Original Article

Effects of Renin-Angiotensin System Blockade on Macrophage Infiltration in Patients with Hypertensive Nephrosclerosis

Toshihiko IMAKIIRE[1)], Yuichi KIKUCHI[1)], Muneharu YAMADA[1)], Taketoshi KUSHIYAMA[1)], Keishi HIGASHI[1)], Naomi HYODO[1)], Kojiro YAMAMOTO[1)], Takashi ODA[1)], Shigenobu SUZUKI[1)], and Soichiro MIURA[1)]

The mechanisms of hypertensive nephrosclerosis are not fully understood. In experimental models of the disease, inflammatory reactions such as macrophage infiltration play an important role. In human hypertensive nephrosclerosis, however, there have been few studies examining the role of inflammation histologically. We investigated whether the number of infiltrating macrophages was increased in human hypertensive nephrosclerosis, and evaluated the effects of a blockade of the renin-angiotensin system on clinical and histological findings. We examined macrophage infiltration using immunohistochemistry in renal biopsy specimens obtained from 16 patients with hypertensive nephrosclerosis, 5 patients with IgA nephropathy, 5 patients with membranous nephropathy, and 5 patients with minimal change nephrotic syndrome. The number of infiltrating macrophages in glomeruli was significantly larger in the patients with hypertensive nephrosclerosis than in those with minimal change nephrotic syndrome. The patients with hypertensive nephrosclerosis were divided into groups based on their use of antihypertensive agents at the time of renal biopsy. We investigated the effects of antihypertensive agents on clinical findings, macrophage infiltration, and monocyte chemoattractant protein-1 expression. There was no difference in clinical findings between the hypertensive groups. The numbers of infiltrating macrophages and monocyte chemoattractant protein-1–positive cells in glomeruli were significantly smaller in patients treated with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker, whereas calcium channel blockers had no influence on histological findings. In conclusion, inflammation is involved in the progression of human hypertensive nephrosclerosis and the inflammatory process is inhibited by blocking the renin-angiotensin system. (*Hypertens Res* 2007; 30: 635–642)

***Key Words*: angiotensin-converting enzyme inhibitor, angiotensin II type 1 receptor blocker, hypertensive nephrosclerosis, macrophage, monocyte chemoattractant protein-1**

Introduction

Hypertensive nephrosclerosis is one of the most important causes of end-stage renal failure (*1*). In addition, systemic hypertension affects renal function in patients with other chronic renal diseases (*2*, *3*). However, the mechanisms behind the development and progression of hypertensive renal injury have not been fully elucidated. During the last decade, several studies have suggested that inflammatory reactions involving macrophage infiltration play an important pathogenic role in the development and progression of hypertensive nephrosclerosis (*4*, *5*). Monocyte chemoattractant protein-1 is a chemokine that strongly attracts monocytes/

From the [1)]Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan.

Address for Reprints: Toshihiko Imakiire, M.D., Department of Internal Medicine, National Defense Medical College, 3–2 Namiki, Tokorozawa 359–8513, Japan. E-mail: grd1701@ndmc.ac.jp

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Table 1. Clinical Data of 31 Patients

	HTN	IgAN	MN	MCNS
Number	16	5	5	5
Age (years)	57.7±13.0	34.3±11.6	59.2±14.9	24.8±13.0
BMI (kg/m^2)	25.4±3.7	23.5±3.8	24.2±2.7	22.8±3.8
SBP (mmHg)	157.0±24.4	127.0±23.6	136.8±24.1	117.6±17.3
DBP (mmHg)	89.6±14.3	78.7±15.9	77.6±16.1	66.0±14.0
BUN (mmol/L)	6.21±1.96	6.18±1.32	6.07±2.36	5.36±1.93
Cr (μmol/L)	103.4±44.2	82.2±27.5	83.1±9.7	60.1±8.8
T-Cho (mmol/L)	5.13±0.89	5.09±1.09	7.93±2.75	11.27±3.24
Glu (mmol/L)	5.82±1.05	5.22±0.28	5.53±1.70	5.25±0.95
CCr (mL/s)	1.00±0.26	1.34±0.21	1.36±0.53	1.75±0.42
UP (g/day)	0.95±1.25	0.73±0.54	5.64±5.30	7.23±2.60

HTN, hypertensive nephrosclerosis; IgAN, immunoglobulin A nephropathy; MN, membranous nephropathy; MCNS, minimal change nephrotic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; Cr, creatinine; T-Cho, total cholesterol; Glu, glucose; CCr, creatinine clearance; UP, urinary protein.

macrophages, and its expression is upregulated in the kidneys of many patients with renal diseases, including hypertensive renal injury (*5*). Activation of the renin-angiotensin system is a major cause of systemic hypertension and local activation in the kidneys induces renal tissue damage *via* immunological mechanisms such as the activation of nuclear factor κB (NFκB) (*6*). In addition, renal monocyte chemoattractant protein-1 expression is increased in an experimental rat model of renin-angiotensin system–dependent hypertension, and angiotensin II type 1 receptor blocker inhibits the production of monocyte chemoattractant protein-1 protein and decreases macrophage infiltration (*7*). Furthermore, large clinical trials have confirmed that angiotensin-converting enzyme inhibitors inhibit the renin-angiotensin system, and that angiotensin II type 1 receptor blockers have renoprotective effects in diabetic and non-diabetic renal diseases, with some of these renoprotective effects appearing to be independent of the blood pressure–lowering effects (*8*, *9*).

Despite many clinical and experimental findings, there have been few histological investigations of human hypertensive nephrosclerosis. It is still unknown whether inflammatory cells are actually involved in hypertensive renal injury. Thus, we studied the involvement of macrophage infiltration in hypertensive nephrosclerosis in comparison with that in various glomerulonephritides. We also investigated the effects of inhibition of the renin-angiotensin system by angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers on macrophage infiltration and the expression of monocyte chemoattractant protein-1 in human hypertensive nephrosclerosis.

Methods

Patients

We retrospectively studied 24 subjects histologically diagnosed with benign hypertensive nephrosclerosis from among patients undergoing renal biopsy at the Department of Internal Medicine of the National Defense Medical College between 1995 and 2003. Renal biopsies were performed on these hypertensive patients to test for other renal diseases. The diagnosis was based on clinical symptoms, laboratory data, and histological findings. Among the 24 patients with hypertensive nephrosclerosis, 8 with decreased renal function (serum creatinine concentration >2 mg/dL) were excluded because their glomeruli were largely obsolescent. In the remaining 16 patients, there was no evidence of secondary hypertension or other systemic diseases. We also studied 5 randomly selected patients with IgA nephropathy, 5 with membranous nephropathy, and 5 with minimal change nephrotic syndrome. Renal samples obtained from the healthy poles of nephrectomized kidneys from 4 patients with renal cell carcinoma were also examined as a normal control. Clinical and laboratory findings on all patients are summarized in Table 1.

To study the effects of angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers on the renal histopathology, the 16 patients with hypertensive nephrosclerosis were divided into two groups based on their use of angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers at the time of renal biopsy. Eight patients were being treated with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker at the time of renal biopsy. These patients with hypertensive nephrosclerosis were also divided into two groups based on their use of calcium channel blockers.

The protocol was approved by the local ethics committee, and informed consent was obtained from each patient.

Light Microscopy and Immunohistochemistry

For light microscopic examination, renal biopsy specimens

were stained with hematoxylin and eosin, periodic acid-Schiff, and Masson trichrome.

For immunohistochemical analysis, we used monoclonal antibodies against CD68 (macrophage marker, monoclonal mouse antihuman PG-M1; DAKO, Carpinteria, USA), CD3 (T lymphocyte marker, rabbit antihuman, U0026; DAKO), monocyte chemoattractant protein-1 (monoclonal mouse antihuman, MAB2791; R&D systems, Minneapolis, USA), and transforming growth factor β1 (polyclonal rabbit antihuman, sc-146; Santa Cruz Biotechnology, Santa Cruz, USA). Kidney specimens fixed in 10% formalin and embedded in paraffin were sectioned and stained using the labeled streptavidin biotin method. The sections were deparaffinized with xylene and ethyl alcohol. The endogenous peroxidase activity was blocked by incubation with 3% hydrogen peroxide for 10 min. After further blocking with 10% non-immune serum in phosphate-buffered saline for 10 min, the sections were incubated with primary antibodies for CD68 (1:100), CD3 (ready-to-use), monocyte chemoattractant protein-1 (1:100), and transforming growth factor β1 (1:100) for 45 min at 37°C. These staining procedures for CD68 and monocyte chemoattractant protein-1 required pretreatment with 0.04% proteinase K for 7 min and those for CD3 required autoclave (121°C, 10 min) pretreatment for optimal antigen retrieval. Then, all sections except those for CD3 were incubated with DAKO LSAB system link–biotinylated secondary antibody (DAKO) for 10 min, followed by peroxidase-conjugated streptavidin at room temperature for 10 min. After being washed with phosphate-buffered saline, all of the sections were stained with a 3,3′-diaminobenzidine solution and then counterstained with hematoxylin. To investigate the localization, double staining for monocyte chemoattractant protein-1 and CD68 was performed. Paraffin sections were first stained for monocyte chemoattractant protein-1 with an ENVISION-ALP system (DAKO) and developed with Fast blue BB salt (blue), and then sequentially stained for CD68 (PG-M1 EPOS: DAKO) and developed with a 3,3′-diaminobenzidine solution (brown).

Semi-Quantification and Statistical Analysis

Global glomerulosclerosis was assessed in specimens stained with periodic acid-Schiff and was presented as a percentage of the number of all glomeruli. In each patient, 6–45 glomeruli per specimen with a median of 18 glomeruli were inspected. The degree of interstitial fibrosis was scored semi-quantitatively with the Masson-stained specimens as follows: 0, no fibrosis; 1, mild (<25% fibrotic tissue); 2, moderate (25–50%); 3, severe (>50%). The number of CD68- or monocyte chemoattractant protein-1–positive cells in each glomerulus was counted and averaged for each biopsy specimen. The interstitial CD68-positive area was scored semi-quantitatively as follows: 0, no staining; 1, mild (<25% of area immunostained); 2, moderate (25–50%); 3, severe (>50%). The percentage of the interstitium positive for monocyte chemoattractant protein-1 was evaluated by using Lumina Vision software (Mitani Corp., Tokyo, Japan). These microscopic evaluations were performed by histologists without prior prejudicial information.

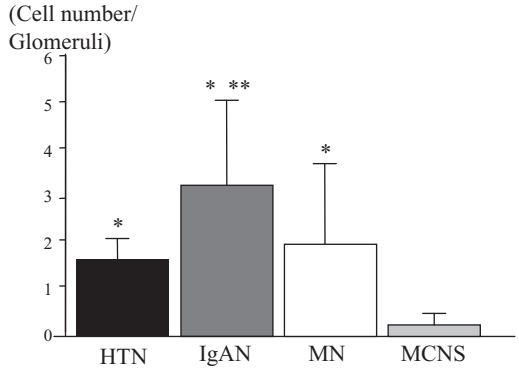

Fig. 1. *The number of CD68-positive cells in glomeruli in the four groups. Hypertensive nephrosclerosis (HTN), 1.64±0.95; IgA nephropathy (IgAN), 3.00±1.85; membranous nephropathy (MN), 1.98±1.43; minimal change nephrotic syndrome (MCNS), 0.27±0.17. *p<0.05 vs. MCNS, **p<0.05 vs. HTN.*

Results are expressed as the mean±SD. Statistical analyses were performed using an analysis of variance (ANOVA) followed by Fisher's PLSD test as appropriate. A *p*-value of <0.05 was considered significant.

Results

In normal kidneys, CD68-positive cells were undetectable in glomeruli, and monocyte chemoattractant protein-1–positive cells were undetectable in glomeruli and very sparse in the interstitium. Numbers of CD68-positive cells in glomeruli were significantly increased among the patients with hypertensive nephrosclerosis, IgA nephropathy, and membranous nephropathy compared with the patients having minimal change nephrotic syndrome. There was no significant difference in the number of CD68-positive cells in glomeruli between the patients with hypertensive nephrosclerosis and those with membranous nephropathy, whereas the number was significantly increased in patients with IgA nephropathy compared with patients with hypertensive nephrosclerosis (Fig. 1).

Table 2 shows the clinical data and pathological findings of patients with hypertensive nephrosclerosis divided into two groups according to their use of angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers. In regard to the clinical data, blood pressure and urinary protein excretion were higher in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group than the angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker (–) group. However,

Table 2. Comparison of Clinical Data and Pathological Findings between 16 Patients with HTN Divided by ACEI/ARB Usage

	ACEI/ARB (−)	ACEI/ARB (+)
Number	8	8
Age (years)	59.5±13.0	55.9±13.9
BMI (kg/m^2)	25.9±3.4	24.8±4.0
SBP (mmHg)	151.0±23.8	163.0±25.2
DBP (mmHg)	87.3±16.6	92.0±12.1
BUN (mmol/L)	6.46±2.07	6.00±1.90
Cr (μmol/L)	106.1±44.2	97.2±44.2
T-Cho (mmol/L)	5.13±0.67	5.13±1.12
Glu (mmol/L)	5.90±1.35	5.73±0.73
CCr (mL/s)	0.98±0.20	1.03±0.32
UP (g/day)	0.71±1.00	1.18±1.50
Global GS (%)	23.0 ±12.8	19.3±20.1
T-I change (score)	2.25±0.71	1.75±0.89

HTN, hypertensive nephrosclerosis; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; Cr, creatinine; T-Cho, total cholesterol; Glu, glucose; CCr, creatinine clearance; UP, urinary protein; GS, glomerulosclerosis; T-I, tubulo-interstitial.

the difference was not significant. Regarding renal pathology, the score of tubulointerstitial fibrosis was lower in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group than the (−) group, but again the difference was not significant. Similarly, when these patients were divided into two groups according to their use of calcium channel blockers, there was no significant difference between the calcium channel blocker (+) group ($n=6$) and the calcium channel blocker (−) group ($n=10$) in either clinical data or pathological findings (data not shown).

Glomerular immunostainings of CD68 and monocyte chemoattractant protein-1 in patients with hypertensive nephrosclerosis are shown in Fig. 2. Some CD68-positive cells were observed in the angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker (−) group (Fig. 2A, arrows), but few in the (+) group (Fig. 2B). In the angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker (−) group, partial staining of monocyte chemoattractant protein-1 was observed in mesangial cells (Fig. 2C, arrows). On the other hand, only sparse glomerular staining of monocyte chemoattractant protein-1 was detected in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group (Fig. 2D). The observation of staining for CD68 (brown) adjacent to that for monocyte chemoattractant protein-1 (blue) indicated their close relationship (Fig. 2E). The number of CD68-positive cells in glomeruli was significantly lower in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group than the angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker (−) group (1.14±0.73 *vs*. 2.14±0.91, $p<0.05$) (Fig. 3A). Similarly, the score of the interstitial CD68-positive area tended to be lower in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group (1.75±0.71) than the (−) group (2.38±0.52), although the difference did not reach the level of statistical significance (Fig. 3B). In contrast, there was no difference in the number of CD68-positive cells in glomeruli between the calcium channel blocker (+) group and the calcium channel blocker (−) group (1.64±1.17 *vs*. 1.65±0.87). The number of monocyte chemoattractant protein-1–positive cells in glomeruli was significantly smaller in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group than the angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor blocker (−) group (0.58±0.25 *vs*. 1.06±0.54, $p<0.05$) (Fig. 4A). However, there was no significant difference in the interstitial monocyte chemoattractant protein-1–positive area between the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) and (−) groups (0.72±0.23% *vs*. 0.75±0.34%) (Fig. 4B). And as before, there was no significant difference in monocyte chemoattractant protein-1–positive cell numbers in glomeruli between the calcium channel blocker (+) group and the calcium channel blocker (−) group (0.85±0.52 *vs*. 0.81±0.48).

In hypertensive kidneys, CD3-positive cells and transforming growth factor β1–positive cells were undetectable in glomeruli. Those cells were locally observed only in fibrotic areas in the interstitium. There were no significant differences between groups in either CD3-positive cells or transforming growth factor β1–positive cells (data not shown).

Discussion

In this study, we found that the number of macrophages in glomeruli was significantly greater in patients with hypertensive nephrosclerosis than those with minimal change nephrotic syndrome. In addition, the numbers of infiltrating macrophages and monocyte chemoattractant protein-1–positive cells in glomeruli were significantly decreased in hypertensive patients treated with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker compared to patients not treated with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker. On the other hand, these agents did not affect T lymphocyte infiltration and transforming growth factor β1 expression. The effects of these agents on macrophage infiltration and monocyte chemoattractant protein-1 expression might be comparatively specific to human hypertensive nephrosclerosis.

Several studies have suggested that macrophages infiltrating the kidneys play an important role in the progression of many glomerulonephritides and diabetic nephropathy (*10–12*). Macrophages produce a variety of cytokines and nitric

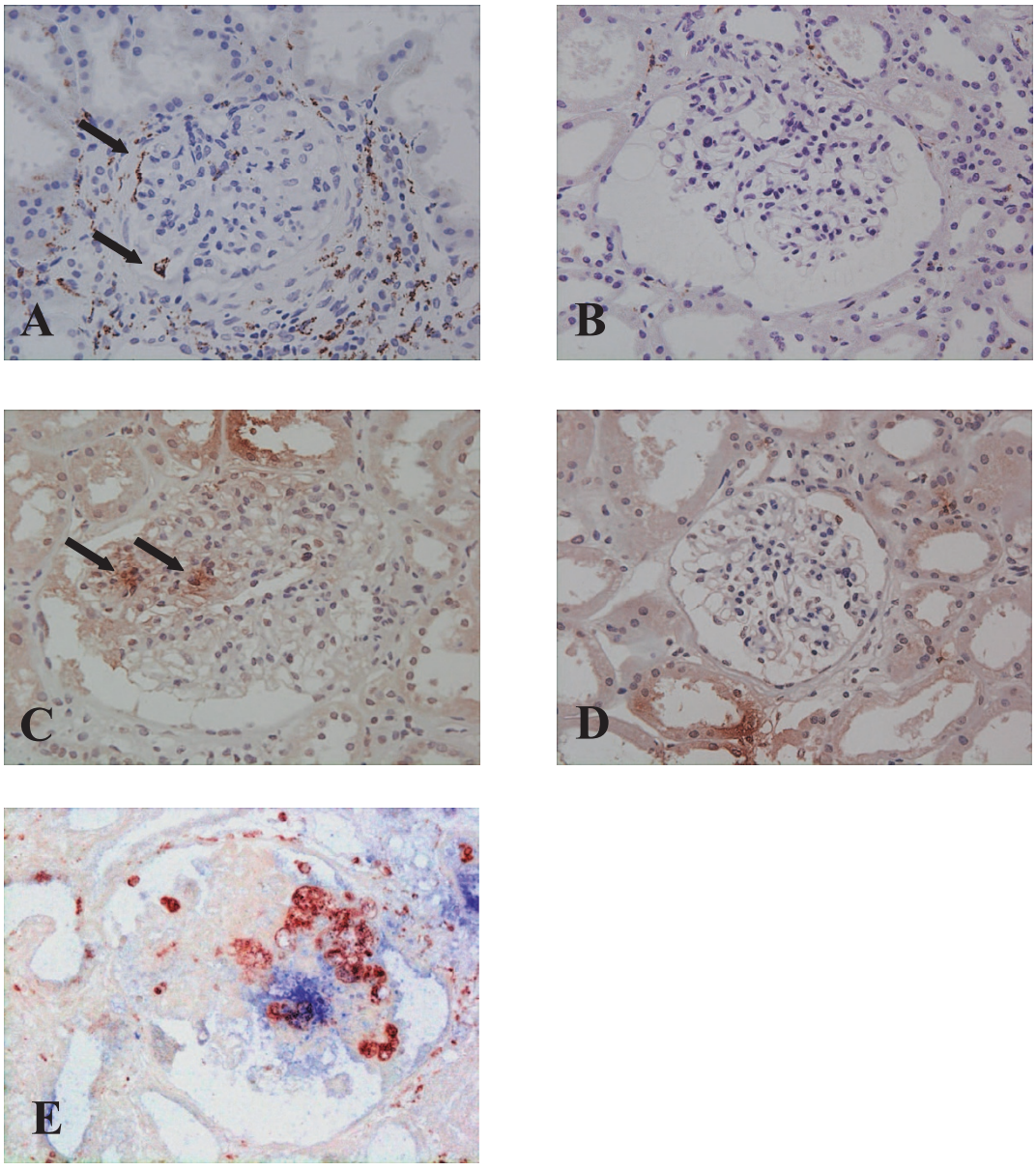

Fig. 2. *Representative immunohistochemical photomicrographs of CD68 (A, B) and monocyte chemoattractant protein-1 (MCP-1) (C, D) in hypertensive nephrosclerosis. A: Immunostaining of CD68 in a patient with angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (ACEI/ARB) (–). Some CD68-positive cells were observed (arrows). B: Immunostaining of CD68 in a patient with ACEI/ARB (+). C: Immunostaining of MCP-1 in a patient with ACEI/ARB (–). A few MCP-1–positive cells were observed (arrows). D: Immunostaining of MCP-1 in a patient with ACEI/ARB (+). E: Double immunostaining for CD68 (brown) and MCP-1 (blue). Original magnification, × 400.*

oxygen, and thereby contribute to tissue damage. Furthermore, recent studies suggest that inflammatory mechanisms, including macrophage infiltration, are involved in the development of hypertensive kidney injury (*5*, *13*), as well as in other glomerulonephritides, where they are though to contribute primarily to the disease progression. According to our data, the degree of macrophage infiltration in glomeruli was greater in patients with hypertensive nephrosclerosis than those with minimal change nephrotic syndrome, suggesting that inflammation was involved, at least in part, in the development of human hypertensive renal injury.

Angiotensin II has a key role in the development of chronic kidney diseases, exerting both hemodynamic and non-hemodynamic effects. The hemodynamic effect of angiotensin II on efferent arterioles raises intraglomerular pressure (*14*) and accelerates glomerulosclerosis. Moreover, mechanical stretch

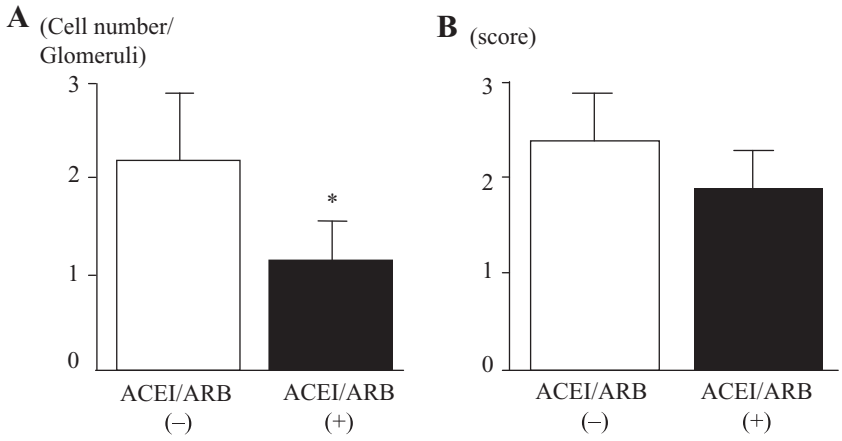

Fig. 3. *The number of CD68-positive cells in glomeruli (A) and the score of the CD68-positive area in the interstitium (B) in hypertensive nephrosclerosis. *p < 0.05 vs. the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (ACEI/ARB) (–) group.*

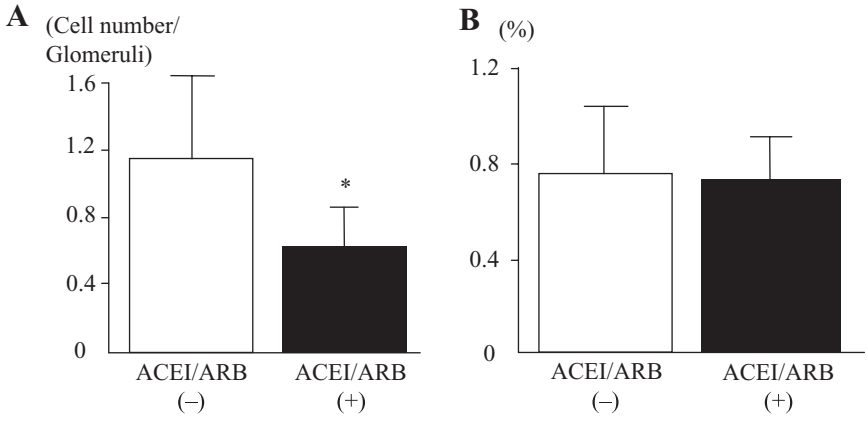

Fig. 4. *The number of monocyte chemoattractant protein-1 (MCP-1)–positive cells in glomeruli (A) and the percentage of the interstitium positive for MCP-1 (B) in hypertensive nephrosclerosis. *p < 0.05 vs. the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (ACEI/ARB) (–) group.*

in mesangial cells induces monocyte chemoattractant protein-1 expression and macrophage infiltration *in vitro* (*15*). Non-hemodynamic effects of angiotensin II, including induction of the expression of chemokines, are thought to be involved in the pathogenesis of various renal diseases. Inhibition of angiotensin II by angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers attenuates the decline in renal function associated with diabetic and non-diabetic chronic kidney diseases (*8*, *9*, *16–19*). Monocyte chemoattractant protein-1 is an important chemoattractant for macrophages in a variety of kidney diseases (*20*), and its expression is induced by activation of the renin-angiotensin system (*21*, *22*). In an experimental model, monocyte chemoattractant protein-1 expression in kidneys was increased in hypertensive nephrosclerosis and was related to macrophage infiltration. Angiotensin II type 1 receptor blocker blocked the expression of monocyte chemoattractant protein-1 and decreased macrophage infiltration (*7*). Transforming growth factor β1 also plays an important role in renal fibrosis in various diseases, including hypertensive nephrosclerosis (*23*), and is induced by angiotensin II (*24*); however, transforming growth factor β1 expression did not appear to be affected by inhibition of the renin-angiotensin system in the present study.

In the present study, we observed a close relationship between macrophage and monocyte chemoattractant protein-1 by means of double staining and demonstrated that the numbers of infiltrating macrophages and monocyte chemoattractant protein-1–positive cells in glomeruli were significantly decreased in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group compared

with the (–) group. On the other hand, these effects were not seen in patients treated with calcium channel blocker. There was no significant difference in clinical and biochemical parameters, including blood pressure, either between the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group and (–) group or between the calcium channel blocker (+) group and (–) group. Therefore, the blood pressure–lowering effect of antihypertensive drugs seemed to have little influence on macrophage infiltration and monocyte chemoattractant protein-1 expression in our study. Similarly, the quantity of proteinuria was not related to macrophage infiltration and monocyte chemoattractant protein-1 expression in this study. There was a trend for urinary protein excretion to be greater in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group than the (–) group. This difference was attributed to patient selection bias. That is, the baseline urinary protein excretion in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group was a little greater. Thus, our data suggest that inflammatory mechanisms contribute to human hypertensive nephrosclerosis, and a blockade of the renin-angiotensin system might improve hypertensive renal injury *via* a reduction of monocyte chemoattractant protein-1 expression and macrophage infiltration regardless of the level of blood pressure and proteinuria. As large clinical trials have shown that a blockade of the renin-angiotensin system has great advantages in diabetic and non-diabetic kidney diseases (*8*, *9*, *17*, *18*), it is feasible that an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker could improve the prognosis of hypertensive nephrosclerosis not only by lowering blood pressure but also by inhibiting inflammatory mechanisms.

Histologically, hypertensive nephrosclerosis is characterized by arteriolar and tubulointerstitial changes as well as glomerular lesions. In this study, there was no significant difference in the degree of macrophage infiltration or monocyte chemoattractant protein-1 expression in the interstitium, although fibrosis and macrophage infiltration in the interstitium tended to be less extensive in the angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker (+) group. The reason for these slight differences in results between the glomeruli and the interstitium is not exactly clear. But we speculate that the effects of angiotensin II might be more profound in the glomeruli than in the interstitium in human hypertensive nephrosclerosis, because the constriction of the efferent arterioles by angiotensin II directly influences glomerular cells.

Our data suggested that a macrophage-mediated inflammatory process might be involved in hypertensive nephrosclerosis. The involvement of an inflammatory process in the progression of hypertensive nephrosclerosis has been suggested based on findings mainly obtained from experimental models of hypertension, and there have been few reports referring to histological findings on inflammatory cell infiltration in human hypertensive nephrosclerosis (*25*). This is because a renal biopsy is not performed for the diagnosis of hypertensive nephrosclerosis, and hypertensive nephrosclerosis can generally be diagnosed by excluding other glomerulonephritides using the medical history and clinical presentation, as it was in the present cases. In this study, all 16 patients were clinically and histologically diagnosed with benign hypertensive nephrosclerosis. Human benign hypertensive nephrosclerosis is thought to develop gradually as a consequence of long-term hypertension, and thus shows a considerably different progression from experimental hypertension, which is generally rapid and short-term (*4*, *5*, *7*). The present data are interesting, because they suggest that, in addition to the role played by the renin angiotensin system, an inflammatory process could also contribute to the progression of human benign hypertensive nephrosclerosis, although the mechanisms are not likely to completely correspond with those in experimental models.

The main limitation of this study is that it was cross-sectional in a small number of patients. Although some patients had been prescribed an angiotensin-converting enzyme inhibitor and/or angiotensin II type 1 receptor blocker after renal biopsy, rebiopsy was not be performed because we could not obtain their consent. In addition, there are some differences between the actions of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers, and thus it is possible that their influences on macrophage infiltration are different. Additional prospective studies with large cohorts will be needed to elucidate the effects of renin-angiotensin system blockade on the inflammatory reaction in human hypertensive nephrosclerosis.

In conclusion, an inflammatory process is involved in the progression of renal injury in patients with benign hypertensive nephrosclerosis, and inhibition of the renin-angiotensin system decreases glomerular macrophage infiltration *via* a reduction in monocyte chemoattractant protein-1 expression. In addition to lowering systemic and intraglomerular blood pressure, antihypertensive treatment with an angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker might retard deterioration in renal function by suppressing inflammatory cell infiltration in the kidneys.

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