Original Article

Comparison of Renal and Vascular Protective Effects between Telmisartan and Amlodipine in Hypertensive Patients with Chronic Kidney Disease with Mild Renal Insufficiency

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The present study was conducted to compare the renal and vascular protective effects of telmisartan and amlodipine in untreated hypertensive chronic kidney disease (CKD) patients with moderate renal insufficiency. Thirty hypertensive CKD patients were randomly assigned to receive telmisartan 40 mg (*n*=15) or amlodipine 5 mg (*n*=15) once daily for 12 months. Changes in blood pressure, serum creatinine, 24-h creatinine clearance (Ccr), proteinuria, brachial-ankle pulse wave velocity (baPWV), intima-media thickness (IMT), plasma interleukin-6 (IL-6), plasma matrix metalloproteinase (MMP)-9 and lipid profiles were monitored in all patients. Before treatment, there were no significant differences in these parameters between the telmisartan and amlodipine groups. Over the 12 month observation period, blood pressure decreased equally in both groups. However, serum creatinine, proteinuria, baPWV, IMT, plasma levels of IL-6 and MMP-9 and total cholesterol decreased and 24-h Ccr increased more strikingly in the telmisartan group than the amlodipine group. These data suggest that telmisartan is more effective than amlodipine for protecting renovascular functions, and potentially for ameliorating atherosclerosis, in hypertensive CKD patients with moderate renal insufficiency. (*Hypertens Res* 2008; 31: 841–850)

***Key Words*: chronic kidney disease, angiotensin receptor antagonist, proteinuria, atherosclerosis**

Introduction

Chronic kidney disease (CKD) is associated with increased risk of cardiovascular morbidity and mortality. It has been suggested that cardiovascular risk factors and cardiac, renal and arterial abnormalities should be evaluated from the beginning of CKD (*1*). Inflammation, hypertension, and increased pulse pressure have been associated with vascular dysfunction and may be targets for future interventional strategies to reduce cardiovascular risk in patients with CKD (*2*). Pulse wave velocity (PWV) and intima-media thickness (IMT) are important vascular markers in CKD patients (*3*, *4*). Metalloproteinase (MMP)-9 is an extracellular matrix–degrading enzyme that plays an important role in renal diseases (*5*). MMP-9 expression in the arterial wall is elevated in unstable coronary atherosclerosis and the upregulation of MMP-9 in arterial wall inflammation has been shown to raise blood MMP-9 levels (*6*).

Since the purpose of antihypertensive therapy is to prevent cardiovascular complications, the organ protective effect of antihypertensive drugs is very important (*7*). In this regard,

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telmisartan, an angiotensin type 2 receptor blocker (ARB), has been shown to have a unique property: it is a partial agonist of peroxisome proliferator–activated receptor γ (PPARγ) (*8*). Telmisartan has been shown to effectively and safely reduce blood pressure and regress proteinuria in hypertensive proteinuric patients with CKD, even in those with mild-to-moderate chronic renal failure (*9*). Amlodipine is one of the most popular calcium channel blockers (CCBs). Some investigators have reported that amlodipine induced a significant increase in proteinuria in hypertensive patients with CKD (*10*) and that amlodipine failed to slow the progression of CKD (*11*). However, there have been few studies directly comparing the renovascular effects of telmisartan and amlodipine in hypertensive CKD patients. The present study was therefore conducted to compare the renovascular protective effects of telmisartan and amlodipine in CKD patients.

Methods

Patients

We enrolled 30 non-diabetic CKD patients with hypertension with moderate renal insufficiency (18 males and 12 females; age: 47±10 years; systolic blood pressure [SBP]: 161±9 mmHg; diastolic blood pressure [DBP]: 97±6 mmHg; serum creatinine:1.7±0.3 mg/dL). CKD was diagnosed by renal biopsy. For light microscopic examination, renal biopsy specimens were stained with hematoxylin and eosin, periodic acid-Schiff, and Masson trichrome. Global glomerulosclerosis was assessed in specimens stained with periodic acid-Schiff and was presented as a percentage of the number of all glomeruli (*12*). In each patient, 8–35 glomeruli per specimen with a median of 16 glomeruli were inspected. The degree of interstitial fibrosis was scored semiquantitatively with the Masson-stained specimens as follows (*12*): 0, no fibrosis; 1, mild fibrosis (25% fibrotic tissue); 2, moderate fibrosis (25–50%); 3, severe fibrosis (>50%). The subjects were selected from among untreated CKD patients with hypertension who were visiting our hospitals for the first time. The exclusion criteria were an age younger than 20 years, serum creatinine >2.5 mg/dL (severe renal failure), proteinuria >2.0 g/d (severe proteinuria), histopathologically global glomerulosclerosis >50%, the use of any drugs, myocardial infarction or a cerebrovascular accident within the preceding 6 months, congestive heart failure, liver diseases, chronic pulmonary diseases, cancer, pregnancy, and collagen diseases. Initially, 38 non-diabetic CKD patients were enrolled, but 8 patients were excluded because of severely decreased renal function, high proteinuria and/or severe histopathology.

Study Design

The subjects were randomly assigned to two groups in a blinded fashion: 1) a group receiving amlodipine 5 mg once daily, or 2) a group receiving telmisartan 40 mg once daily. Any other antihypertensive therapy could be added if required to attain a blood pressure goal of less than 140/90 mmHg, including α-blockers, β-blockers and diuretics. We excluded angiotensin-converting enzyme inhibitors (ACEIs), other ARBs and other CCBs. During treatment, all patients were advised to follow moderate salt (4 to 6 g/d) and protein restriction (0.7 to 0.8 g/kg/d) in the diet (*13*). Table 1 summarizes the clinical and laboratory findings of the subjects. Informed consent was obtained from each patient and the local ethical committee approved the study protocol. The doses of other antihypertensive agents, drugs for glomerulonephritis, and statins were held constant during the study period. Treatment was continued for 12 months, during which period clinical and laboratory parameters were monitored once per month, and there were no changes in medication during the experimental period.

Measurements

Outpatient blood pressure measurements were obtained twice in the sitting position after 2 min of rest at 2 h after administration of the test drug, and the mean of 2 values was determined (*7*). Serum creatinine, 24-h creatinine clearance (Ccr), and urinary protein excretion were determined as parameters of the renal protective effect of these drugs. Carotid artery IMT and brachial-ankle PWV (baPWV) were determined as parameters of atherosclerosis. High-resolution B-mode ultrasound examination was done with a 7.5-MHz mechanical sector transducer on an Aloka SSD-2000 (Aloka Co., Ltd., Tokyo, Japan). An experienced technologist who was kept unaware of the patients' clinical data made all ultrasound measurements (scans and image analyses) using the same equipment as described previously (*14*, *15*). Carotid IMT was measured at points 20, 25 and 30 mm proximal to the flow divider on the far wall of the right and left common carotid arteries at the end of the diastolic phase (*16*), and the mean IMT was calculated for each individual. The greatest value from the 6 averaged IMTs (3 from the left and 3 from the right) was used as the representative value for each individual. When a plaque was observed in the region of common carotid artery measurements, IMT was not determined. baPWV was measured by means of a pulse pressure analyzer (model BP-203RPE; Nihon Colin, Tokyo, Japan). This instrument records PWV, blood pressure, electrocardiogram, and heart sounds simultaneously. Patients were examined in a supine position. Electrocardiographic electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the left edge of the sternum, and sphygmomanometer cuffs were wrapped on both upper arms and ankles. Pulse waves were recorded *via* sensors placed on both posterior tibial arteries. The time intervals required for the pulse waves to travel from the heart to both posterior tibial arteries was estimated on the basis of the patient's height. The best 10 consecutive pulses were analyzed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing

the distance by the time interval. Two measurements were taken in each leg, and the average value was used for analysis. PWV was expressed in cm/s. The PWV coefficient of variation was less than 5%. IMT and PWV studies were performed by a single trained observer at Shinmatsudo Central General Hospital who was unaware of the clinical and biochemical data.

Specific Plasma Markers

Plasma interleukin-6 (IL-6) and MMP-9 were determined as inflammation and atherosclerosis markers. Plasma IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Quantikine Human IL-6 Immunoassay; R&D Systems, Minneapolis, USA). This assay can detect IL-6 at a concentration as low as 7 pg/mL. The upper limit of normal plasma IL-6 levels is 10 pg/mL. Plasma MMP-9 levels were measured by a one-step sandwich enzyme immunoassay as previously reported (*17*, *18*). The sensitivity of the assay was 0.24 ng/mL and linearity was obtained from 0.24 ng/mL to 250 ng/mL. The intraassay coefficients of variation were 1.8–3.9%, and the interassay coefficients of variation were 1.8–6.2%. Blood total cholesterol (T-chol) and triglycerides (TG) were determined as metabolic factors.

Statistical Analysis

Intent-to-treat analysis includes data from all randomized patients in the group to which they were randomly assigned, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. Data are shown as the means±SD. To compare the parameters between two groups and between before and after treatment, we used the Mann-Whitney *U* test for unpaired data and the Wilcoxon signed-rank test for paired data. A p-value of <0.05 was considered significant.

Results

All 30 patients completed the study period without experiencing adverse side effects. As shown Table 1, there were no differences in the baseline characteristics, including age, sex, primary renal disease, SBP and DBP, serum creatinine, 24-h Ccr, urinary protein, PWV, IMT, serum T-chol, serum TG, plasma IL-6 and plasma MMP-9 between the amlodipine group and telmisartan group. Histopathological data were also not different between the two treatment groups. The percentage of patients taking steroids for glomerulonephritis and statins, was also not different between the two groups. Figure 1 shows the changes of SBP and DBP. Blood pressure showed a similar gradual and significant decrease with time in both groups ($p<0.001$), and there was no difference in the extent of changes between the two groups. Figure 2 shows the changes of serum creatinine, 24-h Ccr and urinary protein excretion as renal markers. Serum creatinine levels increased significantly after 12 months when compared with baseline in the amlodipine group ($p<0.001$). Serum creatinine levels showed little difference throughout the experimental period in the telmisartan group. Serum creatinine levels showed a significantly greater decline in the telmisartan group than in the amlodipine group (6 months: $p<0.05$; 12 months: $p<0.001$). Twenty-four–hour Ccr increased significantly

Table 1. Clinical and Laboratory Findings of CKD Patients

	Amlodipine	Telmisartan
n	15	15
Sex (male/female)	9/6	9/6
Age (years)	47±10	45±11
Dose (mg/d)	5	40
SBP (mmHg)	160±8	162±10
DBP (mmHg)	96±6	98±6
Heart rate (beats/min)	72±4	74±4
Serum creatinine (mg/dL)	1.6±0.3	1.7±0.3
24 h Ccr (mL/min)	48.5±8.5	47.4±7.4
Proteinuria (g/d)	1.3±0.3	1.4±0.4
PWV (cm/s)	1,620±196	1,680±168
IMT (mm)	0.620±0.048	0.610±0.052
Plasma IL-6 (pg/mL)	45.0±10.0	44.6±8.8
Plasma MMP-9 (pg/mL)	42.0±9.8	42.4±10.2
Total cholesterol (mg/dL)	218±13	219±15
Triglyceride (mg/dL)	145±18	148±20
BMI (kg/m^2)	24.8±4.2	25.4±3.8
Histopathology		
Global GS (%)	14.0±6.2	15.2±7.4
Tubulointerstitial score	2.10±0.82	2.32±0.90
Antihypertensive drugs (*n*)		
α-Blocker	6	5
β-Blocker	4	4
Diuretics	6	5
Anti-glomerulonephritis drugs (*n*)		
Anti-platelet	10	9
Steroids	2	2
Immunosuppressants	1	1
Statins (*n*)	3	2
Primary disease (*n*)		
IgA nephropathy	8	8
Non-IgA PGN	4	3
MN	1	2
MPGN	1	1
FGS	1	1

Data are expressed as mean±SD. CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; Ccr, creatinine clearance; PWV, pulse wave velocity; IMT, intima-media thickness; IL-6, interleukin-6; MMP, metalloproteinase; BMI, body mass index; GS, glomerulosclerosis; PGN, proliferative glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; FGS, focal glomeruosclerosis.

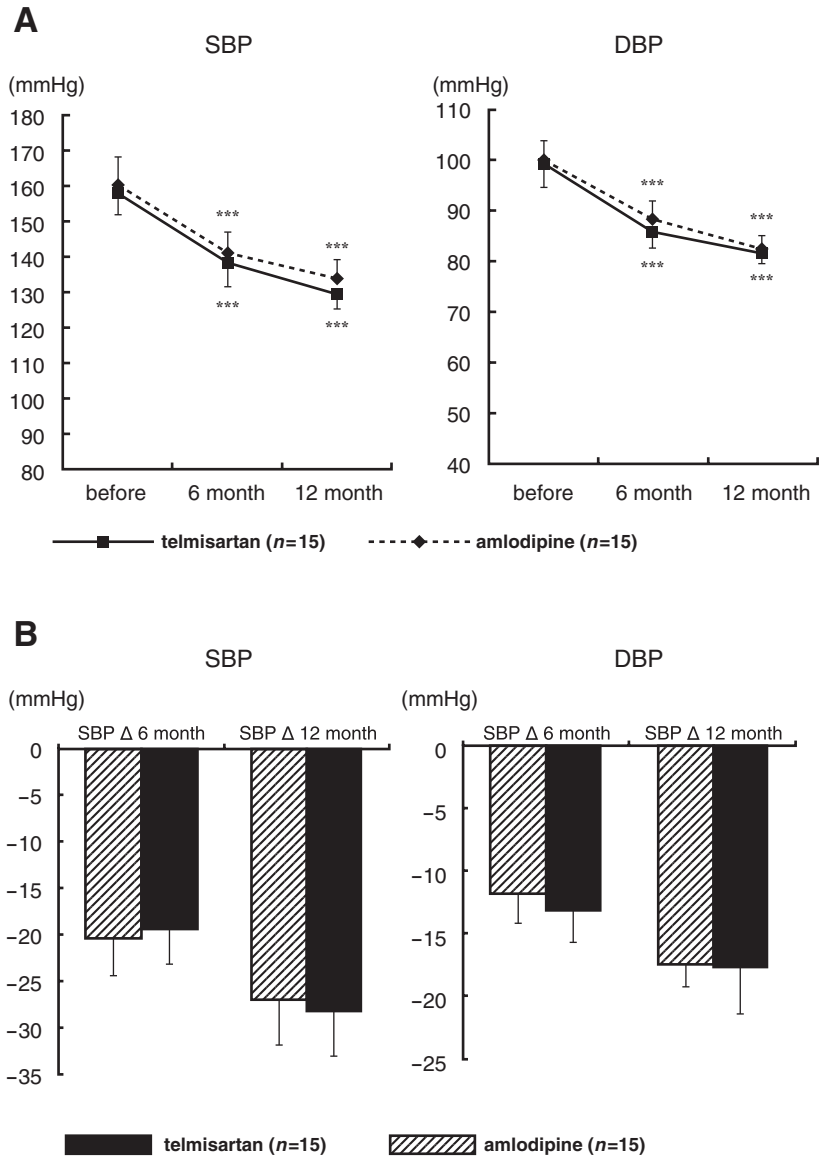

Fig. 1. *A: Time course of blood pressure changes by treatment with amlodipine or telmisartan. ***$p<0.001$ vs. before treatment. B: Changes of blood pressure at 6 and 12 months after treatment. There was no difference between the two treatment groups at either time point. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

after 6 months when compared with baseline in the telmisartan group ($p<0.001$), whereas 24-h Ccr decreased significantly after 12 months in the amlodipine group ($p<0.01$). The 24-h Ccr showed a significantly greater increase in the telmisartan group than in the amlodipine group (6 and 12 months: $p<0.001$). To assess the changes of nutrition, we measured BMI. BMI was found to be slightly reduced in both groups, but this change did not reach the level of statistical significance (amlodipine: from 24.8±4.2 to 23.6±3.8 kg/m^2; telmisartan: from 25.4±3.9 to 24.6±3.2 kg/m^2). Urinary protein excretion increased significantly after 12 months when compared with baseline in the amlodipine group ($p<0.01$), whereas it decreased significantly after 6 and 12 months (both $p<0.001$) in the telmisartan group. Urinary protein excretion showed a significantly greater decline in the telmisartan group than in the amlodipine group (6 and 12 months: $p<0.001$). Figure 3 shows the changes of PWV and IMT. PWV increased significantly after 6 ($p<0.05$) and 12 months ($p<0.01$) when compared with baseline in the amlodipine group, whereas this parameter decreased significantly after 6 ($p<0.001$) and 12 months ($p<0.001$) in the telmisartan group. PWV showed a significantly greater decline in the telmisartan group than in the amlodipine group (6 and 12 months: $p<0.001$). IMT showed the same pattern in the amlodipine and telmisartan groups. Figure 4 shows the changes of plasma IL-6 and MMP-9 levels. Plasma IL-6 levels increased

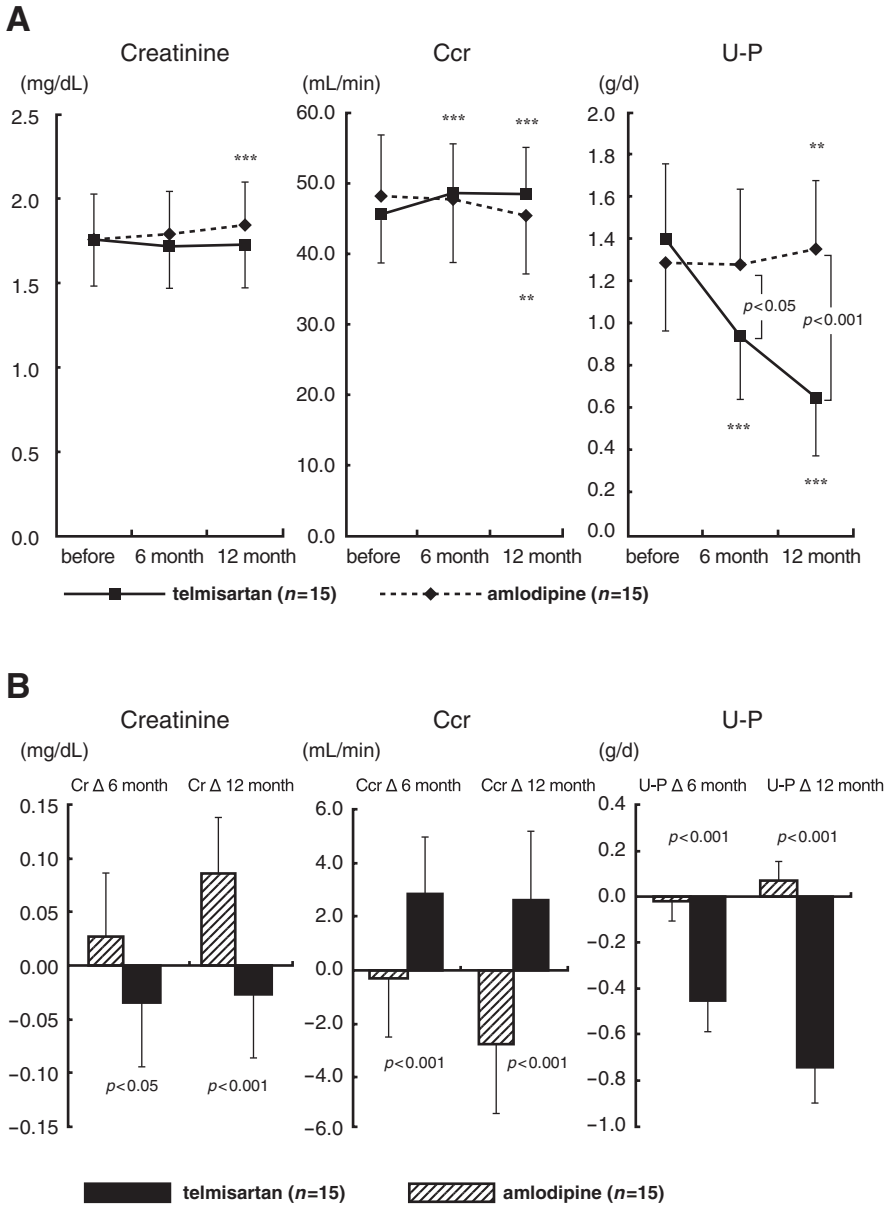

Fig. 2. *A: Time course of serum creatinine, 24-h Ccr and U-P excretion changes by treatment with amlodipine or telmisartan. **p < 0.01 and ***p < 0.001 vs. before treatment. B: Changes of serum creatinine, 24-h Ccr and urinary protein excretion at 6 and 12 months after treatment. Ccr, creatinine clearance; U-P, urinary protein.*

significantly after 6 and 12 months (both $p<0.05$) when compared with baseline in the amlodipine group, whereas they decreased significantly after 6 and 12 months in the telmisartan group (both $p<0.001$). Plasma IL-6 levels showed a significantly greater decline in the telmisartan group than in the amlodipine group (6 and 12 months: $p<0.001$). Plasma MMP-9 levels showed almost the same pattern in the amlodipine and telmisartan groups. Figure 5 shows the changes in serum T-chol and TG levels. Serum T-chol levels showed a significant decrease with time in the amlodipine group (6 and 12 months: $p<0.05$) and in the telmisartan group (6 and 12 months: $p<0.001$) when compared with baseline. Serum T-chol levels showed a significantly greater decline in the telmisartan group than in the amlodipine group (6 and 12 months: $p<0.001$). Serum TG levels decreased significantly after 6 and 12 months (both $p<0.01$) when compared with baseline in the telmisartan group, whereas these parameters showed little change throughout the experimental period in the amlodipine group. The changes of serum TG levels were not significantly different between the two treatment groups.

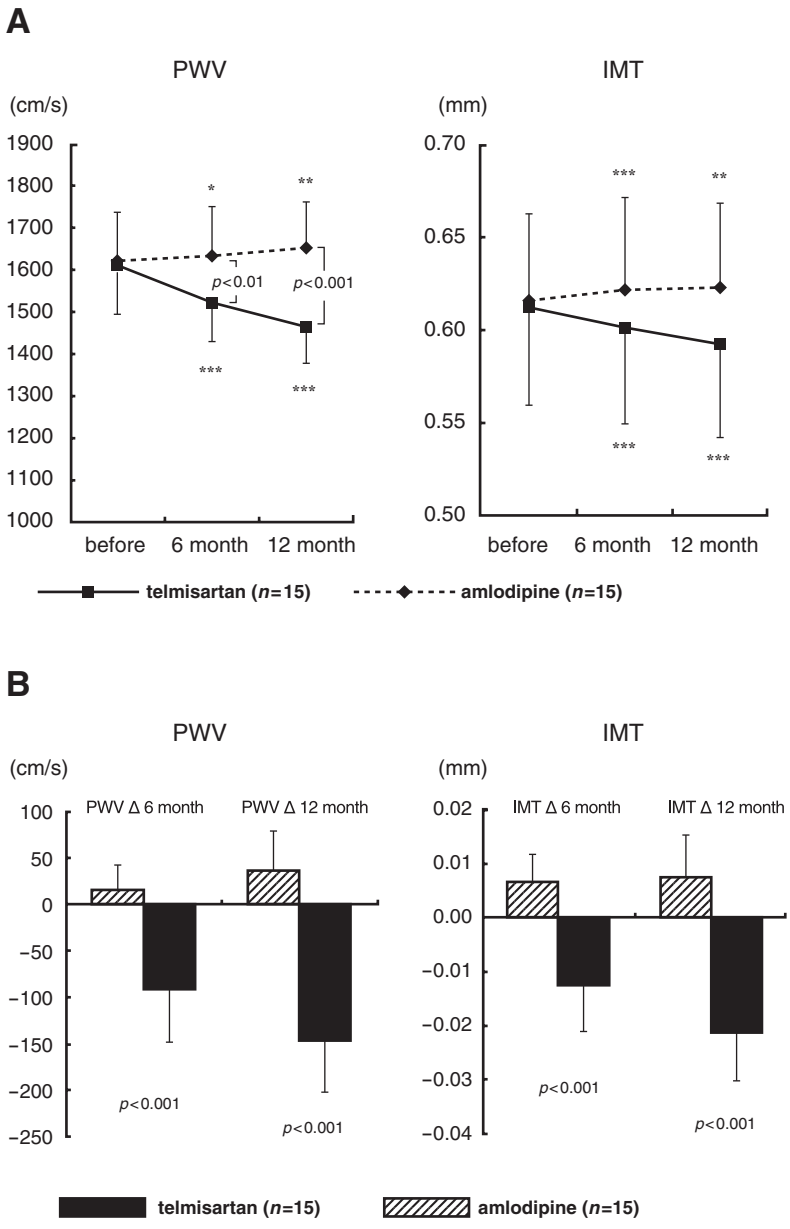

Fig. 3. *A: Time course of PWV and IMT changes by treatment with amlodipine or telmisartan. *p < 0.05, **p < 0.01, ***p < 0.001 vs. before treatment. B: Changes of PWV and IMT at 6 and 12 months after treatment. PWV, pulse wave velocity; IMT, intima-media thickness.*

Discussion

In the present study, we first demonstrated that an ARB, telmisartan, is more effective at protecting renal and vascular functions and at improving atherosclerosis lesions than the CCB, amlodipine, in hypertensive CKD patients with moderate renal insufficiency despite both drugs having a similar antihypertensive effect. Many investigators have reported the beneficial renoprotective effects of blocking the renin-angiotensin-system (RAS) (*19*, *20*). Telmisartan has been shown to have a unique property: it is a partial agonist of PPARγ (*8*). Activators of PPARγ exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risk for atherosclerosis (*21*). In addition to the antidiabetic properties, PPAR activators may improve renal disease and reduce proteinuria (*22*). A subgroup of ARBs including telmisartan have been characterized as PPARγ ligands independent of their angiotensin II type 1 (AT1) receptor–blocking actions (*22*) It is possible that some of the protective effects of AT1 receptor blockers in slowing the progression of CKD are due to actions that are independent of

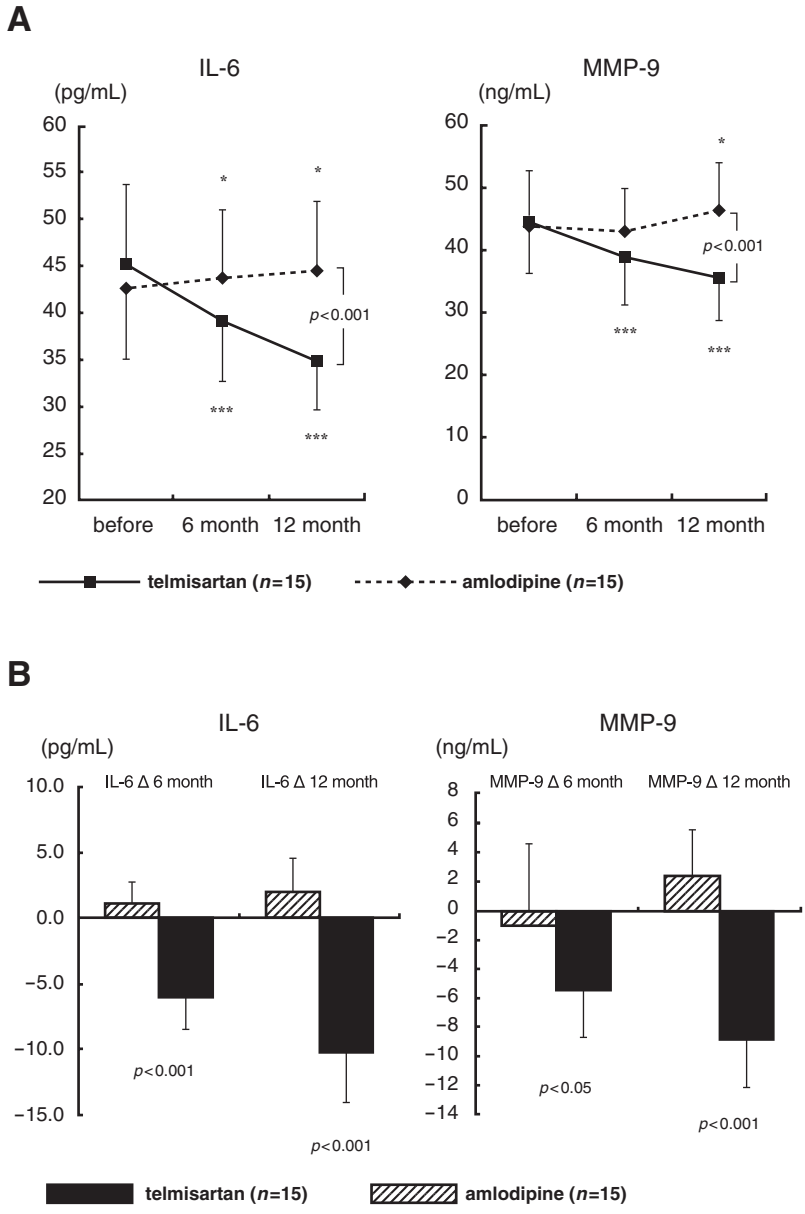

Fig. 4. *A: Time course of plasma IL-6 and MMP-9 changes by treatment with amlodipine or telmisartan. *p < 0.05, ***p < 0.001 vs. before treatment. B: Changes of IL-6 and MMP-9 at 6 and 12 months after treatment. IL-6, interleukin-6; MMP-9, metalloproteinase-9.*

the RAS action (*23*). Sharma *et al*. (*24*) have reported that once-daily telmisartan provided effective and well-tolerated treatment of mild/moderate CKD patients with hypertension, with no worsening renal function. Our data were coincident with theirs. Arterial changes occur early in the course of renal disease progression and may be related to dyslipidemia in the early stage (*4*). In the present study, we showed that telmisartan significantly reduced IMT, baPWV and serum T-chol. In a previous report, it was shown that telmisartan 40 mg/d was effective for reducing PWV in patients with mild-to-moderate hypertension, and that telmisartan may also be effective for improving cerebrovascular mortality (*25*). Candesartan, another ARB, has been shown to significantly decrease PWV and urinary albumin excretion, but did not affect IMT in hypertensive patients (*26*). Some investigators have reported that amlodipine reduced IMT in hypertensive patients (*26*), whereas others have reported that IMT was unaffected by amlodipine (*27*). In addition, some investigators have reported that amlodipine reduced PWV in hypertensive patients (*27*), whereas others have reported that PWV was unaffected by amlodipine (*28*). In the present study, amlodipine reduced neither IMT nor PWV in the hypertensive

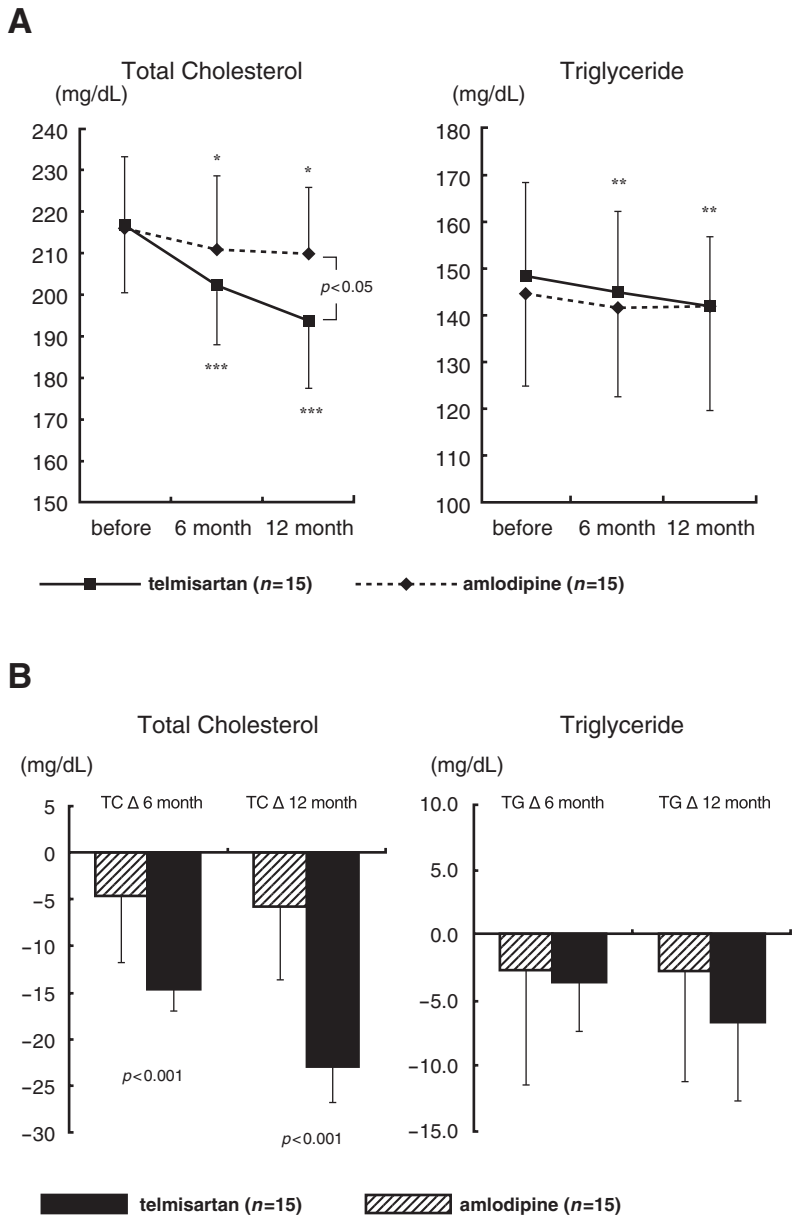

Fig. 5. *A: Time course of serum total cholesterol and triglyceride changes by treatment with amlodipine or telmisartan. *p < 0.05, **p < 0.01, ***p < 0.001 vs. before treatment. B: Changes of serum total cholesterol and triglyceride at 6 and 12 months after treatment. TC, total cholesterol; TG, triglycerides.*

CKD patients. However, some of these discrepancies may be related to differences in the patient backgrounds.

MMP-9 has been implicated in the pathogenesis of atherosclerosis (*29*). We have previously reported that MMP-9 may be associated with arteriosclerosis obliterans (*30*). Cytokines play important roles in cardiovascular diseases, including arteriosclerosis obliterans, by inducing inflammation, cell proliferation, and apoptosis (*31*). Many cytokines, including IL-6, stimulate MMP-9 (*32*). Lee *et al*. (*33*) have reported that carotid IMT increased significantly with increasing IL-6 levels and that IL-6 may be associated with an early state of atherosclerosis. In the present study, we first demonstrated that telmisartan, but not amlodipine, reduced plasma IL-6 and MMP-9 levels in hypertensive CKD patients, suggesting that telmisartan may have contributed to the prevention of atherosclerosis in these patients

In 2007, the Japanese Society of Nephrology published a CKD guide which stipulated that an ARB or ACEI be the first choice drug for CKD patients. Nonetheless, while CCBs have varying individual pharmacological and therapeutic properties, as a group they are also effective antihypertensive agents in CKD patients (*34*). Current studies suggest that CCBs do

not worse the progression of renal disease but rather may provide benefit when the SBP has been tightly normalized (*34*). Krimholtz *et al*. (*35*) have reported that candesartan and amlodipine lowered the urinary albumin excretion rate and blood pressure to a similar degree. Previous studies appearing in *Hypertension Research* compared the renoprotective efficacy of CCBs in CKD patients (cilnidipine *vs*. amlodipine or efonidipine *vs*. amlodipine) (*36*, *37*). In spontaneously hypertensive rat (SHR), amlodipine was shown to preserve the glomerular number and decrease the serum creatinine levels (*38*). Recently, Ichihara *et al*. (*39*) reported that addition of a low-dose of amlodipine to ARB treatment in hypertensive patients had benefits on the vascular function and vascular structure that were independent of amlodipine's depressor effects. Based on these findings, we consider that add-on CCB treatment should be considered for all CKD patients treated with an ARB.

Decline of renal function is inevitable in patients with CKD, and while ARBs can attenuate the decline of renal function, they cannot actually reverse the damage and improve renal function. Some investigators have reported that Ccr did not change significantly after telmisartan treatment in CKD patients (*19*, *40*). However, others have reported that Ccr and estimated glomerular filtration rate (eGFR) were increased slightly by telmisartan treatment (*41*, *42*). In the present study, telmisartan increased Ccr significantly. These discrepant results may be partly related to differences in the patient profiles, telmisartan dose, renal function or degree of diet therapy. However, the precise causes are unclear.

In the present study, we showed that telmisartan induced greater reductions in T-chol and TG when compared with amlodipine. We and other investigators have previously reported that telmisartan significantly reduced T-chol and TG levels in hypertensive patients (*43*, *44*). Telmisartan has a specific ability to partially activate receptors stimulating the proliferation of peroxisomes and improve the regulation of carbohydrate and lipid metabolism (*45*). However, the precise mechanisms of this effect are still unknown.

The present study has some limitations. First, the sample size was small. A large-scaled multicentered double-blinded study will be needed in the future. Second, whether the present results were due to class effects of ARBs in general or specific to telmisartan also remains to be determined. Third, we did not maximize the doses of either telmisartan or amlodipine, although such escalation will be needed to determine whether or not the effects are dose-dependent. Fourth, none of our findings suggested that there were changes in the renal injuries. In future studies on this topic, post-treatment renal biopsy will be needed.

In summary, the present study indicated that telmisartan is more effective at protecting renal and vascular function than amlodipine in hypertensive CKD patients with moderate renal insufficiency.

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