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The Urine Urokinase Concentration in End Stage Renal Disease with Acquired Renal Cyst

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To see whether there was any difference in the urine urokinase concentration between acquired cystic kidney disease (ACKD) group and control (non cyst) group in end stage renal disease patients (ESRD), we evaluated fifty ESRD patients who had been maintained on chronic hemodialysis for various period. The urine urokinase concentration was higher in the ACKD group (17.5±14.7 unit/ml, range 13.5~47.0 unit/ml, n=9) than the control group (4.1±3.4 unit/ml, range 0.5~12.0 unit/ml, n=36) (p<0.001), and polycyst group (2.6±1.8 unit/ml, range 1.0~5.1 unit/ml, n=5) (p<0.01).

But there was no difference between the control group and polycyst group. In the control group and the ACKD group, there was a direct relation between the dialysis duration and the urokinase concentration and the longer the dialysis duration, the higher the urine urokinase concentration (r squared=0.424, p=0.0001). The hemodialysis duration was longer in the ACKD group (42±17.0 months) than the control group (20.0±12.5 months) (p<0.005). These findings suggest that urokinase may be responsible for cystogenic degeneration in ESRD.

Key Words: *Urine urokinase concentration, End Stage Renal Disease (ESRD), Acquired Cystic Kidney Disease (ACKD)*

INTRODUCTION

It is generally accepted that acquired cystic kidney disease (ACKD) is a natural consequence of long standing end stage renal disease (ESRD) regardless of its underlying disease[1]. Recent reports about ACKD arouse clinician's interest because it often lead to the complication of hemorrhage and it appear to increase the incidence of association with renal malignancy[1~3]. However, the mechanism leading to cyst formation in ESRD remain uncertain[3,4]. Urokinase is a serine protease cleave the peptide bond Arg-560-Val-561 of plasminogen to produce plasmin which is the main component of the fibrinolysis system[5,6].

It is also known that urokinase plays an important role in extravascular fibrinolysis such as tissue remodeling, cell migration[7~9] and degradation of the structural protein[10,11]. The urokinase production in the kidney is so great that the concentration in the urine is several times higher than in the

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plasma[12~14].

Recently, we reported[15] that, as the renal mass decreases during the progression of ESRD, regardless of its underlying diseases, the remnant nephrons produce a larger amount of urokinase than the normal nephrons. With this result, if renal tubules were exposed to relatively high concentrations of urokinase, it might accelerate the cystogenic degenerative change of the renal tubules. This study was undertaken to see whether there is any difference in urine urokinase concentration between the ACKD group and non cyst (control) group in ESRD.

METHOD

1. Patients

Fiffy ESRD patients who had been maintained on chronic hemodialysis at Soonchunhyang university Chunan hospital for various periods of between 4 months and 70 months were chosen for this study. Causes for the underlying disease were various and ages ranged between 20 and 68 years old. The details of underlying diseases and sex distribution are summarized in Table 1.

2. Detection of Renal Cyst

Sonogram for the detection of renal cyst was performed by a radiologist (one of the authors of this study), using the 3.5 MHz linear and conex transducer (ALOKA SSD-270). Special attention was paid to rule out hydronephrosis and adult type polycystic kidney disease from ACKD.

3. Urokinase Activity

The urine urokinase activity was measured by a chromogenic peptide substrate, S-2444[16]. 100 ul of urine, from 24 hours urine collection and standard urokinase in PBS were allowed to react with a defined amount of colorless substrate, S-2444 to release the colored p-nitroaniline which is measured spectrophotometrically at 405 nm. The absorbance was converted to urokinase activity (unit/ml) by the standard curve constructed from standard urokinase (product of Korean Green Cross CO.) in PBS.

4. Urokinase Concentration

It was derived from the following equation;

$$\text{urokinase activity (unit/ml)} \times \frac{\text{urine osmolarity}}{\text{plasma osmolarity}}$$

Our preliminary study showed that the urokinase activity was stable at room temperature for several weeks.

5. Statistics

Datas are expressed as mean±one standard daviation of mean. Difference of urine urokinase concentration, dialysis duration and urine volume between groups were evaluated by the Mann-Whitney U test (between 2 groups), through the software stativew 512+ (Brain power, calabasas, CA) operating on a Macintosh PC. Statistical significance was considered to be present if $p<0.05$.

RESULTS

Out of fifty patients, nine patients have ACKD, five patients had polycystic renal disease (underlying disease of ESRD) and there was no cyst in thirty six patients (control group). TIhe cyst (ACKD) was single in six cases, unilateral in eight cases and the diameter was less than 2 cm in ten cases(Table 2).

The duration of hemodialysis was 42.2±17.0 month (range 19~70 months) in the ACKD group, 39.0±10.3 months (range 24~54 months) in the

Table 1. Underlying Diseases and Sex Distribution of the Cases

Underlying dz	Male	Female	Total No.
CGN	6	4	10
Hypertension	2	–	2
DM	4	2	6
Cystic dz	4	1	5
Unknown	11	16	27
Total No.	27	23	50

Table 2. Characteristics of the Cyst in ACKD

	2 cm >	2 cm <
Unilateral		
Single	4	1
Multiple	2	–
Bilateral		
Single	–	–
Multiple	2	0
Total No.	8	1

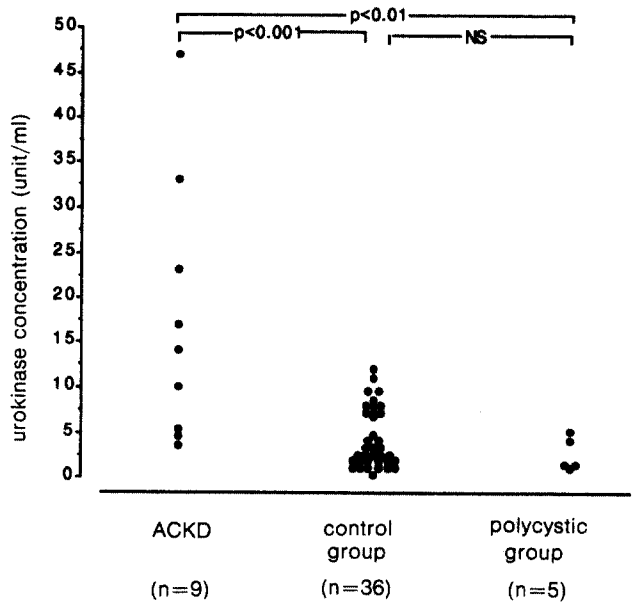

Fig. 1. *Urine urokinase concentration in ACKD group, control group and polycystic group. It is higher in the ACKD group than the control group and The polycystic group.*

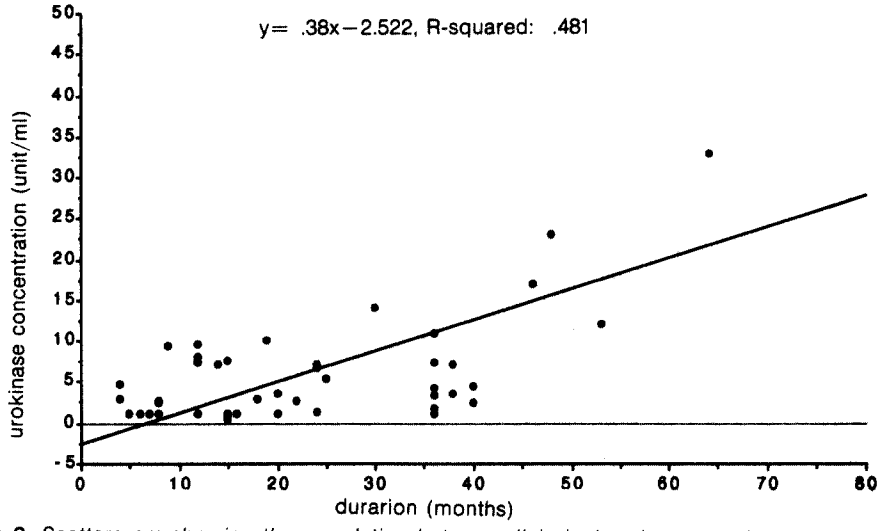

Fig. 2. *Scattergram showing the correlation between dialysis duration and urine urokinase concentration. The longer the dialysis duration the higher the urine urokinase concentration (p=0.0001)*

polycyst group, and 20.0±12.5 months (range 4 ~53 months) lin the control group. It was longer in ACKD group than the control group ($p<0.005$).

The 24 hour urine volume was 181±131 ml (range 50~400 ml) in the ACKD group, 450±250 ml (range 100~800 ml) in the polycyst group, and 697±472 ml (range 100~1,500 ml) in the control group. It was smaller in ACKD group than contro group ($p<0.001$) and polycyst group ($p<0.05$).

The urine osmolality was 323.3±59.1 mOsm/L

(range 250~429 mOsm/L) in ACKD group, 311.2±53.1 mOsm/L (range 237~520 mOsm/L) in control group, 366.3±70.6 mOsm/L (range 286~419 mOsm/L) in polycyst group. There was no difference of urine osmolality between groups.

The urine urokinase concentration was 17.5±14.7 unit/ml (range 3.5~47 unit/ml) in the ACKD group, 2.6±1.8 unit/ml (range 1.0~5.1 unit/ml) in the polycyst group and 4.1±3.4 unit/ml (range 0.5~12.0 unit/ml) in the control group. It was higher in the ACKD group than the polycyst group ($p<0.01$) and control group ($p<0.001$), but there was no difference between the control group and polycyst group(Fig. 1).

The urine urokinase concentration showed a direct relation with hemodialysis duration and the longer the dialysis duration, the higher the urine urokinase concentration (r squared=0.424, $p=0.0001$) (Fig. 2).

DISCUSSION

Three hypotheses which exist for the mechanism of cyst formaiton in adult polycystic kidney disease[17] may be applid to ACKD; 1) tubular obstuction due to epithelial hyperplasia with subsequent elevated transmural pressure leading to tubular dilatation; 2) increased tubular basement membrane compliance with tubular dilatation at normal transmural pressure leading to tubular dilatation; 3) increased radial growth of epithelial cells and basement membrane due to an unknown stimulus, resulting in dilatation in parts of the tubules.

There have been many reports supporting these hypothesis in ACKD[18~25], but non are coinclusive. Ishikawa et al[26] reported two cases of ACKD which regressed after renal transplation; one recurred when the graft failed. This finding support a role for the uremic milieu or hemodialysis in the genesis of acquired cystic disease.

But there is good evidence that tubule obstruction could occur in ACKD, by epithelial hyperplasia[19], intraluminal casts[1], calcium oxalate deposits[27] or tubular atrophy and associated interstitial fibrosis[1]. Whether tubule basement membrane compliance is increased in ACKD is unknown. If the increased compliance of basement membrane were the important factor for cystic degeneration in ACKD, possible factos suggested in literature, are hyperfiltration in remnant nephrons[28], acute and chronic renal ischemia[3], compensatory renal growth factor[3], abnormal hormone level[3], uremic toxin and some exogenous substance introduced by hemodialysis procedure[18,20,29,30].

Urinary plasminogen activator is principally urokinase which is not filtered but is mainly produced in tubular epithelial cells[31] and act on its main substrate plasminogen to produce plasmin. Considering that urokinase play an important role in tissue remodeling, cell migration[7~9], and structural protein destruction[10,11] and ACKD arises from renal tubule of ESRD, the urokinase concentration in the tubule might be a cystogenic factor in some situation. The urokinase production was reported to decrease in ESRD[32,33]. Recently we found[15] that as the GFR decreases, total urokinase in urine decreases, but the total urokinase divided by GFR (total u-PA/Ccr) increases abruptly when the GFR falls below 25L/day. This finding suggests that as the renal mass decrease, remnant nephron produce larger amount of urokinase than do normal nephron.

Even in ESRD, as long as urine formation is continued, there may be functioning nephrons on the way to functional loss. The deterioration of renal function will reach the point at which urine volume will be zero due to complete renal loss. We believe that this is the reasoin for decreased urine volume and longer duration of dialysis in ACKD group in our study. During this period, the tubules face a higher concentration of urokinase than the tubules of normal nephrons, and the longer the duration of ESRD (hemodialysis), the higher the expected urokinase concentration.

Our results show that the ACKD group had a higher concentration of urokinase and longer duration of hemodialysis than the control group.

With this concept, transformation of the control group into the ACKD group after some period of dialysis during which, remnant nephron produces much more urokinase is expected. Higher urokinase concentration in the ACKD group might be a result rather than a cause of ACKD. But there was no difference in the between the polycyst group and control group. This finding suggests that the increased urine urokinase concentration in the ESRD is rather the cause of ACKD than the result of ACKD.

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