Original Article

Impact of Hypertension and Hypertension-Related Vascular Lesions in IgA Nephropathy

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It remains poorly understood whether vascular pathology plays an important role in the progression of renal parenchymal disease in humans. Moreover, in the case of hypertensive patients with mild proteinuria, nephrologists tend to make a diagnosis of benign nephrosclerosis without renal biopsy. Among 172 patients who were treated at our hospital for biopsy-proven IgA nephropathy, we performed quantitative histopathological analysis in 38 patients with mild proteinuria of less than 0.5 g/day. We related these histopathological parameters with clinical data at biopsy and also with follow-up data. The percentage of glomeruli showing global sclerosis exceeded 10% of total glomeruli in 15 of the patients (39.5%) and exceeded 20% in 9 (23.7%). Arteriosclerosis and tubulointerstitial changes significantly correlated with glomerular sclerosis, but mesangial cell proliferation did not. Among the 38 patients, the 12 with hypertension showed more severe glomerular sclerosis, tubulointerstitial changes and arteriosclerosis compared with the 26 without hypertension, but the mesangial cell proliferation was identical between the two groups. Stepwise multiple regression analysis revealed that hypertension and urinary protein excretion (UPE) were independent risk factors for arteriosclerosis. The follow-up data of a mean period of 27.6 months showed that 9 of the 38 patients (23.7%) had an increase in UPE. Hypertension, arteriosclerosis, age, and UPE at biopsy were selected as the important risk factors for an increase in UPE in the follow-up. Our results provide not only clinical but histopathological evidence that hypertension affects the prognosis of mild proteinuric nephropathy through vascular lesions. (*Hypertens Res* 2006; 29: 15–22)

***Key Words*: arteriosclerosis, IgA nephropathy, glomerular sclerosis, proteinuria, tubulointerstitium**

Introduction

In renal parenchymal disease, several studies have stressed the impact of blood pressure and blood pressure-related vascular lesions on renal injury and outcome (*1–4*). However, more powerful independent clinical predictors of renal outcome are elevated serum creatinine (S-Cr) level at presentation and severe proteinuria (*5*). Therefore, the degree of proteinuria should be taken into consideration as an indication for renal biopsy. In some institutes or localities, however, even isolated hematuria is considered as an indication for renal biopsy. Some nephrologists consider that this policy results in early detection of glomerular disease (*6*), but others doubt the necessity for renal biopsy in patients with isolated hematuria (*7–9*). Indeed, unexpectedly severe renal injury has been observed in the absence of clinically overt proteinuria (*10*, *11*).

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Table 1. Clinical and Histopathological Features of 38 Patients with IgA Nephropathy Showing Mild Proteinuria

Clinical parameters	
Male:female	21:17
Age (years)	34.7±17.3 (9–65)
Body mass index (kg/m^2)	22.8±2.2 (19.7–28.4)
Systolic blood pressure (mmHg)	124.0±21.3 (92–160)
Diastolic blood pressure (mmHg)	77.0±9.7 (58–96)
Duration prior to biopsy[a] (year)	4.7±5.1 (0.1–20)
UPE (g/day)	0.26±0.12 (0–0.5)
U-RBC (grade)	2.8±1.4 (1–5)
S-Cr (mg/dl)	0.81±0.25 (0.41–1.57)
Ccr (ml/min/1.73 m^2)	84.4±30.1 (24.3–156.9)
NAG (U/day)	6.2±5.4 (1.7–34.5)
U-β_2MG (μg/day)	92.3±94.2 (12–508)
Hypertension	12
Macrohematuria	9
Histopathological parameters	
Glomerular sclerosis (%)	11.3±17.2 (0–71.4)
Mesangial score	0.43±0.24 (0.1–0.95)
Interstitial fibrosis/tubular atrophy (grade)	0.9±0.7 (0–3)
Interstitial infiltration (grade)	1.1±0.8 (0–3)
Arteriosclerosis (%)	14.4±20.4 (0–66.6)
Crescent formation	3

The figure in parenthesis indicates the range of each parameter. Ccr, creatinine clearance; NAG, *N*-acetyl-β-glucosaminidase; S-Cr, serum creatinine; U-β_2MG, urinary β_2-microglobulin; UPE, urinary protein excretion; U-RBC, urinary red blood cells. [a]Data of 4 patients were not obtained. To convert serum creatinine in mg/dl to μmol/l, multiply by 88.4.

We previously reviewed histopathological findings in 58 patients (male:female=29:29, age 33.4±18.4 years, S-Cr 0.74±0.20 mg/dl [65.4±17.6 μmol/l]) with mild proteinuria less than or equal to 0.5 g/day (*12*). This study showed that only a small number of the patients had minor glomerular abnormality (10.3%), whereas 58.6% of the patients had IgA nephropathy (IgAN). Surprisingly, global sclerosis exceeding 10% of total glomeruli was found in 16 of the 58 patients (27.6%). Further, 10 of the patients (17.2%) showed global sclerosis exceeded 20% of total glomeruli. After the study, there remained an essential question: What factors contributed to the severe lesions in the patients with mild proteinuria? Apart from animal models, characteristics of vascular lesions have not been fully investigated in human renal parenchymal disease. In particular, there is little clinicopathological evidence regarding the degree to which hypertension affects vascular lesions. In the present study, therefore, we wanted to investigate the relationship between vascular lesions and hypertension in renal parenchymal disease. To avoid unnecessary complexity of the histopathological findings, we chose IgAN, which is known as the most common primary glomerular disease in Japan (*13*), as a single disease entity of renal parenchymal disease. Moreover, although nephrologists tend to regard patients with hypertension and mild proteinuria as having benign nephrosclerosis, it is important to reveal whether this diagnosis is correct. In consideration of the above, we selected IgAN showing mild proteinuria as a single disease entity to identify factors contributing to severe lesions. Indeed, since mild urinary abnormalities are common signs during the onset of IgAN (*14*, *15*), renal biopsy in patients with mild proteinuria may be critical to detect the disease in an early stage and clarify the clinical course of cases with latent progression. Szeto *et al*. have recently reported that a proportion of cases of IgAN presenting with mild proteinuria show disease progression (*6*). However, the histopathological factors relating to the disease progression are still unknown. Therefore, we investigated clinicopathological findings and follow-up data of IgAN patients with mild proteinuria. In the present study, we showed that hypertension and hypertension-related vascular lesions result in severe renal lesions even if proteinuria is mild.

Methods

Patients

Of 571 patients who underwent renal biopsy in our hospital from April 1997 to May 2003, 172 (30.1%) were given a diagnosis of IgAN (male:female=94:78, age 37.8±17.2 years, urinary protein excretion [UPE] 0.85±0.84 g/day, S-Cr 1.02±0.57 mg/dl [90.1±50.3 μmol/l]). Histopathology of IgAN was defined by mesangial cell proliferation and/or mesangial matrix expansion on light microscopy, predominant mesangial IgA deposition with C3 deposition on immunofluorescence, and electron-dense deposits in the mesangium on electron microscopy. The inclusion criteria were: patients with proteinuria less than or equal to 0.5 g/day, and light microscopic specimens including more than 10 glomeruli. The exclusion criteria were: patients with diabetes mellitus, Henoch-Schonlein purpura nephritis, chronic liver disease, collagen disease, renal artery stenosis, or previous treatment with steroids or immunosuppressants. Finally, we analyzed 38 patients with primary IgAN showing mild proteinuria less than or equal to 0.5 g/day. We performed renal biopsy in these patients because of longstanding mild urinary abnormalities, macrohematuria even without overt proteinuria, or the patient's hope for future pregnancy. Retrospective post-biopsy follow-up was performed. Informed consent for renal biopsy and the present study was obtained from all patients.

Clinical Evaluation

At the time of biopsy, we evaluated patients' sex, age, duration of abnormal urinalysis prior to biopsy, presence of hyper-

Table 2. Correlation Coefficients between Clinical and Histopathological Parameters

	Glomerular sclerosis	Mesangial score	Interstitial fibrosis/ tubular atrophy	Interstitial infiltration	Arteriosclerosis
Age	0.654***	NS	0.565***	0.485**	0.642***
Duration prior to biopsy[a]	0.484**	NS	0.412*	NS	0.536**
UPE	0.550***	NS	0.419*	NS	0.452**
U-RBC	−0.404*	NS	−0.505**	NS	−0.465**
S-Cr	0.409*	NS	0.454**	0.455**	0.430**
Ccr	−0.488**	NS	−0.633***	−0.572***	−0.550***

Ccr, creatinine clearance; S-Cr, serum creatinine; UPE, urinary protein excretion; U-RBC, urinary red blood cells; NS, not significant. *$p<0.05$, **$p<0.01$, ***$p<0.001$. [a]Data of 4 patients were not obtained.

Table 3. Comparisons of Histopathological Parameters Based on Categorical Parameters

	Sex		Hypertension		Macrohematuria	
	Male ($n=21$)	Female ($n=17$)	+ ($n=12$)	− ($n=26$)	+ ($n=9$)	− ($n=29$)
Glomerular sclerosis (%)	10.8±17.1	11.8±17.8	24.6±23.4	5.1±8.5	3.7±8.7	13.6±18.6
	NS		$p<0.001$		$p<0.05$	
Mesangial score	0.42±0.27	0.44±0.20	0.47±0.23	0.41±0.25	0.39±0.26	0.44±0.24
	NS		NS		NS	
Interstitial fibrosis/tubular atrophy (grade)	0.8±0.7	1.0±0.6	1.5±0.7	0.6±0.4	0.4±0.5	1.0±0.7
	NS		$p<0.001$		$p<0.05$	
Interstitial infiltration (grade)	1.1±0.9	1.1±0.6	1.6±0.6	0.9±0.7	0.7±0.8	1.2±0.7
	NS		$p<0.05$		NS	
Arteriosclerosis (%)	17.4±24.7	10.6±13.0	38.6±20.1	3.2±4.8	3.1±5.2	17.9±22.1
	NS		$p<0.001$		NS	

NS, not significant.

tension as defined by a systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg or current use of antihypertensive drugs, episodes of macrohematuria, S-Cr, and the number of urinary red blood cells (U-RBC) in urine sediment. S-Cr was measured by an auto-analyzer using a kit coupled with creatininase, creatinase, and sarcosine dehydrogenase. Before biopsy, a 24-h urine collection was performed at least thrice to measure UPE, creatinine clearance (Ccr), *N*-acetyl-β-glucosaminidase (NAG), and urinary β_2-microglobulin (U-β_2MG), and we recorded the mean values of these parameters. Urine collection was also performed at the outpatient follow-up after renal biopsy. The number of U-RBC in urine sediment was semiquantitatively graded as follows: grade 0, absent; grade 1, less than 5 cells per high-powered field (HPF); grade 2, 5 to 9 cells per HPF; grade 3, 10 to 19 cells per HPF; grade 4, 20 to 29 cells per HPF; grade 5, over 30 cells per HPF; grade 6, over 100 cells per HPF.

Histopathological Evaluation

All renal biopsy specimens were reviewed by a single pathologist unaware of the patients' clinical condition. Glomerular sclerosis, mesangial cell proliferation, crescent formation, interstitial infiltration, interstitial fibrosis/tubular atrophy, and arteriosclerosis were evaluated using quantitative or semiquantitative methods as follows.

Regarding glomerular sclerosis, we evaluated the percentage of globally sclerotic glomeruli (%GS). Mesangial cell proliferation was graded in each glomerulus as follows: grade 0, absent; grade 1, mild; grade 2, moderate; grade 3, severe. We then calculated the mesangial score according to the equation used in Wada's study (*16*) with modifications:

$$\text{Mesangial score} = (1 \times N_1 + 2 \times N_2 + 3 \times N_3)/N$$

N_1 to N_3 are the numbers of the glomeruli in grade 1 to 3, respectively. N is the total number of glomeruli included in the specimen. The score indicates the mean grade of mesangial cell proliferation in each specimen.

Interstitial infiltration was graded according to Nieuwhof's study (*17*): grade 0, absent; grade 1, focal interstitial infiltration; grade 2, multiple foci of interstitial infiltration; grade 3, diffuse interstitial infiltration.

Interstitial fibrosis/tubular atrophy was semiquantitatively graded according to Katafuchi's study (*18*): grade 0, absent; grade 1, involving less than 25% of the interstitium/tubules in

Table 4. Correlation Coefficients between Histopathological Parameters

	Glomerular sclerosis	Mesangial score	Interstitial fibrosis/ tubular atrophy	Interstitial infiltration	Arteriosclerosis
Glomerular sclerosis	—	NS	0.677***	0.528**	0.680***
Mesangial score	NS	—	0.521**	NS	NS
Interstitial fibrosis/ tubular atrophy	0.677***	0.521**	—	0.538**	0.630***
Interstitial infiltration	0.528**	NS	0.538**	—	NS
Arteriosclerosis	0.680***	NS	0.630***	NS	—

NS, not significant. **$p<0.01$, ***$p<0.001$.

Table 5. Stepwise Multiple Regression Analysis for Risk Factors for Arteriosclerosis

	β	F
Hypertension	0.712	66.3***
UPE	0.321	13.4**
Ccr	−0.128	0.5
S-Cr	0.088	0.2
Interstitial fibrosis/tubular atrophy	0.068	0.1
Age	−0.062	0.1
U-RBC	0.052	0.09
Glomerular sclerosis	0.037	0.04

$r^2=0.749$. Ccr, creatinine clearance; S-Cr, serum creatinine; UPE, urinary protein excretion; U-RBC, urinary red blood cells. **$p<0.01$, ***$p<0.001$.

the cortical area; grade 2, involving between 25% and 50%; grade 3, involving over 50%. Interstitial fibrosis was defined by the presence of interstitial collagen as determined by Masson trichrome staining.

Regarding arteriosclerosis, the percentage of vessels with hyaline change and/or wall thickening was evaluated in each specimen. Wall thickening was evaluated as the ratio of luminal diameter to outer diameter, and was considered to be present when the ratio was less than 0.5 (*18*).

Statistical Analysis

Data are shown as the mean±SD. In comparisons between 2 groups, Student's *t*-test, Mann-Whitney's *U*-test, or Fisher's exact test was used as appropriate. In comparisons among 3 groups, one-way analysis of variance (ANOVA) with Bonferroni correction was used. Correlations between variables were tested by Spearman's correlation rank test. Stepwise multiple regression analysis was used to select an independent risk factor among parameters selected by univariate analyses. The parameters with an F value of more than 4 were adopted. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 10.0 software.

Results

As shown in Table 1, the 38 patients included 21 males and 17 females, and their mean age was 34.7 years (range 9–65). The duration of abnormal urinalysis prior to biopsy was 4.7 years (range 0.1–20). The mean Ccr was 84.4 ml/min/1.73 m^2 (range 24.3–156.9). There were 12 patients with hypertension (male 8, female 4) and 9 with episodes of macrohematuria (male 4, female 5). Eleven of the hypertensive patients were over 40 years of age. The patients with hypertension were older than those without hypertension (53.1±9.2 *vs.* 26.3±13.0 years, $p<0.001$). On the other hand, the patients with episodes of macrohematuria were less than 40 years of age. Before biopsy, antihypertensive drugs had been administered in 3 patients: a calcium channel blockade in 1 and angiotensin converting enzyme-inhibitor (ACE-I)/angiotensin-II receptor blockade (ARB) in 2. In all 3 cases, however, proteinuria did not exceed 0.5 g/day before the commencement of these drugs. Regarding the histopathological features, all parameters but mesangial score ranged from mild to severe. The highest mesangial score, which has a highest possible value of 3, was 0.95, and the mean value was 0.43±0.24. The mean %GS was 11.3%. In 15 of the 38 patients (39.5%), %GS exceeded 10%, and it exceeded 20% in 9 (23.7%). The highest %GS was 71.4% in a 60-year-old man and a 63-year-old woman, both with hypertension. Crescent formation was observed in 3 patients.

Subsequently, we tested the correlations between clinical parameters and histopathological parameters (Table 2). Age, S-Cr, and Ccr were correlated with glomerular sclerosis, interstitial fibrosis/tubular atrophy, interstitial infiltration, and arteriosclerosis, but not correlated with mesangial score. UPE and duration prior to biopsy correlated with glomerular sclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis. U-RBC showed negative correlations between the histopathological parameters. However, NAG and U-β_2MG did not correlate with any histopathological parameters. Similarly, mesangial score did not correlate with any clinical parameters. Table 3 shows the comparisons of histopathological parameters based on categorical parameters. Male sex, a predictor for poor outcome in some studies on IgAN (*19*, *20*),

Table 6. Comparisons of Parameters at Renal Biopsy According to Changes in Urinary Protein Excretion during the Follow-Up Period

	Group A (n=9)	Group B (n=20)	Group C (n=9)
Follow-up period (month)	38.4±22.0	22.6±18.7	28.2±20.2
Clinical parameters			
Male:female	7:2	9:11	5:4
Age (year)	23.0±14.8	35.1±14.9	45.7±18.5*
Duration prior to biopsy[a] (year)	2.6±4.2	5.3±5.7	5.7±4.2
UPE (g/day)	0.18±0.15	0.27±0.09	0.33±0.13*
U-RBC (grade)	3.6±1.4	2.6±1.4	2.3±1.4
S-Cr (mg/dl)	0.76±0.30	0.76±0.16	0.97±0.34
Ccr (ml/min/1.73 m^2)	94.9±30.9	89.6±27.1	62.6±27.9
NAG (U/day)	4.4±1.8	5.7±3.3	9.0±9.7
U-β_2MG (μg/day)	55.2±37.3	79.6±42.7	157.7±169.1
Hypertension	1	4	7**,††
Macrohematuria	3	4	2
Histopathological parameters			
Glomerular sclerosis (%)	6.7±11.1	7.4±9.6	24.4±27.8†
Mesangial score	0.33±0.23	0.42±0.22	0.56±0.28
Interstitial fibrosis/tubular atrophy (grade)	0.4±0.5	0.9±0.3	1.3±1.1*
Interstitial infiltration (grade)	0.6±0.8	1.1±0.7	1.6±0.7*
Arteriosclerosis (%)	7.8±18.7	9.9±14.0	30.8±26.5*,†
Therapy			
PSL	1	3	1
Anti-platelet drug	5	15	8
ACE-I or ARB	2	9	8*
Icosapentate	0	4	2
Tonsillectomy	0	2	0
None	4	2*	0*

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; Ccr, creatinine clearance; NAG, *N*-acetyl-β-glucosaminidase; PSL, prednisolone; S-Cr, serum creatinine; U-β_2MG, urinary β_2-microglobulin; UPE, urinary protein excretion; U-RBC, urinary red blood cells. Group A: the patients with disappearance of proteinuria in the follow-up; Group B: those with persisting proteinuria less than or equal to 0.5 g/day in the follow-up; Group C: those with an increase in urinary protein excretion in the follow-up. *$p<0.05$, **$p<0.01$ as compared with Group A. †$p<0.05$, ††$p<0.01$ as compared with Group B. [a]Data of 2 patients in both Group B and C were not obtained. To convert serum creatinine in mg/dl to μmol/l, multiply by 88.4.

was not associated with severe histopathological changes. Hypertension was associated with glomerular sclerosis, interstitial fibrosis/tubular atrophy, interstitial infiltration, and arteriosclerosis, but was not associated with mesangial score. In the patients with episodes of macrohematuria, glomerular sclerosis and interstitial fibrosis/tubular atrophy were less severe. Table 4 shows the correlation coefficients between the histopathological parameters. Interstitial fibrosis/tubular atrophy correlated with all other parameters. Arteriosclerosis showed significant correlations with glomerular sclerosis and tubulointerstitial changes. However, mesangial score did not correlate with glomerular sclerosis.

The results obtained by univariate analysis in Tables 2 to 4 showed that age, UPE, U-RBC, S-Cr, Ccr, hypertension, glomerular sclerosis, and interstitial fibrosis/tubular atrophy were associated with arteriosclerosis. We then analyzed the independent risk factors for arteriosclerosis. By stepwise multiple regression analysis (Table 5), hypertension and UPE were selected as the independent risk factors for arteriosclerosis.

The mean follow-up period was 27.6±20.4 months (range 1–67). As shown in Table 6, after biopsy, 5 patients received prednisolone therapy because of active lesions represented by severe mesangial cell proliferation, interstitial infiltration, or cellular crescents. In the absence of these findings, anti-platelet drugs (n=28) and ACE-I/ARB (n=19) were administered. Six patients were observed without medication because they showed almost normal findings on light microscopy with IgA deposition on immunofluorescence. During the follow-up period, S-Cr exceeded 1.5 mg/dl in 3 patients, all of whom had already shown a slight increase in S-Cr at biopsy. However, ΔS-Cr did not exceed 50% in these patients. UPE

increased in 9 patients. It exceeded 1 g/day in 4, all of whom had had hypertension at biopsy, and 2 of these had shown the highest %GS of 71.4%. On the other hand, proteinuria disappeared in 9 patients. None of the patients without hypertension at biopsy became hypertensive during the follow-up period. Two patients with hypertension at biopsy needed an additional administration of an antihypertensive drug.

According to the change in proteinuria during the follow-up period, the patients were divided into 3 groups: Group A, those with disappearance of proteinuria; Group B, those with persisting proteinuria less than or equal to 0.5 g/day; Group C, those with an increase in UPE (Table 6). Then, we compared clinical and histopathological data at biopsy among these groups. Although there was no difference in the duration of follow-up among these groups, a significant difference was found in age, UPE, hypertension, and tubulointerstitial and arteriosclerotic changes between Group A and C. In the comparison between Group B and C, hypertension, glomerular sclerosis, and arteriosclerosis were related to an increase in UPE. Among them, hypertension was most significant ($p=0.003$) followed by arteriosclerosis ($p=0.02$). There is no possibility that treatment modalities affected the clinical course of proteinuria, because ACE-I/ARB was given to 2 of 9 patients in Group A, while these drugs were given to 8 of 9 in Group C.

Discussion

Two previous studies have reported mild histopathological lesions and good renal outcome in patients with IgAN with mild proteinuria (*7*, *8*). Recently, however, two studies on IgAN with mild proteinuria have shown contradictory results (*6*, *21*). These studies included a relatively large number of patients with hypertension or renal insufficiency at biopsy, which was not the case in the aforementioned studies (*7*, *8*). In Usui's study (*21*), renal histopathology showed severe mesangial involvement or glomerular sclerosis in 6.1% of 197 patients. In Szeto's study (*6*), severe renal injury was observed in 12.5% of 72 patients. During the mean follow-up for 7 years, renal impairment and end-stage renal failure (ESRF) developed in 6.9% and 1.4% of the patients, respectively. However, neither of these studies attempted to identify the pathological factors contributing to severe lesions. In the present study, therefore, we attempted to identify these factors.

We found an unexpectedly large number of patients showing severe renal lesions in IgAN, despite their having only mild proteinuria. It is of interest to note that, despite the mild mesangial cell proliferation, both arteriosclerosis and tubulointerstitial changes were severe in most of the cases. Our histopathological study also clearly showed that arteriosclerosis was well correlated with glomerular sclerosis. In our study, %GS exceeded 10% in 15 patients (39.5%), and it exceeded 20% in 9 (23.7%). Surprisingly, the highest %GS was 71.4%. This is noteworthy considering the fact that the percentage of glomeruli showing focal or global sclerosis was 5.0±6.8% in Nieuwhof's study on IgAN patients with proteinuria of less than 0.5 g/day (*7*). However, it seems unlikely that these severe lesions were solely ascribable to IgAN, because mesangial cell proliferation, the primary histopathological finding in IgAN, did not correlate with any of the histopathological parameters in our study. In the previous studies on IgAN (*14*, *19*), it has been reported that mesangial cell proliferation correlated with glomerular sclerosis, interstitial fibrosis, and arteriosclerosis. Therefore, the present finding of severe glomerular sclerosis with disproportionate mesangial cell proliferation conflicted with the previous results. Our study suggests that some factor other than IgAN might contribute to the formation of severe glomerular sclerosis. We conclude that hypertension was a main contributor to the severe lesions, because: 1) the severe lesions were observed particularly in hypertensive patients; 2) the histopathology of tubulointerstitial changes accompanying correlated arteriosclerosis is not discrepant with renal injury induced by hypertension; 3) hypertension-induced renal injury, rather than IgAN, would more reasonably explain mild proteinuria despite severe histopathological changes; and 4) hypertension and arteriosclerosis at biopsy were most significantly related to an increase in UPE during the follow-up period. Benign nephrosclerosis may be superimposed with IgAN. Hypertension is a well known risk factor for renal prognosis (*4*, *5*, *22–24*). In our study, we histopathologically showed that vascular lesions, rather than mesangial cell proliferation, play an important role in glomerular sclerosis. The patients with hypertension showed more severe vascular lesions than those without hypertension. Hypertension and hypertension-related vascular lesions thus seem to play an important role in the progression of renal histopathology in IgAN patients with mild proteinuria.

There is a limitation regarding the mean follow-up period of 27.6 months. However, the increase in UPE in 9 patients (23.7%) was notable, because an increase in UPE is the most powerful predictor of renal outcome (*5*). The clinical risk factors for an increase in UPE were hypertension and age at biopsy. Histopathologically, more severe vascular lesions were shown at biopsy in the patients with an increase in UPE. Our results provide not only clinical but also histopathological evidence that blood pressure control affects the prognosis of IgAN through vascular lesions. From a clinical standpoint, hypertensive patients with mild proteinuria are commonly given a diagnosis of benign nephrosclerosis. However, our study suggested that "presumable" benign nephrosclerosis without renal biopsy may include many cases of IgAN.

It is interesting that age at biopsy was not selected as an independent risk factor for arteriosclerosis, although in both healthy and diseased individuals, aging induces functional and histopathological changes (*25*). Compared with healthy individuals in Kaplan's study (*26*), which has reported a relation between age and glomerular sclerosis, our patients showed higher %GS. Therefore, we can exclude the possibil-

ity that glomerular sclerosis is not solely related to aging. Thus far, it has been reported that in IgAN, age at onset or biopsy is well correlated with proteinuria (*21*, *27*), renal function (*19*, *27*, *28*), blood pressure (*19*, *27*, *28*), histopathological changes (*6*, *19*, *28*), and poor prognosis (*19*, *28*). Although age at biopsy was not selected as an independent risk factor for arteriosclerosis, we do not exclude the possibility that age affects the prognosis in IgAN. Indeed, in our study, age at biopsy was associated with hypertension, severe histopathological changes, and an increase in UPE during follow-up.

In conclusion, we found severe glomerular sclerosis, tubulointerstitial changes, and arteriosclerosis disproportionate to mild proteinuria in IgAN patients. In such patients, we showed that hypertension, hypertension-related arteriosclerosis, and tubulointerstitial changes, rather than mesangial cell proliferation could play an important role in the natural history of renal disease. Even if proteinuria is mild, we should carefully observe vascular lesions, particularly in hypertensive patients.

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