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Original article

SERUM UROMODULIN – A MARKER FOR THE EARLY DETECTION OF CHRONIC KIDNEY DISEASES

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ABSTRACT

Chronic damage in different renal diseases leads to a change in urinary and serum uromodulin (sUmod). This indicates that sUmod plays an important role in the development of chronic kidney disease (CKD), and can probably be used as an early marker for detecting renal impairment.

Purpose: to assess the role of sUmod as a marker for early CKD detection.

Materials/Methods: A total of 207 patients were enrolled in this prospective observational study in the Clinic of Nephrology of the University Hospital "St. Ivan Rilski", Sofia, Bulgaria. The mean age of the patients was 56.81 ± 14.24 years, with the male/female ratio 99/108 (47.8% / 52.2%). Laboratory blood and urine tests, abdominal ultrasound with resistive index (RI) measurement and sUmod investigations were performed.

Results: There was a strong negative correlation between sUmod and serum creatinine (r= -0.712, p<0.0001) and moderate correlation – with urea (r= -0.680, p<0.0001) and cystatin C (r= -0.680, p<0.0001). Correspondingly, a strong positive relationship with estimated glomerular filtration rate (r=0.713, p<0.0001) was found. Moderate negative correlations were found between sUmod, RI (r = -0.511, p<0.0001) and parathyroid hormone (r = -0.449, p<0.0001). Correlations between continuation of CKD or hypertension, systolic or diastolic blood pressure or 24-hour proteinuria with sUmod were significant but not strong (r < 0.7; p < 0.05 for all).

Conclusions: sUmod correlates well with all commonly known markers of kidney damage, and its values decrease significantly with increasing CKD severity. It allows sUmod to be used as an early diagnostic marker for CKD.

Keywords: serum uromodulin, chronic kidney disease, correlation, early diagnosis

INTRODUCTION

Chronic kidney disease (CKD) remains one of the leading causes of morbidity and mortality worldwide. Epidemiological data show that CKD affects all age groups, and according to published studies, the total number of patients with CKD continues to increase globally, generating high economic costs for treatment. Despite the development of medicine, the search for modern diagnostic markers that prove early kidney damage continues to this day. In recent years, new markers for the assessment of kidney function have been introduced for scientific purposes and in practice. They are tested in blood, serum or urine, and in some cases in more than one body fluid [1].

Uromodulin or Tamm-Horsfall protein is a glycoprotein produced exclusively in the kidneys, mainly in the epithelial cells of the thick ascending limb of the loop of Henle. Under physiological conditions, it is found mainly in urine and only a small part in the blood. Chronic damage in different renal diseases leads to a change in urinary and serum uromodulin (sUmod). This indicates that uromodulin plays an important role in the development of CKD, and can be one of the potential biomarkers in the assessment of kidney function in CKD [1, 2, 3, 4, 5, 6].

The aim of the study was to assess the role of sUmod as a marker for early CKD detection.

MATERIAL AND METHODS

This prospective observational study was conducted in the period from 2018 to 2021 at the Nephrology Clinic, University Hospital "St. Ivan Rilski", Medical University – Sofia. 207 patients with varying degrees of CKD were included. All participants gave written informed consent. The study was approved by the Ethics Committees of the Medical University of Sofia in compliance with the Declaration of Helsinki. The mean age of the participants was 56.81 ± 14.24 years, with a men/femail ratio of 99(47.8%) /108 (52.2%) .

Inclusion criteria:

1. Patients with CKD

2. In cases of diabetes mellitus – glycated hemoglobin up to 7.0%

3. Absence of infections in the previous three months

4. Normal or drug-controlled blood pressure (BP) with BP values †< 150/100 mm Hg

Exclusion criteria:

1. Type 1 or type 2 diabetes mellitus with poor metabolic control

2. Uncontrolled hypertension with BP values e" 150/100 mm Hg

3. Alcohol or drug addiction

4. Immunocompromised diseases

5. Patients after organ transplantation

6. Neoplastic processes

7. Active treatment of acute/chronic inflammation

8. Chronic liver diseases

9. Refusal to participate in the clinical study

Anamnesis was taken, and physical examination was done in all patients. Main laboratory haematological and biochemical parameters - hemoglobin, hematocrit, leukocytes, platelets, urea and serum creatinine (SCr), uric acid, total protein and albumin; Cystatin C (CysC); parathyroid hormone and 24-hour proteinuria were tested. Glomerular filtration rate (eGFR) was calculated using the MDRD formula: GF (mL/min/1.73 m2) = 175 õ (SCR)-1, 154 õ (age) – 0,203 õ 0,742 (if the tested subject is a woman). Abdominal ultrasound with renal resistive index (RI) measurement was performed in all patients.

An Enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun AG, Lübeck, Germany) for the study of sUmod was used. A 96-well plate was pre-coated with uromodulin and blocked to reduce non-specific binding. Plasma samples were diluted 1:101 using dilution buffer. A total of 100 ìL of calibrators, controls or diluted samples was pipetted into the wells of the microtiter plate, which were initially coated with uromodulin. Subsequently, 100 ìL of antibody was added to a final concentration of 50 ng/mL. The microtiter plate was covered with foil and incubated for 120 minutes at 450 revolutions per minute (rpm) at room temperature (+18°C to +25°C) on a rotary shaker. After 2 hours, the microtiter plate was washed 3 times using 300 ìL of wash buffer. A total of 100 µL of streptavidin-peroxidase (final concentration 67 ng/mL) was pipetted into each well, followed by another incubation for 30 minutes at 450 rpm. The microtiter plate was washed three times with 300 ìL of wash buffer. 100 µL of substrate solution (containing the chromogen tetramethylbenzidine and hydrogen peroxide as a substrate for streptavidin-peroxidase) was added and pipetted into each well. The microtiter plate was incubated in the dark for 15 minutes at room temperature. The reaction was stopped by adding 100 µL of stop solution. This caused a color change from blue to yellow. Finally, the substrate solution is measured using a photometer at a wavelength of 450 nm and a reference wavelength between 620 nm and 650 nm. The lower limit of detection of uromodulin in this test is 2.0 ng/mL.

IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA) software package was used to perform all statistical analyses. The data description was displayed as n (%), mean ± standard deviation. Frequency analysis of qualitative variables; nonparametric methods - Kolmogorov-Smirnov and Shapiro-Wilk methods; Mann-Whitney method; Kruskal-Wallis Test and Correlation analysis were used. The critical significance level used by us is $\alpha = 0.05$. The corresponding null hypothesis is rejected when the P-value is less than α.

The strength of the correlation was assessed using the following scale:

$|r| \leq 0.3$ – weak correlation

$0.3 < |r| \leq 0.7$ – moderate correlation

$0.7 < |r| \leq 1.0$ – strong correlation

RESULTS

The characteristics of the study population are presented in Table 1.

Table 1. Demographic data of the patients

Parameter	Mean ± SD
Age	56.81 ± 14.24
Weight (kg)	80.86 ± 18.45
Height (sm)	168.89 ± 8.84
BMI	28.25 ± 5.85
Systolic blood pressure (mmHg)	137.00 ± 18.03
Diastolic blood pressure (mmHg)	86.45±10.05

Note: BMI – body mass index

Mean continuation of CKD was 94.45 ± 57.87 months.

The results of the patients' hematological and biochemical laboratory parameters, parathyroid hormone levels and 24-hour proteinuria are presented in Table 2.

Table 2. Main laboratory data

Laboratory parameter	Mean ±SD
Leukocytes	8.56 ± 2.68
Platelets	271.17 ± 92.54
Hemoglobin	127.70 ± 21.99
Hematocrit	0.37 ± 0.059
Erythrocytes	4.33 ± 0.77
Blood sugar	6.09 ± 2.19

Total protein	69.94 ± 7.34
Albumin	41.72 ± 5.83
Uric acid (μmol/L)	382.51 ± 121.21
SCr (μmol/L)	193.93 ± 164.69
Urea (mmol/L)	11.53 ± 7.66
eGFR (mL/min/1.73m2)	50.73 ± 31.46
CysC (mg/L)	2.28 ± 1.52
sUmod (ng/ml)	123.71 ± 110.34
parathyroid hormone	186.61 ± 234.25
proteinuria (g/24 h)	1.32 ± 1.75

Note: SCr – serum creatinine; eGFR – Glomerular filtration rate; CysC – Cystatin C; sUmod – serum uromodulin.

The average size of the left kidney, determined by abdominal ultrasound test, was 106.92 ± 12.33 mm, with a parenchymal thickness of 14.96 ± 3.52 mm, and for the right kidney, respectively, the size was 106.00 ± 14.77 mm, with a parenchymal thickness of 14.96 ± 3.52 mm. The average resistive index determined during the ultrasound examination was 0.79 ± 0.13.

The main results from the correlation analysis are shown in Table 3.

Table 3. Correlations between sUmod and other parameters

Parameter	R	p	Correlation strength
Duration of CKD	-0.307	<0.0001	moderate
Duration of hypertension	-0.208	0.005	weak
Systolic arterial pressure	-0.387	<0.0001	moderate
Diastolic arterial pressure	-0.297	<0.0001	weak
Albumin	0.274	<0.0001	weak
SCr	-0.712	<0.0001	strong
Urea	-0.68	<0.0001	moderate
Uric acid	– 0.297	<0.0001	weak
CysC	-0.68	<0.0001	moderate
eGFR	0.713	<0.0001	strong
Proteinuria	-0.351	<0.0001	moderate
parathyroid hormone	-0.449	<0.0001	moderate
RI	– 0.511	<0.0001	moderate

Note: CKD – chronic kidney disease; SCr – serum creatinine; eGFR – Glomerular filtration rate; CysC – Cystatin C; RI – resistive index

DISCUSSION

Our study included 207 patients with CKD with a mean age of 56.81 ± 14.24 years and female predominance (52.2% women). The gender distribution is in line with the population-based studies reported so far, according to which CKD is more prevalent among women [7]

Our results showed that uromodulin levels were significant but weakly or moderately negatively correlated with the duration of CKD ($r = -0.307$, $p < 0.0001$) and hypertension ($r = -0.208$, $p = 0.005$), systolic BP ($r = -0.387$, $p < 0.0001$) or diastolic BP ($r = -0.297$, $p < 0.0001$) and 24-hour proteinuria. Leiherer A, et al. also found differences in serum uromodulin levels in patients with hypertension compared to those without (160.9 ± 74.0 vs 181.8 ± 87.8 ng/ml, P = 0.037) [8]. In a study by Lv L, et al. patients with lower sUmod values (sUmod ≤ 52.7 ng/ml) had higher systolic and diastolic BP values compared to those with higher uromodulin (sUmod > 52.7–100.8 ng/ml or uromodulin > 100.8 ng/ml) [9].

According to our results a negative correlation with some of the well established markers for kidney damade was found – strong correlation with serum creatinine ($r = -0.712$, $p < 0.0001$), moderate with urea values ($r = -0.680$, $p < 0.0001$) and CysC ($r = -0.680$, $p < 0.0001$), weak with uric acid ($r = – 0.297$, $p < 0.0001$). At the same time, a strong positive correlation was found between sUmod and eGFR ($r = 0.713$, $p < 0.0001$). Similar results have been obtained by other authors [8, 9, 10, 11, 12, 13, 14, 15]. Steubl et al. conducted a study in which 426 patients were included – 71 with CKD stage 0 and 355 with other stages of CKD. They examined the values of plasma uromodulin, serum creatinine, CysC, urea and eGFR. They found that uromodulin correlated with all biomarkers, as well as with glomerular filtration (eGFR: r = 0.80, creatinine: r = -0.76, urea: r = -0.72 and cystatin C: r = -0.79) [14].

In a single-center, prospective, observational study, conducted in patients with CKD, older than 18 years of

age, Rajayapandian et al. investigated the estimation of sUmod, Glucose, Urea, and Creatinine. Their results were very close to ours. They found that upon univariate analysis, sUmod concentrations were significantly associated with urea (r = -0.783), creatinine (r = -0.686) and eGFR (r = 0.866). There was a significant negative correlation between sUmod with SBP, Serum creatinine, Blood urea, and a positive correlation with eGFR [16].

With the progression of CKD, sUmod levels decrease. This was first reported in 2014 by Swedish authors and has since been confirmed in a number of other studies [10, 11]. Leiherer et al. found significantly lower sUmod levels in patients with CKD (eGFR < 60 ml/min/1.73 m2) compared to those with normal renal function (71.9 ± 29.0 vs 169.1 ± 76.1 ng/ml, P < 0.001). They reported a decrease in sUmod with increasing CKD severity. The difference in sUmod between patients with moderately impaired renal function (CKD grade 3a) and mildly impaired function (CKD grade 2) was significant (85.4 ± 34.8 vs 152.3 ± 67.3 ng/ml, P = 0.004). In addition, patients with mildly impaired renal function had statistically lower sUmod values than those with normal renal function (152.3 ± 67.3 vs 176.4 ± 78.6 ng/ml, P = 0.001). The authors prospectively followed 529 coronary patients and reported that low serum uromodulin levels were associated with an increased risk of future renal failure [8]. Only Prajczer et al. reported that sUmod values were low in healthy controls and increased with the progression of CKD. The results they reported are most likely due to the different ELISA methods used in the studies, as well as other factors in their study design [12]. In one study of •eravica et al., significantly lower Umod levels were detected in patients with CKD compared to the healthy population and showed a significant correlation with GFR values [1].

sUmod and the RI are both markers of renal function that generally show an inverse relationship in the context of CKD progression. In our study, a moderate negative correlation was found between sUmod values and the RI (r = – 0.511, p < 0.0001). As RI values increase, sUmod values decrease and the degree of renal damage increases. In their study, Khan et al. found a statistical correlation between RI and creatinine level, which again indirectly proves the connection between sUmod and RI [17].

A statistically significant but moderate inverse correlation was found between sUmod and parathyroid hormone (r = -0.449, p < 0.0001).

In a study of Delgado GE, et al., sUmod was measured in patients admitted for coronary angiography. The results showed that higher sUmod was found in patients with lower parathyroid hormone. At the same time, Uromodulin was inversely correlated with serum creatinine and CysC, and correlated directly with eGFR [18].

In the population-based KORA study, the higher sUmod was inversely associated with progression to advanced kidney disease [19]. There is a relationship between uromodulin and renal function, making it a specific and sensitive indicator of kidney health. It can be used for standard diagnostic of kidney function and renal diseases [20].

CONCLUSION

sUmod correlates well with all commonly known markers of kidney damage. Its values †decrease significantly with increasing CKD severity. It allows sUmod to be used as an early diagnostic marker for CKD detection.

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