Clinical Kidney Journal, 2023, vol. 17, no. 1, 1–6

https://doi.org/10.1093/ckj/sfad027
Advance Access Publication Date: 10 February 2023
Original Article

ORIGINAL ARTICLE

Urinary matrix metalloproteinase-7 is a sensitive biomarker to evaluate renal tubular injury in patients with minimal change disease and focal segmental glomerulosclerosis

Dan-yang Yin[1,*], Gai-ling Hou[1,*], Xiao-qing Yang[2], Liang-liang Bi[2], Xiao-feng Mei[2], Meng-ke Bai[2], Li Zhou[3], Shan Zhu[4] and Yan-jie Huang[1,2]

[1]Department of Pediatrics, Henan University of Chinese Medicine, Zhengzhou, Henan, China, [2]Department of Pediatrics, The First Affiliated Hospital of Henan University of CM, Zhengzhou, Henan, China, [3]School of Pharmacy China Pharmaceutical University, Nanjing, Jiangsu, China and [4]Department of Pediatrics, Henan Province Hospital of TCM, Zhengzhou, Henan, China

*Dan-yang Yin and Gai-ling Hou contributed equally to this work and are both to be considered first authors.
Correspondence to: Yan-jie Huang; E-mail: huangyanjie69@hotmail.com; Shan Zhu; E-mail: zhshteacher@163.com; Gai-ling Hou; E-mail: erkehgl2818@163.com

ABSTRACT

Objective. To explore the advantages of urinary matrix metalloproteinase-7 (MMP-7) in evaluating renal tubular injury in minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) patients compared with urinary cystatin C (CysC) and retinol-binding protein (RBP).

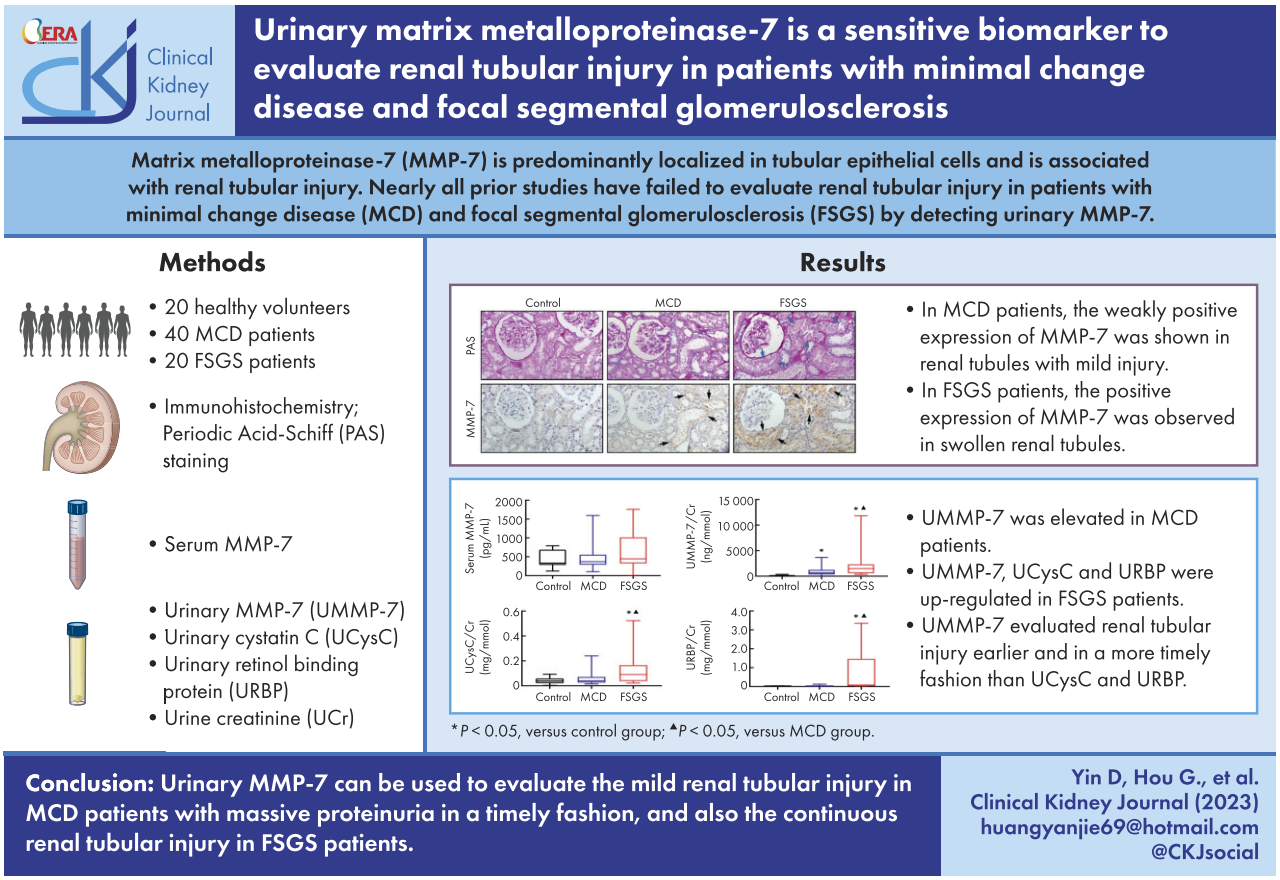
Methods. Serum and urine samples were collected from 20 healthy volunteers, and 40 MCD and 20 FSGS patients. Serum and urinary MMP-7 levels were measured by enzyme-linked immunosorbent assay. Urinary total protein, CysC and RBP levels were measured by automatic specific protein analyzer and compared with urinary creatinine level for calibration. The renal tissue serial sections were stained by MMP-7 immunohistochemistry and periodic acid–Schiff.

Results. Under light microscopy, MMP-7 granular weak positive expression was showed sporadically in the cytoplasm of a few renal tubular epithelial cells without obvious morphological changes in MCD patients, and MMP-7-positive expression was observed in the cytoplasm of some renal tubular epithelial cells in FSGS patients. There was no significant difference in serum MMP-7 level among the three groups. Compared with the control group, the urinary MMP-7 level in MCD patients was higher, but urinary CysC and RBP levels were not increased significantly. Compared with the control group and MCD patients, urinary MMP-7, CysC and RBP levels in FSGS patients were upregulated significantly.

Conclusions. Urinary MMP-7 could not only evaluate the mild renal tubular epithelial cells injury in MCD patients with massive proteinuria, but also evaluate the continuous renal tubular epithelial cells injury in FSGS patients.

Received: 25.8.2022; Editorial decision: 29.1.2023

GRAPHICAL ABSTRACT



Keywords: cystatin C, focal segmental glomerulosclerosis, matrix metalloproteinase-7, minimal change disease, renal tubular injury

INTRODUCTION

In some patients minimal change disease (MCD) can be accompanied by mild tubular injury [1–4]; however, tubular injury is usually more obvious in patients with focal segmental glomerulosclerosis (FSGS) [5, 6]. Renal tubular lesions affect the progress of MCD and FSGS [7–10]. Therefore, it is of great significance to explore sensitive biomarkers to evaluate renal tubular injury in patients with MCD and FSGS. Matrix metalloproteinase-7 (MMP-7) is mainly expressed in injured renal tubular epithelial cells [11–13]. MMP-7 can cleave E-cadherin [12], and degrade tight junction protein 1 (TJP1) by activating matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) [14], which ultimately disrupts the integrity of the renal tubular epithelial cells. The degradation of nephrin by MMP-7 leads to the excretion of proteinuria increases, which further causes renal tubular cell apoptosis and renal tubular fibrosis [15–17]. Our previous study showed that the level of urinary MMP-7 (UMMP-7) was higher in some MCD and FSGS children with massive proteinuria than that in normal children. Urinary cystatin C (UCysC) and retinol-binding protein (URBP) are common biomarkers to estimate the reabsorption function of renal tubular epithelial cells in clinic [18–21]. Therefore, it is useful to determine whether UMMP-7 evaluates renal tubular injury in a more timely manner than UCysC and URBP, and what is the difference in the level of UMMP-7 between MCD and FSGS patients. The purpose of this study was to explore whether UMMP-7, UCysC and URBP can be used to accurately evaluate tubular injury in patients with MCD and FSGS by measuring the UMMP-7, UCysC and URBP levels in normal subjects, MCD and FSGS patients and combining with renal pathology and the expression of MMP-7 in renal tubules.

MATERIALS AND METHODS

Patient characteristics

A total of 60 patients were enrolled from The First Affiliated Hospital of Henan University of CM from February 2017 to April 2022 in this study. Among them, 40 patients had been diagnosed as MCD, and 20 patients had been diagnosed as FSGS. Twenty healthy volunteers were recruited as a control group. The following clinical features were collected from the medical records: age, gender, 24-h proteinuria, serum total protein, serum albumin, blood urea nitrogen, serum creatinine and the estimated glomerular filtration rate (eGFR). The eGFR was calculated by

using the Modification of Diet in Renal Disease formula based on serum creatinine (sCr): $175 \times sCr^{(-1.154)} \times age^{(-0.203)} \times 0.742$ (if female) [22, 23]. This study was approved by ethics committees from The First Affiliated Hospital of Henan University of CM (2014HL-024) and conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consents.

Inclusion criteria

Diagnostic criteria were as follows. (i) MCD: light microscopy showed no glomerular lesions, or only minimal mesangial prominence. Immunofluorescence microscopy was negative. Electron microscopy demonstrated extensive foot process effacement but no electron-dense deposits, and in the presence of unremarkable light and immunofluorescence, findings were diagnostic for MCD [24]. (ii) FSGS: FSGS lesions were classified into collapsing, tip lesion, cellular, perihilar lesion and not otherwise specified variants, following the criteria of D'Agati *et al.*, except secondary FSGS [25, 26]. All healthy volunteers, MCD and FSGS patients agreed to provide serum and urine samples.

Exclusion criteria

(i) Urinary tract infection was excluded in both subjects and controls. (ii) Transient abnormalities on routine urine test were excluded in the control group. (iii) Patients with abnormal heart function and urinary tract or kidney tumors were excluded in subjects.

Serum and urine samples retention

Serum and mid-morning urine of healthy volunteers, and MCD and FSGS patients were collected, and the supernatant was collected after centrifugation at 2000 r.p.m. for 5 min and stored in a refrigerator at –80 °C.

Assay characteristics

Serum and urinary MMP-7 levels were measured by enzyme-linked immunosorbent assay (ELISA) kits (EK1M07-96; MULTI SCIENCES, Hangzhou, China). Urinary total protein (UTP), UCysC, URBP and urinary creatinine (UCr) levels were measured by using an automatic specific protein analyzer (BA400, Biosystems S.A., Spain). The above UTP, UCysC, URBP and UCr kits were purchased from Biosystems S.A. of Spain. UMMP-7, UTP, UCysC and URBP levels were compared with UCr level for calibration.

Periodic acid–Schiff (PAS) staining of renal tissue

Paraffin sections (4 μm) were deparaffinized. They were oxidized with 1% periodic acid aqueous solution for 10 min, then stained with Schiff reagent for 15 min. Nuclei were counterstained with hematoxylin solution. The renal tubular injury was observed under light microscope. The acute injury was characterized by renal tubular epithelial cells swelling and granular degeneration, absence of the brush border and tubulitis [27]. The chronic lesion was characterized by thickening of renal tubular basement membrane and tubular atrophy. The severity of renal tubular injury was divided into (i) no obvious pathological change; (ii) mild pathological changes (lesions involving <25% of the area); (iii) moderate pathological changes (lesions involving ≥25% and <50% of the area); and (iv) severe pathological changes (lesions involving ≥50%) [28].

Immunohistochemistry of MMP-7

Serial sections of renal tissue were stained with MMP-7 immunohistochemistry. Paraffin sections (4 μm) were deparaffinized, then exposed to heat antigen retrieval in 0.01 M citrate buffer (pH 6.0) for 5 min. After cooling to room temperature, the tissue sections were incubated with rabbit anti-MMP-7 antibody (1:100, SAB4501894, Sigma, USA) overnight at 4°C. After washing, the tissue sections were incubated with horseradish peroxidase-conjugated goat anti-mouse/rabbit IgG polymer (PV-9000, ZSGB-BIO, Beijing, China) for 30 min at 37°C. Then, diaminobenzidine (DAB) was added chromogenic for visualization in a color reaction, followed by hematoxylin dye. The distribution of MMP-7 was observed under light microscope.

Statistical analysis

SPSS 25.0 statistical software was used for data statistical analysis. Age, serum total protein, serum albumin, blood urea nitrogen and serum creatinine were expressed as mean ± standard deviation (SD), and 24-h proteinuria, UTP, UMMP-7, UCysC and URBP were expressed as median and interquartile range (IQR). Quantitative variables conforming to normal distribution were compared using Student's *t*-test for independent data, and quantitative variables which do not conform to normal distribution were compared using the Mann–Whitney U test. Qualitative variables were presented as frequencies (*n*) and percentages (%) and they were compared using Chi-squared test. A *P*-value <.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics of the study population

Forty patients with MCD, 20 patients with FSGS and 20 healthy volunteers were included in the study. The average age of the control group was (10.95 ± 10.24) years old, including 12 males and 8 females. There were no significant differences in age, gender, 24-h proteinuria, serum total protein, serum albumin, blood urea nitrogen and serum creatinine between MCD and FSGS patients ($P > .05$). The stages of chronic kidney disease (CKD) were confirmed by eGFR. In MCD patients, two patients (5%) had progressed to Stage 2 CKD. In FSGS patients, one patient (5%) had progressed to Stage 2 CKD and four patients (20%) to Stage 3 CKD. Pathologically, non-specific swelling and granular degeneration of some renal tubular epithelial cells were observed in all patients with MCD and FSGS. Among 40 patients with MCD, mild tubular atrophy was seen in 8 cases. Among 20 FSGS patients, 3 patients had mild brush border absence of renal tubular epithelial cells and 1 patient had moderate brush border absence of renal tubular epithelial cells. Renal tubular atrophy was observed in 17 FSGS patients, 14 of which were mild and 3 were moderate (Table 1).

Positive expression of MMP-7 in renal tubular of patients with MCD and FSGS

Renal tissue serial sections stained with MMP-7 immunohistochemistry and PAS were observed under light microscope. MMP-7 negatively expressed in normal renal tissue. However, in MCD patients, MMP-7 granular weak positive expression was showed

Table 1: Clinical baseline and pathological characteristics of patients with MCD and FSGS.

Characteristics	MCD ($n = 40$)	FSGS ($n = 20$)	P-value
General characteristics			
Age (years), mean ± SD	14.23 ± 8.04	19.15 ± 16.62	NS
Gender: male, *n* (%)	24 (60)	10 (50)	NS
Biochemical characteristics			
24-h proteinuria (mg/24 h), median (IQR)	2668.84 (1547.88–6290.34)	2979.42 (1218.02–4233.25)	NS
Serum total protein (g/L), mean ± SD	49.72 ± 11.29	55.82 ± 12.38	NS
Serum albumin (g/L), mean ± SD	25.81 ± 9.93	32.04 ± 9.54	NS
Blood urea nitrogen (mmol/L), mean ± SD	4.69 ± 1.93	7.72 ± 5.8	NS
Serum creatinine (μmol/L), mean ± SD	44.89 ± 22.90	71.18 ± 60.86	NS
Pathology			
Glomerular segmental sclerosis, *n* (%)	0	17 (85)	$P < .001$
Glomerular balloon adhesion, *n* (%)	0	12 (60)	$P < .001$
Absence of the brush border of the renal tubular epithelial cells			
Mild, *n* (%)	0	3 (15)	$P = .033$
Moderate, *n* (%)	0	1 (5)	NS
Severe, *n* (%)	0	0	
Thickening of renal tubular basement membrane and tubular atrophy			
Mild, *n* (%)	8 (20)	14 (70)	$P < .001$
Moderate, *n* (%)	0	3 (15)	$P = .033$
Severe, *n* (%)	0	0	

NS, not significant.

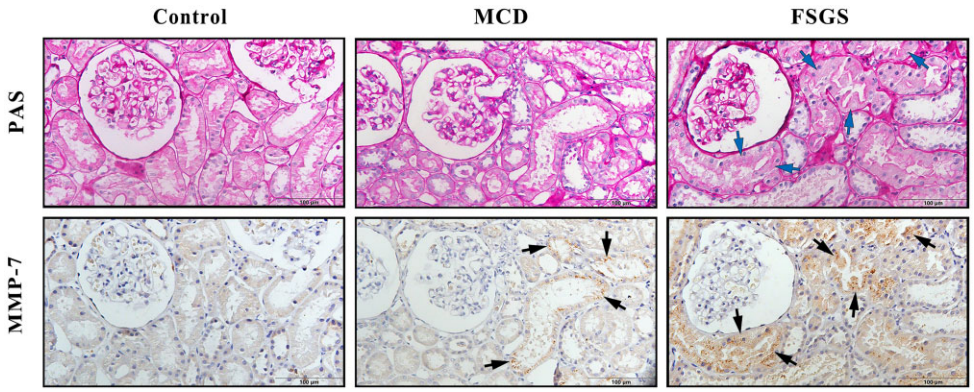


Figure 1: Expression of MMP-7 in renal tubules of patients with MCD and FSGS. Control, nontumor kidney tissues from the patients who had renal cell carcinoma used as normal controls. Blue arrows indicated swollen tubular epithelial cells. Black arrows indicated MMP-7-positive expression. Magnification, ×400; Scale bars, 100 μm.

sporadically in the cytoplasm of a few renal tubular epithelial cells. In FSGS patients, MMP-7-positive expression was observed in the cytoplasm of some renal tubular epithelial cells. PAS staining showed that no obvious morphological change was seen in renal tubular epithelial cells with MMP-7-positive expression sites in MCD patients, while obvious renal tubular epithelial cells swelling was observed in FSGS patients (Fig. 1).

Serum MMP-7, UMMP-7/Cr, UCysC/Cr, URBP/Cr and UTP/Cr levels in each group.

There was no significant difference in serum MMP-7 level among the control group, MCD and FSGS group. Compared with the control group, the UMMP-7 level in MCD patients was higher, but UCysC and URBP levels did not enhanced significantly. Compared with the control group and MCD patients, all the UMMP-7, UCysC and URBP levels were markedly elevated in patients with FSGS (Table 2).

DISCUSSION

Our data showed that there was no significant difference in serum MMP-7 level among the control group, MCD and FSGS patients, while the UMMP-7 level in MCD and FSGS patients was higher than that in the control group. The results of MMP-7 immunohistochemistry and PAS staining in renal tissue serial sections showed that MMP-7 was up-regulated in the cytoplasm of swelling renal tubular epithelial cells. The above-mentioned results suggested that the enhanced UMMP-7 may mainly derived from the damaged renal tubular epithelial cells in MCD and FSGS patients, rather than the circulation. In MCD patients, MMP-7 weak positive expression was observed in the cytoplasm of renal tubular epithelial cells without obvious morphological change under light microscope. Compared with the control group, UMMP-7 level was enhanced about 25-fold in MCD patients, while UCysC and URBP levels were not increased significantly, suggesting that UMMP-7 could evaluate renal tubular injury earlier and in a more timely manner than UCysC and

Table 2: Serum MMP-7, UMMP-7/Cr, UCysC/Cr, URBP/Cr and UTP/Cr levels in each group.

	Control ($n = 20$)	MCD ($n = 40$)	FSGS ($n = 20$)	P1	P2	P3
Serum MMP-7 (pg/mL), median (IQR)	332.23 (282.55–688.37)	370.32 (288.08–556.50)	445.68 (321.89–1015.12)	NS	NS	NS
UMMP-7/Cr (ng/mmol), median (IQR)	26.19 (13.61–99.83)	667.22 (342.65–1256.57)	1485.85 (572.87–2325.09)	$P < .001$	$P < .001$	$P = .004$
UCysC/Cr (mg/mmol), median (IQR)	0.04 (0.02–0.06)	0.04 (0.03–0.07)	0.09 (0.04–0.17)	NS	$P = .002$	$P = .001$
URBP/Cr (mg/mmol), median (IQR)	0.009 (0.005–0.02)	0.01 (0.008–0.03)	0.08 (0.03–1.47)	NS	$P < .001$	$P < .001$
UTP/Cr (mg/mmol), median (IQR)	9.37 (5.86–11.40)	326.55 (59.03–654.97)	289.39 (170.17–637.95)	$P < .001$	$P < .001$	NS

P1, MCD versus control; P2, FSGS versus control; P3, FSGS versus MCD; NS, not significant.

URBP. One study has shown that UCysC and URBP levels in patients with MCD were lower than those in patients with diabetes nephropathy, but this study did not compare UCysC and URBP levels between MCD and normal subjects [29]. Yang *et al.* found that the UMMP-7 level in those with severe acute kidney injury (AKI) was characterized by a peak within 6 h after cardiac surgery, whereas the peak in sCr rise occurred after 24 h of surgery [30]. Zhou *et al.* demonstrated that UMMP-7 was already elevated substantially in patients with CKD when renal impairment is mild (eGFR >90 mL/min/1.73 m^2) and free of robust tissue fibrosis [12]. In a rabbit model of renal ischemia–reperfusion (IR) injury, MMP-7 in renal tissue reacted to IR injury earlier than MMP-2 and MMP-9 [14]. Our data and the above reports suggest that MMP-7 can sensitively evaluate renal tubular injury in the early stage.

By observing serial sections of renal tissue stained with MMP-7 immunohistochemistry and PAS under light microscope, we found that compared with the control group and MCD patients, the expression of MMP-7 in renal tubular epithelial cells of FSGS patients with more observable tubular injury was significantly increased. And the results of measuring UMMP-7 levels in three groups showed that UMMP-7 level in FSGS patients was significantly higher than that in the control group and MCD patients, suggesting that UMMP-7 could continuously estimate the injury of renal tubular epithelial cells in FSGS patients. One study has shown that patients with high levels (>3.9 μg/g) of UMMP-7 had 2.7-fold higher risk for IgAN progression compared with those with lower levels (≤3.9 μg/g) of UMMP-7 [31]. It was reported that compared with that in the healthy controls, the UMMP-7 level in patients with myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis (MPO-AAV) was markedly elevated by more than 10-fold, and the degree of tubular atrophy and interstitial fibrosis in patients with high UMMP-7 level was greater than that in patients with low UMMP-7 level. Correlation analysis showed that UMMP-7 excretion was positively correlated with MMP-7 expression in renal tubular epithelial cells ($r = 0.678$, $P < .001$), but not with serum MMP-7. Double-label experiments showed that tubular MMP-7 did not colocalize with megalin, an endocytic receptor that mediates resorption of MMPs, suggesting that the elevated UMMP-7 level may mainly be derived from the enhanced synthesis of renal tubular epithelial cells, rather than the increased filtration or decreased tubular reabsorption [32]. Our data and the above studies suggested that the increase of UMMP-7 may be related to the damage of renal tubular epithelial cells. Nearly all prior studies have failed to evaluate renal tubular injury in patients with MCD and FSGS by detecting UMMP-7.

UCysC and URBP are low-molecular-weight proteins of 13 kDa and 21 kDa, respectively. They can freely pass through the glomerular filtration membrane and are decomposed after having been reabsorbed by the proximal tubular epithelial cells. However, the proximal tubular epithelial cells cannot secret CysC and RBP. Therefore, the levels of UCysC and URBP are generally used to evaluate the renal tubular reabsorption function. Compared with the control group, UCysC and URBP levels in MCD patients had no significant up-regulation, while UCysC and URBP levels in FSGS patients were markedly elevated. The reason for this may be that the direct toxic effect of a large amount of proteinuria on renal tubular epithelial cells in MCD patients led to transient renal tubular injury, but it had not caused the reabsorption disorder of low-molecular-weight protein by renal tubular epithelial cells, or the damage of renal tubular epithelial cells was repaired quickly. However, the renal tubular epithelial cells injury in FSGS patients was more serious, and had affected the reabsorption function of renal tubular epithelial cells. Zhang *et al.* found that the URBP level in patients with primary FSGS was higher than that in patients with MCD [33]. Our study also showed that the URBP level was higher in patients with FSGS than that in patients with MCD, while there was no significant differences in URBP level between MCD and the control group, suggesting that URBP is not sensitive to mild renal tubular injury, but it can evaluate the renal tubular reabsorption disorder.

In conclusion, UMMP-7 can be used to evaluate the mild renal tubular injury in MCD patients with massive proteinuria in a timely manner, and the continuous renal tubular injury in FSGS patients as well. UMMP-7 combined with UCysC and URBP can dynamically monitor renal tubular injury in patients with MCD and FSGS, and also evaluate whether renal tubular reabsorption function is damaged or not in patients with MCD and FSGS. Further study is needed to verify these results with a larger sample size and a multi-center approach. Whether UMMP-7 is suitable for the assessment of tubular lesion in all kidney diseases and its specificity needs to be confirmed by more clinical studies. On the other hand, the increased expression of MMP-7 in AKI was also involved in survival and regeneration of renal tubules [34]. Therefore, the underlying pathological effects of MMP-7 need to be clarified further in renal tubular cells.

ACKNOWLEDGEMENTS

The authors thank Professor Haibo Mu, who provided helpful comments for revising the paper.

FUNDING

General Projects of National Natural Science Foundation of China in 2021 (82174187); Leading Talent Project of Traditional Chinese Medicine in Henan Province [(2021) No. 8]; 2022 special scientific research project of national clinical research base of traditional Chinese medicine of Henan Provincial Health Commission (2022JDZX014).

AUTHORS' CONTRIBUTIONS

Y.-j.H. conceived the idea and designed the experiments. D.-y.Y., G.-l.H. and X.-q.Y. collected clinical urine and renal tissue samples, and provided clinical interpretation of the data. D.-y.Y and X.-q.Y performed MMP-7 immunohistochemistry and PAS staining. G.-l.H., L.-l.B., X.-f.M. and M.-k.B. performed ELISA experiments. D.-y.Y. and G.-l.H. analyzed data and wrote the manuscript. L.Z. and S.Z. helped to correct the grammar mistakes. Y.-j.H. contributed to revised the final manuscript. All authors have reviewed the manuscript and agreed on submission.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest (financial or otherwise) are declared by the authors.

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