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BLADDER

Adverse Childhood Experiences and Lower Urinary Tract Symptoms and Impact Among Women

Brady SS, Arguedas A, Huling JD, Shan L, Lewis CE, Fok CS, **Van Den Eeden SK**, Markland AD

This study utilizes Coronary Artery Risk Development in Young Adults (CARDIA) cohort study data to examine whether (1) family-based adverse childhood experiences (ACEs), recalled by women aged 32 to 47, are associated with lower urinary tract symptoms (LUTS) and their impact, a composite variable with 4 levels (bladder health and mild, moderate, or severe LUTS/impact), and (2) extensiveness of women's social networks in adulthood attenuates an association between ACEs and LUTS/impact. Recall of more frequent family-based ACEs was associated with report of more LUTS/impact over 10 years later (OR=1.26, 95% CI=1.07, 1.48). Social networks during adulthood appeared to attenuate the association between ACEs and LUTS/impact (OR=0.64, 95% CI=0.41, 1.02). Among women with less extensive social networks, estimated probability of experiencing moderate or severe LUTS/impact versus bladder health or mild LUTS/impact was 0.29 and 0.21 for those reporting an ACEs frequency corresponding to more than "a little" versus "rarely or none of the time," respectively. Among women with more extensive social networks, estimated probabilities were 0.20 and 0.21, respectively.

Clinically Important Differences for Pain and Urinary Symptoms in Urologic Chronic Pelvic Pain Syndrome: A MAPP Network Study

Stephens-Shields AJ, Lai HH, Landis JR, Kreder K, Rodriguez LV, Naliboff BD, Afari N, Sutcliffe S, Moldwin R, Griffith JW, **Clemens JQ**, Bradley CS, Quallich S, Gupta P, Harte SE, Farrar JT

Symptom heterogeneity in interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, collectively termed urologic chronic pelvic pain syndrome (UCPPS), has resulted in difficulty in defining appropriate clinical trial endpoints. We determine clinically important differences (CIDs) for 2 primary symptom measures, Pelvic Pain Severity (PPS) and Urinary Symptom Severity (USS), and evaluate subgroup differences. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain Symptom Patterns Study enrolled individuals with UCPPS. We defined CIDs by associating changes in PPS and USS over 3 to 6 months with marked improvement on a global response assessment using regression and receiver operating characteristic curves. We evaluated CIDs for absolute and percent change and examined differences in CIDs by sex-diagnosis, presence of Hunner lesions, pain type, pain widespreadness, and baseline symptom severity. The conclusion showed that a reduction of 30-50% in PSS is a clinically meaningful endpoint for future therapeutic trials in UCPPS. USS CIDs are more appropriately defined separately for male and female participants.

Deep Learning of Videourodynamics to Classify Bladder Dysfunction Severity in Patients with Spina Bifida

Weaver JK, Martin-Olenski M, Logan J, Broms R, Antony M, Van Batavia J, Weiss DA, Long CJ, Smith AL, Zderic SA, Huang J, **Fan Y**, **Tasian GE**

Urologists rely heavily on videourodynamics (VUDS) to identify patients with neurogenic bladders who are at risk of upper tract injury, but their interpretation has high interobserver variability. Our objective was to develop deep learning models of VUDS studies to categorize severity of bladder dysfunction. Among 306 VUDS studies, the accuracy and weighted kappa of the ensemble model classification of bladder dysfunction when at least 75% expected bladder capacity was reached were 70% (95% CI 66%,76%) and 0.54 (moderate agreement), respectively. The performance of the clinical model built from data extracted by pediatric urologists was the poorest with an accuracy of 61% (55%, 66%) and a weighted kappa of 0.37. Our models built from urodynamic pressure-volume tracings and fluoroscopic images were able to automatically classify bladder dysfunction with moderately high accuracy.

Effects of aging on urinary tract epithelial homeostasis and immunity

Ligon MM, **Joshi CS**, **Fashemi BE**, **Salazar AM**, **Mysorekar IU**

A global increase in older individuals creates an increasing demand to understand numerous healthcare challenges related to aging. This population is subject to changes in tissue physiology and the immune response network. Older individuals are particularly susceptible to infectious diseases, with one of the most common being urinary tract infections (UTIs). Postmenopausal and older women have the highest risk of recurrent UTIs (rUTIs); however, why rUTIs become more frequent after menopause and during old age is incompletely understood. In this review, we highlight our understanding of bladder innate and adaptive immunity and the impact of aging and hormones and hormone therapy on bladder epithelial homeostasis and immunity. In particular, we elaborate on how the cellular and molecular immune landscape within the bladder can be altered during aging as aged mice develop bladder tertiary lymphoid tissues (bTLT), which are absent in young mice leading to profound age-associated change to the immune landscape in bladders that might drive the significant increase in UTI susceptibility. Knowledge of host factors that prevent or promote infection can lead to targeted treatment and prevention regimens. This review also identifies unique host factors to consider in the older, female host for improving rUTI treatment and prevention by dissecting the age-associated alteration of the bladder mucosal immune system.

Longitudinal urinary microbiome characteristics in women with urgency urinary incontinence undergoing sacral neuromodulation

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The objective was to evaluate the stability of the urinary microbiome communities in women undergoing sacral neuromodulation (SNM) for urgency urinary incontinence (UUI). We hypothesized that clinical response to SNM therapy would be associated with changes in the urinary microbiome. Nineteen women who underwent SNM and provided both baseline and 3-month urine samples were included in this analysis. Women reported improvement in objective (number of UUI episodes) and subjective (symptom severity and health-related quality of life) measures. Ninety percent of the bacteria were classified as Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. No significant differences were observed in each subject's beta-diversity at 3 months compared with their baseline microbiome. Our descriptive pilot study of a cohort of women who had achieved objective and subjective improvements in UUI following SNM therapy demonstrates that the urinary microbiome remains relatively stable, despite variability amongst the cohort.

The role of the bladder diary in phenotyping men with LUTS

Khosla L, Lee P, Farooq M, Rychik K, Daniel R, Vizgan G, Prishtina L, **Bushman W**, Weiss JP, Blaivas JG

The aim of this study was to compare the clinical characteristics of men with lower urinary tract symptoms (LUTS) grouped by 24-h urine output determined from a bladder voiding diary. An online database was queried to identify men who completed a 24-hour bladder diary (24HBD), and the Lower Urinary Tract Symptom Score (LUTSS) questionnaire from 2015 to 2019 using a mobile app. Data from the bladder diary and questionnaire were contemporaneously matched within a 2-week period. Additional data, including maximum uroflow (Qmax) and postvoid residual urine (PVR), were obtained from the electronic medical record (EMR). The cohort was divided into three groups: normal, oliguria, and polyuria based on their 24-hour voided volume (24HVV). The LUTSS, 24HVV, maximum voided volume (MVV), maximum flow rate (Qmax), and PVR were compared between those with oliguria and polyuria. These observations suggest that men with oliguria or polyuria and LUTS constitute easily distinguished phenotypes that might require different diagnostic and therapeutic algorithms. Those with oliguria were older, and had lower MVVs and much lower uroflows, suggesting that they are more likely to have underlying disorders such as bladder outlet obstruction and detrusor underactivity or may be patients with overactive bladder who reduced fluid intake to improve symptoms.

KIDNEY

Clinical and Genetic Characteristics of CKD Patients with High-risk APOL1 Genotypes

Elliott MD, Marasa M, Cocchi E, Vena N, Zhang JY, Khan A, Murthy SK, Bheda S, **Rasouly HM**, Povysil G, Kiryluk K, **Gharavi AG**

APOL1 genotype has significant effects on kidney disease development and progression that vary among specific causes of kidney disease, suggesting the presence of effect modifiers. We assessed the risk of kidney failure and eGFR decline rate in patients with chronic kidney disease (CKD) carrying high-risk (N=239) and genetically matched low-risk (N=1187) APOL1 genotypes. Exome sequencing revealed monogenic kidney diseases. Exome-wide association studies and gene-based and gene-set based collapsing analyses evaluated genetic modifiers of the effect of APOL1 genotype on CKD.In this genetically matched cohort, high-risk APOL1 genotypes were associated with an increased risk of kidney failure and eGFR decline rate, with a graded risk between specific high-risk genotypes and a lower rate of monogenic kidney disease. Rare missense variants in the inflammasome pathway may act as genetic modifiers of APOL1 effect on kidney disease.

Genetics of Kidney Disease: The Unexpected Role of Rare Disorders

Elliott MD, **Rasouly HM**, **Gharavi AG**

Hundreds of different genetic causes of chronic kidney disease are now recognized, and while individually rare, taken together they are significant contributors to both adult and pediatric diseases. Traditional genetics approaches relied heavily on the identification of large families with multiple affected members and have been fundamental to the identification of genetic kidney diseases. With the increased utilization of massively parallel sequencing and improvements to genotype imputation, we can analyze rare variants in large cohorts of unrelated individuals, leading to personalized care for patients and significant research advancements. This review evaluates the contribution of rare disorders to patient care and the study of genetic kidney diseases and highlights key advancements that utilize new techniques to improve our ability to identify new gene-disease associations.

The impact of genetic education on referral of patients to genetic evaluation: Findings from a national survey of nephrologists

Milo Rasouly H, Balderes O, Marasa M, Fernandez H, Lipton M, Lin F, **Gharavi AG**, Sabatello M

The success of genomic medicine hinges on implementation of genetic knowledge in clinical settings. In novel subspecialties, it requires that clinicians refer patients to genetic evaluation or testing, but referral is likely to be impacted by genetic knowledge. 201 nephrologists completed the survey. All reported treating patients with genetic forms of kidney disease, but 37% have referred less than 5 patients to genetic evaluation. A third had limited basic genetic knowledge. Most nephrologists (85%) reported concerns regarding future health insurance eligibility as a barrier to referral to genetic testing. Most adult nephrologists reported insufficient genetic education during residency (65%) and fellowship training (52%). Lower rating of genetic education and lower knowledge in recognizing signs of genetic kidney diseases were significantly associated with lower number of patients referred to genetic evaluation (p-value<0.001). Most nephrologists reported that improving their genetic knowledge is important for them (>55%). The conclusion showed that there is a need to enhance nephrologists' genetic education to

increase genetic testing utilization in nephrology.

Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial

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Primary hyperoxaluria type 1 (PH1) is a rare genetic disease characterized by excessive hepatic oxalate production that frequently causes kidney failure. Lumasiran is an RNA interference therapeutic that is administered subcutaneously for the treatment of PH1. Lumasiran has been shown to reduce oxalate levels in the urine and plasma of patients with PH1 who have relatively preserved kidney function. In the ILLUMINATE-C study, the efficacy and safety of lumasiran were evaluated in patients with PH1 and advanced kidney disease, including a cohort of patients undergoing hemodialysis. During the 6-month primary analysis period, lumasiran resulted in substantial reductions in plasma oxalate with acceptable safety in patients with PH1 complicated by advanced kidney disease. Lumasiran resulted in substantial reductions in POx with acceptable safety in patients with PH1 who have advanced kidney disease, supporting its efficacy and safety in this patient population.

Primary Hyperoxaluria Type 3

Milliner DS, Harris PC, Sas DJ, **Lieske JC**

Primary hyperoxaluria type 3 (PH3) is characterized by recurring calcium oxalate stones beginning in childhood or adolescence and, on occasion, nephrocalcinosis or reduced kidney function. PH3 most often presents in childhood (median age 2 to 3 years) with signs or symptoms related to stones including hematuria, frequent urination, dysuria, blood visible in the urine, or stone-associated pain. Some individuals with PH3 do not present until adulthood, usually with stone-related symptoms or findings. Over time, frequent stones and/or nephrocalcinosis may compromise kidney function, resulting in chronic kidney disease. To date, systemic oxalosis has not been reported in PH3.

PROSTATE

Impact of the bladder detrusor muscular ring on lower urinary tract symptoms due to benign prostatic hyperplasia: A quantitative MRI analysis

Nandalur KR, Walker D, Ye H, Al-Katib S, Seifman B, Gangwish D, Dhaliwal A, Connor E, Dobies K, Sesoko C, Dejoie W, **Zwaans B**, Nandalur S, Nguyen J, Hafron J

The etiology of lower urinary tract symptoms secondary to benign prostatic hyperplasia (LUTS/BPH) remains uncertain. The purpose of our study was to quantitatively analyze anatomic characteristics on magnetic resonance imaging (MRI) to assess novel independent factors for symptoms. This retrospective single-institution study evaluated treatment-naïve men who underwent prostate MRI within 3 months of international prostate symptom score (IPSS) scoring from June 2021 to February 2022. Factors measured on MRI included: size of the detrusor muscular ring (DMR) surrounding the bladder outlet, central gland (CG) mean apparent diffusion coefficient (ADC), levator hiatus (LH) volume, intrapelvic volume, intravesicular prostate protrusion (IPP) volume, CG volume, peripheral zone (PZ) volume, prostate urethra angle (PUA), and PZ background ordinal score. Multivariable logistic regression and receiver operating characteristic analysis were used to analyze factors for moderate/severe (IPSS ≥ 8) and severe LUTS/BPH (IPSS ≥ 20). Expansion of the DMR surrounding the bladder outlet is a novel anatomic factor independently associated with moderate and severe LUTS/BPH, taking into account prostate volumes, including quantified IPP volume, which were unrelated. Detrusor ring diameter, easily and reliably measured on routine prostate MRI, may relate to detrusor dysfunction from chronic stretching of this histologically distinct smooth muscle around the bladder neck.

Steroid hormone imbalance drives macrophage infiltration and Spp1/osteopontin+ foam cell differentiation in the prostate

Popovics P, **Skalitzky KO**, **Schroeder E**, Jain A, **Silver SV**, Van Fritz F, Uchtmann KS, **Vezina CM**, **Ricke WA**

Benign Prostatic Hyperplasia (BPH) occurs progressively with aging in men and drives deteriorating symptoms collectively known as Lower Urinary Tract Symptoms (LUTS). Age associated changes in circulating steroid hormones, and prostate inflammation have been postulated in the etiology of BPH/LUTS. The link between hormones and inflammation in the development of BPH/LUTS is conflicting because they may occur independently or as sequential steps in disease pathogenesis. This study aimed to decipher the prostatic immune landscape in a mouse model of lower urinary tract dysfunction (LUTD). Steroid hormone imbalance was generated by the surgical implantation of testosterone (T) and estradiol (E2) pellets into male C57BL/6J mice and gene expression analysis was performed on ventral prostates (VP). These experiments identified an increase in the expression of macrophage markers and Spp1/osteopontin (OPN). Localization studies of OPN pinpointed that OPN+ macrophages travel to the prostate lumen and transition into lipid accumulating foam cells. We also observed a significantly increase in number of tissue macrophages in the VP which was prevented in OPN knockout (OPN-KO) mice. In contrast, mast cells, but not macrophages, were significantly elevated in the dorsal prostate of T+E2 treated mice which was diminished in OPN-KO mice. Steroid hormone implantation progressively increased urinary frequency, which was ameliorated in OPN-KO mice. Our study underscores the role of age associated steroid hormone imbalances as a mechanism of expanding the prostatic macrophage population, their luminal translocation and foam cell differentiation.

Toxicoproteomics of Mono(2-ethylhexyl) phthalate and Perfluorooctanesulfonic Acid in Models of Prostatic Diseases

Thomas S, **Ricke WA**, Li L

Benign and malignant prostatic diseases are common, costly, and burdensome; moreover, they share fundamental underlying molecular processes. Several ubiquitous contaminants may perturb these processes, possibly via peroxisome proliferator-activated receptor (PPAR) signaling, but the role of environmental exposures–particularly mixtures–in prostatic diseases is undefined. In the present study, nontumorigenic prostate stromal cells and metastatic prostate epithelial cells were exposed to ubiquitous exogenous PPAR ligands under different dosing paradigms, including a mixture, and effects were assessed via mass spectrometry-based global proteomics. In prostate stromal cells, environmentally relevant levels of mono(2-ethylhexyl) phthalate (MEHP), alone and in combination with perfluorooctanesulfonic acid, led to significant changes in proteins involved in key processes underlying prostatic diseases: oxidative stress defense, proteostasis, damage-associated molecular pattern signaling, and innate immune response signaling. A follow-up experiment in metastatic prostate epithelial cells showed that the occupationally relevant levels of MEHP perturbed similar processes, including lipid, cholesterol, steroid, and alcohol metabolism; apoptosis and coagulation regulation; wound response; and aging. This work shows that environmental exposures may contribute to prostatic diseases by perturbing key processes of a proposed adverse outcome pathway, including lipid metabolism, oxidative stress, and inflammation. Future in vivo research will investigate the role of contaminants in prostatic diseases and in preventative agents.

STONES

Pediatric Nephrolithiasis

Cao B, Daniel R, McGregor R, **Tasian GE**

The prevalence of pediatric nephrolithiasis has increased dramatically in the past two decades for reasons that have yet to be fully elucidated. Workup of pediatric kidney stones should include metabolic assessment to identify and address any risk factors predisposing patients to recurrent stone formation, and treatment should aim to facilitate stone clearance while minimizing complications, radiation and anesthetic exposure, and other risks. Treatment methods include observation and supportive therapy, medical expulsive therapy, and surgical intervention, with choice of treatment method determined by clinicians' assessments of stone size, location, anatomic factors, comorbidities, other risk factors, and preferences and goals of patients and their families. Much of the current research into nephrolithiasis is restricted to adult populations, and more data are needed to better understand many aspects of the epidemiology and treatment of pediatric kidney stones.

Ureteral Stent Placement Prior to Definitive Stone Treatment is Associated with Higher Post-Operative Emergency Department Visits and Opioid Prescriptions for Youth Having Ureteroscopy or Shockwave Lithotripsy

Tasian GE, Maltenfort MG, Rove K, Ching CB, Ramachandra P, DeFoor B, Fernandez N, Forrest CB, **Ellison JS**

Little is known about the impact of ureteral stents on youth having stone surgery. We evaluated the association of ureteral stent placement before or concurrent with ureteroscopy (URS) and shockwave lithotripsy (SWL) with emergency department (ED) visits and opioid prescriptions among pediatric patients. We conducted a retrospective cohort study of individuals aged 0-24 years who underwent URS or SWL from 2009-2021 at 6 hospitals in PEDSnet, a research network that aggregates electronic health record data from children's health systems in the United States. The exposure, primary ureteral stent placement, was defined as a stent placed concurrent with or within 60 days before URS or SWL. Associations between primary stent placement and stone-related ED visits and opioid prescriptions within 120 days of the index procedure were evaluated with mixed-effects Poisson regression. The conclusion showed that primary ureteral stent placement was associated with more frequent ED visits and opioid prescriptions, driven by pre-stenting. These results support elucidating situations where stents are not necessary for youth with nephrolithiasis.

- Jennifer Allmaras MPH, Muen Wang, 2/28/2023

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