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Matrix metalloproteinases in nephrotic syndrome; a vital but obscure field of research

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ABSTRACT

Context: Matrix metalloproteinases (MMPs) are involved in the remodelling of the glomerular basement membrane (GBM) by tightly regulating the metabolism of extracellular matrix (ECM) of the GBM.

Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, PubMed, EBSCO, Scopus and Web of Science have been searched.

Results: Gelatinases (MMP-2 and MMP-9) are mainly found involved in the remodelling of GBM and therefore this review focuses on these two MMPs and their action in nephrotic syndrome (NS), which is a protein losing enteropathy occurring due to the loss of integrity of GBM. In addition to the blood corpuscles, glomerular epithelial cells and mesangium are also expressing MMPs, and various cytokines and growth factors are involved in addition to tissue inhibitors of metalloproteinases (TIMPs) in regulating the metabolism of ECM via MMPs. While examining the results of MMP activity and expression in NS, except diabetic nephropathy (DN), membranoproliferative glomerulonephritis (MPGN) and hereditary NS where there was a clear down-regulation of MMP, all the other types of NS showed conflicting results. Both suppression and induction of MMPs are finally leading to GBM thickening, loss of integrity and proteinuria. Enhanced MMP activity leads to increase in matrix turnover and accumulation of ECM remnants and apoptotic cells leading to fibrosis. On the other hand, diminished expression of MMPs prevents the normal ECM turnover and matrix accumulation. The review compiled the mechanisms of action of both downregulation and upregulation of MMPs.

Conclusions: Imbalance of ECM metabolism due to varied expression levels and activities of MMPs in different types of primary NS might contribute to the progression of nephropathies. Further studies are required to identify the potential and usage of MMPs as a diagnostic/prognostic/therapeutic tool.

Review

Implication for health policy/practice/research/medical education:
The role of MMPs in glomerular disease is increasingly appreciated. MMPs mediate both degradation of ECM components and cell proliferation and facilitate leukocyte function. Imbalance of metabolism in the ECM, in various nephropathies might direct the long-term disease course and contribute to the progression of nephropathies.

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1. Background

In normal adults, the average excretion rate of protein is less than 150 mg/d, even though an amount up to 300 mg/d is considered to be normal. However, loss of integrity of the filtration machinery causes important increase in the excretion rate of proteins (1). Rather than a disease, nephrotic syndrome (NS) is an umbrella term used for a group of signs and symptoms displayed, when the rate of protein loss through urine exceeds the rate of albumin synthesis in the liver (2). NS affects 1–3 per 100 000 children below the age of 16 years (3). According to the most recent report, the annual incidence of NS in adults is also 3 per 100 000 out of which 80-90% of the cases are idiopathic (4). Despite being considered as a rare

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disease, NS accounts for significant morbidity which is mostly due to complications like infections, thrombotic events, cardiovascular diseases, hypertension, side effects of prolonged corticosteroid therapy, reduced quality of life and early mortality.

2. The filtering unit

The glomerulus of the kidney is a very complex organelle consisting of unique cellular and extracellular elements. The glomerular filtration barrier (GFB) is a macromolecular sieve (pore size is about 8 nm) which retards the passage of large plasma proteins and some exogenous tracers while permits the free passage of water and small solutes (5). It consists of three layers as mentioned below.

a. Fenestrated endothelium of the capillary: The fenestrations are too large to prevent the passage of plasma proteins, but they are enriched with surface glycocalyx which is having a strong negative charge and thus endows charge selectivity.
b. Glomerular basement membrane (GBM): It is an extracellular matrix composed of a meshwork of collagen IV, proteoglycans like perlecan (heparan sulfate proteoglycan), glycoproteins like agrin, fibulin-1, fibrillin-1, fibronectin, ECM protein FRAS 1(Fraser ECM complex subunit 1), hemicentin-1, laminin, nidogen (Entactin) 1&2, tubulointerstitial nephritis antigen and von Willebrand factor A domain (6). All these proteins are heavily glycosylated and compared to other tissues, they are far more abundant in the GBM, suggesting a functional role of these proteins in kidney filtration (7).
c. Podocyte foot processes: It is a layer of epithelial cells surrounding the outer layer of the glomerulus. These cells have long foot like processes called podocytes. The spaces between the podocytes are called slit diaphragms which are again enriched with negatively charged proteins (Figure 1).

GFB selectively filters the molecules based on their charge and size (8). In an average adult human, the normal glomerular filtration rate (GFR) is about 125ml/min or 180 L/day. It is almost 20% of the renal plasma flow (9). The structural integrity of GFB is disrupted in NS, which leads to elevated pore size, loss of charge selectivity, effacement of podocyte foot processes, scarring and sclerosis of mesangial matrix. This further leads to the loss of albumin and even proteins with high molecular weight through the urine causing a spectrum of symptoms.

The integrity and quantity of ECM components in the GBM is stringently maintained in a normal condition which helps the proper functioning of kidney. This is achieved by regulating cell migration, proliferation and apoptosis thereby maintaining the tissue homeostasis (10). This homeostasis is disrupted in NS when the glomerular balance between ECM synthesis and ECM degradation shifts towards ECM synthesis. The equilibrium between matrix synthesis and degradation is achieved with the help of two major ECM proteases. They are plasmin and matrix metalloproteinases (MMPs). Accumulation of ECM occurs if there is (1) increase in ECM protein synthesis, (2) decrease in the production of proteases or (3) augmented synthesis or availability of ECM protease inhibitors (11).

The stimuli for increased ECM synthesis are glomerular hypertension (12), hypertrophy (13), hyperfiltration (14), remnant kidneys (15), hypercholesterolemia, products of lipid metabolism, aging (16), oxidant injury (17) increased concentration of growth factors or cytokines, eicosanoids, alteration in local matrix composition and glucose concentration. According to the study of Uchio et al (18), ECM components mount up in the glomeruli

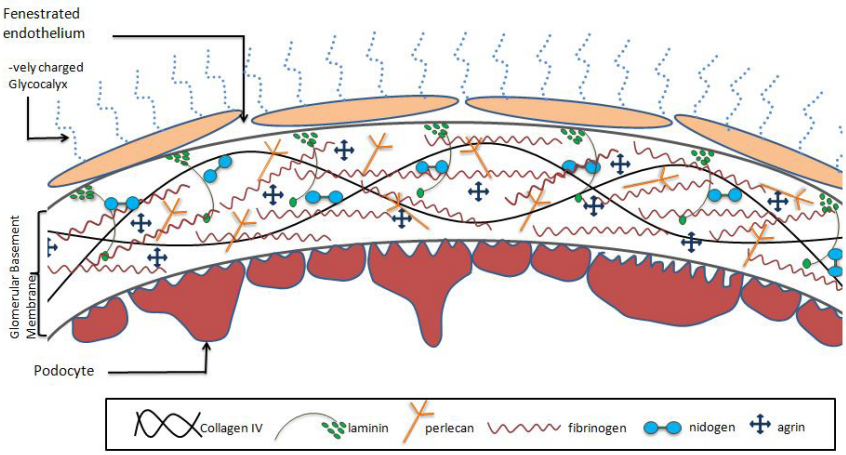

Figure 1. The glomerular filtration barrier: Figure shows the three layers of GFB, i.e., Fenestrated endothelium with surface glycocalyx, glomerular basement membrane and podocyte foot processes.

and tubulointerstitium of immune complex glomerulo nephritis (ICGN) kidneys, due to increased production and decreased degradation of ECM and finally leads to ECM augmentation. Changes in renal blood flow, hemodynamic and direct effect of glucose on tubular structures results in an escalation of collagen deposition and activation of cytokines leading to interstitial expansion. The intensity of interstitial expansion is correlated with the severity of glomerulosclerosis (19). In an experimental rat model of overload proteinuria, the total collagen content in the kidney doubled after three weeks when compared to control kidneys (20).

3. Matrix metalloproteinases

MMPs are a large family of genetically related zinc dependent endopeptidases, involved in ECM remodelling, tissue homeostasis, morphogenesis and embryonic development in normal and pathological conditions, the prototype of latter being inflammatory and neoplastic diseases (21). Initially thought to cleave only ECM proteins, MMPs are now found to disrupt non-ECM proteins like cell adhesion molecules (cadherins and integrins) and growth factors (transforming growth factor-β, TGF-β; fibroblast growth factor-R1, FGF-R1) and their receptors. More than 28 types of MMPs are identified till date and they are classified into subgroups based on their substrate specificity. The potential sources of circulating MMPs found in the plasma are fibroblasts (MMP-1,2,8,9,14), eosinophils (MMP-9), neutrophils (MMP-8,9), macrophages (MMP-2,9,12,14), endothelial cells (MMP-2,8,9,14), smooth muscle cells (MMP-1,2,3,9,14), cardiomyocytes (MMP-2,7,9) and monocytes (MMP-1,2,3 and 9) (22). MMPs are also expressed in the glomerulus and mesangial cells, but the type of MMP and the extent of expression vary depending on the normal or specific pathogenic condition of the tissue as well as it is species dependent, and the localization of these proteins have not been completely elucidated (23). MMPs are secreted as inactive pro-MMP with an amino terminal pro-peptide (inhibitory prodomain), which is cleaved irreversibly to activate the enzyme and expose the active site containing Zn ion. This is performed by plasmin or other active MMPs. There are some endogenous proteins which are involved in the inhibition of MMPs, i.e., TIMPs (tissue inhibitors of metalloproteinases) and α macroglobulins. The compounds which help in detaching the inhibitory pro-domains are heavy metals, alkylating agents, reactive oxygen species (ROS), peroxynitrite, and disulfides (24). Thereof 4 different types of TIMPs (TIMP 1-4) exerting its action on different MMPs. TIMPs exerts its action either by binding to zymogen form of MMP to prevent activation, or by binding to its activated form to prevent further activity (25, 26). Thus the MMP expression is regulated at 3 levels 1) gene expression 2) activation of pro-enzyme by plasmin or other MMPs and 3) inhibition by TIMP.

4. Action of MMPs in glomerular basement membrane

The mesangial cells and tubular epithelial cells of the kidney usually express gelatinases (MMP-9 and MMP-2) (27). MMPs are mainly synthesized from candidate cells like mesangial cells, podocytes and macrophages (28) while monocytes and activated granulocytes also express MMPs on it (29,30). According to Suto et al MMP-9 is produced under mutual regulation by mesangial cells and macrophages (31). The synthesis of MMPs is stimulated by inflammatory cytokines including TGF-β1 and IL-1β (interleukin-1β) (32). Membrane type 1 MMP (MT1-MMP) is involved in the activation of the secreted MMP-2 on the cell surface (33) while aP-1 (activator protein-1) and NF-κB are important regulators of MMP-9 expression. NF-κB upregulates MMP-9 mRNA and protein expression promoted by IL-1 and TNF-α (tumour necrosis factor-α) (34-36). IL-1 upregulates the production of proto-oncogenes c-fos and c-jun which combine to form protein complexes of homodimers and heterodimers. These transcription factors bind to the (activation protein) aP-1 binding site or TPA (12-*O*-tetradecanoylphorbol-13-acetate) responsible element of the promoter region of the genes. This promoter region is present on MMP-9 gene, but not on MMP-2. MMP-2 has aP-2 and SP-1 (specificity protein) site where there is different mechanism for regulation. Both TIMP-I and II genes possess aP-1 binding site that might be expected to increase inhibitor synthesis after treatment with IL-1β (37, 38). Induction of MMP-9 by PDGF (Platelet derived Growth Factor) or FGF also occurs through aP-1 element. Ogata et al proposed that MMP-3 is the most likely candidate that participate in activation of MMP-9 in cell lines (39). Same cytokines exert a differential regulation on the secretion of TIMP-1 and TIMP-II by the glomerular cells. This suggests that the regulation of metabolism of glomerular ECM by these cells is a highly controlled event. MMP activity is also largely regulated at post-translational level and interaction with endogenous inhibitors (21).

Reduced barrier function of peritubular capillaries and endothelial dysfunction, caused due to kidney damage in various nephropathies, suggests that MMPs leak into the vascular system. Since circulating levels of MMPs reflects the tissue levels in various nephropathies, circulating MMPs can be considered as a biologically relevant parameter of connective tissue metabolism in them (40). A significant relationship between serum MMP-2 and estimated glomerular filtration rate (eGFR) implies that kidneys clear off these biomarkers (40,41). Sekiuchi et al

(42) studied the localization of MMP-2, MMP-9, TIMP-1 and TIMP-2 in kidneys and reported that irrespective of the histopathology, the pattern of distribution of each enzyme was similar while the intensity of staining differed with each case and each disease. As per the study it was observed that MMP-2 and TIMP-1 are localized in the glomerular capillary loops (GCL), Bowman's capsule (BC) and mesangium. TIMP-2 is localized in mesangium and BC whereas MMP-9 in mesangium and GCL. MMP-2 and MMP-9 degrade type IV, V, and VI collagens as well as gelatine (40). MMP-2 targets fibronectin and laminin while MMP-9 targets type IV and V collagen. TIMP-1 is involved in the inhibition of MMP-9 while TIMP-2 inhibits pro MMP-2 (43). Upcoming evidence implicates the anti-fibrotic as well as pro-inflammatory activities of some MMPs (44-46). Based on the data, it is suggested that MMP-2 induces degradation of GBM and MMP-9 plays a role in the decomposition of the mesangial matrix.

5. MMPs in different types of nephrotic syndrome

Based on primary and secondary causes and renal histopathology NS is subdivided into discrete categories. The primary causes are minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN) and congenital NS. The major secondary causes include diabetes mellitus (DM), systemic lupus erythematosus (SLE) and Amyloidosis.

After thoroughly studying the previous articles about MMPs in NS, it was observed that the expression and activity of MMPs varied drastically among different types of NS. Since gelatinases (MMP-9 and MMP-2) were found to play the primary role in all the glomerulonephritis, this review focuses mainly on the expression and activity of MMP-2 and MMP-9 in different types of NS.

6. Minimal change disease

In MCD, minimal mesangial prominence is detected along with effacement of foot processes within the epithelial cells. Table 1 shows the results of various animal and human studies conducted on the activities and expressions of MMPs in MCD.

7. Focal and segmental glomerulosclerosis

There is segmental accumulation of ECM in the mesangium with destruction of the capillaries, sclerosis, hyalinosis and foam cells with deposition of IgM and C3 in the sclerotic segments (49). It was also found that there is an accumulation of type IV collagen in the mesangium and type III in periglomerular synechiae. Table 2 enlists the experiments conducted on MMPs in FSGS. According to Liu et al, the deposition of fibronectin within the injured glomeruli was proposed to be due to increased crosslinking of ECM by tissue transglutaminase and reduced degradation due to diminished expression of MMP-9 (50). Qin et al reported that treatment with all-trans retinoic acid induced the protein and enzymatic activity of MMP-2 and MMP-9, which otherwise was found reduced in FSGS (51). According to the study by Czech et al, increased levels of MMPs and TIMPs may be the early non-invasive biomarkers for diagnosis of FSGS in SSNS patients and they also may represent therapeutic targets for preventing chronic kidney disease progression in FSGS (52). Benazeprils are angiotensin-converting enzyme (ACE) inhibitors which decreased proteinuria and mesangial cell proliferation. It also adjusted the expression and activity of MMPs and TIMPs and maintained their dynamic balance (53). Absence of MMP-9 increases vascular stiffness and pulse pressure. Increased MMP activity at initial stages of hypertension may be protective because it could allow the vessels to adapt to increased BP (54). Both ACE and MMP-9 are Zn dependent endopeptidases. It explains how ACE inhibitor may inhibit MMP-9 (56).

8. Membranous nephropathy

GBM is thickened and there is granular deposition of IgG in MN. In an animal study conducted by Adler et al it was found that there is an accumulation of type IV collagen in the glomerulus and this could be due to the increased synthesis (60). The role of MMP-9 in the GBM breakdown was suggested by McMillan et al, who reported a temporary correlation of MMP-9 expression in cultured glomerular epithelial cells with proteinuria (61). Zakiyanov et al also reported that MMP-2 was found negatively correlating with estimated glomerular filtration rate (eGFR) (32). Fibrinolytic activity of MMP-9 was also reported by Lelongt et al who observed that MMP-9 was protective against anti-GBM antibody induced glomerular injury in mice. Impaired collagen degradation due to reduced MMP-9 can be the major mechanism

Table 1. MMPs in minimal change disease

Type of Study	Author	Sample	MMP-2	MMP-9	TIMP-1	TGF-β
Animal study	Uchio et al (47)	Renal tissue extracts	↓	↓	-	
Human study	Zakiyanov et al (32)	Serum	No change	No change	-	
	Bauvois et al (48)	Plasma	↑	Normal	↑	Normal

Table 2. MMPs in focal segmental glomerulosclerosis

Type of Study	Author	Sample	MMP-2	MMP-9	TIMP-1	TIMP-2	TGF-β
Animal study	Uchio et al (47)	Kidney tissue extracts	↓	↓	-	-	
Transgenic GH mouse model	Jacot et al (55)	mRNA expression in mesangium	No change	↓			
Transgenic GH mouse model	He et al (57)	mRNA expression in glomerulus	No Change	↑			
Glomerulosclerosis rat model	Adhikary et al (58)	Protein expression	No Change	↓			
Glomerulosclerosis rat model	Qin YH et al (51)	Protein expression	↓	↓	↑		
PAN induced FSGS rat mode	Liu S et al (50)	Glomerular expression of protein		↓			
Human study (paediatrics)	Czech et al (52)	Urine concentration	↑	↑	↑	↑	
Human study (paediatrics)	Wasilewska et al (59)	Urine concentration		No Change			
Human study (adults)	Zakiyanov et al (32)	Serum	No change	No change	-	-	
Human study (adults)	Bauvois et al (48)	Plasma	↑	Normal	↑	-	↓

Table 3. MMPs in membranous nephropathy

Type of Study	Author	Sample	MMP-2	MMP-9	TIMP-1	TIMP-2	TGF-β
Human study (adults)	Zakiyanov et al (32)	Serum	No change	↑	-	-	
Human study (adults)	Bauvois et al (48)	Plasma	↑	↓	↑	-	Normal
Human study (adults)	Akiyama et al (64)	Serum	↑		↑		
Human study (adults)	Koide et al (67)	mRNA expression in PBMC	No change	No change			
MN Cell culture model	McMillan et al (61)	Cell culture		↑			

leading to prolonged mesangial matrix expansion. In anti-GBM nephritis model of MMP-9 knock-out mice, MMP-9 administration slowed down the fibrin induced glomerular lesions (62). In Heymann nephritis model of MN, there was 9-fold increase in gelatinase activity (63). Glomerular injury in Thy 1 nephritis and MN was found to be the after effect of increased secretion of MMP-2 and MMP-9 from human mesangial cells and glomerular epithelial cells (65). Endo et al detected MMP-9 expression in lesions of mesangial matrix and MMP-2 expression was revealed along the GCLs in patients with IgAN and MN (66). Table 3 presents the studies conducted on MMPs in MN.

9. Membranoproliferative glomerulonephritis

Immune complex glomerulonephritis occurring with chronic infections (HIV, hepatitis B and C, SLE and malignancies) and associated with sub-endothelial and mesangial immune deposits (49). IL-1, epidermal growth factor, and IL-6 are found to promote mesangial proliferation (68). TGF-β is also found associated with gene expression and mesangial expression in glomerulonephritis (69). A comparative study of two rat models with reversible or prolonged mesangial matrix expansion by Tomita et al showed that, there is decreased expression of MMP-9 and decreased urinary type I collagen degrading activity in prolonged model than reversible while there was no difference in MMP-2, MMP-13, MT-1 MMP, TIMP-1, mRNA of type I collagen and type IV collagen between the models. Even though there was no significant change in the mRNA expressions of type I and IV collagens between two models, there was enhanced an accumulation of these collagens in the mesangial area in the prolonged model when compared to the reversible ones. Additionally, urinary type I collagen degrading activity was significantly correlating with matrix expansion. Therefore impaired MMP-9 expression might be a causative factor for prolonged collagen accumulation in the glomeruli and it can be used as a prognostic indicator to distinguish reversible alterations from prolonged alterations (28). Yagi et al proposed that collagen accumulation was on peak on 4th day and normalized by 5th week in a chronic model of glomerulonephritis (71). All these findings point to a decreased degradation of the collagen, being

the primary cause for development of chronic glomerular lesions rather than increases synthesis. Thus the impaired expression of MMP-9 may contribute to the development of prolonged mesangial matrix expansion indirectly through the increased mesangial deposition of fibrin (50).

10. IgA Nephropathy

In IgAN there are prominent and diffuse granular deposits of IgA in the glomerular mesangium. Table 4 shows the results of various animal and human studies conducted on MMPs in IgAN. Koide et al in their study observed an increase in expression of MMP-9 mRNA in peripheral blood monocytes of patients with IgAN and it positively correlated with urinary protein excretion. Probable explanation is that the activated monocytes in the glomerular microvascular bed release MMP-9 locally and accesses the glomerulus, interstitium or blood vessel walls, leading to their degradation and further proteinuria. Activated monocytes or macrophages also produce IL-1 and TNF-α along with MMP-9. It is therefore possible that these cytokines up-regulate MMP-9 mRNA in peripheral blood mononuclear cells from patients with IgAN. PBMC from IgAN also showed increased expression of TGF-β mRNA. MMP-9 mRNA decreased gradually with steroid treatment but not with other drugs which can be due to the immune suppressive effect of the steroids (67). Arima et al reported that monocytes play a leading role in the pathogenesis of mesangial hypercellularity, irreversible glomerular damage and interstitial tissue injury in IgAN. According to them TGF-β enhances MMP-9 transcripts in monocytes which causes persistent leucocyte accumulation (72). Lai et al reported that CD4+ T cells from IgAN increased TGF-β mRNA when compared to healthy controls and other types of glomerulonephritis (73).

11. Rapidly progressive glomerulonephritis (crescentic glomerulonephritis)

Ahuja et al examined a subject who was on steroid treatment for crescentic glomerulonephritis. He was administered doxycycline (an MMP inhibitor) for acne treatment and on commencement of the treatment, proteinuria stopped. Surprisingly when doxycycline was stopped, proteinuria resumed (75). Doxycycline inhibits glomerular proliferation and prevents fibrosis which was proved by Fundo Saglam et al who reported a decline in total glomerular cell numbers, as well as accumulation of IgG and C3 in immune complex nephritis rats treated by doxycycline. Also there was insignificant glomerular proliferation with interstitial inflammation in doxycycline treated group and an up-regulated expression of TIMP-1 in the glomerulus (65). Floege et al reported, a reduction of type IV collagen by MMP inhibitors (76). According to a study by Zhang et al, increased activities of gelatinases contribute to glomerular injury and it plays a role in the development of RPGN (77). Sanders et al observed an increased MMP-2,3,9 and TIMP-1 activity in ANCA associated crescentic glomerulonephritis and it correlated with inflammatory activity (78). Injection of anti-GBM antiserum induced the secretion of MCP-1 from mesangial cells, which lead to macrophage infiltration, which in turn adhered to glomerular endothelial cells through LFA-1 (lymphocyte function-associated antigen 1) and ICAM-1 (Intercellular Adhesion Molecule 1) (79,80). Hayashi et al reported an elevated MT-1 MMP mRNA level 7 days after the injection of anti-GBM antibody, when massive infiltration of macrophages and increased cellularity was observed with the formation of cellular crescents. Pro-MMP-2 activation was proportional to the increase of MT-1 MMP and MMP-2 gene expression. Although the mRNA expression and enzymatic activity of MMP-2 were enhanced with disease progression, the progressive matrix accumulation may be due to the impairment of ECM turnover by resident glomerular cells. This concept is supported by the fact that apoptotic cells increased with disease progression in this model (81). Wang et al also reported that MMP-9 expression was observed in the mesangial proliferative lesions of the glomeruli whereas TIMP-1 was slightly expressed (82). Miyazaki et al also supported the findings by observing increased TIMP-1 in

Table 4. MMPs in IgA nephropathy

Type of Study	Author	Sample	MMP-2	MMP-9	TIMP-1	TIMP-2	TGF-β
Human study (adults)	Bauvois et al(48)	Plasma	↓	↓	↑		↓
Human study (adults)	Akiyama et al(64)	Serum	↓		↑		
Human study (adults)	Koide et al (67)	mRNA expression in PBMC	↓	↑			↑
Human study (adults)	Urushihara et al (70)	Kidney biopsy of mesangium		↑			
Human study (adults)	Zakiyanov et al (32)	Serum	↓	↑			
Human study (adults)	Koide et al (67)	mRNA expression in PBMC		↑			↑
Mouse model of MPGN	Tomita et al (28)	mRNA expression in mesangium		↓			
Rat model of chronic IgAN	Harendza et al (74)	mRNA expression in mesangium	↑	↓			↑

mesangial proliferative lesions, glomerular epithelium as well as BC (83).

12. Diabetic Nephropathy

The classical changes seen in the glomerular compartment in DN are glomerular hypertrophy, thickening of GBM and mesangial expansion with formation of Kimmelstiel Wilson nodules. The tubulointerstitium undergoes fibrosis with increased deposition of laminin, fibronectin, type IV and type V collagen in the mesangium (84,85). Diabetes is accompanying by accumulation of ECM, which because of its slow turnover, is predominantly vulnerable to advanced glycation end-product (AGE) accumulation (86). High glucose concentration induces the synthesis of ECM proteins in both mesangial and tubular epithelial cells (87, 88). Howard et al proved that exposure of mesangial cells to high glucose resulted in increased mRNA of matrix proteins (89). Another experiment by Wahab et al found that high glucose reduced the activity of degradative enzymes such as collagenase and cathepsins in mesangial cells (90,91). According to Rysz et al circulating TIMP-1, TIMP-2 and MMP-2 are decreased in patients with DN, when compared with either chronic renal failure or diabetes (92). High glucose concentration acts on mesangial cells directly to decrease the activities of MMPs (93) which in turn leads to enlargement of mesangium in diabetes (94). This was evident from the observation that aminoguanide, an inhibitor of advanced glycation, was able to prevent the changes. McLennan et al observed a decrease in mRNA expression and enzymatic activity of MMP-9 and increased mRNA expression of MMP-2 but a decreased activity of MMP-2 after 6 months of diabetes. It was also found that activation of MMPs by aminophenyl mercuric acetate, increased the matrix degradation by 2 fold, even then it was less than that of the controls (95). High glucose can also affect MMP activation by decreasing plasmin availability and by reducing the expression of MT1-MMP. Karamessini et al reported that high glucose reduces MMP-2 and TIMP-2 expression and related these changes to tubular basement membrane thickening in DN (96). Phillipis et al concluded that exposure of proximal convoluted tubule to high glucose induces induce TIMP synthesis which leads to deposition of type IV collagen and fibronectin and reduces the degradation of matrix proteins (93). In another study by Kitsiou et al, TIMP-2 was found up-regulated in high glucose media in cultured podocytes which may have contributed to ECM accumulation (98). Caenazzo et al noticed that increased TGF-β1 expression is associated with glomerular hypertrophy in diabetic rodents, whereas treatment with anti-TGF-β1 Ab can decrease the hypertrophy (99,100). The mechanism behind this as suggested by Ziyadeh et al is, TGF-β1 can increase the levels of plasminogen activator inhibitor which decreases the plasminogen antigen which in turn decreases the plasmin and MMP-2 levels (101). TNF-α, IL-1 and IGF-1 synthesis increased in the mouse mesangial cells (102). High glucose can also enhance TGF-β, which may in turn modify promoter activity of MMP (95,103,104). Glycation of the matrix and accumulation of AGE leads to 1) inhibition of angiogenesis (105) 2) perturbation of the stretch receptors of the fibroblasts, impairing the ability to contract collagen (90) 3) decreases tyrosine phosphorylation and 4) activates MAPK pathway (106). AP-1 binding sites are present in the promoter region of some MMPs. High glucose via Angiotensin II and AT-1 receptor stimulates TGF-β expression in mesangial cells (107-110), Proximal convoluted tubules and renal interstitial fibroblasts (111). There are studies which proved that decreased MMP, increased TIMP and thereby increased ECM synthesis in diabetes is attenuated by ACE inhibitors (95,112,113). ACE inhibitor also diminished the overexpression of TGF-β (113).

13. Other types of nephrotic syndrome

13. 1. Lupus Nephritis

Zakiyanov et al observed a decrease in levels of MMP-2 and MMP-9 in SLE (32). Robak et al (114) also reported a decrease in MMP-9 while Fabermann et al (115) reported an increased activity of serum MMP-9 in SLE. The study by Makowski et al (116) showed that neutrophil MMP-9 was inversely associated with anti dsDNA antibodies which is a diagnostic indicator of SLE. Additionally, Jiang et al (117) reported a heightened expression of MMP-2 and MMP-9 in lupus nephritis.

13.2. Henoch–Schönlein Purpura

Danilewicz et al reported an increased glomerular expression of MMP-2 but not MMP-9 in HSP (118).

13.3. Hereditary nephrotic syndrome

Uchio et al found that there is decreased MMP-1, MMP-2 and MMP-9 in ICGN kidneys when compared with normal ICR mice (11,47). In another study Uchio et al published an in situ hybridization data showing ECM production in the glomeruli and tubule interstitium of ICGN mice to be upregulated (10). In ICGN mice, MT-1 MMP level decreased causing a down regulation of MMP-2 action (10). TGF-β1 is also found increased in ICGN mice (11).

14. Conflicting results of MMP increase and MMP decrease

Except DN, MPGN and Hereditary NS, where there was

a clear down-regulation of MMP expression and activity, all the other types of NS showed a conflicting report on MMP action in matrix degradation. One of our studies also demonstrated a decrease in MMP-9 levels in primary NS patients before initiation of steroid therapy (119). Therefore, the results are contradictory on the levels of MMPs in NS. One probable reason for the difference in findings is that the representation levels of MMPs vary depending on the balance between the attenuation of matrix accumulation and proliferation of mesangial cells via a transient stimulation of synthesis of MMP proteins. Another reason is that, increased MMP levels in the circulation might be due to enhanced inflammatory process, whereas decreased MMP levels result from accumulation of MMP in inflamed blood vessels and tissues (32).

Thus there can be two possible reasons of MMP action in NS leading to GBM degeneration and proteinuria (Figure 2).

1. There are reduced expression and activity of MMPs leading to ECM augmentation and further sclerosis and destruction. Hence, in conditions like DN, MPGN and hereditary NS, this might be the mechanism of action by MMP.
2. MMP activity and expression is increased in NS, leading to increased matrix turnover, increased apoptosis and deposition of ECM protein remnants leading to thickening of GBM. In both cases, the final effect is GBM thickening and damage leading to proteinuria.

15. Concluding remarks

The role of MMPs in glomerular disease is increasingly appreciated. MMPs mediate both degradation of ECM components and cell proliferation and facilitate leukocyte function. Imbalance of metabolism in the ECM, in various nephropathies might direct the long-term disease course and contribute to the progression of nephropathies. From the above findings it is clear that MMPs play an important role in the pathogenesis of NS. However, the expression level and activities of the enzyme varies depending on the type of NS and its severity. Being proved as a primary player in the pathogenesis of NS, further human studies are recommended to utilize the strong potential of MMPs as a diagnostic/prognostic/therapeutic tool.

Authors' contribution

SS: Idea of the manuscript, literature search, manuscript writing, tables and figures. BD: Manuscript review, major corrections. VD: Manuscript review, major corrections.

Conflicts of interest

The authors declare that they have no competing interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

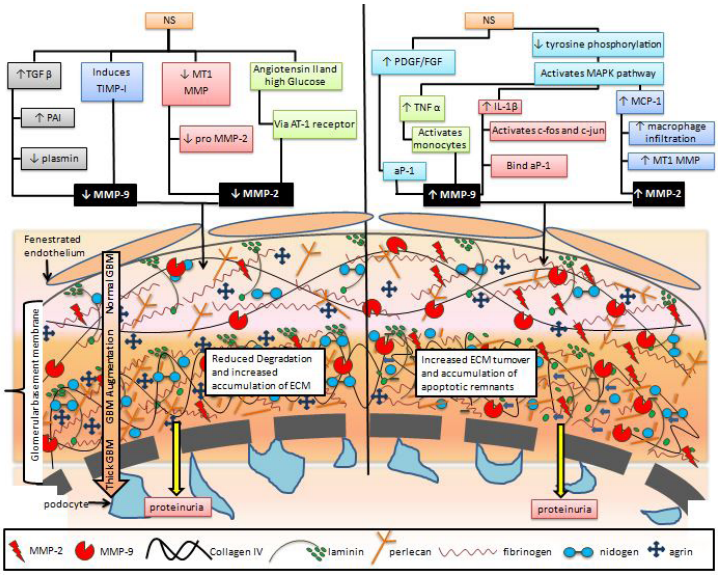

Figure 2. Mechanism of Action of MMPs in NS: The figure depicts the different pathways by which MMPs are suppressed or induced. Glomerular Filtration barrier is also illustrated with different ECM components. After entering the Glomerular Basement membrane, MMPs exerts its action (MMP-9 cleaving collagen IV and MMP-2 cleaving fibronectin and laminin) leading to ECM augmentation and thickening. This causes loss of integrity of the filtration barrier and protein loss.

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