

UROTHELIAL DYSFUNCTION AND PROTEIN EXPRESSIONS IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE AND DIFFERENT SENSORY DYSFUNCTION

Hypothesis / aims of study

Patients with chronic kidney disease (CKD), and end-stage renal disease (ESRD) frequently present with bladder dysfunction in terms of low capacity, low compliance and also high incidence of detrusor overactivity (DO). Previous study reported the cause may be due to the vessel diseases among CKD/ESRD patients such as subclinical multiple cerebral infarctions, diabetes mellitus and arteriosclerosis which may induce DO. Urothelial dysfunction is a reason and also a possible pathophysiology for lower urinary tract dysfunction which may induce a vicious cycle. However, it is still little evidence to correlate the urothelium function with low urinary tract symptoms in CKD/ESRD patients. This study is to investigate the relationships between urothelial dysfunction and sensory protein expressions in CKD/ESRD patients compared with normal controls.

Study design, materials and methods

Immunofluorescence staining of E-cadherin, zonula occludens-1 (ZO-1), tryptase for mast cell activation), and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) for urothelial apoptosis tests on bladder biopsy specimens were performed in 20 CKD/ESRD patients and 10 controls. Other sensory proteins including purinergic and muscarinic receptors (P2X3, M2, M3), β 3-adrenoceptor, endothelial nitric oxide synthases (eNOS) were determined by Western blot and immunohistochemistry.

Results

There were totally twenty patients with CKD/ESRD (including 9 CKD, and 11 ESRD patients) with a mean age of 54.85 ± 13.11 enrolled in this study. Ten other women with stress urinary incontinence with a mean age of 52.4 ± 10.51 without DO served as the controls. In immunofluorescence staining, patients with CKD/ESRD had significantly lower expression of E-cadherin (22.05 ± 22.74) vs control group (41.3 ± 8.4) ($P=0.024$). No specific difference was found in the suburothelial inflammation of activated mast cells, apoptotic cell numbers, and tight junction protein ZO-1 (Table 1). In Western blot and immunohistochemistry study, muscarinic receptor M3 was significantly higher in ESRD groups (4.75 ± 3.95) compared with control group (1.47 ± 1.07) and CKD group (1 ± 1.23) ($P=0.003$). P2X3 receptor expression was lower in CKD/ESRD group (0.87 ± 0.88) vs control group (1.66 ± 1.17) ($P=0.039$). On the other hand, β 3-adrenoceptor was significantly higher in CKD/ESRD groups (1.58 ± 0.97) compared with control group (0.46 ± 0.56) ($P=0.008$). M2 receptors and eNOS did not show significant differences between each group.

Interpretation of results

In this study, CKD/ESRD patients revealed lower E-cadherin expression, which was associated with bladder sensation and junctional function impairment of the urothelium. No evidence of increased inflammatory and apoptosis process was detected by immunofluorescence staining. On the other hand, M3 receptor was highly expressed in CKD/ESRD, which may be associated with detrusor hypertonicity in the CKD/ESRD with a contracted bladder. Interestingly, β 3-adrenoceptor was significantly higher in CKD/ESRD patients. Until now, the role of β 3-adrenoceptor in the urothelium is still unclear. Further study to correlate with clinical lower urinary tract dysfunction and urodynamic study is needed to clarify this issue.

Concluding message

This is the first study to investigate the urothelial dysfunction and sensory protein expressions in CKD/ESRD patients. These preliminary data may provide evidence for the pathophysiology of low urinary tract dysfunction in CKD/ESRD patients.

Table 1. The expression of E-cadherin, activated mast cells, apoptosis (TUNEL), and zonula occludens-1 (ZO-1) in the controls and CKD/ESRD patients

	Normal (N=10)	CKD&ESRD (N= 20)	CKD (N= 9)	ESRD (N=11)	P-value
E-cadherine	41.3 ± 8.4	22.05 ± 22.74	20.33 ± 17.22	23.45 ± 27.22	0.024
Mast-cell	5.9 ± 4.92	8.43 ± 6.68	8.75 ± 7.02	8.18 ± 6.72	0.683
TUNEL	1 ± 1.35	2.19 ± 1.92	3.04 ± 1.82	1.5 ± 1.79	0.057
ZO-1	6.37 ± 1.72	4.43 ± 3.29	4.62 ± 3.53	4.28 ± 3.25	0.145

Table 2. The expression of proteins of M2, M3, P2X3, eNOS, β 3 in uroethial cells in the controls and CKD/ESRD patients

	Normal (N= 10)	CKD&ESRD (N= 20)	CKD (N=9)	ESRD (N=11)	P-value
M2	1.22 \pm 0.59	2.43 \pm 2.41	1.38 \pm 1.85	3.28 \pm 2.55	0.105
M3	1.47 \pm 1.07	3.06 \pm 3.54	1 \pm 1.23	4.75 \pm 3.95*	0.003
P2X3	1.66 \pm 1.17	0.87 \pm 0.88	0.84 \pm 1.13	0.89 \pm 0.67	0.09
eNOS	0.34 \pm 0.17	0.27 \pm 0.27	0.23 \pm 0.29	0.3 \pm 0.27	0.427
β 3	0.46 \pm 0.56	1.58 \pm 0.97	1.37 \pm 0.85	1.75 \pm 1.07	0.008

Disclosures

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