Virchows Arch (1996) 427:567–573

ORIGINAL ARTICLE

Hideo Shiiki · Toshihiko Nishino · Hideto Uyama
Toshihiko Kimura · Kazuo Nishimoto
Toshio Hashimoto · Yoshihiro Fujii · Kazuhiro Dohi

Alterations in extracellular matrix components and integrins in patients with preeclamptic nephropathy

Received: 21 August 1995 / Accepted: 30 October 1995

Abstract The glomerular features of patients with preeclampsia consist of swelling of endothelial cells, subendothelial deposits of incompletely defined material, and thickening of the capillary walls. These abnormalities are thought to resolve in the postpartum period. The distribution of extracellular matrix (ECM) components and integrins was investigated in 10 such patients. Frozen sections and paraffin-embedded sections were stained with antibodies to type IV collagen, laminin (LN), fibronectin (FN), vitronectin (VN), tenascin (TN), fibronectin receptor (FNR), and vitronectin receptor (VNR). In preeclamptic nephropathy, the accumulation of type IV collagen, LN, FN, TN, and FNR was observed in the thickened capillary walls, particularly in the subendothelial layer and, to some extent, in the mesangium. However, deposits of VN were sparse and the distribution of VNR was similar to that in normal kidney. In segmental sclerotic lesions, the amounts of type IV collagen, LN, FN, VN, and TN were increased, whereas those of FNR and VNR were markedly decreased. These results suggest that the materials deposited in the subendothelial space consist of ECM components as well as of plasma-derived proteins, and that the deposition of ECM components and of FNR may be involved in the development and the reparative process of the characteristic glomerular lesions. The formation of sclerotic lesions was linked to the accumulation of ECM components, but not to an interaction with integrins.

Key words Preeclamptic nephropathy · Extracellular matrix components · Fibronectin · Tenascin · Integrins

Introduction

The nephropathy seen in patients with preeclampsia is characterized by swelling of the endothelial cells, subendothelial deposits, and thickening of the capillary wall, which occasionally exhibits a double-contour appearance [5, 13, 24]. Electron microscopy demonstrates an extensive widening of the subendothelial space, which is filled with dense, finely granular, fibrillar or electron-lucent subendothelial deposits [5, 13]. The subendothelial deposition of fibrin and IgM is frequently detected by immunofluorescence microscopy [5, 13, 27]. However, the constituents of the subendothelial deposits are poorly defined. Because the glomerular changes disappear in the postpartum period, materials deposited in the subendothelial layer may play a key part in the evolution and resolution of preeclamptic nephropathy.

Evidence indicates that extracellular matrix (ECM) components are involved in the progression and aggravation of glomerulonephritis in humans and experimental animals [3, 11, 23, 30]. To our knowledge only one report has focused on the distribution of type IV collagen, laminin (LN), fibronectin (FN), and proteoglycan in patients with preeclamptic nephropathy [10]. Changes in new components of ECM, including vitronectin (VN) and tenascin (TN), and integrins, cell surface receptors of ECM, have not been documented in such patients. We, therefore, evaluated the alterations in ECM components and integrins of patients with preeclampsia.

Materials and methods

Patients

Thirty-six Japanese women in whom pure preeclampsia characterized by hypertension, oedema, and nephrotic-range proteinuria was diagnosed between 1983 and 1994 underwent a renal biopsy in the postpartum period. Some of these cases have been reported elsewhere [27]. Of the 36 patients, 10 for whom both frozen and paraffin-embedded sections were available were selected for this study. The 10 patients ranged in age from 26 to 32. Seven were primiparas and three, multiparas. Proteinuria appeared in the 30th to 35th (average, 32th) week of gestation and increased progressively to 3.5–10 g/day. All patients had hypertension (160/100 mmHg or more) and severe oedema. Serum creatinine was normal (less than 1.0 mg/dl) and serum uric acid was markedly elevated in all patients, ranging from 6.4 to 10.6 mg/dl. All patients delivered in the 31st to 37st (average, 35th) week of gestation, but 8 required Cesarean section for fetal distress.

H. Shiiki (✉) · T. Nishino · H. Uyama · T. Kimura · K. Nishimoto
T. Hashimoto · Y. Fujii · K. Dohi
First Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara 634, Nara, Japan

Light microscopy

Percutaneous renal biopsy was performed between 7 and 14 days after delivery. For light microscopy, renal tissue fixed in formalin and embedded in paraffin was stained with haematoxylin-eosin, periodic acid-Schiff, and periodic acid silver methenamine.

Immunofluorescence studies

Tissue for immunofluorescence microscopy was snap-frozen in OCT compound and cut at a thickness of 4 μm with a cryostat. Air-dried sections were washed with phosphate-buffered isotonic saline (PBS, pH 7.2). Immunoglobulins, complement factors, and fibrinogen/fibrin-related antigen (FRA) were detected by a direct method using fluorescein-conjugated antisera to IgG, IgA, IgM, C1q, C3, and FRA (MBL, Nagoya, Japan). Sections were incubated with these antibodies in a moist chamber for 1 h at room temperature.

To study the localization of ECM components in the glomeruli, frozen sections were stained by an indirect method. Air-dried sections were allowed to react overnight in a moist chamber at 4° C with rabbit anti-human polyclonal antibodies to type IV collagen, LN, FN, VN, and TN (Chemicon, Calif.). After being washed with PBS, the sections were incubated with fluorescein-conjugated goat affinity-purified antibody to rabbit IgG (Cappel, Calif.).

Immunohistochemical studies

To observe the precise localization of integrins and ECM components and to examine focal and segmental glomerulosclerotic (FSGS) lesions, immunohistochemical staining was also carried out on formalin-fixed paraffin-embedded sections by the streptoavidin-biotin (SAB) method, as previously described [28]. Sections were deparaffinized and endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min. Next, the sections were incubated for 10 min at room temperature with 0.4% proteinase K (DAKO, Calif.) and allowed to react overnight with polyclonal antibodies to human fibronectin receptor (FNR; Chemicon, Calif.), vitronectin receptor (VNR; Telios, Calif.), type IV collagen, LN, FN, VN, and TN in a moist chamber at 4° C. This procedure was followed by incubation with biotinylated goat anti-rabbit immunoglobulin for 10 min and with peroxidase-labelled streptoavidin for 15 min (DAKO LSAB Kit, Calif.), with thorough washing in PBS between the steps. The colour reaction was developed with a 3,3'-diaminobenzidine-peroxide substrate. Mayer's haematoxylin was used for counterstaining.

The intraglomerular distribution of immunoglobulins, complement factors, FRA, ECM components, and integrins was graded according to the extent and intensity of staining, as follows: 0, negative; 1+, weakly positive; 2+, positive; 3+, strongly positive.

As normal control tissue we used apparently normal portions of kidneys removed from three patients with renal cell carcinoma.

Results

Light microscopy

All 10 patients exhibited the typical glomerular features of preeclamptic nephropathy, including swelling of the glomerular endothelial cells (endotheliosis), mesangial widening, and diffuse thickening of the capillary walls observed as a double contour on silver staining although biopsy was performed on relatively late stage of preeclamptic nephropathy. FSGS lesions were present in all patients, as described previously [27]. The early stage of FSGS lesions predominated. In such an early lesion, the affected tufts were either filled with hyaline-like material, or solidified by capillary collapse accompanied by an increase in the mesangial matrix. Most FSGS lesions showed adhesion to Bowman's capsule.

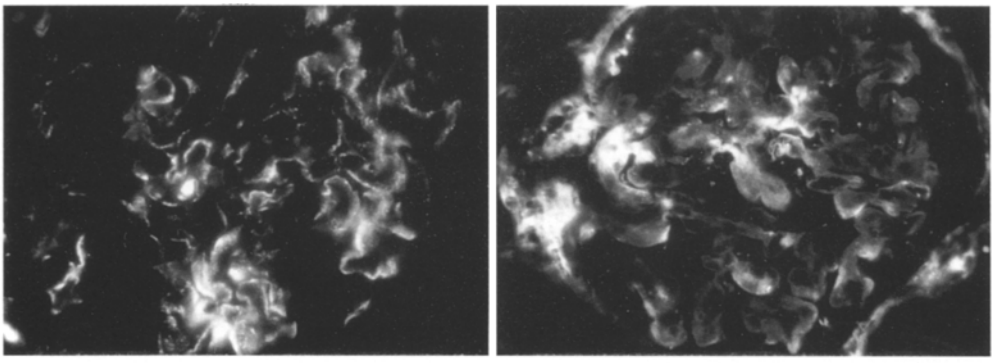

Fig. 1 Fine granular deposits of IgM are observed along the capillary walls (*left*). FRA are deposited segmentally along the capillary walls and in the mesangium (*right*). (Frozen sections: *left* ×210, *right* ×210)

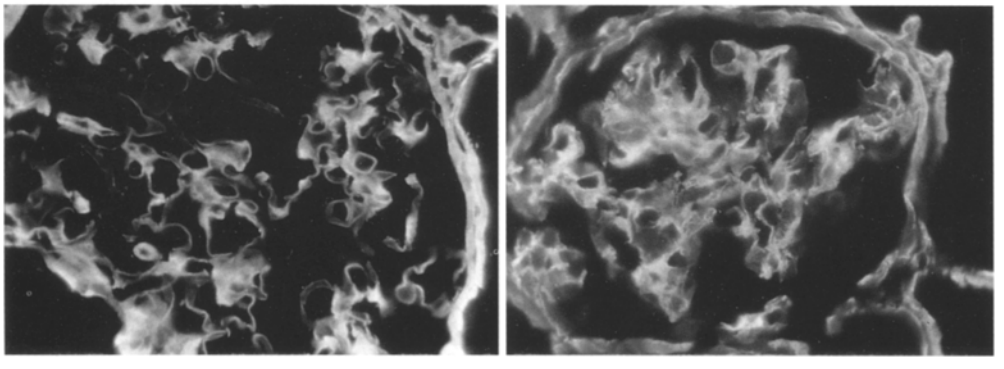

Fig. 2 Normal glomerulus (*left*) and a glomerulus from a patient with preeclampsia (*right*), stained with antibody to type IV collagen. Staining of type IV collagen of preeclamptic nephropathy is increased along the capillary walls and in the mesangium. (Frozen sections: *left* ×270, *right* ×210)

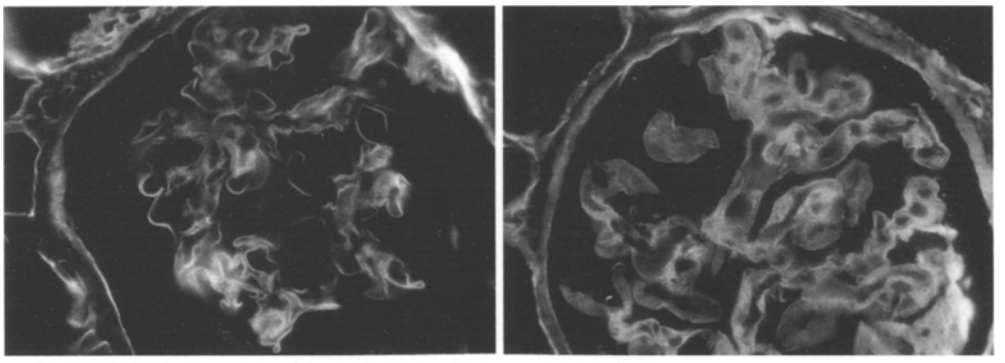

Fig. 3 Compared with a normal glomerulus (*left*), LN is increased in the subendothelial space of the GBM in preeclampsia (*right*). (Frozen sections: *left* ×270, *right* ×270)

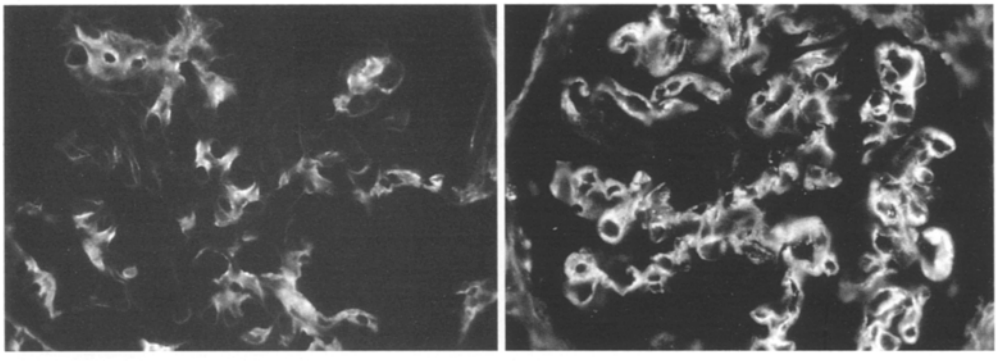

Fig. 4 A normal glomerulus showing mesangial staining of FN (*left*). In preeclampsia, massive deposition of FN is observed in the subendothelial layer of the GBM (*right*). (Frozen sections: *left* ×270, *right* ×210)

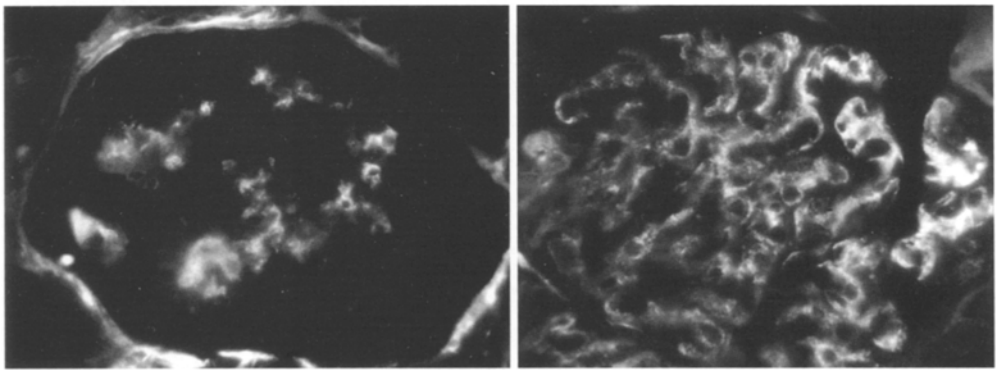

Fig. 5 A normal glomerulus shows mesangial staining of TN (*left*), while a glomerulus from a preeclamptic patient displays granular and diffuse staining in the subendothelial and in the mesangial areas (*right*). (Frozen sections: *left* ×250, *right* ×250)

Table 1 Distribution of extracellular matrix (*ECM*) components and integrins in patients with preeclamptic nephropathy (grade of intraglomerular deposition: 0, negative; 1+, weakly positive; 2+, positive; 3+, strongly positive; *FSGS* focal and segmental glomerulosclerotic)

ECM and integrins	Intraglomerular localization				
	Preeclamptic nephropathy			Normal control	
	Mesangium	Capillary wall	FSGS lesion	Mesangium	Capillary wall
Type IV collagen	1+~2+	2+~3+	3+	0~1+	2+
Laminin	1+	2+~3+	3+	0	2+
Fibronectin	2+~3+	3+	3+	2+	0
Vitronectin	0~1+	0~1+	2+	0	0
Tenascin	2+~3+	3+	3+	2+	0
Fibronectin receptor	3+	3+	0~1+	2+	1+~2+
Vitronectin receptor	0~1+	1+	0~1+	0~1+	1+

Direct immunofluorescence

All patients exhibited granular and discontinuous depositions of FRA and IgM along the capillary walls and in the mesangium (Fig. 1). The staining intensity was 1+ to 2+, often showing a segmental pattern. Deposition of FRA appeared less prominent in our patients [27]. IgA, C1q and C3 were deposited, in a more markedly segmental fashion, in one patient each.

ECM components and integrins in normal renal tissue

The staining patterns of ECM components in frozen sections were identical to those in paraffin sections. Type IV

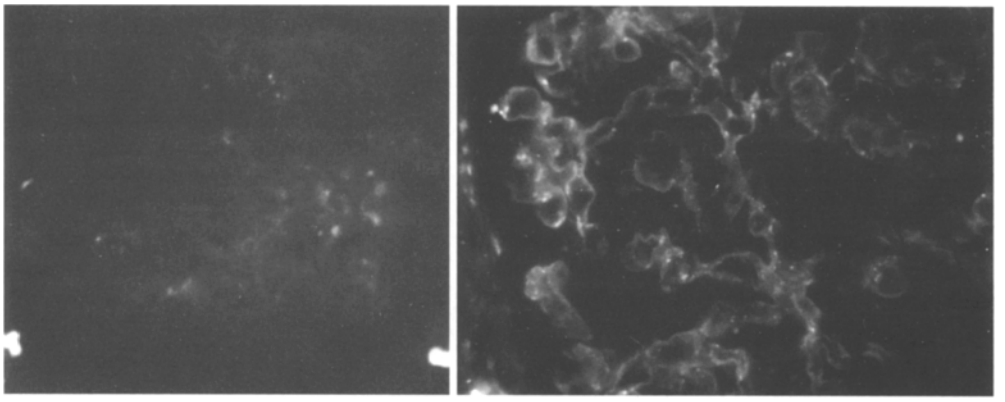

Fig. 6 VN is negative in a normal glomerulus (*left*). A glomerulus from a preeclamptic patient shows weak and granular staining of VN along the capillary walls (right). (Frozen sections: *left* ×200, *right* ×250)

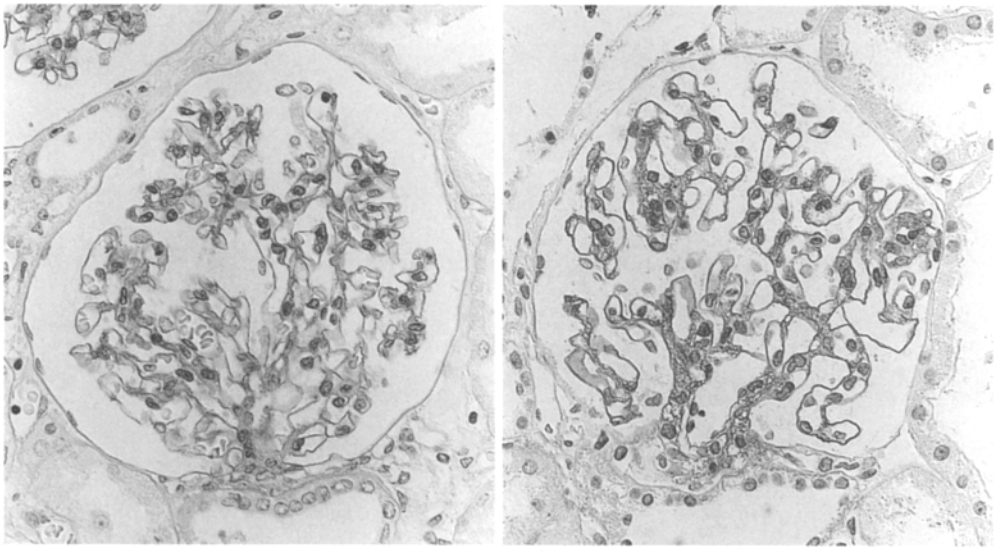

Fig. 7 A normal glomerulus exhibits staining of FNR in the mesangial areas and along the capillary walls (*left*). A marked increase in FNR expression is observed in a glomerulus obtained from a preeclamptic patient (*right*). (Paraffin sections: *left* ×220, *right* ×220)

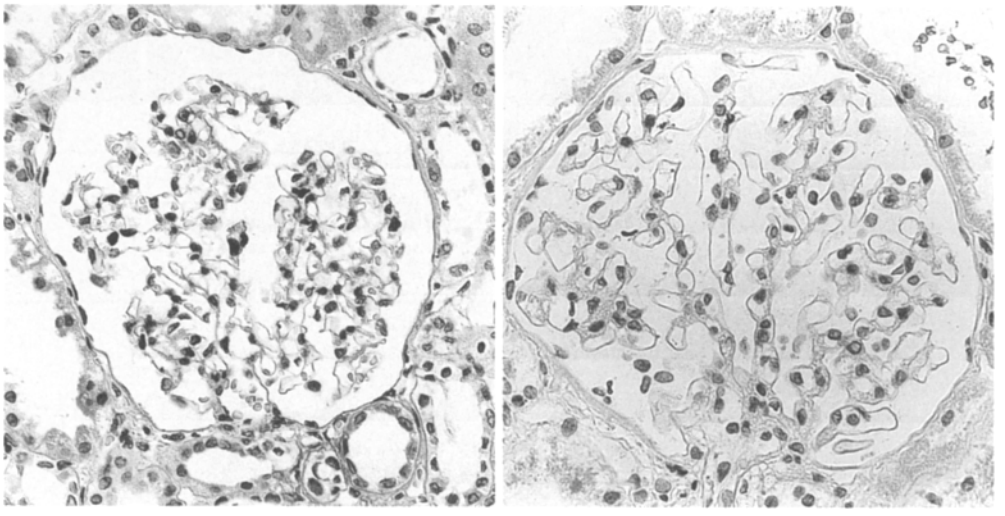

Fig. 8 In a normal glomerulus (*left*) and a glomerulus obtained from a preeclamptic patient (*right*), VNR is weakly positive in the capillary walls. (Paraffin sections: *left* ×210, *right* ×210)

collagen was detected in a linear pattern along the glomerular basement membrane (GBM), Bowman's capsule, and tubular basement membrane (Fig. 2). The distribution of LN was identical to that of type IV collagen (Fig. 3). Staining of FN and TN was limited to the mesangial areas (Figs. 4, 5). VN was not detected in the glomeruli (Fig. 6). FNR was observed in the mesangial areas and along the capillary walls (Fig. 7). VNR was weakly positive in the mesangial areas and along the capillary walls (Fig. 8).

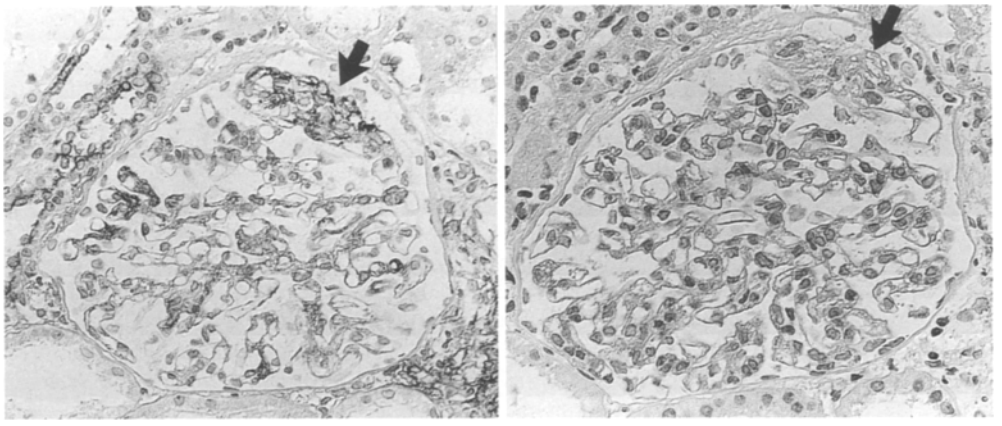

Fig. 9 TN is strongly positive in a FSGS lesion (*left*), whereas staining of FNR is markedly decreased (*right*). *Arrows* indicate FSGS lesion. (Paraffin sections: *left* ×160, *right* ×200)

ECM components and integrins in preeclamptic nephropathy

Immunofluorescence and immunohistochemical findings in preeclamptic nephropathy are summarized in Table 1. Distribution patterns and intensities of each material were similar in all patients. Type IV collagen and LN extended diffusely in the thickened capillary walls involving the subendothelial space as well as the GBM, and in the widened mesangial areas (Figs. 2, 3). FN and TN were strongly positive in the subendothelial space and in the mesangium (Figs. 4, 5). Although exact localization of the staining in the capillary wall was not always possible in frozen sections, careful examination of paraffin sections under an oil-immersion lens suggested that the staining corresponded to a widened subendothelial layer. FN and TN were more predominant in the subendothelial space than in the mesangial region. However, VN was detected in only a few patients and showed weak and granular immunoreaction along the capillary walls (Fig. 6). FNR was strongly positive in the thickened capillary walls and also in the widened mesangial areas (Fig. 7). The distribution of VNR in preeclamptic nephropathy was similar to that in the normal kidney (Fig. 8).

In FSGS lesions, strong staining of type IV collagen, LN, FN, VN, and TN was observed in all patients. TN showed the strongest immunoreaction among these ECM components (Fig. 9). Conversely, FNR and VNR were negative or weakly positive in FSGS lesions (Fig. 9).

Discussion

The distribution of ECM components and integrins has been described in normal and diseased kidneys [4, 6, 23, 29, 30]. In the normal kidney, type IV collagen, LN, FN, and TN, a recently described ECM component, are present within the glomeruli. Type IV collagen and LN are major constituents of the GBM, while FN and TN form the mesangial matrix [4, 23, 31]. FN, an adhesive glycoprotein, is involved in cellular adhesion, cellular proliferation, phagocytosis, wound healing, and clot formation [26]. TN is also a glycoprotein with multiple functions, including cell attachment and detachment, cell growth stimulation, wound healing, and haemoagglutination [25]. VN is a cellular adhesive glycoprotein that possesses various physiological actions, including cellular adhesion, inhibition of cellular injury by C5b-9 complex, and facilitation of blood coagulation [16, 22], and is not found within normal glomeruli [2, 16]. FNR ($\alpha 5\beta 1$ integrin) and VNR ($\alpha v\beta 3$ integrin) bind specifically with FN and VN, respectively, and are distributed along the capillary walls [6, 16, 29].

The staining patterns of ECM components and integrins in normal renal tissues examined were identical to those mentioned above.

The present study demonstrated that in patients with preeclampsia, type IV collagen, LN, FN, TN, and FNR were increased mainly in the thickened capillary walls, especially in the subendothelial space and, to some extent, in the mesangial areas. Direct immunofluorescence also showed that IgM, IgA, and FRA were deposited in the subendothelial layer of the GBM. These findings indicated that the materials deposited consisted not only of plasma-derived proteins, but also of ECM components and integrins. These findings supported the previous report by Foidart et al. [10] that structural proteins of the GBM are present in the thickened capillary walls.

It is unclear whether the increased ECM components and FNR in the thickened capillary walls resulted merely from the entrapment of plasma materials or from collaborative actions with local production by glomerular cells. Plasma FN is markedly elevated in patients with preeclampsia and is considered to indicate damage to endothelial cells [7]. Some recent papers have reported that plasma or serum levels of type IV collagen, LN, and FNR were increased in toxaemia of pregnancy [12, 17] and their authors have presumed that these materials are released from injured placental tissue into the general circulation [12, 17]. However, mesangial cells, epithelial cells and, probably, endothelial cells synthesize type IV collagen, LN, FN, TN, and proteoglycans in cell culture [9, 30]. Foidart et al. [10] also reported that the addition of FN to culture media stimulated the production of collagen by mesangial and epithelial cells. Increased levels of messenger RNA of type IV collagen, LN, and TN

were observed in the glomeruli of various renal diseases and were up-regulated by transforming growth factor (TGF)-β1 [8, 32, 33]. TGF-β1 also may promote the induction of FNR expression [14]. Nevertheless, there is no information concerning the significance of TGF-β1 in preeclamptic nephropathy. Although a precise mechanism has not been determined, we suggest that, in preeclamptic nephropathy, the majority of type IV collagen, LN, TN and, probably, FNR are synthesized by the glomerular cells (mesangial cells, epithelial cells, and endothelial cells) and that a minority of these substances may be deposited by an increased permeability of damaged endothelial cells with insudation of plasma contents. Because of the increased expression of FNR, it seems likely that the massive deposition of FN is caused by cooperative actions with exudation of plasma, local production, and specific binding with FNR.

In FSGS lesions, the amounts of type IV collagen, LN, FN, VN and TN were increased considerably, whereas the amounts of integrins, FNR, and VNR had either decreased markedly or disappeared. Several authors have demonstrated that ECM components were increased in the early stages of sclerotic lesions of glomerulonephritis in humans and experimental animals [3, 11, 31]. In contrast to ECM components, integrins are reported to be decreased in sclerotic lesions [18, 19]. Our observations support those reports with respect to ECM components and integrins in FSGS lesions. It seems likely, therefore, that the accumulation and/or overproduction of ECM components is ubiquitous in FSGS lesions, regardless of the underlying pathologic processes and morphologic type of renal disease. The mechanisms involved may be independent of interaction with integrins.

Apart from FSGS lesions, VN was deposited in very small amounts, and VNR, its cell surface receptor, was unchanged. VN binds to thrombin-antithrombin III complex and facilitates coagulation by protecting the activity of thrombin and by inhibiting the activity of plasminogen activator [15]. Thus, the deposition of VN may cause local hypercoagulability [16]. It is well known that patients with preeclampsia have chronic intravascular coagulation [13, 20], and we thus expected that VN and VNR would be increased in preeclamptic nephropathy as in other renal diseases [16, 22]. The measurement of plasma VN in patients with preeclampsia could help to explain our contrasting findings.

The significance of the accumulation of ECM and integrins in preeclamptic nephropathy is not well understood. It is generally accepted that both clinical symptoms and characteristic glomerular changes of preeclampsia resolve in the postpartum period [5, 13, 24], suggesting that the thickened capillary walls are completely repaired. The processes involved may consist of disposal of ECM components and plasma materials, adhesion of the newly evident subendothelial space, and repair of the damaged GBM. In the present study, deposition of FN, TN, and FNR in the thickened capillary walls was the most conspicuous finding. Foidart et al. [10] demonstrated massive deposition of FN in the subendothelial space. Truong et al. [31] reported extensive deposition of TN in that space induced by thrombotic microangiopathy, which may result from pathogenetic mechanisms similar to those in preeclampsia [20]. Concerning the reparative process of various pathologic conditions, FN and TN are thought to have key roles in the repair of tissue [25]. Several recent studies suggest an important role for β1 integrins, including FNR, in maintaining the adhesion of endothelial cells and epithelial cells to the GBM [1, 21]. Our results suggest that an increase in FN, TN, and FNR may be involved in the attachment and repair of the separated space. The synthesis of type IV collagen and LN may be related to the regeneration of the damaged GBM. It is also possible that subendothelial deposits are eliminated by the glomerular cells and/or are passed through the GBM to the urinary space.

In summary, the results of this study suggest strongly that ECM components and integrins are closely linked to the development and reparation of glomerular lesions in patients with preeclamptic nephropathy. Additional studies of the mechanisms responsible for the synthesis of ECM components and integrins may provide insights into the pathogenesis of this disorder, as well as in similar conditions such as thrombotic microangiopathy.

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