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URINARY BIOMARKERS IN PATIENTS WITH DETRUSOR UNDERACTIVITY WITH AND WITHOUT BLADDER FUNCTION RECOVERY

Hypothesis / aims of study
Detrusor underactivity (DU) is frequently encountered in elderly patients with chronic medical disease or neurological diseases. The pathophysiology of DU may involve neurogenic, myogenic and bladder outlet pathologies. Part of patients with DU might have bladder function recovery after treament. This study investigated the urinary proteins in these patients in comparison with patients with detrusor overactivity (DO), detrusor hyperactivity and inadequate contractility (DHIC), and patients with normal urodynamic tracing.

Study design, materials and methods
A total of 374 men with mild to moderate LUTS were initially treated with alpha-blocker A total of 37 patients with chronic urinary retention and urodynamically proven DU were enrolled. After medical or surgical treatment, 24 DU patients had bladder function recovery whereas 13 had not, after one-year follow-up. Urine collection at baseline was performed and the urinary protein including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and prostaglandin E2 (PGE2) were measured by ELISA. Twenty urodynamically normal, 34 DO and 15 DHIC patients served as comparative groups.

Results
A total of 106 patients were enrolled in this study, including 37 with DU, 34 with DO, 15 DHIC and 20 normal tracing. The age and gender distribution are listed in Table 1. The age of patients with DHIC was significantly older than the other groups. Among patients with DU, 17 had chronic urinary retention and the others had large PVR requiring indwelling Foley catheter or clean intermittent catheterization. As expected, patients with DO had earlier perception of bladder fullness, urgency sensation and bladder capacity, higher Pdet and smaller PVR than patients with DHIC and DU. Patients with DHIC and DU had similar volume of bladder sensation and capacity, Qmax, voided volume and PVR, however, Pdet was significantly lower in patients with DU than DHIC (Table 1). When we divided patients with DU into bladder function recovery and non-recovery group, there was no significant difference in the baseline urodynamic parameters between groups (Table 2). In DU patients with bladder function recovery, the urinary levels of BDNF and PGE2 were significantly higher than the normal group (153.4 ± 199.1 v 77.4 ± 47.7, $p = 0.033$; 971.4 ± 811.4 v 525.3 ± 269.3, $p < 0.0001$, respectively). The urinary NGF and BDNF levels in the recovery DU group were similar to, but PGE2 was significantly higher than non-recovery group (1290 ± 836.3 v 382.8 ± 237.0, $p = 0.001$) or DO group (1290 ± 836.3 v 740.8 ± 597.1, $p = 0.020$).

Interpretation of results
In this study we found urinary NGF levels were significantly increased in patients with DU, DHIC and marginal elevated in DO. However, no significant difference of urinary NGF was noted between DU patients with and without bladder function recovery. Although NGF is associated with nerve regeneration, this protein might not act as a biomarker to predict bladder function recovery in DU bladders. Interestingly, we found urinary BDNF level was significantly elevated in patients with DU but not in DHIC and DO. The urinary BDNF level in DU patients with bladder function recovery was significantly higher than that in the control group and patients without recovery. These results suggest that urinary BDNF might be a better biomarker to predict bladder function recovery in patients with DU. Increase of urinary NGF and BDNF levels not only reflect the increase of protein secretion under pathological conditions, but also is seen in part of DU patients with bladder function recovery, suggesting a process of nerve regeneration is undergoing. The results of this study revealed that urinary PGE2 was significantly elevated in patients with DU, DHIC and marginal elevated in DO. Patients with DU and bladder function recovery had significantly higher urinary PGE2 level than patients without recovery and DO, suggesting the factors contributing to detrusor contractility are not completely lost in these bladders. The highly secreted PGE2 in DU bladders might reflect a compensatory response to certain bladder pathological conditions causing temporary low detrusor contractility. Through increase of PGE2 secretion from the urothelium or detrusor patients with DU may regain detrusor contractility gradually. Measurement of baseline urinary PGE2 level might predict the recovery of bladder function in patients with DU.

Concluding message
Patients with DU had significantly elevated urinary NGF, BDNF and PGE2 levels. DU patients with bladder function recovery had significantly higher urinary PGE2 and BDNF levels. Among the three urinary proteins, PGE2 provides the most prognostic value for bladder function recovery in patients with DU. Urinary protein levels provide prognostic value of bladder function and dysfunction.

Table 1. The urinary biomarkers and urodynamic parameters in different study groups

	Normal (N= 20)	DO (N= 34)	DHIC (N= 15)	DU (N= 37)	P value
Male/Female	8/12	23/11	9/6	12/25	
Age	61.8± 11.5	72.5±13.6	80.5±8.59	68.1±15.4	0.016
Urine proteins					
NGF (pg/mL)	1.85±2.9	6.1±13.5	10.3±16.1	9.2±20.3	0.655
BDNF(pg/mL)	77.4±47.7	97.7±88.6	99.1±109	153±199	0.242
PGE2 (pg/mL)	525±269	741±597	992±607	971±811	0.313
Urodynamics					
FSF (mL)	148±55.4	74.9±44.5	142±123	175±98.4	0.000
FS (mL)	254±94.9	128±70.5	189±117	260±125	0.000
US (mL)	310±119	146±90.6	220±164	324±136	0.000
Compliance	98.9±62.3	63.7±56.9	64.0±97.3	74.5±95.0	0.850
Pdet(cmH_2O)	15.2±8.2	43.9±36.9	17.5±14.2	9.53±11.8	0.000
Qmax(mL/s)	17.1±9.24	8.57±5.6	4.33±3.56	3.88±4.66	0.001
PVR (mL)	41.7±55.7	42.1±78.1	281±310	321±200	0.000
Volume(mL)	318±204	184±156	114±127	112±148	0.126
CBC (mL)	359±174	226±154	395±312	421±160	0.001

NGF: nerve growth factor, BDNF: brain derived neurotrophic factor, PGE2: prostaglandin E2, FSF: first sensation of filling, FS: full sensation, US: urge sensation, Pdet: detrusor pressure, Qmax: maximum flow rate, PVR: post-void residual, CBC: cystometric bladder capacity, DO: detrusor overactivity, DU: detrusor underactivity, DHIC: detrusor hyperactivity and inadequate contractility

Table 2. The urinary biomarkers and urodynamic parameters in normal and detrusor underactivity with and without bladder function recovery

	Normal (N= 20)	DU recovery (N= 24)	DU non-recovery (N= 13)	P value
Age	61.8± 11.5	71.5±10.8	61.7±20.4	0.986
Urine proteins				
NGF (pg/mL)	1.85±2.9	7.85±14.57	11.7±28.5	0.239
BDNF(pg/mL)	77.4±47.7	190± 239	85.8±43.7	0.612
PGE2(pg/mL)	525±269	1290±836	383±237	0.130
Urodynamics				
FSF (mL)	148±55.4	163±93.5	195±108	0.195
FS (mL)	254±94.9	241±133	297±105	0.304
US (mL)	310±119	313±158	345±84.6	0.503
Compliance	98.9±62.3	80.9±113	62.4±47.8	0.121
Pdet(cmH_2O)	15.2±8.2	10.7±13.3	6.89±7.29	0.027
Qmax (mL/s)	17.1±9.24	3.82±4.13	4.0±5.81	0.001
PVR (mL)	41.7±55.7	309±216	342±178	0.000
Volume (mL)	318±204	126±136	87±174	0.008
CBC (mL)	359±174	420±186	389±160	0.660

Disclosures

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