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Mesangial accumulation of GA-pyridine, a novel glycolaldehyde-derived AGE, in human renal disease

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Mesangial accumulation of GA-pyridine, a novel glycolaldehyde-derived AGE, in human renal disease.

Background. Advanced glycation end products (AGEs) contribute to diabetic and atherosclerotic end-organ damage, but the mechanisms of AGE-formation and AGE-induced damage are unclear. Glycolaldehyde (GA) is a Maillard-reaction intermediate and can be formed by reaction of L-serine with the myeloperoxidase-system. GA reacts with proteins to form AGEs, such as GA-pyridine, which is specific for protein modification by GA. GA-pyridine accumulates in human atherosclerotic lesions. As atherosclerosis and progressive glomerulosclerosis share many similarities, we hypothesized that GA-pyridine accumulates in renal diseases, especially those with prominent mesangial involvement.

Methods. Paraffin-embedded renal biopsies from 55 patients with various renal diseases, as well as control tissue, obtained from the unaffected part of kidneys from 10 patients with renal cell carcinoma were immunohistochemically stained with a monoclonal antibody directed against GA-pyridine and were scored semiquantitatively. Additional sections were scored for mesangial matrix expansion (MME) and focal glomerular sclerosis (FGS).

Results. In normal human kidneys, GA-pyridine was mainly localized in tubular epithelial cells, but not in the glomerular mesangium. Significant mesangial GA-pyridine accumulation was found in disorders with mesangial involvement as a common denominator. In contrast, mesangial GA-pyridine accumulation was less prominent in renal diseases without prominent mesangial involvement. Moreover, mesangial GA-pyridine accumulation was more pronounced in kidneys with higher MME and FGS scores across the different diagnoses.

Conclusion. GA-pyridine accumulates in the mesangium in human renal disease, in particular in disorders with mesangial involvement. Further studies should elucidate whether mesangial GA-pyridine plays a role in the progression of glomerular damage.

Key words: advanced glycation end products, Maillard, diabetic nephropathy, mesangial matrix expansion, nonenzymatic glycosylation.

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Advanced glycation end products (AGEs), formed in the Maillard reaction, accumulate with normal aging [1], but accelerated AGE formation is seen in diabetes [2] and uremia [3]. In normal physiologic conditions, AGEs are cleared by the kidney, implicating that deterioration in renal function results in AGE accumulation [4, 5]. Furthermore, the AGE inhibitor pyridoxamine diminishes end-organ damage of the kidney [6, 7], supporting its pathophysiologic significance.

There are at least 2 mechanisms by which AGEs may contribute to tissue injury. First, AGE modification directly alters the structure and function of extracellular matrix proteins [4, 8]. Second, AGEs modulate cellular functions through ligation of specific cell surface receptors, such as RAGE [9], SR-A (scavenger receptor A) [10], CD36 [11], and LOX-1 [12]. By binding to these receptors, AGEs could give rise to altered gene expression [9], tubular epithelial mesenchymal transformation (TEMT) [13], monocyte migration [14], cellular oxidative stress, increased vascular permeability, and up-regulation of cell adhesion molecules [8, 15].

Many different AGEs, formed in various pathways, have been identified so far [4]. Glycolaldehyde formed either as a fragmentation product in the Maillard reaction [16] or as a result of the myeloperoxidase-hydrogen peroxide-chloride (MPO) reaction [17] can react with proteins to yield various AGEs. Recently, a novel specific GA-derived AGE, called GA-pyridine, has been described in foam cells and in the extracellular matrix of human atherosclerotic fibrotic lesions [18]. The presence of GA-pyridine in atherosclerotic lesions suggests an active participation of this AGE in the initiation and progression of atherosclerosis [18].

Progressive glomerulosclerosis shares many similarities with atherosclerosis, including enhanced extracellular mesangial matrix deposition and macrophage infiltration [19]. However, until now no data have been available on GA-pyridine in the human kidney, so it is unknown whether GA-pyridine accumulates in renal disorders as well. Therefore, to elucidate a possible

contributing role of GA-pyridine in the pathogenesis of renal diseases, in particular those with prominent mesangial involvement, we studied the accumulation of GA-pyridine in various renal disorders and in control renal tissue. Moreover, we studied whether mesangial GA-pyridine deposition was related to the extent of glomerular damage assessed as mesangial matrix expansion (MME) and focal glomerular sclerosis (FGS). Finally, to reveal possible involvement of the MPO-system in the formation of renal GA-pyridine in human renal diseases, we studied the colocalization of GA-pyridine and MPO.

METHODS

Patients

Renal biopsies from 55 patients with various renal diseases who were admitted and examined in the University Medical Center Groningen served as the study group. Morphologic diagnoses were made by a qualified pathologist, unrelated to the present study. Patients were selected to represent a variety of disorders with prominent mesangial involvement ($N = 32$) [diabetic nephropathy ($N = 10$), Wegener's granulomatosis ($N = 8$), mesangial proliferative glomerulonephritis ($N = 7$), focal glomerulosclerosis ($N = 7$)], as well as disorders without prominent mesangial involvement ($N = 23$) [membranous glomerulonephritis ($N = 7$), minimal change disease ($N = 8$), and chronic allograft rejection ($N = 8$)]. Control renal tissue ($N = 10$) was obtained from the unaffected part of kidneys from patients undergoing surgery for renal cell carcinoma. Tissue was fixed in 4% paraformaldehyde and processed for paraffin embedding according to standard procedures. Clinical parameters (blood pressure, serum creatinine, and proteinuria), obtained at the time of biopsy were determined for all different groups.

Assessment of renal morphologic damage

Renal biopsies, routinely stained with hematoxylin and eosin, methanamine-silver, or periodic acid–Schiff (PAS), were blindly scored by a qualified pathologist for glomerular MME and FGS. MME was scored positive if the broadening of the mesangial areas was 2 to 3 times that of the mesangial width seen in control glomeruli. FGS was scored positive when collapse of capillary lumens, mesangial matrix expansion, hyalinosis, and adhesion formation were simultaneously present. Glomeruli were scored for MME and FGS as follows: unaffected glomeruli were scored as 0, if 1 quadrant was affected with MME or FGS a score of 1 was adjusted, 2 quadrants affected was scored as 2, 3 quadrants as 3, and if all quadrants were positive for MME or FGS, a score of 4 was given. The means for MME or FGS of all scored glomeruli of 1 biopsy were calculated.

Immunohistochemistry

Paraffin sections (4 μm) were dewaxed, rehydrated, and endogenous peroxidase was blocked with 0.3% H_2O_2 in phosphate-buffered saline (PBS) for 30 minutes. Sections were incubated with a mouse monoclonal anti-GA-pyridine antibody (0.5 μg/mL) [18] for 60 minutes. Antibody dilutions were made in PBS, and supplemented with 1% normal human serum. The specificity of this antibody has been confirmed previously by noncompetitive enzyme-linked immunosorbent assay (ELISA) [18]. Binding of the antibody was detected using sequential incubations with peroxidase (PO)-labeled rabbit antimouse and PO-labeled goat antirabbit antibodies; both for 30 minutes. Peroxidase activity was developed by using 3,3′-diaminobenzidine tetrachloride for 10 minutes. Sections were counterstained with hematoxylin.

Three types of control tests were performed to determine the specificity of the antibody in tissue sections. First, control sections were incubated with anti-GA-pyridine antibody solutions, after being preincubated with the antigen to which it is directed i.e. GA-BSA [18]. Second, sections were incubated with unrelated mouse monoclonal antibody (antirat macrophages, ED-1), and third, sections were incubated with PBS, both in absence of primary antibodies.

Immunohistochemical staining intensity in glomeruli and interstitium was assessed by semiquantitative scoring on a scale of 0 to +++, 0 (absent), ± (occasionally weak), + (weak), ++ (moderate), +++ (strong staining). Data were converted to percentages [8], moderate to strong staining (++ to +++), and any positive staining (± to +++) (Tables 2 and 3, respectively).

To determine any colocalization of GA-pyridine with MPO, consecutive sections were stained for MPO (α-MPO, 1:4800; Dako, Glosstrup, Denmark) and GA-pyridine, using the same protocol as above. Binding of the MPO antibody, however, was detected using a single incubation with peroxidase (PO)-labeled rabbit antimouse.

Statistics

One-way analysis of variance (ANOVA) was used to detect differences in clinical parameters, and Kruskal-Wallis was used to detect differences in pathologic parameters between the patient groups.

To test for the effect of age on mesangial GA-pyridine accumulation in diseases with prominent mesangial involvement, the study subjects were grouped by a break-up according to age being above or below the median value of the group. Mann-Whitney test was used for comparison between the 2 age groups.

To detect associations between MME or FGS and GA-pyridine accumulation, MME and FGS were split into quartiles, the first quartile representing the biopsies with the lowest MME and FGS scores and the fourth quartile

Table 1. Clinical and pathologic data

	M/F *N*	Age *year*	SBP *mm Hg*	DBP *mm Hg*	Serum creatinine *μg/L*	Proteinuria *g/day*	Mesangial matrix expansion	Focal glomerular sclerosis
Control	5/5	66 (29–73)	135 (105–180)	75 (65–80)	104 (73–156)	–	0.06 (0.0–0.21)	0.0 (0.0–0.0)
Diabetic nephropathy	4/6	51 (42–70)	170 (120–185)	92 (50–105)	119 (89–406)	3.8 (0.1–10)	3.61 (1.92–4.0)	1.61 (0.33–3.33)
Wegener's granulomatosis	5/3	71 (55–81)	118 (100–130)	63 (60–95)	389 (110–550)	0.5 (0.3–6.1)	1.47 (0.20–2.71)	0.91 (0.0–2.47)
Mesangial proliferative glomerulonephritis	6/1	45 (34–83)	134 (110–170)	80 (75–86)	141 (121–264)	2.8 (1.0–6.3)	2.26 (0.30–3.08)	0.36 (0.09–2.0)
Focal glomerular sclerosis	6/1	51 (23–80)	148 (115–180)	80 (60–110)	273 (76–896)	6.4 (1.8–11.6)	2.83 (1.25–3.39)	2.50 (0.25–3.32)
Membranous glomerulonephritis	5/2	51 (33–69)	120 (100–164)	80 (70–82)	137 (69–339)	5.1 (3.1–13.8)	2.15 (0.46–3.33)	1.02 (0.0–3.0)
Minimal change	7/1	7 (2–14)	124 (94–160)	70 (50–80)	37 (33–68)	2.65 (0–8.9)	0.46 (0.0–2.44)	0.0 (0.0–0.89)
Allograft rejection	4/4	59 (40–67)	145 (105–170)	80 (70–90)	207 (149–473)	0.2 (0.1–0.2)	0.42 (0.18–0.83)	0.0 (0.0–0.42)

Abbreviations are: M/F, male-to-female ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are expressed as median and range.

Table 2. Percentage of moderate to strong GA-pyridine staining in control and human renal disease

	GA-pyridine staining							
	Glomerulus				Interstitium			
			Epithelium				Vessels	
	Mesangium	Endothelium	Visceral	Parietal	Tubular epithelium	Peritubular capillaries	SMC	Endothelium
Control	0	0	30	20	100	0	50	30
Diabetic nephropathy	50	0	30	50	100	0	20	30
Wegener granulomatosis	38	0	38	38	100	0	50	17
Mesangial proliferative glomerulonephritis	43	0	14	57	100	0	14	14
Focal glomerular sclerosis	28	0	14	14	100	0	50	17
Membranous glomerulonephritis	0	14	0	0	100	0	14	14
Minimal change	0	13	0	0	100	0	13	0
Allograft rejection	0	0	0	0	100	0	33	0

Abbreviations are: SMC, smooth muscle cells.

representing the highest scores. Kruskal-Wallis test was used for comparison between the quartiles.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 1. No significant differences in age were present between the groups, including controls, except for the patients with minimal change disease, who were significantly younger. Blood pressure and plasma creatinine were not significantly different between the groups. Proteinuria (not measured in controls) did differ between the groups (Table 1). As expected, MME and FGS scores were different between the different diagnostic categories ($P < 0.001$).

GA-pyridine in the normal human kidney

Strong staining of GA-pyridine was seen in proximal and distal tubular epithelial cells (Table 2, Fig. 1A). Also, strong GA-pyridine staining was found in the endothelium and smooth muscle cells of renal vessels and in the visceral and parietal glomerular epithelium (Table 2). In only 1 patient weak GA-pyridine staining was noted in the peritubular capillaries and the glomerular mesangium (Table 3). No staining was present in the glomerular endothelium in any of the control sections (Table 3).

GA-pyridine in renal diseases with prominent mesangial involvement

Strong glomerular mesangial GA-pyridine accumulation was present in patients with diabetic nephropathy (Table 2, Fig. 1C). Mesangial staining was not just limited to areas with expanded mesangium but was also present in the nonexpanded mesangium. The classical noduli, known as Kimmelstiel-Wilson lesions, were occasionally encountered: these were negative for GA-pyridine (Fig. 1D). In addition, glomerular mesangial GA-pyridine accumulation was also prominent in Wegener's granulomatosis (Fig. 1B), mesangial proliferative glomerulonephritis (Fig. 1E), and focal glomerular sclerosis. Weak staining of GA-pyridine was observed in the glomerular endothelium and the peritubular capillaries in these diseases (Table 3). Strong GA-pyridine staining was observed in tubular epithelial cells (Table 2), in the renal vasculature, and in the visceral and parietal glomerular epithelium (Table 2), which was similar to the staining in normal kidneys. GA-pyridine staining

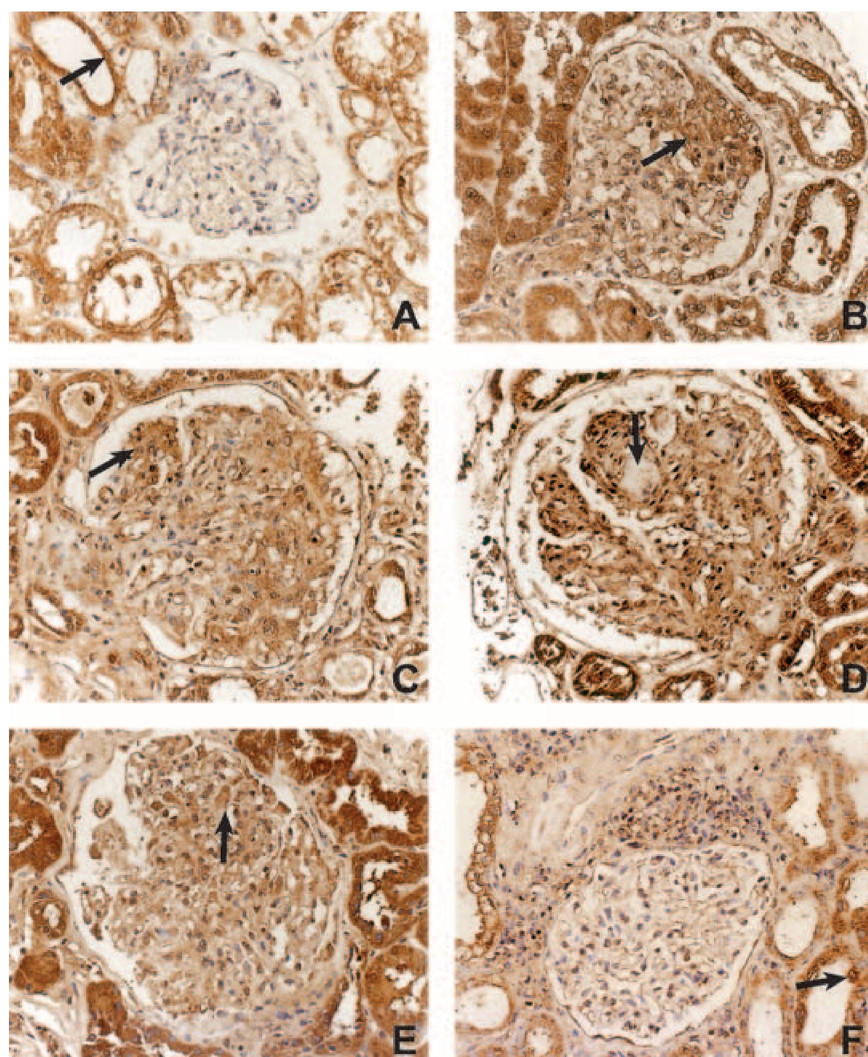

Fig. 1. Staining of GA-pyridine. (*A*) Representative photograph of a section from a control kidney. GA-pyridine is abundantly present in cortical tubular segments (arrow). No glomerular mesangial staining is present. (*B*) Example of a section from a renal biopsy from a patient with Wegener's granulomatosis. In addition to tubular staining, abundant accumulation of GA-pyridine is found in the glomerular mesangium (arrow). (*C*) Photograph of a section from a diabetic kidney. In addition to the tubular staining, abundant accumulation of GA-pyridine is found in the glomerular mesangium (arrow). (*D*) Photograph of a section from a diabetic kidney, with a Kimmelstiel-Wilson nodulus (arrow). Although no GA-pyridine accumulation is seen within the nodulus, staining is obvious in the outer layers. (*E*) Example of a section from a patient with mesangial proliferative glomerulonephritis. In addition to tubular staining, abundant accumulation of GA-pyridine is found in the glomerular mesangium (arrow). (*F*) Photograph of a section from a patient with chronic renal allograft rejection. Strong GA-pyridine staining is seen in the tubular cells (arrow), whereas, in contrast to B, C, and E, no glomerular GA-pyridine staining is seen in this biopsy.

Table 3. Percentage of any positive GA-pyridine staining in control and human renal disease

	GA-pyridine staining							
	Glomerulus				Interstitium			
			Epithelium				Vessels	
	Mesangium	Endothelium	Visceral	Parietal	Tubular epithelium	Peritubular capillaries	SMC	Endothelium
Control	10	0	60	80	100	10	100	80
Diabetic nephropathy	100	100	100	100	100	90	90	100
Wegener's granulomatosis	75	100	88	88	100	100	100	100
Mesangial proliferative glomerulonephritis	71	100	71	100	100	57	100	86
Focal glomerular sclerosis	86	86	71	100	100	71	100	100
Membranous glomerulonephritis	57	100	86	71	100	71	100	100
Minimal change	38	75	38	75	100	75	100	100
Allograft rejection	13	100	57	75	100	63	100	100

Abbreviations are: SMC, smooth muscle cells.

of older patients (age > median) was compared to GA-pyridine staining in younger patients (age < median). GA-pyridine staining was significantly more pronounced in the mesangium of older patients ($N = 14$, median 69, range 55–83) than in younger patients ($N = 14$, median 44, range 23–51) ($P = 0.05$). GA-pyridine staining was not significantly associated with the indices for the severity of renal damage, such as creatinine and proteinuria.

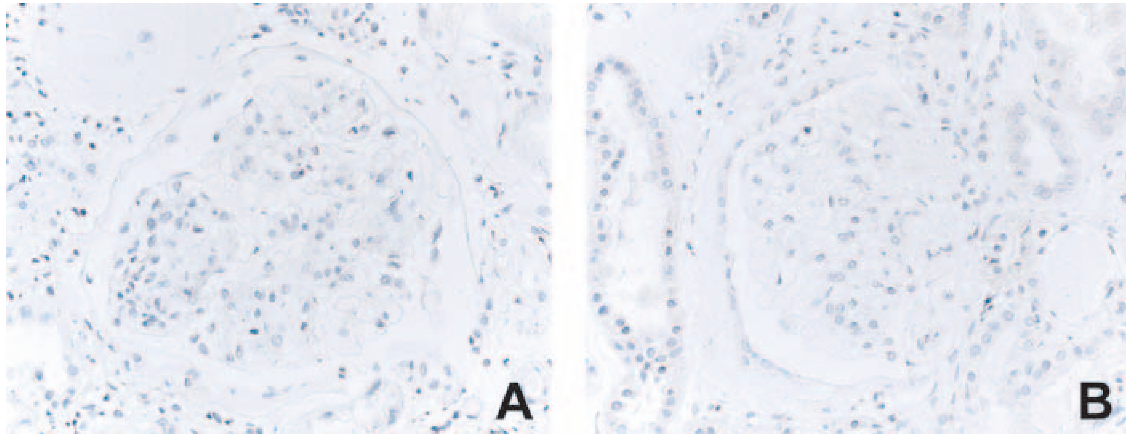

Fig. 2. Control sections. (*A*) Photograph of a section from a patient with diabetic nephropathy, stained with anti-GA-pyridine antibody solutions, preincubated with GA-BSA. No staining at all is present. (*B*) Photograph of a section from a patient with diabetic nephropathy, incubated with an irrelevant mouse monoclonal antibody as a negative control. Also, no GA-pyridine staining is present.

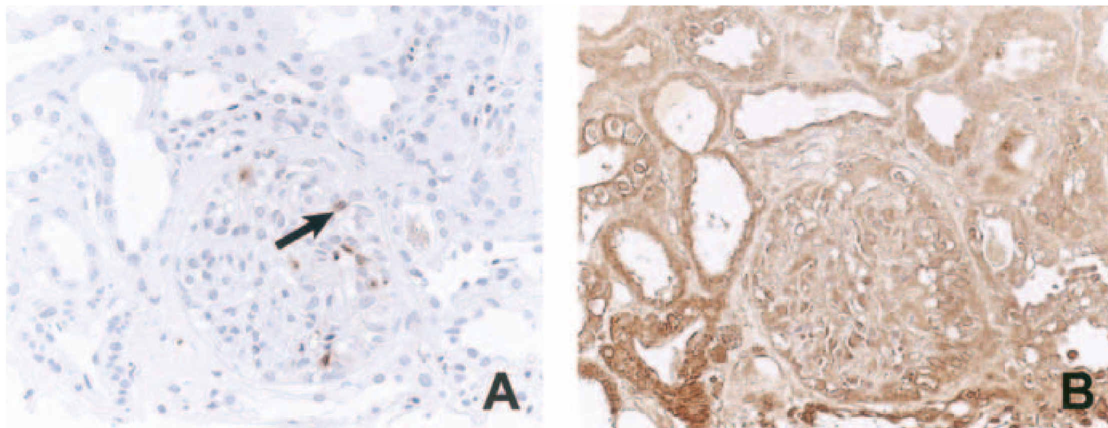

Fig. 4. Colocalization studies for GA-pyridine with MPO. (*A*) Photograph of a section from a patient with Wegener's granulomatosis. Multiple MPO-positive cells (arrow) are present in the glomerulus. (*B*) Photograph of the same glomerulus (stained in serial sections), stained for GA-pyridine. Note the difference in staining pattern when compared to MPO staining (A).

GA-pyridine in diseases without prominent mesangial involvement

Weak GA-pyridine accumulation was observed in the glomerular mesangium and endothelium in patients with membranous glomerulonephritis, minimal change nephropathy, and renal allograft rejection (Table 3, Fig. 1F). Again, strong GA-pyridine staining was observed in tubular epithelial cells (Table 2), which was similar to the staining in normal kidneys. In addition, GA-pyridine was present in the renal vasculature and in the visceral and parietal glomerular epithelium (Table 3). Glomerular mesangial GA-pyridine staining (which was similarly weak in this group) showed no significant differences between biopsies from older or younger patients.

Control sections

Control sections, incubated with anti-GA-pyridine antibody solutions that were preincubated with GA-BSA (Fig. 2A), sections incubated with irrelevant mouse monoclonal antibodies instead of anti-GA-pyridine antibody (Fig. 2B), and sections incubated with only PBS were consistently negative.

Association between glomerular pathology and mesangial GA-pyridine

The association between mesangial GA-pyridine staining and glomerular pathology, estimated as MME and FGS, is given in Figure 3, providing a semiquantitative assessment of GA-pyridine staining per quartile of MME and FGS, respectively. This shows that enhanced mesangial GA-pyridine accumulation is associated with increasing MME and FGS (Kruskal-Wallis, $P = 0.001$).

Colocalization studies with MPO

Using an anti-MPO antibody, we found MPO-positive cells in the glomeruli and in the interstitium in a variety of renal diseases. Consecutive sections, however,

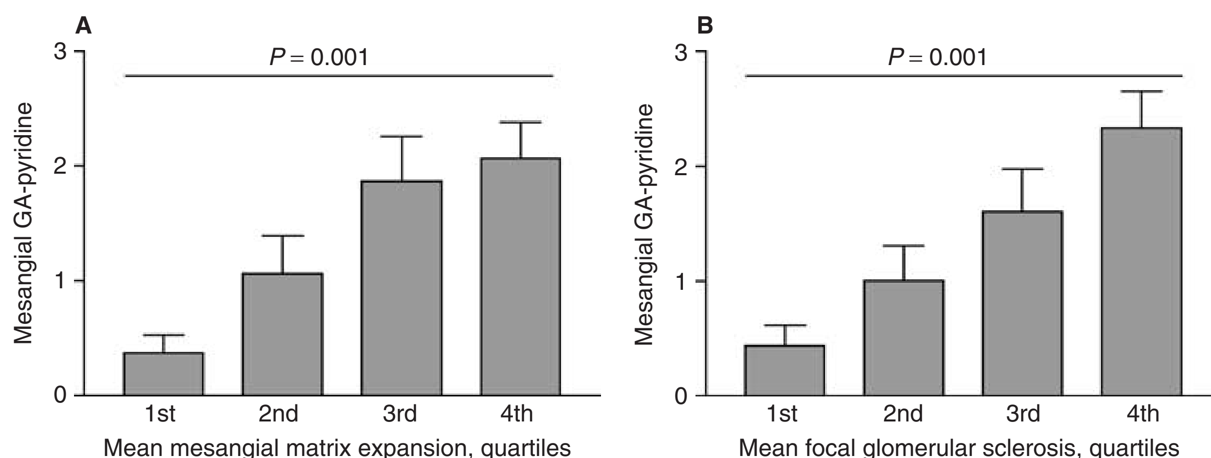

Fig. 3. Mesangial GA-pyridine staining (mean and standard deviation) by a break-up in quartiles of MME (*A*) and FGS (*B*). (A) A significant difference in GA-pyridine staining was present between the quartiles of MME (Kruskal-Wallis, $P = 0.001$). (B) A significant difference in GA-pyridine staining was present between the quartiles of FGS (Kruskal-Wallis, $P = 0.001$).

revealed no colocalization of these cells (Fig. 4A) with GA-pyridine (Fig. 4B) (photographs shown are from a patient with Wegener's granulomatosis).

DISCUSSION

The present study describes for the first time the distribution of a novel AGE, GA-pyridine in the normal human kidney and in human renal diseases. Most importantly, we showed significant accumulation of GA-pyridine in the glomerular mesangium in renal diseases, in particular those with prominent mesangial involvement. This mesangial accumulation was related to the degree of glomerular MME and FGS. In addition, GA-pyridine was found in tubular epithelia and in the renal vasculature: this staining was present in both normal and diseased kidneys, and appears, therefore, not to be related to renal pathology.

Under physiologic conditions, circulating AGEs are cleared by the kidney by glomerular filtration, and are subsequently actively reabsorbed and metabolized by proximal tubular cells [20, 21] GA-pyridine was abundantly and consistently present in cortical tubular cells from normal and diseased human kidneys in our study. This is in concordance with data on other AGEs and advanced lipoxygenation end products (ALEs), such as pentosidine and MDA-lysine, which are also present in proximal tubular cells from normal renal tissue, as well as tissue from patients with diabetic nephropathy and mesangial proliferative glomerulonephritis [22]. The tubular accumulation of GA-pyridine in normal and diseased human kidneys, therefore, may reflect the normal tubular uptake of this AGE from the plasma, as GA-modified proteins have been shown to be present in human serum [23].

Based on the parallel between atherosclerosis, where GA-pyridine accumulation was previously described [18], and glomerulosclerosis [19], we expected to find GA-pyridine accumulation in the glomerular mesangium of renal diseases with prominent mesangial involvement. This would be in concordance with previous reports describing the accumulation of AGEs such as CML, pentosidine, and pyrraline in the expanded mesangial areas of patients with diabetic nephropathy and IgA nephropathy (mesangial proliferative glomerulonephritis) [24, 25]. Furthermore, AGEs have been described in the mesangium of aging rat [26, 27]. Significant GA-pyridine accumulation was indeed found in diabetic nephropathy, Wegener's granulomatosis, mesangial proliferative glomerulonephritis, and focal glomerulosclerosis. Renal disorders without significant glomerular mesangial involvement, such as renal transplantation, membranous glomerulonephritis, and minimal change nephropathy only revealed minor mesangial GA-pyridine accumulation. Moreover, mesangial GA-pyridine accumulation appeared to be related to higher scores for MME and FGS across the different disorders. This suggests that mesangial GA-pyridine accumulation is more closely related to the severity of glomerular mesangial pathology, as such, than to the classifying diagnosis.

In our patients with renal diseases with mesangial involvement, GA-pyridine localization was not only limited to areas with mesangial matrix expansion, but was also present in areas with morphologically intact mesangium. This is compatible with the assumption that GA-pyridine accumulation is not merely an epiphenomenon to damage, but can precede mesangial expansion and may, thus, play a role in the pathogenesis of these lesions. Studies demonstrating protection against diabetic renal damage by intervention in AGE formation by pyridoxamine [6, 7] and, specifically, reduction of mesangial matrix expansion

by aminoguanidine [28], support the pathogenetic relevance of AGEs for renal damage. The mechanisms of the pathogenetic role of AGEs in renal damage have been subject of many studies. It has been found that nonenzymatic glycation (i.e., by glycolaldehyde) could influence the growth of mesangial cells, which could contribute to the mesangial abnormalities of diabetic glomerulopathy [29]. Also, AGE-modified proteins have been demonstrated to up-regulate mesangial growth factor [30], and to stimulate synthesis of fibronectin and type IV collagen by glomerular mesangial cells [31]. AGEs could give rise to cellular responses through binding to receptors, and recent data show that, among the different receptors for cellular AGE uptake, at least 3 of them, RAGE [32], SR-A [10], and CD36 [33] not only recognize glucose-modified protein but also GA-modified proteins.

In diabetic nephropathy nodular mesangial lesions, known as intercapillary glomerulosclerosis or Kimmelstiel-Wilson lesions, are sometimes present. Although these lesions are essentially similar to the diffuse mesangial lesions, we did not detect GA-pyridine staining in those lesions. However, the outer layers were positively stained for GA-pyridine. Strong nodular immunostaining by anti-pentosidine and anti-AGE polyclonal antibodies has been described [25]. In contrast, Uesugi et al noted the absence of CML in some nodular lesions [24]. These results indicate that the pattern of distribution may vary between various AGEs. Also, differences in staining methods cannot be excluded.

The renal vasculature was of special interest, considering the accumulation of GA-pyridine in atherosclerotic lesions [18]. We found GA-pyridine in the renal vessels of both patients and controls, despite the absence of foam cells. GA-pyridine staining was present in the endothelium and in the smooth muscle cells, and in the cells of the thickened intima (mainly fibroblasts) in normal as well as diseased kidneys. These data are in concordance with the literature, reporting accumulation of pentosidine, CML, and pyrraline in thickened intima of renal arteries in DN [25]. Unlike mesangial GA-pyridine, GA-pyridine in the renal vasculature was present in both normal and diseased kidneys and seems, therefore, not to be related to renal pathology. This was also the case for tubular GA-pyridine accumulation.

In our renal patients, accumulation of GA-pyridine was slightly increased in the glomerular endothelium compared to control kidneys. This is in accordance with previous studies showing AGEs in glomerular endothelial cells in diabetic rat [34]. It is also known that CML and CEL plasma levels are associated with markers of endothelial activation [35]. Moreover, AGEs are known to induce increased permeability and enhance endothelium-dependent procoagulant activity through endothelial cell AGE-receptors in cultured endothelial cells [36]. So a possible pathogenetic role of GA-pyridine in renal damage might involve effects on the endothelium of renal vessels and glomerulus.

In our study, a higher age was associated with more GA-pyridine accumulation in the diseases with prominent mesangial involvement, but not in the other patient groups or in controls. This suggests that mesangial pathology may act as a permissive factor in age-related accumulation of GA-pyridine and vice versa.

One of the factors involved in the formation of GA-pyridine is the MPO system [18]. To reveal its possible role in GA-pyridine formation in renal diseases, we performed MPO staining and GA-pyridine staining in consecutive sections. However, MPO did not colocalize with GA-pyridine in the renal disorders studied here. In fact, most GA-pyridine was found in DN, in which MPO activity is known to be decreased [37]. Our results suggest that, in the renal conditions studied here, the MPO system is not crucially involved in the formation of GA-pyridine. This indicates that other mechanisms, such as the Maillard reaction, could be more important in its formation in renal disease.

CONCLUSION

The newly discovered AGE, GA-pyridine, is present in diseased kidneys, especially those with prominent mesangial involvement**.** Moreover, its accumulation in the mesangium is related to the severity of MME and FGS. Further studies, aimed at intervention in the formation of GA-pyridine, or preventing its binding to specific receptors, may provide new therapeutic strategies and shed new light on its possible role in the pathogenesis of renal lesions.

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