Serum Uromodulin Is a Possible Auxiliary Diagnostic Tool for Acute Tubular Injury and Acute Interstitial Nephritis: A Case Series

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Abstract
Recently, the usefulness of serum uromodulin (sUmod) as a novel renal biomarker has been attracting attention. Clinical evidence regarding sUmod measurements has been accumulated by analyzing cross-sectional data. However, little is known about the longitudinal data on sUmod. Therefore, we decided to investigate the variability of sUmod in patients with acute kidney injury due to different causes. High concentrations of sUmod have been observed in patients with acute tubular injury (ATI) and/or acute interstitial nephritis (AIN). sUmod could be used as an auxiliary diagnostic tool for ATI and AIN.

Introduction
Serum uromodulin (sUmod) levels in subjects with stable physical conditions have a good correlation with estimated glomerular filtration rate (eGFR) and can be a novel renal biomarker [1, 2]. We additionally conducted a clinical study using a custom-made ELISA and reported similar results [3]. However, little is known about the fluctuation of sUmod levels.
El-Achkar et al. [4] reported changes in sUmod in a mouse model of acute kidney injury (AKI). However, it is unknown how sUmod levels fluctuate in human cases of AKI.

Uromodulin is a protein exclusively expressed in tubular epithelial cells, and almost all of it is released into the urine by proteolytic cleavage. The derivation of sUmod has not been fully elucidated; however, two mechanisms have been documented to date. The first is the back-leakage mechanism: a portion of urinary UMOD back leaks from the intraluminal area to the interstitial region via the intercellular space of the tubular epithelium and enters the circulation via blood vessels in the interstitium [5]. The second is the secretion mechanism; a portion of intracellularly processed uromodulin migrates to the basement membrane and is secreted into the interstitial region and enters the circulation via blood vessels in the interstitium [2, 4]. These mechanisms suggest that tubulointerstitial conditions would affect sUmod concentration.

### Case Report

#### Materials and Methods

sUmod was measured using a custom-made ELISA [3]. To help readers understand the relationship between sUmod levels and eGFR values in subjects with stable renal function, a comparison table based on previous reports is shown in Table 1. Additional information is provided in online supplementary information (for all online suppl. material, see www.karger.com/doi/10.1159/000523855).

#### Case 1

A 70-year-old man was treated for type 2 diabetes mellitus, hyperlipidemia, and hypertension. He was receiving the following medications: saxagliptin, ipragliflozin, rosuvastatin, irbesartan/trichlormethiazide, atenolol, and omeprazole. In January, he was admitted for rhabdomyolysis (creatine kinase [CK] 85,528 IU/L) and AKI (creatinine [Cr] 2.44 mg/dL). His renal function just before this episode was Cr 0.9 mg/dL and eGFR 64 mL/min/1.73 m². Although therapeutic infusion was initiated, oliguria persisted. He was then transferred to our hospital on the second day of hospitalization. Laboratory data on admission to our hospital showed CK 91,880 IU/L, myoglobin 50,250 ng/mL, Cr 4.74 mg/dL, urine α1-microglobulin (MG) 4.4 mg/L (normal range <8), and N-acetyl-β-D-glucosaminidase (NAG) 3.4 IU/L (normal range <11). sUmod on admission was 366.1 ng/mL, which seemed high compared to the value estimated from eGFR just prior to this episode. It then reached 585.7 ng/mL on the seventh hospital day. Therapeutic infusions improved the patient’s condition. sUmod gradually decreased and stabilized at approximately 90 ng/mL (Fig. 1; online suppl. Table S1).

### Table 1. Median sUmod concentrations in eGFR stages

| CKD stage | Median sUmod concentration, ng/mL |
|-----------|----------------------------------|
| Non-CKD   | 257.7                            |
| eGFR ≥ 90 | 256.3                            |
| 90 > eGFR ≥ 60 | 248.3       |
| 60 > eGFR ≥ 45 | 165.9       |
| 45 > eGFR ≥ 30 | 119.3       |
| 30 > eGFR ≥ 15 | 56.7        |
| 15 > eGFR  | 32.9                             |

References: Usui et al. [3], Fedak et al. [1], Scherberich et al. [2]

ELISA kit: Custom-made BioVendor EUROIMMUN AG
Case 2
A 73-year-old man was on medication for hypertension. His occupation was gardening. His appetite had gradually decreased since early August, and later in the same month, he collapsed at an outdoor work site. He was admitted due to heatstroke and prerenal AKI (oliguria, Cr 8.66 mg/dL, fractional excretion of sodium [FeNa] 0.5%, and fractional excretion of urea nitrogen 12%). Tubular injury markers were not assessed. His recent renal function just before this episode was Cr 0.8–0.9 mg/dL and eGFR 65–75 mL/min/1.73 m². sUmod on admission was 195 ng/mL, which was comparable to the value estimated from eGFR just before this episode. Therapeutic infusion rapidly improved renal function and sUmod declined for a while, then turned upward and recovered to the same level as at the time of admission (Fig. 2; online suppl. Table S2).

Case 3
(Fig. 3; online suppl. Table S3) An 84-year-old woman had a thoracolumbar compression fracture in May. She was prescribed tiaramide, loxoprofen, and eldecalcitol for back pain and osteoporosis, but her pain persisted. The nerve block temporarily relieved her pain. In November, although she was administered 1,500 mg/day acetaminophen, her condition
gradually worsened, and she was admitted for orthopedic surgery. On the day of admission, AKI was confirmed (Cr 0.88 mg/dL and eGFR 46.2 mL/min/1.73 m² in October, and Cr 8.05 mg/dL on admission), and she was transferred to our hospital to undergo hemodialysis. There was mild edema in the lower limbs, but no inferior vena cava collapse and oliguria. An FeNa of 8% was observed. Postrenal and prerenal AKI were ruled out, and renal AKI was suspected. Tubular injury markers were as follows: α1-MG 10.3 mg/L and NAG 15.0 IU/L. sUmod on admission was 787 ng/mL, which was very high compared to the value estimated from eGFR just before this episode, which then reached 897 ng/mL on the third hospital day. Positive results of gallium scintigraphy (Fig. 3a) and drug-induced lymphocyte stimulation test for acetaminophen were confirmed. She was diagnosed with AKI due to drug-induced allergic acute interstitial nephritis (AIN). After discontinuing the suspected drug, acetaminophen, renal function improved, and withdrawal from hemodialysis was achieved. However, because the Cr level did not improve well, steroid pulse therapy was performed, and both Cr and sUmod decreased (Fig. 3b).

Case 4
(Fig. 4; online suppl. Table S4) A 58-year-old man with no history of illness. On a recent physical examination, his renal function was Cr 1.0 mg/dL and eGFR 60.5 mL/min/1.73 m². In April, he developed fever, cough, and nausea and was prescribed loxoprofen, rebamipide, and mosapride, but his symptoms persisted. Later, he was admitted to our hospital because of pneumonia and AKI (Cr 10.52 mg/dL) and underwent hemodialysis. Because there were no signs of dehydration, oliguria, and FeNa 1.3%, postrenal and prerenal AKI were ruled out, and renal AKI was suspected. Urinary findings were unremarkable (protein ±, occult blood ±, white blood cells [-]). Tubular injury markers were as follows: α1-MG, 17.3 mg/L and NAG, 16.4 IU/L. sUmod on admission was 1,218 ng/mL, which was extremely high compared to the value estimated from eGFR just before this episode. On the day of admission, rhabdomyolysis (CK 15,344 IU/L, myoglobin 11,610 ng/mL) and several bruises on his extremities due to a fall from a bicycle were observed. The cause of rhabdomyolysis is thought to be traumatic and/or drug-induced. Negativity for the drug-induced lymphocyte stimulation test and
positivity for gallium scintigraphy (Fig. 4a) were observed. Respiratory symptoms improved immediately with meropenem, but a fever of 38°C and high CRP persisted (37.7 mg/dL on admission and 35.53 mg/dL on the fourth hospital day). Since AIN was thought to be the cause of AKI, high fever, and elevated CRP, steroid pulse therapy was administered. He achieved rapid resolution of fever, improvement of CRP levels, and renal function; thus, hemodialysis was discontinued. A renal biopsy performed after withdrawal from hemodialysis showed severe tubular damage and focal inflammatory cell infiltration in the interstitium (Fig. 4b) compatible with acute tubular injury (ATI) and AIN. sUmod decreased with improvement in renal function and stabilized at approximately 250 ng/mL.

**Case 5**

(Fig. 5; online suppl. Table S5) A 41-year-old woman had not undergone a medical checkup for more than 10 years. She started taking several supplements (details unknown) in November. In March of next year, she visited a dermatologist because of a generalized skin...
rash with severe desquamation and significant lower limb edema and was diagnosed with erythroderma, nephrotic syndrome (urinary protein 12.9 g/gCr, total protein 5.0 g/dL, albumin 0.9 g/dL, and marked generalized edema), with impaired renal function (Cr 5.96 mg/dL). She was admitted and underwent hemodialysis. Minimal change disease (MCD) was suspected to be the cause of nephrotic syndrome, but she did not consent to steroid use. Moreover, she had severe anemia (Hb 8.3 g/dL) on admission, which subsequently decreased to 5.6 g/dL. On the tenth hospital day, renal biopsy performed after blood transfusion showed advanced ATI/AIN (Fig. 5b). Tubular injury markers were markedly elevated (α1-MG 94.5 mg/L and NAG 73.4 IU/L). sUmod on admission was 478.9 ng/mL and reached 1,336 ng/mL on the 21st hospital day. Based on skin rash, elevated tubular injury markers, renal biopsy findings, and positivity for gallium scintigraphy (Fig. 5a), she was diagnosed with nephrotic syndrome due to MCD complicated with AIN/ATI. On the 30th hospital day, she consented to steroid use. Administration of steroids improved renal function immediately, and the patient was withdrawn from hemodialysis. sUmod decreased in association with improvement in renal function and stabilized at approximately 400 ng/mL.

**Discussion**

To the best of our knowledge, this is the first report of longitudinal data on sUmod in human AKI cases. sUmod levels were positively correlated with eGFR values. However, sUmod levels in patients with AKI were not consistent with renal function. Based on this discrepancy, the possible utility of sUmod measurement is discussed.

Case 1 was a case of AKI due to rhabdomyolysis. Myoglobin, an endogenous protein with strong tubular toxicity, causes ATI but not glomerular injury or AIN. The increase in sUmod levels in the early phase of ATI was consistent with that reported by El-Achkar et al. [4]. In contrast, as shown in Table 1, post-treatment sUmod levels seemed to be lower. The sUmod level is thought to reflect the surviving nephron mass [1–3]. If advanced ATI leads to irreversible tubular damage and a permanent decrease in UMOD protein expression, the sUmod level may be lower than that estimated from eGFR. Knowing the sUmod value of the patient pre-AKI, sUmod measurement may help to evaluate the number of nephrons lost due to AKI and the treatment given for AKI.

Case 2 was a case of AKI due to dehydration; that is, prerenal AKI. Delayed renal reperfusion results in ATI, and its severity affects the recovery of renal function and AKI sequelae. The therapeutic strategy for prerenal AKI is to promote rapid renal reperfusion to avoid progression to ATI. In this case, the sUmod levels on admission and after treatment were similar. If the sUmod level prior to the onset of AKI is known, sUmod measurement may possibly help determine whether or not to proceed to ATI. In other words, it may be concluded that Case 1 progressed to ATI, but Case 2 did not.

Case 3 was a case of allergic AIN caused by acetaminophen. Although normal doses of acetaminophen do not cause toxic ATI, they can cause allergic AIN [6]. A positive result of gallium scintigraphy is strongly suggestive of AIN, but not ATI [7]. The polypharmacy trend has raised concerns about the increasing number of drug-induced kidney injuries. Toxic ATI and allergic AIN are important causes of drug-induced kidney injuries; however, it is not easy to diagnose AIN. In most cases of AIN, urinary finding abnormalities are insignificant, and the classic triad (fever, rash, and eosinophilia) is reported to be present in less than 10% of cases [8]. Recently, urinary TNF-α and IL-9 have been proposed as diagnostic biomarkers for AIN [9]. In addition, sUmod may contribute to the safety monitoring of drug use.

Case 4 was a case of drug-induced allergic AIN and rhabdomyolysis-caused ATI complicated by bacterial pneumonia, while Case 5 was a case of nephrotic syndrome due to MCD.
complicated by ATI/AIN. ATI and AIN in both cases were confirmed by renal biopsy. Based on post-treatment sUmod levels, high sUmod levels were found in the early stages of ATI/AIN. In Case 5, as in Case 2, the sUmod levels on admission and after treatment were similar. The failure of immediate steroid administration was thought to have resulted in prolonged ATI/AIN.

In summary, sUmod is considered a possible auxiliary diagnostic tool for ATI and/or AIN. However, AKI is a complicated condition, and further studies are required to determine whether sUmod can be a universal indicator of the condition.

**Statement of Ethics**

This observational study was approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 4602) and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

The authors declare no conflicts of interest.

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**Author Contributions**

R.U. performed the analysis of all the data and wrote the manuscript. T.O., K.N., and M.K. supervised the study and edited the manuscript. R.U. and C.I. collected the data and blood samples. All the authors read and approved the final version of the manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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