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UROTHELIAL DYSFUNCTION AND SENSORY PROTEIN EXPRESSIONS IN PATIENTS WITH UROLOGICAL OR SYSTEMIC DISEASES AND HYPERSENSITIVE BLADDER

Hypothesis / aims of study
To investigate the underlying pathophysiology in the urothelium of different lower urinary tract diseases (LUTDs) and in patients with systemic diseases and overactive bladder (OAB) or hypersensitive bladder (HSB), including chronic inflammation, barrier proteins, and sensory functional receptors.

Study design, materials and methods
A total of 156 patients, including 14 with idiopathic OAB, 11 with detrusor overactivity and inadequate contractility (DHIC), 19 with end-stage renal disease (ESRD) and HSB, 26 with spinal cord injury (SCI) and detrusor overactivity (DO), 23 with bladder outlet obstruction (BOO) and DO, 19 with diabetes mellitus (DM) and OAB, 20 with interstitial cystitis (IC), and 16 with ketamine cystitis (KC) were investigated for urothelial dysfunction and sensory protein expressions. All subjects had urodynamically proven DO or increased bladder sensation on video urodynamic studies. The bladder biopsy tissues were investigated for urothelial dysfunction and functional receptor expressions. The variables were compared between the various types of bladder dysfunction and controls.

Results
All patient subgroups had significant increases in mast cell activation and apoptotic cell counts and a decrease in E-cadherin expression. P2X3 expression was significantly decreased in DHIC but was significantly increased in BOO/DO. Urothelial M3 expression was significantly increased in patients with OAB, BOO/DO, DM/OAB, and KC. M2 expression was significantly decreased in DHIC but increased in patients with BOO/DO. β3-AR expression was significantly decreased in patients with OAB and increased in patients with DHIC, ESRD/HSB, DM/OAB, and KC. Patients with OAB and BOO/DO had significantly increased M2/β3-AR. Lower M2/β3-AR was associated with lower voiding efficiency and large PVR in DHIC, ESRD/HSB, and SCI/NDO.

Interpretation of results
Patients with LUTDs and non-urological diseases and bladder overactivity or hypersensitivity showed increased urothelial inflammation and lower barrier protein expressions. The urothelial muscarinic receptors and β3-AR expression were also altered. Increased M3/β3-AR or M2/β3-AR is associated with OAB, whereas decreased M3/β3-AR or M2/β3-AR is associated with poor voiding efficiency and large PVR volume. These changes of urothelial expression contributed to sensory disorders in the bladder storage phase and affected detrusor contractility. Treatment of bladder hypersensitivity or low voiding efficiency in these LUTDs might target at the altered receptor ratio.

Concluding message
Patients with OAB or HSB showed increased urothelial inflammation and lower barrier protein expression. Increased M3/β3-AR or M2/β3-AR in the urothelium was associated with OAB, whereas decreased M3/β3-AR or M2/β3-AR was associated with poor voiding efficiency and large PVR in LUTD.

Table 1. Muscarinic receptor M3 and M2 and β_3-AR adrenoceptor expression in the urothelium of the urinary bladder in patients with different lower urinary tract diseases and controls

LUTD (n)	M3	M2	β_3-AR	M3/β_3	M2/β_3
Control (10)	0.24±0.23	0.31±0.43	0.37±0.19	0.90± 1.36	0.87± 1.33
OAB (14)	0.90±0.61*	0.58±0.68	0.24±0.25*	9.83±10.9*	5.02± 4.93*
Control (10)	1.55±1.03	1.22±0.59	0.57±0.48	3.44±2.28	4.03±4.45
DHIC (11)	0.82±0.35	0.56±0.62*	0.86±0.30*	1.08±0.51*	0.61±0.57*
Control (10)	1.55±1.03	1.22±0.59	0.57±0.48	3.44± 2.28	4.03± 4.45
ESRD/HSB(19)	1.57±1.89	1.61±1.96	1.55±1.0*	0.88± 0.70*	0.85± 1.13*
Control (10)	1.55± 1.03	1.22±0.59	0.57± 0.48	3.44± 2.28	4.03± 4.45
SCI/NDO (26)	0.37± 0.27	0.79± 0.65	0.78± 0.54	0.69± 0.71*	1.38± 1.35*
Control (10)	1.59±0.70	0.41±0.30	0.88±0.58	2.15± 1.42	0.61± 0.55
BOO/DO (23)	0.70±0.31*	1.07±1.18*	0.86±0.27	0.86± 0.50*	1.42± 1.65*
Control (10)	0.24±0.23	0.31±0.43	0.37±0.19	0.90± 1.36	0.87± 1.33
DM/OAB (19)	0.84±0.56*	0.41±0.59	0.86±0.66*	3.06± 5.96*	0.51± 0.46
Control (19)	1.92± 2.23	1.53± 1.83	0.84± 1.10	3.08± 1.82	3.72± 3.83
IC (20)	0.60±0.32*	1.13± 0.42	0.70± 0.40	1.64± 1.89*	2.64± 2.67
Control (10)	0.14±0.93	0.12±0.21	1.06±0.13	0.12± 0.07	0.11± 0.18
KC (16)	0.81±0.46*	0.18±0.21	2.41± 1.79*	0.47± 0.38*	0.12± 0.17

DA: detrusor areflexia, DHIC: detrusor overactivity and inadequate contractility, ESRD: end-stage renal disease, SCI: spinal cord injury, BOO: bladder outlet obstruction, DO: detrusor overactivity, OAB: overactive bladder, DM: diabetes mellitus, IC: interstitial cystitis, KC: ketamine related cystitis.
*Indicates significant difference from the control.

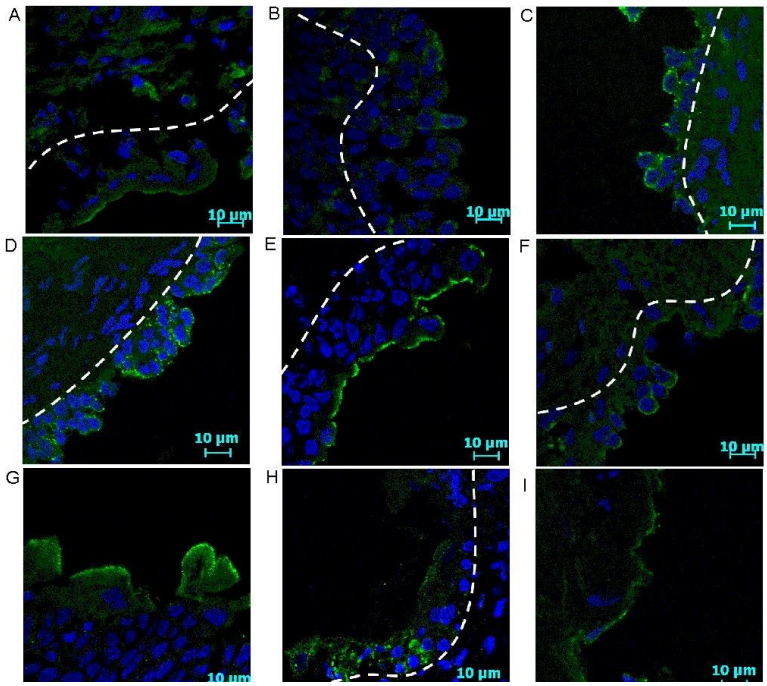

Fig.1. Confocal immunofluorescence microscopy of the β_3-adrenoceptors in the patients with: (A) a normal bladder, (B) overactive bladder, (C) detrusor overactivity and inadequate contractility, (D) end-stage renal disease and hypersensitive bladder (E) spinal cord injury and detrusor overactivity, (F) bladder outlet obstruction and detrusor overactivity, (G) diabetes mellitus and overactive bladder, (H) interstitial cystitis, and (I) ketamine cystitis. White lines represent basement membrane of the uroepithelium. Green color indicates immunofluorescent staining of the β_3-adrenoceptors.

Disclosures
Funding: none **Clinical Trial:** Yes **Public Registry:** No **RCT:** No **Subjects:** HUMAN **Ethics Committee:** Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation **Helsinki:** Yes **Informed Consent:** Yes