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UROTHELIAL DYSFUNCTION, SUBUROTHELIAL INFLAMMATION, AND ALTERED SENSORY PROTEIN EXPRESSION IN MEN WITH BLADDER OUTLET OBSTRUCTION AND VARIOUS BLADDER DYSFUNCTIONS: CORRELATION WITH URODYNAMICS

Hypothesis / aims of study
Bladder outlet obstruction (BOO) causes significant transformation of the morphology and physiology of the urinary bladder. At present, the evidence for urothelium sensory proteins playing a role in bladder dysfunction caused by BOO is mainly based on animal studies. This study investigated urothelial integrity, suburothelial inflammation, and expression of sensory proteins in bladder urothelium of male patients with BOO and various bladder dysfunctions.

Study design, materials and methods
We prospectively enrolled 33 men with urodynamically proven BOO (study group). Bladder biopsies were obtained from all study patients and 10 control patients. The expressions of E-cadherin, zonula occludens-1, tryptase, and apoptosis, and TRPV1, TRPV4, β3 adrenoreceptor, M2, and M3 muscarinic receptors, P2X3 receptor, and inducible/epithelial nitric oxide synthase were compared between study and control patients.

Results
Study patients had significantly lower expression of E-cadherin and higher suburothelial mast and apoptotic cell numbers than controls did (Table 1). Additionally, higher expressions of P2X3 and M2 muscarinic receptors and lower expression of M3 muscarinic receptor were detected in the study patients. Detrusor underactivity subgroup was characterized by significantly higher expression of β3 adrenoreceptors and lower expression of inducible nitric oxide synthase than in controls. In study patients, significantly positive correlation was noted between voided volume and E-cadherin expression ($r = 0.372$), volume at first sensation of filling and expression of β3 adrenoreceptor ($r = 0.386$), and detrusor pressure and expression of M2 muscarinic receptor ($r = 0.496$) in the bladder urothelium (all $p < 0.05$) (Fig. 1).

Interpretation of results
BOO affected the urothelial integrity and altered the sensory receptor expression within the bladder mucosa in both the urothelium and suburothelium. This resulted in various bladder dysfunctions. In BOO, the afferent bladder sensation, which was altered and augmented by purinergic and muscarinic mechanisms, could be responsible for DO/HSB development. Impaired bladder sensory transduction or modulation through β-3 adrenoreceptors and the NOS pathway contributed to the development of DU.

Concluding message
Urothelial dysfunction, suburothelial inflammation, cellular apoptosis, and alterations of sensory proteins are prominent in bladder dysfunction secondary to BOO. Impaired urothelial signaling and sensory transduction pathways appear to reflect the pathophysiology of bladder dysfunction and detrusor underactivity in patients with BOO.

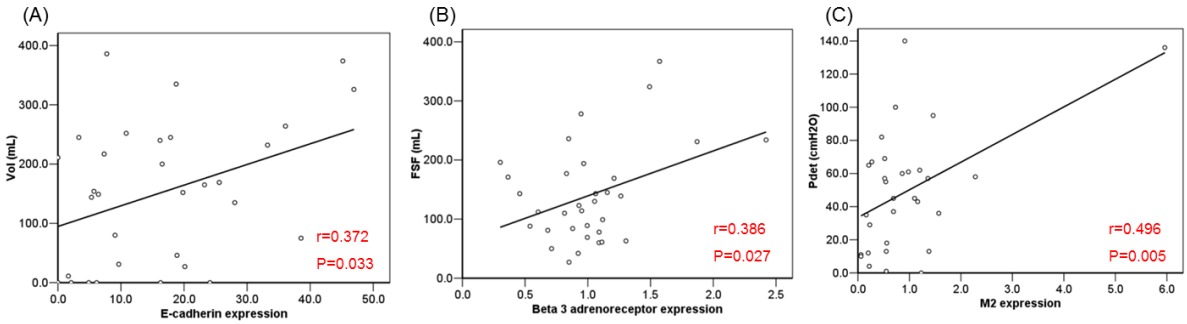

Fig. 1. Correlations of VUDS parameters and sensory proteins in the bladder urothelium of BOO patients. (A) Correlation of voided volume (Vol) and E-cadherin expression. (B) Correlation of the volume of the first sensation of filling (FSF) and β-3 adrenoreceptor expression. (C) Correlation of voiding detrusor pressure (Pdet) and M2 muscarinic receptor expression.

Table 1. Demographic, immunofluorescence, western blotting, and video urodynamic study parameters in BOO patients and control

	Control (n=10)	BOO				
		Overall (n=33)	DO/HSB (n=23)	DU (n=10)	P value[1]	P value[2]
Age	64.6±11.45	68.5 ±11.1	69.0±11.6	67.5±10.5	0.258	0.764
IF findings						
E-cadherin	27.70±10.42	15.93±13.20	18.85±13.60	9.21±9.57*	0.015	0.038
Tryptase	4.16±2.68	15.12±7.89	16.11±6.16*	12.84±10.96	0.000	0.652
TUNEL	0.85±1.31	2.64±2.57	2.47±2.41*	3.03±3.01	0.028	0.844
Western blotting						
ZO-1	6.90±1.82	7.83±3.98	7.29±2.58	9.08±6.14	0.358	0.570
TRPV 1	0.131±0.070	0.139±0.096	0.137±0.102	0.145±0.084	0.840	0.695
TRPV 4	0.188±0.286	0.155±0.243	0.152±0.249	0.164±0.241	0.565	0.570
iNOS	0.258±0.325	0.171±0.332	0.219±0.389	0.062±0.039*	0.128	0.147
eNOS	0.094±0.088	0.104±0.096	0.119±0.107	0.071±0.058	0.885	0.254
P2X3	0.097±0.109	0.257±0.206	0.247±0.145*	0.278±0.315*	0.001	0.456
β3	0.878±0.584	1.012±0.415	0.864±0.269	1.35±0.499*	0.289	0.009
M2	0.405±0.303	0.912±1.043	1.073±1.184*	0.558±0.490	0.041	0.108
M3	1.593±0.708	0.797±0.342	0.703±0.308*	1.013±0.330*	0.000	0.024
M2/ M3	0.313±0.280	1.371±1.610	1.691±1.796*	0.634±0.685	0.001	0.012
VUDS						
FSF (mL)		140.2±81.8	115.2±53.98	197.8±106.9		0.042
FS (mL)		242.5±146.9	190.8±80.3	361.5±195.7		0.025
CBC (mL)		316.0±143.5	284.8±114.6	387.7±181.3		0.036
Pdet (cmH_2O)		48.9±36.0	60.5±33.4	15.6±18.9		0.002
Qmax (mL/s)		5.58±4.68	7.74±3.93	0.60±0.84		0.000
Vol (mL)		152.0±119.6	198.7±101.8	32.8±68.8		0.000
PVR (mL)		175.4±178.8	88.3±89.9	398.0±155.1		0.000

*P value < 0.05 versus control.

[1]P values between control and overall BOO patients.

[2]P values between DO/HSB and DU groups within BOO.

BOO, bladder outlet obstruction; DO/HSB, detrusor overactivity/ hypersensitivity bladder; DU, detrusor underactivity; FSF, first sensation of bladder filling; FS, full sensation; CBC, cystometric bladder capacity; Pdet, detrusor voiding pressure; Qmax, maximal urinary flow rate; Vol, voided volume; PVR, post-void residual volume

Disclosures

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