

BLADDER

[Longitudinal patterns of urinary incontinence and associated predictors in women with type 1 diabetes](#)

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Urinary incontinence (UI) in women is a dynamic condition with numerous risk factors yet most studies have focused on examining its prevalence at a single time. The objective of this study was to describe the long-term time course of UI in women with type 1 diabetes (T1D). Longitudinal data in women with T1D were collected from 568 women in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Over a 12-year period, participants annually responded to whether they had experienced UI in the past year. We identified four categories of UI in this population over time: 205 (36.1%) women never reported UI (no UI), 70 (12.3%) reported it one or two consecutive years only (isolated UI), 247 (43.5%) periodically changed status between UI and no UI (intermittent UI), and 46 (8.1%) reported UI continuously after the first report (persistent UI). Compared to women reporting no/isolated UI, women displaying the intermittent phenotype were significantly more likely to be obese (OR: 1.86, 95% CI: 1.15, 3.00) and report prior hysterectomy (OR: 2.57, 95% CI: 1.39, 4.77); whereas women with persistent UI were significantly more likely to have abnormal autonomic function (OR: 2.36, 95% CI: 1.16-4.80). UI is a dynamic condition in women with T1D. Varying risk factors observed for the different phenotypes of UI suggest distinctive pathophysiological mechanisms. These findings have the potential to be used to guide individualized interventions for UI in women with diabetes.

[Urinary Tract Infections in Children: Testing a Novel, Non-Invasive, Point-Of-Care Diagnostic Marker](#)

Tamar R Lubell, **Jonathan M Barasch**, Benjamin King, Julie B Ochs, Weijia Fan, Jimmy Duong, Manasi Chitre, Peter S Dayan *Acad Emerg Med.* 2021 Oct 19. doi: 10.1111/acem.14402. Online ahead of print. PMID: 34665891

Urinary neutrophil gelatinase-associated lipocalin (uNGAL) appears highly accurate to identify urinary tract infections (UTIs) when obtained via catheterization. Our primary aim was to determine the agreement in uNGAL levels between paired catheter and bag urine specimens. Our second aim was to compare the diagnostic test characteristics of quantitative uNGAL, dipstick uNGAL (a potential point-of-care test) and urinalysis (UA). Prospective study of febrile children <24 months evaluated for UTIs. We evaluated quantitative uNGAL at a previously-identified threshold of 39.1 ng/mL, dipstick uNGAL at its built-in threshold of >50 ng/mL, and UA at standard thresholds for leukocyte esterase (LE). A positive urine culture was defined as >100,000 CFUs/mL of a pathogen. The agreement between catheterized and bagged samples at a quantitative uNGAL cutoff of ≥ 39.1 ng/mL was 0.76 (95% CI: 0.67-0.83) and 0.77 (95% CI: 0.68-0.84) at a uNGAL dipstick threshold of >50 ng/mL. The area under the receiver-operating characteristic curve for uNGAL from a catheterized sample was 0.96 (95% CI: 0.89-1.00) as compared to 0.93 (95% CI: 0.87-0.99) from a bagged sample. The sensitivities of catheterized sample quantitative and dipstick uNGAL (90.5%) were higher than UA at a LE threshold of $\geq 1+$ (57.1%). Bagged sample uNGAL had lower quantitative and dipstick specificities (both 73.8%) than from catheterized samples (94.2% and 95.2% respectively), similar to UA. uNGAL from bagged and catheterized samples showed insufficient agreement to be used interchangeably. Low specificity of uNGAL from bagged samples suggests that sampling technique affects uNGAL levels.

[Effects of low-dose insulin or a soluble guanylate cyclase activator on lower urinary tract dysfunction in streptozotocin-induced diabetic rats](#)

Daisuke Gotoh, Nailong Cao, Eduardo C Alexandre, Tetsuichi Saito, Yosuke Morizawa, Shunta Hori, Makito Miyake, Kazumasa Torimoto, Kiyohide Fujimoto, **Naoki Yoshimura** *Life Sci.* 2021 Oct 3;286:120001. doi: 10.1016/j.lfs.2021.120001. Online ahead of print. PMID: 34614417

To examine the effects of low-dose insulin or a soluble guanylate cyclase activator (sGC) on lower urinary tract dysfunction (LUTD) in rats with diabetes mellitus (DM). Female Sprague-Dawley rats were divided into non-DM control (N), DM induced by streptozotocin (65 mg/kg), with low-dose insulin (DI), DM with vehicle (D), and DM with sGC (GC) groups. In GC group, BAY 60-2770 (1 mg/kg/day) was orally administered in 6-8 weeks after DM. Voiding assay at 2, 4, and 8 weeks after DM, cystometry, and urethral pressure recordings at 8 weeks of DM were performed. mRNA levels of NO-related markers and cGMP protein levels in the urethra, and ischemia and inflammation markers in the bladder were evaluated by RT-PCR. Moderate levels of high blood glucose were maintained in Group DI versus Group D. The 24-h voided volume was significantly higher in Group D versus Groups N and DI. Non-voiding contractions were significantly greater, and voiding efficiency and urethral pressure reduction were significantly lower in Group D versus Groups N, DI, and GC. Urethral cGMP levels were significantly lower in Group D versus Groups N and GC. mRNA levels of PDE5 in the urethra and ischemia and inflammation markers in the bladder increased in Group D versus Group N or DI was reduced after sGC treatment. DI rats with a lesser degree of bladder and urethral dysfunction might be useful as a slow-progressive DM model. sGC activation could be an effective treatment of LUTD in DM.

[Functional and histologic imaging of urinary bladder wall after exposure to psychological stress and protamine sulfate](#)

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To quantify the urinary bladder wall T1 relaxation time (T1) before and after the instillation contrast mixture in rats previously subjected to water avoidance stress (WAS) and/or acute exposure to protamine sulfate (PS). Female Wistar rats were randomized to receive either sham (control) or 1 h of WAS for ten consecutive days before the evaluation of nocturnal urination pattern in metabolic cages. T1 mapping of urinary bladder wall at 9.4 T was performed pre- and post- instillation of 4 mM Gadobutrol in a mixture with 5 mM Ferumoxytol. Subsequently, either T1 mapping was repeated after brief intravesical PS exposure or the animals were sacrificed for histology and analyzing the mucosal levels of mRNA. Compared to the control group, WAS exposure decreased the single void urine volume and shortened the post-contrast T1 relaxation time of mucosa- used to compute relatively higher ingress of instilled Gadobutrol. Compromised permeability in WAS group was corroborated by the urothelial denudation, edema and ZO-1 downregulation. PS exposure doubled the baseline ingress of Gadobutrol in both groups. These findings confirm that psychological stress compromises the paracellular permeability of bladder mucosa and its non-invasive assay with MRI was validated by PS exposure.

PROSTATE

[Therapeutic effects of nerve growth factor-targeting therapy on bladder overactivity in rats with prostatic inflammation](#)

Taro Igarashi, Pradeep Tyagi, Shinsuke Mizoguchi, Tetsuichi Saito, Akira Furuta, Yasuyuki Suzuki, Shin Egawa, **Zhou Wang, Naoki Yoshimura**

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The present study examined the effect of liposomes conjugated with antisense oligonucleotide of nerve growth factor (NGF-OND) on local overexpression of NGF and bladder overactivity using rats with prostatic inflammation (PI). Male Sprague-Dawley rats were divided into three groups: (1) Control group; intact rats, (2) PI-NS group; rats with PI and intravesical instillation of normal saline (NS), (3) PI-OND group; rats with PI and intravesical instillation of NGF-OND. On Day 0, PI was induced by intraprostatic 5%-formalin injection. On Day 14, NGF-OND or NS was instilled directly into the bladder after laparotomy. On Day 28, therapeutic effects of NGF-OND were evaluated by awake cystometry and histological analysis as well as reverse-transcription polymerase chain reaction measurements of messenger RNA (mRNA) levels of NGF in the bladder and prostate, inflammatory markers in the prostate, C-fiber afferent markers, and an A-type K⁺ channel α -subunit (Kv 1.4) in L6-S1 dorsal root ganglia (DRG). Intravesical NFG-OND treatment reduced PI-induced overexpression of NGF in both bladder and prostate, and reduced PI-induced bladder overactivity evident as longer intercontraction intervals in association with reductions of TRPV1 and TRPA1 mRNA expression levels in DRG. mRNA expression of Kv1.4 in DRG was reduced after PI, but improved in the PI-OND group. These results indicate that NGF locally expressed in the bladder is an important mediator inducing bladder overactivity with upregulation of C-fiber afferent markers and downregulation of an A-type K⁺ channel subunit in DRG following PI, and that liposome-based, local NGF-targeting therapy could be effective for not only bladder overactivity and afferent sensitization, but also PI.

KIDNEY

[Longitudinal Outcomes of COVID-19-Associated Collapsing Glomerulopathy and Other Podocytopathies](#)

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The long-term outcome of COVID-19-associated collapsing glomerulopathy is unknown. We retrospectively identified 76 native kidney biopsies from patients with history of COVID-19 between March 2020 and April 2021. Presenting and outcome data were obtained for all 23 patients with collapsing glomerulopathy and for 7 patients with non-collapsing podocytopathies. We performed APOL1 genotyping by Sanger sequencing, immunostaining for spike and nucleocapsid proteins and in situ hybridization for SARS-CoV-2. All but one patient presented with AKI, 17 had nephrotic-range proteinuria, and 6 had nephrotic syndrome. Fourteen (61%) patients required dialysis at presentation. Among 17 patients genotyped, 16 (94%) were high-risk APOL1. Among 22 (96%) patients with median follow-up at 155 days (range 30-412 days), 11 (50%) received treatment for COVID-19 and 8 (36%) received glucocorticoid therapy for podocytopathy. At follow-up, 19 (86%) patients were alive and 15 (68%) were dialysis-free. The dialysis-free patients included 64% (7/11) of those treated for COVID-19 and 75% (6/8) of those treated with glucocorticoids for podocytopathy. Overall, 36% achieved partial remission of proteinuria, 32% had no remission, and 32% reached combined end-points of ESKD or death. Viral infection of the kidney was not detected. Half of 14 patients with COVID-19-associated collapsing glomerulopathy requiring dialysis achieved dialysis-independence, but the long-term prognosis of residual proteinuric CKD remains guarded, indicating a need for more effective therapy.

[Elevated NGAL is Associated with the Severity of Kidney Injury and Poor Prognosis of Patients with COVID-19](#)

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Kidney Int Rep. 2021 Oct 8. doi: 10.1016/j.ekir.2021.09.005. Online ahead of print. PMID: 34642645

Loss of kidney function is a common feature of COVID-19 infection, but serum creatinine (SCr) is not a sensitive or specific marker of kidney injury. We tested whether molecular biomarkers of tubular injury measured at hospital admission were associated with AKI in those with COVID-19 infection. This is a prospective cohort observational study consisting of 444 consecutive SARS-CoV-2 patients enrolled in the Columbia University Emergency Department at the peak of New York's pandemic (March-April 2020). Urine and blood were

collected simultaneously at hospital admission (median time: day 0, IQR 0-2 days) and urine biomarkers analyzed by ELISA and by a novel dipstick. Kidney biopsies were probed for biomarker RNA and for histopathologic acute tubular injury (ATI) scores. Admission uNGAL was associated with AKI diagnosis (267 ± 301 vs. 96 ± 139 ng/mL, $P < 0.0001$) and staging; uNGAL levels >150 ng/mL demonstrated 80% specificity and 75% sensitivity to diagnose AKI-stage 2-3. Admission uNGAL quantitatively associated with prolonged AKI, dialysis, shock, prolonged hospitalization, and in-hospital death, even when admission SCr was not elevated. The risk of dialysis increased almost 4-fold per standard deviation of uNGAL independently of baseline SCr, co-morbidities, and proteinuria [OR(95%CI): 3.59 (1.83-7.45), $P < 0.001$]. In COVID-19 kidneys, NGAL mRNA expression broadened in parallel with severe histopathological injury

(ATI). Conversely, low uNGAL levels at admission ruled out stage 2-3 AKI (NPV 0.95, 95%CI: 0.92-0.97) and the need for dialysis (NPV: 0.98, 95%CI: 0.96-0.99). While proteinuria and uKIM-1 implicated tubular injury, neither were diagnostic of AKI stages. In COVID-19 patients, uNGAL quantitatively associated with histopathological injury (ATI), the loss of kidney function (AKI), and the severity of patient outcomes.

- Jennifer Allmaras, MPH, 10/25/2021

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