bone morphogenic protein-7 (BMP-7) and hepatocyte growth factor (HGF). The present study investigates the potential role of CD44 standard (CD44s) and CD44v3-v10 (CD44v3) isoforms as modulators of the balance between TGF-beta1 and HGF/BMP-7. CD44s is the shortest and most common isoform. CD44v3-v10 (CD44v3) has heparan sulfate moieties, which enable the binding to HGF/BMP-7, and hence, might exert renoprotective effects. Using transgenic mice overexpressing either CD44s or CD44v3 specifically on proximal TEC, we found that in vitro the overexpression of CD44v3 on primary TEC renders cells less susceptible to TGF-beta1 profibrotic actions and more sensitive to BMP-7 and HGF compared with TEC overexpressing CD44s. One day after unilateral ureteric obstruction, obstructed kidneys from CD44v3 transgenic mice showed less tubular damage and myofibroblasts accumulation, which was associated with decreased TGF-beta1 signaling and increased BMP-7 synthesis and signaling compared with kidneys from wild-type and CD44s transgenic mice. These data suggest that CD44v3 plays a renoprotective role in early stage of chronic obstructive nephropathy.

Rodriguez-Pena, A. B., I. Fuentes-Calvo, et al. "Effect of angiotensin II and small GTPase Ras signaling pathway inhibition on early renal changes in a murine model of obstructive nephropathy." *Biomed Res Int.* 2014;2014:124902. doi: [10.1155/2014/124902](https://doi.org/10.1155/2014/124902). Epub 2014 Jul 3.

Tubulointerstitial fibrosis is a major feature of chronic kidney disease. Unilateral ureteral obstruction (UUO) in rodents leads to the development of renal tubulointerstitial fibrosis consistent with histopathological changes observed in advanced chronic kidney disease in humans. The purpose of this study was to assess the effect of inhibiting angiotensin II receptors or Ras activation on early renal fibrotic changes induced by UUO. Animals either received angiotensin II or underwent UUO. UUO animals received either losartan, atorvastatin, and farnesyl transferase inhibitor (FTI) L-744,832, or chaetomelic acid A (ChA). Levels of activated Ras, phospho-ERK1/2, phospho-Akt, fibronectin, and alpha-smooth muscle actin were subsequently quantified in renal tissue by ELISA, Western blot, and/or immunohistochemistry. Our results demonstrate that administration of angiotensin II induces activation of the small GTPase Ras/Erk/Akt signaling system, suggesting an involvement of angiotensin II in the early obstruction-induced activation of renal Ras. Furthermore, upstream inhibition of Ras signalling by blocking either angiotensin AT1 type receptor or by inhibiting Ras prenylation (atorvastatin, FTI o ChA)

reduced the activation of the Ras/Erk/Akt signaling system and decreased the early fibrotic response in the obstructed kidney. This study points out that pharmacological inhibition of Ras activation may hold promise as a future strategy in the prevention of renal fibrosis.

Sabbiseti, V. S., S. S. Waikar, et al. "Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes." J Am Soc Nephrol. 2014 Oct;25(10):2177-86. doi: 10.1681/ASN.2013070758. Epub 2014 Jun 5.

Currently, no blood biomarker that specifically indicates injury to the proximal tubule of the kidney has been identified. Kidney injury molecule-1 (KIM-1) is highly upregulated in proximal tubular cells following kidney injury. The ectodomain of KIM-1 is shed into the lumen, and serves as a urinary biomarker of kidney injury. We report that shed KIM-1 also serves as a blood biomarker of kidney injury. Sensitive assays to measure plasma and serum KIM-1 in mice, rats, and humans were developed and validated in the current study. Plasma KIM-1 levels increased with increasing periods of ischemia (10, 20, or 30 minutes) in mice, as early as 3 hours after reperfusion; after unilateral ureteral obstruction (day 7) in mice; and after gentamicin treatment (50 or 200 mg/kg for 10 days) in rats. In humans, plasma KIM-1 levels were higher in patients with AKI than in healthy controls or post-cardiac surgery patients without AKI (area under the curve, 0.96). In patients undergoing cardiopulmonary bypass, plasma KIM-1 levels increased within 2 days after surgery only in patients who developed AKI ( $P < 0.01$ ). Blood KIM-1 levels were also elevated in patients with CKD of various etiologies. In a cohort of patients with type 1 diabetes and proteinuria, serum KIM-1 level at baseline strongly predicted rate of eGFR loss and risk of ESRD during 5-15 years of follow-up, after adjustment for baseline urinary albumin-to-creatinine ratio, eGFR, and Hb1Ac. These results identify KIM-1 as a blood biomarker that specifically reflects acute and chronic kidney injury.

Sakuraya, K., A. Endo, et al. "The synergistic effect of mizoribine and a direct renin inhibitor, aliskiren, on unilateral ureteral obstruction induced renal fibrosis in rats." J Urol. 2014 Apr;191(4):1139-46. doi: 10.1016/j.juro.2013.10.053. Epub 2013 Oct 16.

**PURPOSE:** Renal fibrosis, the major histopathological change in various renal disorders, is closely related to renal dysfunction. Unilateral ureteral obstruction is a well established model of experimental renal disease that results in tubulointerstitial fibrosis. Previous studies showed that aliskiren and mizoribine

ameliorated unilateral ureteral obstruction induced renal fibrosis. However, to our knowledge the protective effect of combination therapy with aliskiren and mizoribine against renal fibrosis is unknown. We investigated the synergistic effects of aliskiren and mizoribine combination therapy on unilateral ureteral obstruction induced fibrosis in rats. **MATERIALS AND METHODS:** Male Sprague Dawley(R) rats underwent unilateral ureteral obstruction followed by aliskiren and/or mizoribine treatment. Kidney samples were fixed for histopathology and immunohistochemistry of myofibroblasts (alpha-SMA) and macrophages (ED-1). Real-time quantitative reverse transcription-polymerase chain reaction was performed to measure alpha-SMA, TGF-beta1, osteopontin, MCP-1 and renin expression. **RESULTS:** After unilateral ureteral obstruction the tubular dilatation, interstitial volume and alpha-SMA expression scores were significantly decreased by combination therapy compared with monotherapy with aliskiren or mizoribine. Combination therapy caused a significant decrease in the number of ED-1 positive cells and in TGF-beta1 gene expression compared with monotherapy with either drug (each  $p < 0.05$ ). Combination therapy also decreased OPN and MCP-1 gene expression ( $p < 0.05$ ). **CONCLUSIONS:** Aliskiren and mizoribine combination therapy provides increased renal protection against renal fibrosis and unilateral ureteral obstruction induced inflammation.

Saliba, Y., R. Karam, et al. "Evidence of a Role for Fibroblast Transient Receptor Potential Canonical 3 Ca<sup>2+</sup> Channel in Renal Fibrosis." J Am Soc Nephrol. 2014 Dec 5. pii: ASN.2014010065.

Transient receptor potential canonical (TRPC) Ca<sup>2+</sup>-permeant channels, especially TRPC3, are increasingly implicated in cardiorenal diseases. We studied the possible role of fibroblast TRPC3 in the development of renal fibrosis. In vitro, a macromolecular complex formed by TRPC1/TRPC3/TRPC6 existed in isolated cultured rat renal fibroblasts. However, specific blockade of TRPC3 with the pharmacologic inhibitor pyr3 was sufficient to inhibit both angiotensin II- and 1-oleoyl-2-acetyl-sn-glycerol-induced Ca<sup>2+</sup> entry in these cells, which was detected by fura-2 Ca<sup>2+</sup> imaging. TRPC3 blockade or Ca<sup>2+</sup> removal inhibited fibroblast proliferation and myofibroblast differentiation by suppressing the phosphorylation of extracellular signal-regulated kinase (ERK1/2). In addition, pyr3 inhibited fibrosis and inflammation-associated markers in a noncytotoxic manner. Furthermore, TRPC3 knockdown by siRNA confirmed these pharmacologic findings. In adult male Wistar rats or wild-type mice subjected to unilateral ureteral obstruction, TRPC3



expression increased in the fibroblasts of obstructed kidneys and was associated with increased Ca<sup>2+</sup> entry, ERK1/2 phosphorylation, and fibroblast proliferation. Both TRPC3 blockade in rats and TRPC3 knockout in mice inhibited ERK1/2 phosphorylation and fibroblast activation as well as myofibroblast differentiation and extracellular matrix remodeling in obstructed kidneys, thus ameliorating tubulointerstitial damage and renal fibrosis. In conclusion, TRPC3 channels are present in renal fibroblasts and control fibroblast proliferation, differentiation, and activation through Ca<sup>2+</sup>-mediated ERK signaling. TRPC3 channels might constitute important therapeutic targets for improving renal remodeling in kidney disease.

Samarakoon, R., S. Helo, et al. "Loss of Tumour Suppressor PTEN Expression in Renal Injury Initiates SMAD3 and p53 Dependent Fibrotic Responses." *J Pathol.* 2015 Mar 25. doi: 10.1002/path.4538.

Deregulation of the tumour suppressor PTEN occurs in lung and skin fibrosis, diabetic and ischaemic renal injury. However, the potential role of PTEN and associated mechanisms in the progression of kidney fibrosis is unknown. Tubular and interstitial PTEN expression was dramatically decreased in several models of renal injury including aristolochic acid nephropathy (AAN), streptozotocin (STZ)-mediated injury and ureteral unilateral obstruction (UUO), correlating with Akt, p53 and SMAD3 activation and fibrosis. Stable silencing of PTEN in HK-2 human tubular epithelial cells induced dedifferentiation and CTGF, PAI-1, vimentin, alpha-SMA and fibronectin expression compared to HK-2 cells expressing control shRNA. Furthermore, PTEN knockdown stimulated Akt, SMAD3 and p53Ser15 phosphorylation with an accompanying decrease in population density and an increase in epithelial G1 cell cycle arrest. SMAD3 or p53 gene silencing or pharmacological blockade partially suppressed fibrotic gene expression and relieved growth inhibition orchestrated by deficiency or inhibition of PTEN. Similarly, shRNA suppression of PAI-1 rescued the PTEN loss-associated epithelial proliferative arrest. Moreover, TGF-beta1-initiated fibrotic gene expression is further enhanced by PTEN depletion. Combined TGF-beta1 treatment and PTEN silencing potentiated epithelial cell death via p53 dependent pathways. Thus, PTEN loss initiates tubular dysfunction via SMAD3- and p53-mediated fibrotic gene induction with accompanying PAI-1 dependent proliferative arrest, and cooperates with TGF-beta1 to induce the expression of profibrotic genes and tubular apoptosis.

Savic, S., V. Vukotic, et al. "Management of calculus anuria using ureteroscopic lithotripsy as a first line

treatment: its efficacy and safety." *Urol J.* 2014 May 6;11(2):1392-9.

**PURPOSE:** To present our experience with emergency ureteroscopic lithotripsy (URSL) for ureteral calculi associated with acute kidney injury (AKI). **MATERIALS AND METHODS:** We retrospectively evaluated the 61 patients consisted of 90 ureteral units (UU), who underwent URSL. The cause of anuria was bilateral calculus obstructions in 29 cases, and unilateral calculus obstruction with, absent, nephrectomized contralateral kidney in 32 cases. In the case of bilateral synchronous ureteric calculi same-session bilateral ureteroscopy (SBBU) was done. The duration of anuria varied between 12 to 72 hours. At the end of the procedure, ureteral stent was systematically left in place in all patients. Surgery was performed 6-12 hours after admission to hospital. Patients were followed at least 1 month postoperatively. **RESULTS:** The stone free rates (SFR) were determined as baseline, on the first post-operative day, and as overall on the 30 days after procedure. The greatest success was achieved in the distal localization of stones up to 10 mm (93%). Renal function returned in 51 (83.6%) patients within 7 days. In 18 (29.5%) patients [18 (20%) UU] we performed second procedure as extracorporeal shockwave lithotripsy in 16.7% and open surgery in 2.2%. In 43 (70.5%) patients URSL was a successful therapeutic approach in dealing with pain, obstruction and calculus. **CONCLUSION:** Calculus anuria is a medical emergency that requires rapid diagnosis and prompt treatment for the purpose of decompression. URSL is the proper method of choice for selected patients and can be performed safely and has high success rates with minimal morbidity.

Scarpellini, A., L. Huang, et al. "Syndecan-4 knockout leads to reduced extracellular transglutaminase-2 and protects against tubulointerstitial fibrosis." *J Am Soc Nephrol.* 2014 May;25(5):1013-27. doi: 10.1681/ASN.2013050563. Epub 2013 Dec 19.

Transglutaminase type 2 (TG2) is an extracellular matrix crosslinking enzyme with a pivotal role in kidney fibrosis. The interaction of TG2 with the heparan sulfate proteoglycan syndecan-4 (Sdc4) regulates the cell surface trafficking, localization, and activity of TG2 in vitro but remains unstudied in vivo. We tested the hypothesis that Sdc4 is required for cell surface targeting of TG2 and the development of kidney fibrosis in CKD. Wild-type and Sdc4-null mice were subjected to unilateral ureteric obstruction and aristolochic acid nephropathy (AAN) as experimental models of kidney fibrosis. Analysis of renal scarring by Masson trichrome staining, kidney hydroxyproline levels, and collagen immunofluorescence demonstrated progressive

fibrosis associated with increases in extracellular TG2 and TG activity in the tubulointerstitium in both models. Knockout of Sdc-4 reduced these effects and prevented AAN-induced increases in total and active TGF-beta1. In wild-type mice subjected to AAN, extracellular TG2 colocalized with Sdc4 in the tubular interstitium and basement membrane, where TG2 also colocalized with heparan sulfate chains. Heparitinase I, which selectively cleaves heparan sulfate, completely abolished extracellular TG2 in normal and diseased kidney sections. In conclusion, the lack of Sdc4 heparan sulfate chains in the kidneys of Sdc4-null mice abrogates injury-induced externalization of TG2, thereby preventing profibrotic crosslinking of extracellular matrix and recruitment of large latent TGF-beta1. This finding suggests that targeting the TG2-Sdc4 interaction may provide a specific interventional strategy for the treatment of CKD.

Schulte, K., K. Berger, et al. "Origin of parietal podocytes in atubular glomeruli mapped by lineage tracing." *J Am Soc Nephrol.* 2014 Jan;25(1):129-41. doi: 10.1681/ASN.2013040376. Epub 2013 Sep 26.

Parietal podocytes are fully differentiated podocytes lining Bowman's capsule where normally only parietal epithelial cells (PECs) are found. Parietal podocytes form throughout life and are regularly observed in human biopsies, particularly in atubular glomeruli of diseased kidneys; however, the origin of parietal podocytes is unresolved. To assess the capacity of PECs to transdifferentiate into parietal podocytes, we developed and characterized a novel method for creating atubular glomeruli by electrocoagulation of the renal cortex in mice. Electrocoagulation produced multiple atubular glomeruli containing PECs as well as parietal podocytes that projected from the vascular pole and lined Bowman's capsule. Notably, induction of cell death was evident in some PECs. In contrast, Bowman's capsules of control animals and normal glomeruli of electrocoagulated kidneys rarely contained podocytes. PECs and podocytes were traced by inducible and irreversible genetic tagging using triple transgenic mice (PEC- or Pod-rtTA/LC1/R26R). Examination of serial cryosections indicated that visceral podocytes migrated onto Bowman's capsule via the vascular stalk; direct transdifferentiation from PECs to podocytes was not observed. Similar results were obtained in a unilateral ureter obstruction model and in human diseased kidney biopsies, in which overlap of PEC- or podocyte-specific antibody staining indicative of gradual differentiation did not occur. These results suggest that induction of atubular glomeruli leads to ablation of PECs and subsequent migration of visceral podocytes onto Bowman's

capsule, rather than transdifferentiation from PECs to parietal podocytes.

Shiohira, S., T. Yoshida, et al. "Sphingosine-1-phosphate acts as a key molecule in the direct mediation of renal fibrosis." *Physiol Rep.* 2013 Dec 5;1(7):e00172. doi: 10.1002/phy2.172. eCollection 2013 Dec 1.

The major sphingolipid metabolite, sphingosine-1-phosphate (S1P), has important biological functions. S1P serves as a ligand for a family of five G-protein-coupled receptors with distinct signaling pathways regulating important biological pathways. S1P induces renal fibrosis through an inflammatory pathway. However, its direct fibrosis-inducing effect on the kidney has not been shown. The role of S1P as a direct mediator of renal fibrosis was investigated in normal rat kidney interstitial fibroblast (NRK-49F) cells (in vitro) and kidneys of a unilateral ureteral obstruction (UUO) mouse model (in vivo). To clarify the role of S1P in renal fibrosis, we adopted nude UUO mice with immune response deficits. NRK-49F cells were stimulated with various concentrations of exogenous S1P and FTY720 (a S1P receptor agonist) or N,N-dimethylsphingosine (DMS; a sphingosine kinase inhibitor). C57BL6 and nude UUO mice were pretreated with FTY720, DMS, or saline. Expression levels of alpha-smooth muscle actin (a-SMA), E-cadherin, collagen type 1 (COL1), collagen type 4 (COL4), tissue inhibitor of matrix metalloproteinase-1 (TIMP1), and plasminogen activator inhibitor-1 (PAI1) were examined. S1P stimulated fibrosis in NRK-49F cells and UUO mice. Increased a-SMA, COL1, COL4, TIMP1, and PAI1 and decreased E-cadherin expression levels were observed in both the S1P-stimulated cells and UUO mice. Nude UUO mouse kidneys expressed fibrotic markers. Fibrotic changes were successfully induced in both UUO and nude UUO mice, evident through prominent fibronectin and COL1 staining. These S1P-induced fibrotic changes were suppressed by FTY720 and DMS both in vitro and in vivo. Thus, S1P essentially and directly mediates renal fibrosis.

Tammaro, A., I. Stroo, et al. "Role of TREM1-DAP12 in renal inflammation during obstructive nephropathy." *PLoS One.* 2013 Dec 16;8(12):e82498. doi: 10.1371/journal.pone.0082498. eCollection 2013.

Tubulo-interstitial damage is a common finding in the chronically diseased kidney and is characterized by ongoing inflammation and fibrosis leading to renal dysfunction and end-stage renal disease. Upon kidney injury, endogenous ligands can be released which are recognized by innate immune sensors to alarm innate immune system. A new family

of innate sensors is the family of TREM (triggering receptor expressed on myeloid cell). TREM1 is an activating receptor and requires association with transmembrane adapter molecule DAP12 (DNAX-associated protein 12) for cell signaling. TREM1-DAP12 pathway has a cross-talk with intracellular signaling pathways of several Toll-like receptors (TLRs) and is able to amplify TLR signaling and thereby contributes to the magnitude of inflammation. So far, several studies have shown that TLRs play a role in obstructive nephropathy but the contribution of TREM1-DAP12 herein is unknown. Therefore, we studied TREM1 expression in human and murine progressive renal diseases and further investigated the role for TREM1-DAP12 by subjecting wild-type (WT), TREM1/3 double KO and DAP12 KO mice to murine unilateral ureter obstruction (UUO) model. In patients with hydronephrosis, TREM1 positive cells were observed in renal tissue. We showed that in kidneys from WT mice, DAP12 mRNA and TREM1 mRNA and protein levels were elevated upon UUO. Compared to WT mice, DAP12 KO mice displayed less renal MCP-1, KC and TGF-beta1 levels and less influx of macrophages during progression of UUO, whereas TREM1/3 double KO mice displayed less renal MCP-1 level. Renal fibrosis was comparable in WT, TREM1/3 double KO and DAP12 KO mice. We conclude that DAP12, partly through TREM1/3, is involved in renal inflammation during progression of UUO.

Thangada, S., L. H. Shapiro, et al. "Treatment with the immunomodulator FTY720 (fingolimod) significantly reduces renal inflammation in murine unilateral ureteral obstruction." *J Urol.* 2014 May;191(5 Suppl):1508-16. doi: 10.1016/j.juro.2013.10.072. Epub 2014 Mar 26.

**PURPOSE:** The S1P signaling pathway represents an important potential target for the modulation of tissue inflammation/injury. The immunomodulator FTY720, also known as fingolimod, is a potent agonist for multiple S1P receptors that was approved by the Food and Drug Administration to treat multiple sclerosis. We examined the therapeutic role of FTY720 for renal injury secondary to unilateral ureteral obstruction. **MATERIALS AND METHODS:** CB57BL/6 mice underwent a sham procedure or unilateral ureteral obstruction and were treated with FTY720 by gavage for 1, 3 and 5 days. Control groups received vehicle. Ligated and unligated renal tissue was examined for histopathological changes, inflammatory and fibrotic markers, TGF-beta1, alpha-SMA, and macrophage infiltration by Western blot and immunohistochemistry. Proinflammatory and profibrotic cytokines were profiled by quantitative

reverse transcriptase-polymerase chain reaction. **RESULTS:** Pathological evaluation revealed that FTY720 treatment resulted in a significant reduction in inflammatory infiltration in obstructed kidneys compared to controls. Immunohistochemical and Western blot showed that TGF-beta1 and alpha-SMA protein levels were similarly decreased, as was macrophage infiltration into the renal interstitial space, compared to untreated mice. In agreement with these observations quantitative reverse transcriptase-polymerase chain reaction revealed that inflammatory and fibrotic cytokines (MCP-1, IL-1beta, CXCL1, TNF-alpha and TGF-beta1) were also significantly decreased in the FTY720 group. **CONCLUSIONS:** This study suggests that in a murine ureteral obstruction model FTY720 significantly inhibited the production of inflammatory cytokines and factors regulating interstitial fibrosis and extracellular matrix accumulation. These findings were associated with decreased evidence of renal injury on pathological examination, suggesting that FTY720 or related compounds may be valuable modulators of obstruction induced renal injury.

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