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UROTHELIAL DYSFUNCTION AND CHRONIC INFLAMMATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE – A CLINICAL AND HISTOPATHOLOGICAL STUDY

Hypothesis / aims of study
Patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) are at risk of urinary tract infection (UTI) and have bladder irritative symptoms. Knowledge about the change of bladder urothelium in patients with CKD or ESRD is limited. The aim of this study was to evaluate the change of the urothlium in bladder between the patients with CKD or ESRD and the normal variants by histopathological parameters.

Study design, materials and methods
All adult patients with CKD or ESRD with or withour voiding dysfunction, who admitted to our urologic inpatient ward of a tertiary referral centre, underwent videourodynamic study (VUDS) and bladder biopsy, were included retrospectively in this study. The normal variants were the patients with normal renal function defined as estimated glomerular filtration rate greater than 60ml/min received bladder biopsy by other demand. The patients with symptomatic UTI with febrile episode were excluded. The voiding dysfunction was evaluated by VUDS was classified into detrusor underactivity (DU) and detrusor overacitivity (DO) based on the definition by International Incontinence Society. The specimens were prepared in immunohistochemistry (IHC) protocols to mark E-cadherin, tryptase and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). We analyzed and compared the strength of the signals of the three markers between the patients with CKD or ESRD and the normal variants.

Results
A total of forty-seven patients were included in this study. Twenty-seven patients with CKD or ESRD and the other twenty were normal variants. The mean age was 59.2±15.0 and 57.9±11.7 years, respectively. The comparative data in three IHC markers, E-cadherin, tryptase, and TUNEL was tabulated in Table 1. The expression level of tryptase was higher in CKD/ESRD patients than the normal variants (8.45±6.88 vs 3±2.83, p=0.001) as well as of the TUNEL assay (1.96±1.86 vs 0.49±0.99, p=0.001). In the subgroups of patients with CKD/ESRD classified as DU and DO, the expression of E-cadherin was lower in patients with CKD/ESRD and DU than in the normal variants (14.7±25.5 vs 38.4±19.2, p=0.013). Instead of in patients with CKD/ESRD and DU, in those with DO had higher expression of tryptase (8.42±6.73 vs 3±2.83, p=0.003) and TUNEL assay than in the normal variants (2.38±1.95 vs 0.49±0.99, p=0.01).

Interpretation of results
We successfully utilize three IHC markers, E-cadherin, tryptase, and TUNEL to demonstrate the differences in urinary bladder urothelium between the patients with CKD/ESRD and the normal variants: Higher expression of tryptase from mast cell indicates higher prevalence of chronic inflammation in patients with CKD/ESRD than that in the normal variants. Interestingly, it shows different trend in the expression of TUNEL and E-cadherin in the subgroups of patients with DU and DO that may imply higher urothelial apoptosis activity in CKD/ESRD patients with DO. The lower expression of E-cadherin and lower apoptotic cells in DU patients may suggest less bladder sensation and low bladder contractility. The defective urothelial function in DU patients might also contribute to the higher prevalence of urothelial metaplasia or oncogenesis in Taiwanese ESRD patients. However, it's restricted by limited markers and small size of patient number.

Concluding message
Urothelail dysfunction and chronic inflammation are highly prevalent in CKD/ESRD patients. In the patients with CKD/ESRD, diffetrent urothelial dysfunction was noted between DO and DU. The clinical implication of this didfference deserves further investigation.

Table 1. The expression of E-cadherin, tryptase and TUNEL in the urothelium of CKD/ESRD patients

	Normal (n=20)	CKD/ESRD (n=27)	CKD/ESRD with DU (n=8)	CKD/ESRD with DO (n=19)	p
E-cadherin	38.4±19.2	27.1±26	14.7±25.5	32.3±25.1	0.107 0.013* 0.39
Tryptase	3±2.83	8.45±6.88	8.52±7.71	8.42±6.73	0.001* 0.085 0.003*
TUNEL	0.49±0.99	1.96±1.86	0.96±1.23	2.38±1.95	0.001* 0.292 0.01*

†Values were expressed as n (individual number), mean±standard deviation.
‡CKD: chronic kidney disease; ESRD: end-stage renal disease; DO: Detrusor overactivity; DU: detrusor underactivity; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling. * p<0.05 manifested statistical significance.

Disclosures
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