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Editorial Comment

EDITORIAL COMMENT

Urine MMP7 as a kidney injury biomarker

Alejandro Avello [1], Juan Guerrero-Mauvecin[1] and Ana Belen Sanz [1,2]

[1]Laboratory of Experimental Nephrology, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain and [2]RICORS2040, Madrid, Spain

Correspondence to: Ana Belen Sanz; E-mail: asanz@fjd.es

ABSTRACT

Matrix metalloproteinase 7 (MMP-7) is a secreted endopeptidase involved in the degradation of extracellular matrix components and the activation of cytokines and growth factors. The regulation of MMP-7 can be transcriptionally regulated by AP-1 or Wnt/β-catenin or post-translationally by proteolytic activation. MMP-7 expression is low or absent in the healthy kidney, but is significantly upregulated in kidney injury, including AKI and CKD. The function of MMP-7 in kidney disease may differ for CKD and AKI; it may have a profibrotic role in CKD and an anti-apoptotic and regenerative function in AKI. Additionally, the potential of MMP-7 as a biomarker has been studied in different kidney diseases, and the results are promising. Recently, combined unbiased kidney proteomics and transcriptomics approaches identified kidney MMP-7 as the protein having the strongest association with both fibrosis and eGFR and confirmed the predictive role of plasma MMP-7 levels for kidney function decline in over 11 000 individuals. Additionally, urinary MMP-7, combined with urinary cystatin C (CysC) and retinol binding protein (RBP) was reported to provide information on tubular injury in focal segmental glomerulosclerosis and minimal change disease. We now present an overview of research on MMP-7 expression and function in kidney diseases and discuss its potential as a biomarker of kidney diseases.

Keywords: chronic kidney disease, focal and segmental glomerulosclerosis, minimal change disease, MMP-7, urine biomarker

Chronic kidney disease (CKD) is one of the fastest growing global causes of death and is associated with increased risk of acute kidney injury (AKI) and cardiovascular and all-cause death [1]. The fast growth of CKD burden implies that current risk stratification and treatment of kidney disease is suboptimal. In the current issue of CKJ, Yin *et al.* assess the biomarker potential of urinary matrix metalloproteinase 7 (MMP-7) in focal and segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) [2]. The topic is relevant, as MCD usually responds to therapy, while FSGS is one of the most common glomerular causes of kidney failure [3].

MATRIX METALLOPROTEINASE 7 (MMP-7): A MODULATOR OF EXTRACELLULAR MATRIX, CYTOKINES, AND GROWTH FACTORS

Matrix metalloproteinase 7 (MMP-7), also known as matrilysin-1, is a 30 kDa secreted zinc- and calcium-dependent endopeptidase that, along with the other MMP family members, is involved in the degradation of extracellular matrix components and the activation of several cytokines and growth factors [4, 5].

Structurally, MMP-7 is smaller than other MMPs, consisting only of a 19 kDa catalytic domain with an active Zinc binding

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site. It is secreted as an inactive zymogen with an additional 9 kDa cysteine-rich pro-domain near its N-terminal domain. These cysteine residues help keep the protein in an inactive state by binding with the catalytic zinc, and its disruption by proteolytic cleavage is required for MMP-7 activation [5, 6]. MMP-7 is activated by multiple proteases, including trypsin, plasmin or even other MMPs [5].

The regulation of MMP-7 is both transcriptional (synthesis of new mRNA) and post-translational (proteolytic activation). The promoter of the human MMP-7 gene contains an activator protein-1 (AP-1) site required for activation by growth factors, and a T-cell factor (TCF)-binding element (TBE) that responds to the Wnt/β-catenin pathway [7]. TGF-β1, which plays a key role in kidney fibrosis, promotes MMP-7 expression [8, 9]. Additionally, endogenous tissue inhibitors (TIMPs) can reversibly inhibit MMP-7. TIMPs are often capable of inhibiting various MMPs [5]. However, there are differences between TIMPs. As an example, while TIMP2 and TIMP3 inhibit MMPs, the impact on pro-MMP-2 activation and unilateral ureteral obstruction-induced kidney injury differs: TIMP3 inhibits activation of pro-MMP-2 and protects from kidney injury, whereas TIMP2 promotes pro-MMP-2 activation and kidney injury through MMP-2 activation [10]. However, the TIMP specificity for MMP-7 is poorly characterized [5]. TIMP-1 is a more potent inhibitor of MMP-7 than TIMP-2 or TIMP-3, but the Ki is still one order of magnitude higher than for MMP-1, MMP-2, or MMP-9, except for the TIMP-1 T2L/V4S variant that is in the same order of magnitude as for the other MMPs [11].

MMP-7 expression is low or absent in the healthy kidney, but it undergoes significant upregulation during kidney injury, including AKI and different forms of CKD such as diabetic, obstructive, or chronic kidney allograft nephropathy [5, 12] (Fig. 1A). The upregulation is mainly observed in the apical region of the dilated (injured) tubular epithelium, although it can also be expressed by other cell types such as podocytes, interstitial cells, or infiltrated inflammatory cells, depending on the specific disorder (Fig. 1A–C) [5, 13–16]. Increased MMP-7 expression has been observed in proximal and distal tubules.

MMP-7 regulates multiple cellular processes due to its ability to target a broad range of substrates. These processes include extracellular matrix remodelling and epithelial-to-mesenchymal transition (EMT) by cleaving E-cadherin, laminin, fibronectin, fibrinogen or entactin, and apoptosis through cleavage of Fas ligand (FasL) and TNFα release [13, 17–22]. E-cadherin, a key target of MMP-7, plays a crucial role in maintaining intercellular adhesions and preserving the structural integrity of epithelium. E-cadherin binds to β-catenin. Upon E-cadherin degradation by MMP-7, β-catenin is released and activates downstream signalling pathways independent of Wnt, leading to expression of genes related to fibrosis, including MMP-7 [8, 9, 23].

MMP7 EXPRESSION AND FUNCTION IN KIDNEY DISEASE

MMP-7 is upregulated in almost all kidney diseases studied so far and it is one of the best characterized MMPs in kidney disease. Kidney MMP-7 overexpression has been detected in human kidney diseases such as ADPKD, lupus nephritis, diabetic nephropathy, IgA nephropathy, thrombotic microangiopathy and focal segmental glomerulosclerosis [13, 14, 24–27]. Additionally, high levels of MMP-7 expression have also been observed in experimental models of CKD and kidney fibrosis such as adriamycin nephropathy, adenine-induced CKD, chronic angiotensin II infusion, and unilateral ureter obstruction (UUO) [25, 27, 28], and in models of AKI induced by folic acid overdose, cisplatin, or ischemia/reperfusion [25, 29]. The Wnt/β-catenin pathway is key for MMP-7 expression in kidney diseases. In adriamycin nephropathy and in human diseased kidneys, MMP-7 expression positively correlated with β-catenin expression levels, and in both folic acid-AKI and UUO, MMP-7 colocalized with Wnt4 expression [25, 27]. In UUO kidneys, the ectopic expression of Wnt1 increased the expression of MMP-7, while inhibition of the Wnt1/β-catenin pathway repressed MMP-7 expression [27]. Moreover, tubule-specific β-catenin deficiency prevents MMP-7 overexpression induced by chronic angiotensin II infusion or Adriamycin [30]. In cultured kidney tubular cells, the ectopic expression of β-catenin promoted TCF binding to TBE domains in the *MMP7* promoter and *MMP7* gene expression [27]. Overall, the Wnt/β-catenin pathway is a key driver of MMP-7 expression in tubular cells during kidney disease and, as it is the case outside the kidneys, this triggers a positive feedback loop of MMP-7 expression through E-cadherin degradation and subsequent β-catenin release [27, 29].

The function of MMP-7 in kidney disease may differ in CKD and in AKI. MMP-7 global knock-out (MMP-7-KO) mice developed less severe kidney injury after UUO, characterized by higher levels of E-cadherin, and lower levels of β-catenin and fibrosis compared with wild type (WT) mice [13]. Moreover, treatment with MMP-7 inhibitor prevented β-catenin release and reduced kidney fibrosis following UUO [13]. MMP-7 degradation of E-cadherin in tubular cells drives loss of cell–cell adhesion, an initial step for tubular atrophy and kidney fibrosis, and the expression of β-catenin-dependent profibrotic genes [5, 13, 27].

MMP-7 also promotes podocyte injury. In isolated glomeruli, MMP-7 degraded the component of the podocyte slit diaphragm nephrin, resulting in increased glomerular permeability and loss of albumin [30]. Indeed, MMP-7-KO mice had better preserved nephrin and WT1 expression and milder albuminuria following chronic angiotensin II infusion than WT mice [30].

In contrast to CKD models, in experimental AKI induced by folic acid, cisplatin, or IRI, MMP-7 deficiency exacerbates early-stage kidney injury, inflammation, and cell death compared to WT mice [29]. Fas ligand (FasL) activation of the Fas receptor promotes kidney cell death [31, 32]. MMP-7 dependent-proteolytic degradation of FasL is suggested as an anti-apoptotic and protective mechanism in AKI, since FasL levels are increased in MMP-7-KO mice and MMP-7 degrades FasL in tubular cells *in vitro* [29]. Additionally, exogenous MMP-7 decreased the severity of kidney injury and apoptosis in MMP-7-KO mice; however, it would be necessary to treat WT mice with MMP-7 to confirm the relevance of this finding [29]. This protective effect for tubular cells contrasts with its ability to induce apoptosis in renal interstitial fibroblasts by increasing the expression and cleavage of FasL, resulting in its soluble active form [33]. In this regard, FasL-induced apoptosis of kidney fibroblasts may limit kidney fibrosis following acute injury [34]. However, knockdown of MMP-7 with a shRNA reduced the AKI-to-CKD progression in folic acid nephropathy at 14 days after injury and, thus, more studies are necessary to clear the role of MMP-7 in AKI and in AKI-to-CKD progression. More recently, MMP-7 has been also related with kidney inflammation by inducing the expression of inflammasome components NLRP6 and NLRP3 [28].

Given the kidney expression and function of MMP-7, it may play a role as a biomarker in kidney injury and, as it induces podocyte injury, it may play such role in podocytopathies, such as MCD and FSGS.

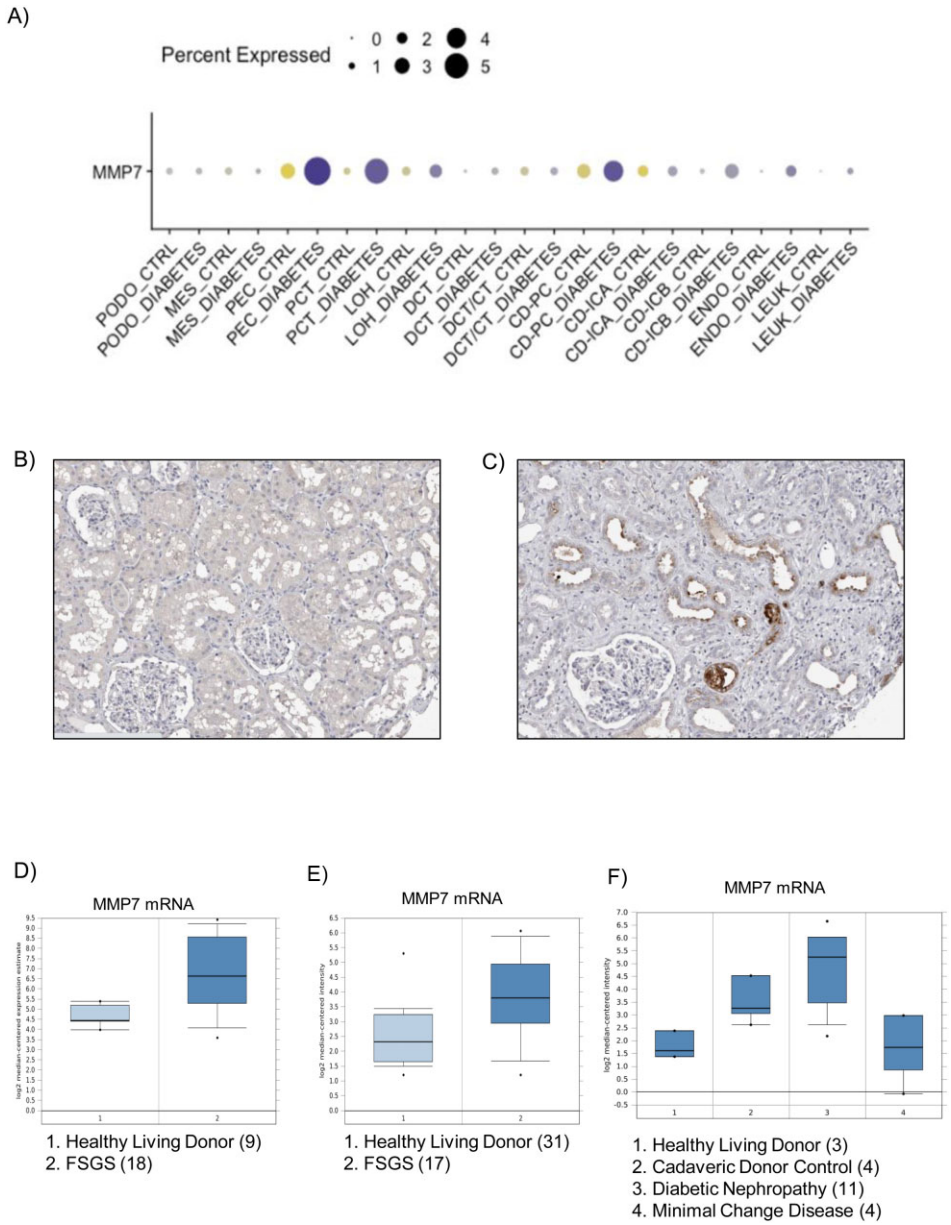

Figure 1: MMP-7 expression in human kidney diseases. **(A)** Human kidney single cell transcriptomics in control and diabetic kidney samples. Multiple cell types appear to express higher levels of MMP-7 mRNA in diabetic kidneys: PEC (parietal epithelial cells), PCT (proximal convoluted tubule), CD-PC (collecting duct principal cell), CD-ICB (collecting duct-intercalated cell type B) and endo (endothelium) [15]. https://humphreyslab.com/SingleCell/. Reproduced with permission from Prof. Ben Humphreys. **(B, C)** Human kidney immunohistochemistry in ProteinAtlas. Although both kidneys were classified as normal, panel A displayed back-to-back tubules, characteristic of healthy kidneys (male, age 16), while panel B shown widened interstitial spaces (female, age 59), characteristic of chronic kidney disease. Intense cytoplasmic staining is observed in distal tubules in panel B. https://www.proteinatlas.org/ENSG00000137673-MMP7/tissue/kidney#img. Image credit: Human Protein Atlas [16]. **(D–F)** MMP7 gene expression of micro-dissected tubulointerstitial samples from: **(D)** 18 focal segmental glomerulosclerosis (FSGS) patients and nine healthy living donors. Fold Change: 5.274; P–value: 7.91E-5. ERCB Nephrotic Syndrome TubInt Dataset. http://v5.nephroseq.org/; **(E)** 17 FSGS patients and 31 healthy living donors. Fold change: 1.93; P–value: 0.006. Ju CKD Tubint dataset [41]. http://v5.nephroseq.org/; **(F)** 3 living donors (controls), 4 minimal change disease (MCD), 4 cadaveric donors, and 11 diabetic nephropathies. Fold change Controls vs MCD: 1.09. Schmid Diabetes TubInt Dataset [42].

MMP7 AS BIOMARKER IN KIDNEY DISEASE: FOCUS ON FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS) AND MINIMAL CHANGE DISEASE (MCD)

In this issue of CKJ, Yin *et al*. explore the use of uMMP-7 to evaluate tubular injury in two diseases that have not been studied before, FSGS and MCD, in young adults as well as in children, a population that is often left out of clinical studies [2]. There were no differences in serum MMP-7 between the control and kidney disease groups, but they did find differences in uMMP-7. Interestingly, the levels of all the urinary small proteins studied, MMP-7, cystatin C and retinol binding protein (RBP) were higher in FSGS than in MCD, despite similar total urinary protein, while only uMMP-7 was increased in MCD. These findings were confirmed by immunohistochemistry, where MMP-7

Table 1: Studies of MMP-7 as biomarker in kidney disease.

Study population	*n*	Sample	Outcome	Comment	Ref
Hydronephrotic kidneys, diverse kidney diseases	3 controls 9 HN kidneys 7 controls 25 renal patients	Kidney tissue mRNA (microarray)	CKD progression	kMMP-7 belongs to a set of 9 genes upregulated in kidney disease and associated with clinical outcomes.	[26]
Kidney transplant recipients	7 Control tx 22 tx with IF/TA 6 Control non-tx 6 Control tx 6 tx with IFTA	Microdissected kidney mRNA (microarray, RT-PCR) Serum (ELISA)	IFTA diagnosis and progression	kMMP-7 increased in all kidney regions of Tx with IFTA. sMMP-7 progressively rise from control non-tx to control tx to IFTA.	[35]
Pediatric kidney transplant recipients	20 stable allografts 20 acute allograft rejection 10 healthy kidney donors 10 stable allografts 14 acute allograft rejection	Kidney tissue mRNA (RT-PCR)	Diagnose rejection of renal allografts	kMMP-7 is increased in acute allograft rejection.	[48]
Lupus nephritis	54 lupus nephritis patients 19 lupus nephritis patients	Kidney tissue mRNA (RT-PCR) Kidney tissue (IHQ)	Prediction of prognosis	kMMP-7 positive correlation with chronicity index and kidney function at time of biopsy.	[24]
Type 1 diabetes Type 2 diabetes with candesartan	91 type 1 diabetes 11 type 2 diabetes	Urine (ELISA)	Risk of DKD	uMMP-7 increased in diabetic patients with DKD compared with patients without DKD. Candesartan did not reduce MMP-7.	[53]
Type 2 diabetes and DKD	141 patients with type 2 diabetes and DKD	Fasting blood and urine (ELISA)	Risk of ESRD and mortality	uMMP-7 associated with increased risk of ESRD and mortality while sMMP-7 was not.	[36]
Renal transplant patient	Discovery: 14 Tx patients Quantitative Test: 133 Tx patients	Urine (proteomic) Urine (ELISA)	Diagnosis of subclinical and clinical inflammation/injury in Tx patients	uMMP-7 increased in inflamed/injured renal allografts compared with normal allografts. Adding urinary MMP7 to CXCL10 improved diagnosis of subclinical and clinical inflammation/injury (improved integrated discrimination).	[39]
Patients receiving cardiac surgery	Stage 1: 721 adults, 323 children Stage 2: 398 adults	Urine and blood (ELISA) Before surgery and at follow-up	Prediction of severe AKI after cardiac surgery	uMMP-7 higher in patients who developed severe AKI within the first 6 hours compared with those with mild or no AKI. However, pMMP-7 not different in patients with or without AKI.	[38]
Various CKDs	102 CKD, 20 healthy 10 CKD, 2 healthy	Urine (ELISA) Kidney tissue (IHQ)	Non-invasive biomarker for kidney fibrosis	uMMP-7 increased in patients with CKD and positively correlated with kidney fibrosis scores	[13]
AKI patients	28 AKI 15 healthy subjects	Urine (time-resolved fluoroimmunoassay (IMPs-TRF) and ELISA	Novel method to quantify uMMP-7	IMPs-TRF good correlation with ELISA	[46]

Table 1: Continued

Study population	*n*	Sample	Outcome	Comment	Ref
Adult patients with stage 1 or 2 AKI after cardiac surgery	121 patients Same cohort that PMID 28 698 269	Urine (ELISA) before surgery and at follow-up	Early detection of high risk for progressive AKI post-heart surgery	uMMP-7 at time of AKI clinical diagnosis predicts AKI progression. uMMP-7 plus with clinical risk factor model identified high risk for progressive AKI post-heart surgery.	[47]
IgA nephropathy	Training set: 554 for 40 months Validation set: 392 for 28 months	Urine (ELISA), at time of biopsy	IgAN progression (composite of >40% loss of eGFR, kidney failure, or death)	uMMP-7 strongest association with IgAN progression compared with other biomarkers. Adding uMMP-7 to MEST-C score and clinical data at time of biopsy improved risk prediction of IgAN progression.	[44]
Lupus nephritis	Stage I: Training set 88 LN, 30 extrarenal SLE, 20 healthy subjects. Bx: 10 LN Validation set: 66	Serum and urine (ELISA) Kidney tissue (IHQ)	Incident renal flare in LN	High uMMP-7 in LN, while sMMP-7 are not. kMMP-7 mainly in tubular cells, correlates with uMMP-7. High uMMP-7 in LN associated with high renal disease activity.	[37]
MPO-AAV	Control:30 Test cohort: 90 MPO-AAV Validation cohort: 60 MPO-AAV	Urine (ELISA)	Predicts kidney prognosis	High uMMP7 level in MPO-AAV independently associated with severe kidney injury and incident ESKD.	[45]
	Control:10 Test cohort: 90 MPO-AAV	Kidney tissue (IHQ)			
General non-diabetic population	Baseline: 1627 subjects, GFR and serum MMP-7 After 5.6 years, in 1324 subjects GFR	Serum (proteomics)	Accelerated GFR decline. Incident CKD	sMMP7 independently associated with GFR loss in persons without diabetes or pre-existing CKD.	[51]
DKD, and general population	23 DKD, 10 healthy Validation set: 433 subjects (Including various CKD and healthy)	Kidney tissue mRNA (RNA-seq)	eGFR decline and kidney fibrosis	kMMP-7 (mRNA and protein) showed the strongest association with both fibrosis and eGFR.	[14]
	23 DKD, 10 healthy Validation set: 23 DKD, 10 healthy.	Kidney tissue (proteomic)			
	ARIC cohort: 1623 diabetic, 9407 non-diabetic After ± 17 years eGFR	Plasma (proteomics)	eGFR decline by 50% or ESKD	pMMP7 levels correlated with both current kidney function and prospective kidney function decline	

Abbreviations. HN: hydronephrotic; IFTA: interstitial fibrosis and tubular atrophy; MPO-AAV: myeloperoxidase–antineutrophil cytoplasmic antibody-associated vasculitis; IHQ: immunohistochemistry; RT-PCR: real time-polymerase chain reaction ELISA: enzyme-linked immunosorbent assay; TX: transplant; RNA-seq: RNA sequencing; kMMP-7, uMMP-7, sMMP-7, pMMP-7: kidney, urine, serum, and plasma MMP-7, respectively; LN: lupus nephritis; SLE: systemic lupus erythematosus; DKD: diabetic kidney disease; IgAN: IgA nephropathy; GFR: glomerular filtration rate; ESRD: end-stage renal disease; ESKD: end-stage kidney disease.

staining was observed in few tubular cells in MCD compared to the higher MMP-7 staining in FSGS.

The potential of serum, tissue, or urine MMP-7 as a biomarker for kidney disease has been studied previously (Table 1). MMP-7 (among other genes) was upregulated in kidney grafts from patients with interstitial fibrosis and tubular atrophy (IFTA). Indeed, serum MMP-7 levels were higher in transplanted patients with IFTA than in non-transplanted patients or transplanted patients without IFTA [35]. Interestingly, among over 11 000 diabetic and non-diabetic participants in the ARIC cohort, plasma MMP-7 levels correlated with both current kidney function and prospective kidney function decline [11]. However, in a smaller cohort of 141 diabetic kidney disease (DKD) patients, no association between serum MMP-7 levels and progression to kidney failure or mortality was found, while uMMP-7 correlated with risk of progression to kidney failure and mortality [36]. Similar findings were obtained when studying other kidney diseases such as lupus nephritis [37] or AKI following cardiac surgery [38]. Now, Yin *et al*. have observed that uMMP-7 levels increase in MCD and FSGS while serum MMP-7 levels do not change. Thus, uMMP-7 appears to be a biomarker of interest in kidney disease, but results with serum MMP-7 are conflicting and further studies are needed to determine its potential as a biomarker. Additionally, uMMP-7 may be informative in kidney transplant recipients. Among 133 kidney transplant recipients, the uMMP-7/uCreatinine ratio was higher in patients with inflammation of any kind, including glomerulonephritis, infections, IFTA, and rejection [39]. Furthermore, the combination of the uMMP-7/uCreatinine and uCXCL10/uCreatinine ratios significantly improved the sensitivity and specificity compared with either biomarker alone. uRBP (molecular weight ∼20 kDa) and uCystC (molecular weight 13 kDa) are promising biomarkers to evaluate proximal tubules injury and the resulting failure to reabsorb small-sized proteins, as they filtered by normal glomeruli and should be fully reabsorbed by proximal tubular cells [40]. Now, Yin *et al*. showed that uMMP-7 combined with uCystC and uRBP can contribute to evaluate renal tubular reabsorption in patients with MCD and FGSG. Circulating MMP-7, as a small protein, is also expected to be filtered by normal glomeruli and reabsorbed by proximal tubules, but MMP-7 of tubular injury may leak into urine. uCysC and uRBP were not significantly elevated in MCD compared to controls, suggesting preserved proximal tubule function. The higher uMMP-7, uRBP, and uCystC levels in FSGS than in MCD support a more severe tubular injury in FSGS.

The mechanisms underlying the observation that only uMMP-7 is elevated in both FSGS and MCD remain unclear. In this regard, data mining of the Nephroseq database (http://v5.nephroseq.org/) disclosed increased tubulointerstitial *MMP7* mRNA expression in human FSGS, which may lead to increased tubular production of MMP-7 that, on top of filtered-but-not-reabsorbed MMP-7, may contribute to increased uMMP-7 (Fig. 1D–E) [41]. However, Schmid *et al*. reported that tubulointerstitial *MMP7* mRNA was not increased in human MCD bulk transcriptomics (Fig. 1F) [42]. This leaves unexplained why uMMP-7, but not urinary levels of other small proteins, was increased in MCD. Yin *et al*. did observe immunostaining for MMP-7 protein in proximal tubules, suggesting that increased local protein production could contribute to increase uMMP-7. Reabsorption of filtered uMMP-7 protein may also lead to tubular MMP-7 immunostaining. Finally, the report by Schmid *et al*. may have lacked sensitivity to detect changes in gene expression in proximal tubular cells as they analysed bulk tubulointerstitial tissue [42].

Yin *et al*. did not estimate GFR by using creatinine or cystatin C-based equations. Given that they have measured urinary levels of small proteins, they could contribute to the ongoing discussion of the so-called selective glomerular hypofiltration syndrome, in which the glomerular filtration of small proteins is hypothesized to be selectively decreased [43].

Further studies showed that uMMP-7 levels correlated with the severity of kidney injury both in AKI and in CKD of diverse causes, such as IgA nephropathy [44], lupus nephritis [37], myeloperoxidase ANCA associated vasculitis (MPO-AAV) [45], and other forms of AKI [46, 47] and of CKD [13]. Among 721 patients undergoing cardiac surgery, including both children and adults, uMMP-7 was high at 6 hours post-surgery in patients that would later develop severe AKI. In addition, higher levels of uMMP-7 had a stronger association with the probability of developing AKI in children (36-fold) than in adults (17-fold) [39]. Overall, the data are consistent with the universality of uMMP-7 as a urinary biomarker of kidney disease.

The increased uMMP-7 levels in various kidney diseases appear to be the result of an increased expression in the kidney, mostly in renal tubular cells [5]. The kidney MMP-7 mRNA expression correlated with the tubular staining by immunohistochemistry of MMP-7 protein [24]. Indeed, kidney MMP-7 staining was increased in patients with CKD of multiple causes and correlated with the degree of fibrosis [13]. Now, Yin *et al*. also observed that in patients with MCD a few cells express MMP-7, whereas in FSGS the tubular expression is higher. Moreover, single cell transcriptomics identified proximal tubules, connecting tubules, and principal cells as likely cellular sources of increased tissue MMP-7 expression [14]. Thus, there may be two sources of uMMP-7: one from *de novo* expression in tubular cells and one from glomerular filtration. MMP-7 has also been found to be a key driver of urine peptidomics patterns. MMP-7 was one of the top differentially expressed peptides in the urine peptidomes of kidney transplant recipients with acute rejection, along with peptides resulting from the proteolysis of uromodulin and various collagens [48]. As MMP-7 is an endopeptidase upregulated in kidney diseases, it may influence the urinary peptidome and analysis of the urine peptidomes in different kidney diseases could also shed light on the activity of MMP-7 and its relationship to kidney injury. In this regard, MMP-7 could explain part of the urinary peptidome characteristic of CKD patients [49]. A biomarker panel composed of 273 urinary peptides (CKD273) and variants has been shown to predict CKD progression even in persons without CKD at baseline [50–52]. Recently, combined unbiased kidney proteomics and transcriptomics identified 14 proteins with kidney tissue levels that correlated with eGFR, and 152 proteins that correlated with interstitial fibrosis in patients with DKD [14]. Of them, MMP-7 showed the strongest association with both fibrosis and eGFR.

CONCLUSION

What is the clinical practice takeaway of the findings reported by Yin *et al*.? We envision two potential contexts of use. First, in children with nephrotic syndrome, the combination of uMMP-7 and either urinary cystatin C or uRBP could help orient the diagnosis (and treatment) towards MCD or FSGS, potentially avoiding a kidney biopsy in the first case. In this regard, kidney biopsy is usually avoided in children, if possible, mostly because of its invasiveness and its potentially harmful, although very rare, complications, but also because of the psychological stress that this diagnostic test provokes in young patients. In a second context of use, the analysis or urinary small proteins may help suspect

an underlying FSGS, even if the biopsy showed MCD, when the clinical course is atypical or eGFR progressively decreases, as the focal and segmental nature of FSGS may limit the sensitivity of the kidney biopsy to diagnose it. In any case, before widespread clinical implementation, the results should be externally validated by independent groups, ideally addressing the impact of these biomarkers in diagnosis, prognosis, treatment, and outcomes of childhood and other nephrotic syndromes in different contexts of use.

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CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests.

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