REVIEW ARTICLE

Matrix metalloproteinases and tissue inhibitors of metalloproteinases in chronic kidney disease and acute kidney injury: a systematic review of the literature

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Abstract

Introduction: Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteinases involved in remodeling the extracellular matrix. Tissue inhibitors of metalloproteinases (TIMPs) are a family of four proteins that act to limit the degradative actions of MMPs. Chronic kidney disease (CKD) and acute kidney injury (AKI) are public health problems worldwide, the prevalence of which has been increasing. Recent concept considers MMPs and TIMPs as critical factors before the onset of microalbuminuria, as well as accelerating factors associated with the breakdown of the glomerular basement membrane, renal scarring, and fibrosis during the progression of kidney diseases. Here we reviewed studies of the expression of MMPs and TIMPs in humans, using as clinical samples serum, plasma, and urine, with a focus on their potential role as molecular markers in CKD and AKI, as non-invasive markers.

Material and methods: We used as data sources, studies at Medline database using combinations of the following keywords: CKD, AKI, MMP, TIMP, serum, plasma, and urine.

Results: Evidence suggests that MMPs/TIMPs could be potential targets for therapeutic intervention in kidney diseases; future studies should attempt to improve the diagnostic or prognostic power of these families.

Discussion: Considering published guides, such as biospecimen reporting for improved study quality (BRISQ), strengthening the reporting of observational studies in epidemiology (STROBE), an updated list of essential items for reporting diagnostic accuracy studies (STARD), transparent reporting of a multivariate prediction model for individual prognosis or diagnosis (TRIPOD), and on the studies reviewed here, we have adapted published recommendations and proposed other news in order to enhance the transparency and quality of MMPs/TIMPs research in CKD and AKI. This review reinforces the complexities of MMPs/TIMPs in the pathobiology of the kidney and the need for well-designed and transparent biomedical studies. HIPPOKRATIA 2018, 22(3): 99-104.

Keywords: Matrix metalloproteinases, tissue inhibitors of metalloproteinases, chronic kidney disease, acute kidney injury

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Introduction

Chronic kidney disease (CKD) is defined as abnormalities in the kidney structure or function, present for three or more months, with implications for health. It is classified based on its cause, glomerular filtration rate (GFR) category, and albuminuria category[1]. The GFR is widely accepted as the best overall index of the kidney's function in terms of health and disease; however, it is difficult to measure and is commonly estimated from the serum creatinine (SCr)[1,2].

The development of CKD eventually progresses to end-stage renal disease and leads to irreversible loss of renal function[1]. Most patients with reduced renal function are not identified in the stages at which it is possible to slow down, or even prevent, the progression of CKD[1]. Chronicity is not synonymous of irreversibility; in some cases, CKD can be reversible[1].

Acute kidney injury (AKI) is defined as an increase in SCr by ≥0.3 mg/dl within a period of 48 hours or an increase in SCr to ≥1.5 times the baseline, that is known or presumed to have occurred within the previous seven days, or a urine volume <0.5 ml/kg/h for six hours[2]. AKI is a predictor of immediate and long-term adverse outcomes and is a significant risk factor for CKD[2]. As with CKD, AKI is amenable to early detection and possible prevention[1,2].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteinases that are involved in the remodeling of the extracellular matrix (ECM). MMPs are multidomain enzymes, generally consisting of a pro-domain, a catalytic domain, a hinge region, and a hemopexin-like domain[3]. To date, over 20 mammalian MMPs have

been described and are subdivided into collagenases, gelatinases, stromelysins, matrilysins, membrane type, and "other MMPs"[4]. MMPs are traditionally conceived as antifibrotic players in the conventional view of progression; however, recent concept considers MMPs as compensatory factors before the onset of microalbuminuria and as accelerating factors associated with the breakdown of the glomerular basement membrane (GBM), renal scarring, and fibrosis during the progression of kidney diseases (KD)[5,6].

Tissue inhibitors of metalloproteinases (TIMPs) are a family of four proteins that their action limits the degradative actions of MMPs. TIMPs interact with MMP active sites to block reversible their proteolytic activity[7]. TIMPs have activities independent of MMPs, including cell growth, migration, and differentiation[8]. Here, we review MMPs and TIMPs expression studies in serum, plasma, and urine, with a focus on their potential role as molecular markers in CKD and AKI. We included diabetes mellitus (DM) and hypertension studies since these diseases are among the most frequent causes of CKD[1].

Methods

Search strategy

The Medline database was searched on the 28 February 2018, using combinations of the following key words: CKD, AKI, MMP, TIMP, serum, plasma, and urine. A total of 284 articles were obtained. The recommendations of the PRISMA group were followed in terms of identification, screening, eligibility, and inclusion criteria[9].

Eligibility, inclusion, and exclusion criteria

The abstract of each article was carefully studied to verify the following eligibility criteria: i) English or Spanish language, ii) original or primary research concerning human renal function, iii) expression of MMPs/TIMPs families, and iv) CKD, AKI, DM or hypertension. The criteria for exclusion from consideration were: i) number of subjects in the group(s) of nine or less cases, ii) DNA sequencing study only, iii) renal transplant study only, and iv) studies performed in patients with a mean or median age under 18 years. Applying these criteria, 247 studies were discarded, and 37 were reviewed to verify the following inclusion criteria: i) reference to the sex and age of the groups, ii) agreement of data in the text and tables. Exclusion criteria were featuring data that, in our judgment, were duplicated. After applying these criteria, 17 studies were included, and a further 37 studies were incorporated into the introduction and conclusions. The description and discussion of these studies include the original name of the study groups, according to their authors.

MMPs and TIMPs in CKD and AKI

While the activity and the spatial and temporal expression of MMP/TIMP families in the human kidney have not been thoroughly characterized, the observational studies reviewed here demonstrated dysregulation of these families in a wide variety of kidney disorders in different fluids (Table 1).

Most of the studies focused on the levels of MMP-2 and MMP-9 quantified using enzyme-linked immunosorbent assay (ELISA) (Table 1); however, for KD type, fluid analyzed [in this case serum ($_S$)] and formula used to calculate the GFR (Modification of Diet in Renal Disease), only three studies were comparable: Peiskerova et al[14] analyzed $_S$MMP-2 and $_S$MMP-9 in non-dialyzed patients with CKD at stages 1-5; Smith et al[19] investigated $_S$MMP-2 in predominantly male and hypertensive pre-dialysis CKD patients with stages 3 and 4; and Gluba-Brzozka et al[25] determined $_S$MMP-2 and $_S$MMP-9 in CKD patients with stages 1-5, where patients at stage 5 had mean dialysis time of 27.9 months. These studies also quantified levels of gelatinase, compared to those of healthy subjects[14,19] or volunteers without CKD[25], noting a consistent increase in the levels of $_S$MMP-2 in CKD, compared to the reference group, while for $_S$MMP-9 they report no differences. These data are of great interest since they are the product of studies conducted in different countries and patients diagnosed with CKD through diverse etiologies, at different stages of the disease, with a wide variety of comorbidities and under different schemes of treatment[14,19,25].

Moreover, other studies report that plasma ($_P$) MMP-2 ($_P$MMP-2) is upregulated in CKD[10], type 1 DM (T1DM)[11] and end-stage kidney disease[18], compared to control subjects[10] or healthy controls (HC)[11,18]. Upregulation of $_P$MMP-2 is also observed in normoalbuminuric hypertensive patients, compared to albuminuric resistant hypertensive patients[24]. On the other hand, urinary ($_U$) MMP-2 ($_U$MMP-2) is proposed as a marker for elevated risk of hyperglycemia, hyperfiltration, and microalbuminuria in patients with T1DM[11]. In subjects with renal impairment living at high altitude $_U$MMP-2 is also associated with microalbuminuria[6].

The fraction sMMP-9 associated with TIMP-1, among other findings, has been reported as a predictor of low GFR in hypertensive patients[21], upregulated in diabetic nephropathy compared to T2DM[12] and chronic renal failure[12], but down-regulated in sepsis-associated AKI, compared to non-sepsis-associated AKI and controls[23].

Data regarding $_U$MMP-9 concentration analyzed in patients with AKI, as an absolute value or normalized to $_U$Creatinine, indicated that the results do not markedly differ, although authors reported that normalizing to $_U$Creatinine is less than ideal due to its non-steady state balance in those patients[13]. An elevated $_U$MMP-9 level could function as a molecular marker of AKI[13], T1DM[15], and urinary tract infection (UTI)[13]. Differential levels according to gender have been reported for $_U$MMP-9 in T1DM[15] and HC[15].

Different proportions have also been observed in detection of the activity of $_U$MMP-9[16] and $_P$MMP-9[24] according to the albuminuria category in T2DM and hypertensive patients, respectively. Most of the studies have likely

Table 1: Observational studies reviewed in this systematic review regarding the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in chronic kidney disease and acute kidney injury.

Ref	Year/ study type	Group studied, age and sex†	Fluid sample/ MMP/ TIMP studied	Main findings
10	2006*	60 CKD (60.5±1.9, 29/31) 40 CS (40.4±2.7, 20/20)	$_{U}$MMP-2[ϗ] $_{P}$MMP-9[ϗ]	↑ MMP-2 in CKD compared to CS ↓ MMP-9 in CKD compared to CS ↗ MMP-2 with SCr ↙ MMP-9 with SCr
11	2007§	93 T1DM (19.3±6.3, 49/44) 50 HC (24.1±6.8, 24/26)	$_{P}$MMP-2[ϗ,ϟ] $_{U}$MMP-2[ϗ,ϟ] $_{U}$TIMP-1[ϟ] $_{P}$TIMP-2[ϟ]	↑ $_{U/P}$MMP-2 level in T1DM compared to HC ↑ $_{P}$MMP-2 activity in T1DM compared to HC ↗ $_{P}$MMP-2 and $_{U}$MMP-2/Cr ↔ TIMP-1 and TIMP-2 in T1DM compared to HC ↙ $_{U}$MMP-2 /Cr and total MMP-2 with age ↑ $_{U}$MMP-2/Cr and total MMP-2 in T1DM >3 years of duration compared to ≤3 years of duration
12	2007*	20 CRF (61.2±12.3, 5/15) 16 T2DM (58.1±6.7, 9/7) 14 DN (T2DM+CRF) (59.2±8.0, 9/5) 20 HC (55.4±11.0, 9/11)	$_{S}$MMP-2[ϟ] $_{S}$MMP-9[ϟ] $_{S}$TIMP-1[ϟ] $_{S}$TIMP-2[ϟ]	↓ TIMP-1 and TIMP-2 in DN compared to T2DM ↑ MMP-9/TIMP-1 and MM-2/TIMP-2 in DN compared to T2DM ↓ TIMP-1 and TIMP-2 in DN compared to CRF ↑ MMP-9/TIMP-1 and MMP-2/TIMP-2 in DN compared to CRF ↓ MMP-2, TIMP-2 and MMP-2/TIMP-2 in T2DM compared to HC
13	2008§	29 AKI (59.0±3.6,19/10) 30 NS (40.8±2.4, 15/15) 15 CKD (69.2±2.4, 10/5) 10 UTI (49.8±8.1, 2/8)	$_{U}$MMP-9[ϟ]	↑ MMP-9 in AKI compared to NS+CKD ↑ MMP-9 in UTI compared to AKI
14	2009§	44 HC age-matched (58±10, 19/25) 80 CKD patients not yet dialyzed (52±16, 37/43)	$_{S}$MMP-2[ϟ] $_{S}$MMP-9[ϟ]	↑ MMP-2 in CKD compared to HC ↔ MMP-9 in CKD compared to HC ↑ MMP-2 and MMP-9 in CKD with DM compared to CKD without DM
15	2010§	121 T1DM (20.8±7.6, 59/62) 55 HC (24.3±7.6, 24/31)	$_{P}$MMP-9[ϟ] $_{U}$MMP-9[ϟ] $_{P}$TIMP-1[ϟ]	↑ $_{U}$MMP-9 in T1DM compared to HC ↑ $_{U}$MMP-9 in female subjects compared to male subjects across the entire population, T1DM and HC ↔ $_{P}$MMP-9 and TIMP-1 in HC compared to T1DM () $_{U}$MMP-9 and glucose in females with T1DM
16	2010§	28 HC age-matched with DM excluded [57,51-61, 24/4] 48 T2DM with normoalbuminuria [62, 53-69, 26/22] 27 T2DM with albuminuria [69,58-73, 18/9]	$_{U}$MMP-2[ʟ] $_{U}$MMP-8[ʟ] $_{U}$MMP-9[ʟ]	-MMP-8 and MMP-9, but not MMP-2, differed among groups, and are highest in albuminuria patients -MMP-9 activity is detectable in 89% of albuminuria patients, 74% of normoalbuminuria and 25% of HC
17	201[1]ö	38 Recovery AKI with renal replacement therapy (52.2±15.7, 23/15) 38 Non-recovery AKI with renal replacement therapy (64.7±16.2, 23/15)	$_{U}$NGAL/MMP-9[ϟ]	∩ Predict renal recovery
18	2012§	98 ESKD (50±9, 81/17) 38 HC (51±11,19/19)	$_{P}$MMP-2[ϟ] $_{P}$TIMP-2[ϟ]	↑ MMP-2 in ESKD compared to HC ↑ TIMP-2 in ESKD compared to HC ↓ MMP-2 after hemodialysis ↔ TIMP-2 after hemodialysis
19	2012§	200 CKD (69±11,144/56) 152 HS (68±12,103/49)	$_{S}$MMP-2[ϟ]	↑ MMP-2 in CKD compared to HS
20	2012ᵇ	20 DKD with normoalbuminuria (72 ±8,8/12) 48 DKD with microalbuminuria (73±9,31/17) 34 DKD with macroalbuminuria (63±11,27/7) 21 DM without KD disease) (65±13,12/9) 21 HC [42.5, 29-56,8/13]	$_{U}$MMP-1[ᶜ] $_{U}$MMP-2[ᶜ] $_{U}$MMP-8[ᶜ] $_{U}$MMP-9[ᶜ] $_{U}$MMP-1[3]ɢ	↑ Overall MMP activity in DKD patients compared to DM and HC ↑ Total MMP activity in normoalbuminuric and microalbuminuric DKD compared to macroalbuminuric DKD ↗ Total MMP activity with interstitial collagenase activity, gelatinase activity and HbA1c
21	2014§	52 Hypertensive GFR< 60 (66.6±11.0,31/21) 335 Hypertensive GFR≥ 60 (53.8±10.2,206/102)	$_{S}$MMP-2[ϟ] $_{S}$MMP-9[ϟ] $_{S}$TIMP-1[ϟ]	↑ TIMP-1 low GFR ↔ MMP-2 and MMP-9 in low GFR ↓ MMP-9/TIMP-1 ratio in low GRF - MMP-9/TIMP-1 ratio is an independent predictor of lower eGFR and albuminuria
22	2015ᵇ	141 DKD (57±8,78/63)	$_{S}$MMP-7[ϟ] $_{U}$MMP-7[ϟ]	() $_{U}$MMP-7 with mortality after adjustment for demographic and clinical covariates and $_{S}$MMP-7
23	2015ᵇ	37 SA-AKI surgical patients [70.0,61.5-75.0,19/18] 16 NSA-AKI surgical patients [70.0,57.5-77.25,9/7] 50 controls without sepsis [65.0, [57.75-74.0,22/28]	$_{S}$MMP-9[ϟ] $_{S}$TIMP-1[ϟ]	↑ MMP-9 in SA-AKI compared to NSA-AKI and controls ↓TIMP-1 and MMP-9/TIMP-1 ratio in SA-AKI compared to NSA-AKI and controls
24	2016*	17 Normoalbuminuric hypertensive patients under long-term RAS blockade (62.24±8.80,7/10) 22 Moderate and severe resistant albuminuric hypertensive patients under long-term RAS blockade, which 14 are moderate (65.72±8.29, 8/6) and 8 are severe (65.72±8.29, 6/2)	$_{P}$MMP-2[ϟ,ϗ] $_{P}$MMP-9[ϟ,ϗ] $_{P}$MMP-1[ɣ] $_{P}$MMP-9/TIMP-1[ᵉ]	^ MMP-2 in conditions of albuminuria ↓ MMP-9/TIMP-1 in normoalbuminuric compared to resistant albuminuric ↔ MMP-2 and MMP-9 levels in normoalbuminuric compared to resistant albuminuric ↑ Total MMP-2 and total MMP-9 activity in normoalbuminuric compared to resistant albuminuric ↑ MMP-9 active form levels in normoalbuminuric compared to resistant albuminuric ↙ GFR and MMP-9 levels
25	2016§	80 CKD (67.2±11.7,45/35) 24 HS (61.2±9.6,7/17)	$_{S}$MMP-2[ϟ] $_{S}$MMP-9[ϟ] $_{S}$TIMP-1[ϟ] $_{S}$TIMP-2[ϟ]	↑ MMP-2 in CKD compared to HC ↑ MMP-2/TIMP-2 ratio in CKD compared to HC ↓ TIMP-1 in CKD compared to HC ↔ MMP-9 and TIMP-2 in CKD compared to HC
6	2017§	28 WRI (55.9±11.5,7/21) 106 NRI (41.2±13.7,23/83)	$_{U}$MMP-2[ϗ] $_{U}$MMP-9[ϗ]	() Presence of MMP-2 or both and gelatinases and arbitrary units of activity ≥P90 with microalbuminuria () Presence of MMP-2 with hyperuricemia

*: The data indicate single measurement, §: cross-sectional study referred by authors; ᶜ: case-control study referred by authors; ᵇ: prospective observational study referred by authors. †: (mean ± standard deviation, No of males/No of females), [median, interquartile range, No of males/No of females]. AKI: acute kidney injury, CKD: chronic kidney disease, CRF: chronic renal failure, Cr: creatinine, CS: control subjects, DM: diabetes mellitus, DKD: diabetic kidney disease, DN: diabetic nephropathy, ESKD: end-stage kidney disease, GRF: glomerular filtration rate, N: normal subjects, HC: healthy controls, HS: healthy subjects, NRI: no renal impairment: GFR ≥60 mL/min/1.73 m^2 and ≤2.9 mg/dL urinary albumin, NSA: non-sepsis associated, P: plasma, S: serum, SA: sepsis associated, U: urine, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus, UTI: urinary tract infection, WRI: with renal impairment: GFR ≥60 mL/min/1.73 m^2 and ≥3.0 mg/dL urinary albumin or with GFR ≤59 mL/min/1.73 m^2, regardless of the level of urinary albumin. NGAL: neutrophil gelatinase-associated lipocalin, SCr: serum creatinine, U: urine. ϗ: enzyme-linked immunosorbent assay, ϙ: zymography, ϓ: fluorokine multianalyte profiling assay, ϔ: biotrak activity assay system, ʟ: Total MMP activity assay, ᶜ: Gelatinase/collagenase assay, ɣ: immunoblotting and immunoprecipitation, ᵉ: MMP/TIMP interaction assay, ↑: increase, ↓: decrease, ↔: no difference, ↗: positive correlation, ↙: inverse correlation, ↕: no correlation, (): associated,)(: non-associated, ∩: area under the curve, ^: non-active enzyme, -: other types of findings.

focused on MMP-2 and MMP-9, due to their action on col-IV, the main ECM protein in the GBM, tubular basement membrane, and mesangium[5,26]. On the other hand, $_{U}$MMP-8 in 24-hour collection is upregulated in T2DM and its levels depend on the albuminuria category[16].

Finally, the only study in which the outcome was death states that $_{U}$MMP-7 is associated with an increased risk of mortality in patients with T2DM and diabetic kidney disease[22]. This association remains robust after adjustment of demographic and clinical covariates, while $_{S}$MMP-7 is not associated with mortality and does not attenuate the association of $_{U}$MMP-7[22].

Since the evidence suggests that progressive glomerulosclerosis is characterized by a profound shift in ECM turnover[27] and that MMPs/TIMPs could be potential targets for therapeutic intervention in KD[28], future studies should attempt to improve the diagnostic or prognostic power of these genetic families through methods to optimize reproducibility, as well as increased sample sizes and greater numbers of MMPs/TIMPs analyzed.

Recommendations to enhance the transparency and quality of MMPs/TIMPs research in CKD and AKI

In this sense, we make some recommendations regarding procurement, storage and quality assurance of frozen biospecimens[29,30] and the guides STROBE[31], STARD[32], TRIPOD[33], adapting these, in some cases, to studies in humans with CKD or AKI:

1. Describe the study design[33] and sample size calculation[31,33]. Some statistical methods for calculating confidence intervals for relative risk and standardized ratios are for large sample approximations and are unreliable for studies with less than 20 cases[34].

2. Describe the criteria of inclusion, exclusion, and elimination of all the groups and how subjects flow through the study; a diagram may be helpful[33,35]. Where applicable, specify whether stratification or matching was carried out. If exist indicate criteria of exclusion about habits, illnesses, and treatments. Note that $_{p}$MMP-9 is up-regulated in tobacco smokers[36] and that significant change in its level is observed 12 weeks after smoking cessation[37].

3. Specify the period of recruitment and the population base, e.g., primary care, secondary care, general, rural or urban population[33].

4. Indicate whether there is control of the conditions that affect pre-analytical and analytical urinary albumin to creatinine ratio, such as UTI, exercise and patients with amputations, which muscle mass could which be lower[1,2].

5. Indicate the formula used to calculate GFR.

6. Provide minimum anthropometric data, such as body mass index and waist size, and minimum sociodemographic information, e.g., sex, age, education level, economic level, and access to health services. Note that the term "race" is controversial in biomedical studies[38,39]. In human genetic research, the use of biological concepts of race has been described as "problematic at best and harmful at worst"[40]. Smart et al argue that "it seems currently unlikely that a genetic concept of race and ethnicity will ever be portable enough to wholly supplant a socio-political one"[39].

7. Indicate whether there are differences between the age and sex proportions in the study groups. Note that renal MMP expression appears to be sex- and age-dependent[15,41].

8. Refer to the duration of the illness[32] or, where appropriate, indicate that this is unknown. Refer similarly to symptoms and comorbidities[32]. In the case of patients undergoing dialysis treatment, indicate the type and duration.

9. Above all, in patients with DM, indicate the glycemic control.

10.Identify the use of certain antibiotics that alter the expression of MMPs, such as doxycycline and minocycline[42,43].

11. Indicate the initial process by which the biospecimens were stabilized during collection; type of long-term preservation, the constitution of preservative time or range between biospecimens acquisition and distribution or analysis and storage duration[13,30,43-45]. Where applicable, the number of freeze/thaw cycles of the biospecimens[6,13,46,47].

12. In studies with clinical blood samples, indicate the fluid type analyzed as well as the preservative, given that some reports indicate discrepancies between levels of certain MMPs/TIMPs in serum and plasma, explained by additional unspecific release during the collection of serum[47,48] and/or by the additive type[48-50].

13. In studies with clinical urine samples, indicate the type: 24-hour collection, minuted; sample isolated by spontaneous micturition in the morning or random, midstream programmed sample, obtained via a probe through a supra-pubic puncture. Indicate whether biospecimens with hematuria were excluded to avoid false positives[6,51]. Indicate whether the analyses were with cell-free urine[20].

14. Indicate whether the assay used has been validated in the fluid studied[11]. Specify whether the assay was performed blinded. Assay methods should be reported completely and transparently with a level of detail that would enable another laboratory to reproduce the measurement technique[35]. It may be helpful to use supplementary material.

15. Studies utilizing ELISA should include the limit of detection, the coefficients of intra- and inter-assay variation.

16. Studies utilizing gel zymography should indicate the limit of detection, concentration, and type of chelant used in the control gels or, where applicable, indicate that they were not conducted[52].

17. Indicate whether the analyses were conducted with the absolute values of the MMPs/TIMPs or whether these were normalized.

Conclusions

MMPs and TIMPs are essential components in many

physiological and pathological processes due to their ability to remodel ECM components[53]. The ECM is not a mere scaffold for cells; it is a versatile and dynamic compartment that harbors cryptic biological functions that can be revealed on proteolysis[53]. ECM is involved in modulating cell proliferation, migration, differentiation, and apoptosis[28,46,54]. MMPs have been associated with renal hypertrophy, renal scarring, tubular cell proliferation, and fibrosis[4]. This sheds new light on the interplay between ECM, cells, and MMPs/TIMPs in renal pathophysiology.

Finally, it is important to highlight that studies in animal models were excluded from this review due to the complexity of MMPs/TIMPs in the kidney and because the expression of these families has been proposed as likely to be species-specific[3]. Moreover, experimental models do not always recapitulate the clinical findings of MMPs/TIMPs[4,28]. Collectively, these data highlight the complexities of MMPs/TIMPs in the pathophysiology of KD and the continued need for biomedical studies. We hope that these recommendations will help the scientific community in planning future research.

Conflict of interest

Authors declare no conflict of interest.

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