SHORT COMMUNICATION

Utility of serum creatinine/cystatin C ratio in diagnosis of postrenal acute kidney injury

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Background: In obstructive uropathy, despite a severe increase in the serum creatinine (Cr) levels, only a mild cystatin C (CysC) increase was previously reported. Therefore, we aimed to determine the availability of serum Cr/CysC ratio in predicting postrenal acute kidney injury (AKI). **Materials and Methods:** This was a cross-sectional study involving 61-adult patients with heterogeneous AKI cases. Patients with bilateral pelvicalyceal dilatation in renal sonography were considered as postrenal AKI group (n = 15) and others were intrinsic AKI group (n = 46). Venous blood sampling for blood urea nitrogen, Cr and CysC measurements were performed on admission. **Results:** The mean age of study population was 66.3 ± 15.5 years; 38 (62%) of which were male. Two groups were similar regarding age, gender, and comorbidities. Cr/CysC ratio was significantly higher in postrenal AKI group (6.9 ± 3.1 vs. 4.4 ± 2.1, P = 0.007). **Conclusion:** We suggest that serum Cr/CysC ratio seems to be a useful diagnostic tool for detection of postrenal AKI cases, especially for the cases without definite hydronephrosis.

Key words: Acute kidney injury, creatinine/cystatin C ratio, cystatin C, obstructive uropathy, postrenal acute kidney injury

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INTRODUCTION

Acute kidney injury (AKI) is a common complication, particularly seen in hospitalized patients, and it increases the mortality rates independent from other factors despite significant advances in medical care.[1-3] Serum creatinine (Cr) is a commonly used marker for estimation of the glomerular filtration rate (GFR); nevertheless, serum Cr is known to be influenced by a number of factors such as age, gender, and muscle mass. Serum cystatin C (CysC) was suggested as an alternative molecule in estimating GFR due to its favorable properties.[4] CysC is less affected by, gender, age, and muscle mass than serum Cr. Its positive charge at physiological pH and lower molecular weight make its glomerular filtration easier, and it is reabsorbed and catabolized in the proximal renal tubule.[5,6] Accordingly, some studies have reported that CysC is more sensitive in determining mild reductions in renal function than serum Cr.[7,8]

However, this seems to be valid in mainly prerenal and intrinsic renal causes of AKI. In cases of postrenal AKI, despite a severe increase in the serum Cr levels, only a mild CysC increase was reported.[9,10] Postrenal AKI usually can be diagnosed by ultrasonic evaluation or computerized tomography scanning. Nevertheless, there may be sophisticated cases without clear hydronephrosis despite postrenal AKI such as retroperitoneal fibrosis.[11] In such confusing cases, the discrepancy between CysC and Cr seems to be useful for supporting diagnosis. Therefore, in the present study we aimed to determine the availability of serum Cr/CysC ratio in predicting postrenal AKI.

MATERIALS AND METHODS

Patients and general characteristics

This was a cross-sectional study involving 61 adult patients (38 men, 23 women) with heterogeneous AKI cases. Patients who were diagnosed as AKI by a consultant nephrologist during their follow-up in different inpatient clinics and patients, who were admitted to the emergency clinic with signs or symptoms of AKI between April and November, 2013 were included to the first evaluation. The patients were scored for AKI using the Cr, and urine output criteria of the AKI network classification system[12] and the diagnosis was established based on these criteria.

As postrenal AKI cases tended to be consist of elderly, patients under age of 30 were excluded in order to avoid heterogeneity between groups. Patients whose renal functions improved in the 1st day of follow-up

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were accepted to be prerenal AKI, and those cases were excluded. Based on the previous reports suggesting that these conditions may be associated with increased or decreased serum CysC levels independent of renal function, we also excluded patients with hyperthyroidism or hypothyroidism, and patients receiving steroid or thyroid hormone therapy.[13-15] In addition, patients whose baseline renal functions could not be documented were also excluded from the study. Finally, 61 AKI patients were enrolled to further investigation. These patients were divided into two groups based on the renal ultrasound evaluation. Of note, at admission some of the patients (6 out of 15) who were subsequently considered as postrenal AKI did not show a definite hydronephrosis in renal sonography. Patients showing bilateral pelvicalyceal dilatation in repeated renal ultrasound evaluations in the period of their clinical follow-up were allocated to postrenal AKI group (n = 15). Others having no signs of urinary obstruction in ultrasound imaging were allocated to intrinsic AKI group (n = 46). Postrenal AKI patients entered the study were all incident obstructive uropathy patients. Afterwards, comparisons were made between these two study groups.

This trial was conducted in accordance with the principles of Helsinki and Istanbul declarations. The study protocol was approved by the local medical Ethics Committee (SDUTF-KAEK/10.04.2013-109) and written informed consents were obtained from all patients or their authorized representatives. Baseline characteristics and medical history of the participants were acquired from hospital records.

Laboratory measurements

Venous blood sampling for blood urea nitrogen, Cr and CysC measurements were performed during admission or at the time of diagnosis of AKI. Samples were centrifuged at 3000 rpm for 10 min. The supernatants were stored at –80°C until the assay. Serum Cr was measured by a modified Jaffe method with protein precipitation. CysC was measured with Human ELISA Cystatin C kit (Biovendor Research and Diagnostic Products, Cat. No: RD191009100, Germany) by the particle enhanced immune - nephelometric method.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 18.0 for Windows (SPSS Inc., Chicago, IL). For the presentation of measurable continuous variables; mean and standard deviation were used. Frequencies and percentages were used while presenting the categorical data. For variables which met parametric test conditions, Student's t-test and for others Mann — Whitney U-test were used for two group comparisons. For the evaluation of categorical variables, Chi-square test and if needed, Fisher's exact test were used. All probability values were calculated by assuming a two - sided $P < 0.05$ with confidence intervals at the 95% level.

RESULTS

The mean age of study population (n = 61) was 66.3 ± 15.5 years; 38 (62%) of which were male. When the patients were divided into two groups as postrenal AKI (n = 15) and intrinsic AKI (n = 46), study groups were similar regarding age, gender and comorbidities of the patients. Postrenal AKI patients tended to be elderly, but the difference did not reach statistical significance (71.3 ± 15.1 vs. 64.6 ± 15.4, P = 0.15). The demographical characteristics and descriptive data of the study groups are shown in Table 1.

Etiologies of AKI for the postrenal AKI group were; bladder carcinoma in 3 out of 15, urolithiasis (bilateral obstruction) in 5 out of 15 and prostatic hyperplasia in the rest 7 patients. For the intrinsic AKI group, the etiology of AKI was mainly acute tubular necrosis (ATN). Based on clinical evaluation, 6 of them were accepted as contrast induced nephropathy, 19 of them were accepted as toxic ATN probably caused by antibiotics (colistin, amikacin), nonsteroid antiinflammatory drugs (diclofenac, flurbiprofen, naproxen sodium) and antineoplastic agents (cisplatin). Etiologies of AKI for the remaining 21 out of 46 intrinsic AKI patients were hypovolemia (prolonged dehydration, massive diarrhea), septic shock and acute cardiorenal syndrome.

Laboratory results of the study participants are shown in Table 2. Serum Cr level was significantly higher in postrenal AKI group compared with intrinsic AKI group, and CysC level was similar between two groups. Cr/CysC ratio was found to be significantly higher in postrenal AKI group (6.9 ± 3.1 vs. 4.4 ± 2.1, P = 0.007).

Table 1: Baseline characteristics of the study groups

	Postrenal AKI	Intrinsic AKI	*P*
Number of patients	15	46	–
Age (years)	71.3±15.1	64.6±15.4	0.15
Gender (male/female)	9/6	29/17	0.83
Weight (kg)	72.2±12.3	77.7±18.3	0.36
Height (m)	166.0±7.6	166.2±9.9	0.95
Body mass index (kg/m^2)	26.0±2.6	27.9±5.3	0.25
Body surface area (m^2)	1.77±0.19	1.86±0.21	0.23
Comorbidities			
Diabetes mellitus (*n*, %)	5 (33)	17 (37)	0.80
Hypertension (*n*, %)	10 (67)	28 (61)	0.68
Coronary artery disease (*n*, %)	6 (40)	9 (20)	0.11

Values are expressed as mean ± SD or number and (%); AKI = Acute kidney injury; SD = Standard deviation

Table 2: Laboratory findings of the study groups

	Postrenal AKI	Intrinsic AKI	*P*
Number of patients	15	46	–
Baseline Cr (mg/dL)	1.08±0.24	1.03±0.22	0.42
BUN (mg/dL)	61.1±20.8	56.4±26.6	0.54
Cr (mg/dL)	5.2±2.5	3.8±2.2	0.03
CysC (ng/mL)	0.79±0.27	0.88±0.25	0.29
Cr/Cysc ratio	6.9±3.1	4.4±2.1	0.007

Cr = Creatinine; CysC = Cystatin C; BUN = Blood urea nitrogen; AKI = Acute kidney injury; SD = Standard deviation; Values are expressed as mean ± SD

DISCUSSION

In the presented study, we primarily aimed to determine the utility of serum Cr/CysC ratio in discriminating postrenal kidney failure from other etiologies of AKI. According to our results, despite similar results for CysC levels, Cr/CysC ratio was found to be significantly higher in postrenal AKI group compared to intrinsic renal AKI patients, thus confirming our hypothesis.

Cystatin C is freely filtered from glomeruli; nearly all is reabsorbed and metabolized by the proximal tubular cells. Therefore, CysC seems to be a better surrogate marker of GFR than serum Cr when its cellular production was accepted to be constant.[5,6] In this context, CysC has been reported to have a significant clinical potential as a biomarker of AKI in clinical studies. In a study of 85 critically ill-patients at risk of developing AKI, increases in serum CysC were demonstrated to predict AKI 1 or 2 days before serum Cr increased.[16] Consistent with this, Villa *et al*. reported that CysC is better than Cr for assessing critically ill patients since only 20% of patients were found to have elevated serum Cr levels, whereas 76% of them had elevated serum CysC levels.[7] In another prospective study of 72 adult patients with cardiac surgery, elevation in urinary CysC levels at the 6th h of Intensive Care Unit (ICU) admission was shown to be a significant predictor of AKI.[17] On the other hand unlike these studies, in a more recent multicenter study in a heterogeneous ICU population, serum CysC and urinary CysC were reported to be poor biomarkers for AKI.[18]

The studies reporting the superiority of serum CysC over Cr in diagnosing AKI earlier are mainly conducted on prerenal or intrinsic causes of AKI. In the case of prerenal or intrinsic renal AKI, CysC cannot even reach glomeruli and, therefore, cannot be filtered and reabsorbed by tubular cells. As a result, CysC cannot be metabolized by tubular cells in intrinsic renal or prerenal AKI, and it increases at a nearly similar rate of the elevation of Cr.[10] Okuda *et al*. has first reported in a Japanese article that, the Cr/CysC ratio in subjects with postrenal AKI was significantly higher than that in subjects with intrinsic renal failure.[19] In addition, recently presented case reports with postrenal AKI reported small increases in serum CysC levels in spite of severely impaired renal functions.[9,10]

It is speculated by Okuda *et al*. that, as Cr is charged neutrally, the permeation of positively charged CysC is may be easier than that of Cr through glomerular basement membrane.[19] Another speculation for this discrepancy was made by Tsuda *et al*. based on an animal study. They suggested that, because nearly all of the glomerular filtrate of CysC is reabsorbed by the tubules, adequate reabsorption in the proximal tubule may lead to a certain amount of degradation of CysC in the early phases of bilateral ureteral obstruction.[20] However, as it is not reabsorbed and metabolized by tubular epithelium, filtered Cr would be returning into the bloodstream because of tubular back leak and contributing to increased serum Cr.[21] Supporting these speculations, the maintenance of glomerular filtration and proximal tubular reabsorption of CysC for a long time after the interruption of Cr excretion seemed to be also involved in our cases of postrenal AKI.

In the case of obstructive uropathy, after complete cessation of Cr excretion, for how long is glomerular filtration and tubular reabsorption of CysC maintained? It cannot be exactly known, but Tsuda *et al*. proposed to be about 48 h based on their rat model of bilateral ureteral obstruction.[20] Fujisawa *et al*. suggested this time to be several days.[10] Our findings support the suggestion of Fujisawa, because the postrenal AKI patients in the present study probably needed more than 3 or 4 days to reach a mean Cr level of 5.2 mg/dL. Of note, 3 out of 15 postrenal AKI patients had Cr levels exceeding 8.5 mg/dL while CysC levels were only at the upper limit of the normal range.

In daily clinical practice, postrenal AKI can usually be easily diagnosed by ultrasonic imaging or computed tomography scans. However, there may be cases without apparent hydronephrosis despite postrenal AKI especially in the earlier phases of obstruction.[22] In the present study as previously mentioned some of our patients with postrenal AKI did not have a clear hydronephrosis on admission. We could achieve to diagnose them in the following days with repeated renal sonography. In such challenging cases, the disparity between CysC and Cr may be a useful tool, and we suggest that the predictive ability of Cr/CysC ratio seems to be strong in earlier discrimination of postrenal failure from other etiologies of AKI.

There were several limitations of our study. First limitation was the somewhat small number of the study patients. Unfortunately, a considerable number of patients could not be included because of the strict exclusion criteria. Second, this study was of cross-sectional design and lacks long-term clinical follow-up. Hence, we cannot say

anything about the predictive value of Cr/CysC ratio on recovery rates of obstructive uropathy. In addition, we did not know the exact time that urinary obstruction occurred. We collected the venous samples as soon as we evaluated and diagnosed patients as AKI; however they probably had urinary obstruction for several days.

CONCLUSION

We suggest that serum Cr/CysC ratio seems to be a useful diagnostic tool for detection of postrenal AKI cases especially for the cases without definite hydronephrosis. As far as we know, higher serum Cr/CysC ratio in postrenal AKI cases was first demonstrated in a clinical study by Okuda *et al*. and it was reported in Japanese.[19] Our results confirm the findings of the previous study[19] and previous case reports.[9,10] However, this suggestion has to be investigated in a larger randomized-controlled study.

AUTHOR'S CONTRIBUTION

SI and MTS carried out the design and coordinated the study, participated in most of the experiments. SI prepared the manuscript. VK, AA and AÖ provide assistance in the design of the study, coordinated and carried out all the experiments. MTS participated in manuscript preparation and finally revised the manuscript. YI provided assistance for all experiments. All authors have read and approved the content of the manuscript.

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