ORIGINAL ARTICLE

The angiotensin II type 1 receptor blocker olmesartan preferentially improves nocturnal hypertension and proteinuria in chronic kidney disease

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Accumulated evidence suggests that an altered ambulatory blood pressure (BP) profile, particularly elevated nighttime BP, reflects target organ injury and is a better predictor of further cardiorenal risk than the clinic BP or daytime BP in hypertensive patients complicated by chronic kidney disease (CKD). In this study, we examined the beneficial effects of olmesartan, an angiotensin II type 1 receptor blocker (ARB), on ambulatory BP profiles and renal function in hypertensive CKD patients. Forty-six patients were randomly assigned to the olmesartan add-on group ($n=23$) or the non-ARB group ($n=23$). At baseline and after the 16-week treatment period, ambulatory BP monitoring was performed and renal function parameter measurements were collected. Although the baseline clinic BP levels and the after-treatment/baseline (A/B) ratios of clinic BP levels were similar in the olmesartan add-on and non-ARB groups, the A/B ratios of ambulatory 24-h and nighttime BP levels in the olmesartan add-on group were significantly lower. Furthermore, the A/B ratios of urinary protein, albumin and type IV collagen excretion in the olmesartan add-on group were significantly lower than those in the non-ARB group (urinary protein excretion, 0.72 ± 0.41 vs. 1.45 ± 1.48 , $P=0.030$; urinary albumin excretion, 0.73 ± 0.37 vs. 1.50 ± 1.37 , $P=0.005$; urinary type IV collagen excretion, 0.87 ± 0.42 vs. 1.48 ± 0.87 , $P=0.014$) despite comparable A/B ratios for the estimated glomerular filtration rate in the two groups. These results indicate that in hypertensive patients with CKD, olmesartan add-on therapy improves the ambulatory BP profile via a preferential reduction in nighttime BP with concomitant renal injury inhibition.

Hypertension Research (2013) 36, 262–269; doi:10.1038/hr.2012.184; published online 15 November 2012

Keywords: ambulatory blood pressure; angiotensin receptor blocker; estimated glomerular filtration rate; proteinuria

INTRODUCTION

Clinical trials have shown that strict blood pressure (BP) control is critical for preventing target organ damage and cardiovascular mortality in hypertensive patients.^{1,2} Hypertensive patients with chronic kidney disease (CKD) are increasing in number, and cardiovascular complications are the most common cause of death in these patients. Thus, it is of considerable importance to identify therapeutic targets in cases of hypertension accompanied by the complication of CKD. Recent studies have indicated that the ambulatory and the clinic BP profiles are important for proper estimation of BP control. In particular, ambulatory BP monitoring has allowed accurate diagnosis of hypertension^{3,4} and determination of the circadian BP rhythm under different pathophysiological conditions, including CKD, and thus may have prognosis predictability superior to clinic BP measurement.^{5,6} The circadian BP pattern in hypertensive patients with CKD has been found to exhibit a blunted nocturnal BP decrease, which is associated with

autonomic neuropathy and nephropathy.^{7,8} Conversely, the loss of nocturnal BP dipping is considered a risk factor for nephropathy progression and is of prognostic value with respect to target organ damage and cardiovascular morbidity in these CKD patients.^{6,9–12}

Activation of the renin–angiotensin system has been demonstrated to be involved in CKD pathogenesis and its cardiovascular complications through the generation of angiotensin II (Ang II), a key regulator of cardiovascular homeostasis. The Ang II type 1 receptor (AT1R) is responsible for most Ang II-mediated pathophysiological effects, and inhibition of the renin–angiotensin system by angiotensin-converting enzyme inhibitors (ACEIs) and AT1R-specific blockers (ARBs) has been shown to exert various protective effects against CKD progression and cardiovascular complications, at least partially through a reduction in urinary protein/albumin excretion.^{13–16}

Furthermore, recent clinical study results and a meta-analysis of several large-scale cohort studies indicated that preservation of the estimated glomerular filtration rate (eGFR), as well as reduction

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Received 11 May 2012; revised 27 July 2012; accepted 27 August 2012; published online 15 November 2012

in proteinuria/albuminuria are important for the suppression of CKD progression and cardiovascular complications in hypertensive CKD patients.^{17–19} Of the clinically available ARBs, olmesartan has been reported to exert a long-lasting BP-lowering effect via its characteristic ‘double-chain domain’ structure²⁰ and is expected to efficiently improve the altered ambulatory BP profile of hypertensive CKD patients.²¹ Previous studies have shown that nocturnal hypertension is closely related to an increase in urinary protein excretion and renal function deterioration in CKD patients. We hypothesized that olmesartan may effectively lower nocturnal BP levels with concomitant renal protective effects such as improvements in proteinuria and markers of renal injury. Therefore, in this study, we examined the therapeutic effects of olmesartan add-on therapy on the ambulatory BP profile and renal function of hypertensive patients with CKD.

METHODS

Study design

This was a randomized open-label parallel-group controlled study; it was conducted at the outpatient clinic of the Department of Internal Medicine, Yokohama City University Hospital (Yokohama, Japan). The study consisted of a 2-week run-in period and a 16-week active treatment period. This study was approved by the Ethics Committees of Yokohama City University Hospital, and written informed consent was obtained from every participant.

Study participants

Inclusion criteria were an age of 20 years or older, a history of mild-to-moderate hypertension (clinic systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 80 mm Hg or receiving antihypertensives) and CKD. When patients were already being treated for hypertension, anti-hypertensive drugs other than ARBs were continued during the run-in period, and then, if the hypertension was still uncontrolled (BP $\geq 130/80$ mm Hg), the patients were considered for recruitment into the study. CKD was diagnosed by the presence of albuminuria (urinary albumin excretion rate (UACR) ≥ 30 mg per g creatinine), proteinuria (urinary protein excretion rate (UPCR) ≥ 0.15 g per g creatinine), or eGFR < 60 ml/min per 1.73 m² for a period of more than 3 months. We calculated the eGFR using a revised equation for the Japanese population: eGFR

(ml min⁻¹ per 1.73 m²) = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).²² Exclusion criteria included patients who were on dialysis, women who were nursing or pregnant, and patients with clinically significant heart disease, stroke, renal artery stenosis, hepatic dysfunction or known hypersensitivity to any ingredient in the study medications.

Study treatment

After the run-in period and the discontinuation of any previous ARB treatment, eligible patients were randomized to the olmesartan add-on group or the non-ARB group. Patients in the olmesartan add-on group were initially given 10 mg of olmesartan once daily in the morning; the dose of olmesartan was titrated up to 40 mg daily, as needed, during the 16-week active treatment period. Patients in the non-ARB group were given either an increased dose of their existing treatment or an additional conventional treatment other than ARB to achieve the BP goal (BP $< 130/80$ mm Hg).

Clinic BP measurement and 24-h ambulatory BP monitoring

Clinic BP was measured at the trough of the medication cycle (24 ± 2 h post dose) using a calibrated standard mercury sphygmomanometer and the recommended cuff sizes in a sitting position.²³ Two measurements were taken at 1- to 2-min intervals, and their average was used to calculate the clinic BP.

The ambulatory BP and heart rate were monitored every 30 min with a fully automated device (TM-2425, A&D, Tokyo, Japan), as described previously.^{24–30} Ambulatory BP monitoring was repeated in patients who had $> 20\%$ of values missing, $> 30\%$ error rate for the total readings, or values missing for more than 2 consecutive hours. The following readings were considered technical artifacts and were omitted: systolic BP > 250 mm Hg or < 70 mm Hg, diastolic BP > 130 mm Hg or < 30 mm Hg, pulse pressure > 160 mm Hg or < 20 mm Hg, systolic differences > 60 mm Hg or diastolic differences > 30 mm Hg compared with the immediately preceding or subsequent values. The patients were instructed to fill out a diary to record the time of sleeping, rising and other daytime activities. Therefore, the terms ‘daytime’ and ‘nighttime’ in the present study reflect the average period during which the subjects were awake/upright and asleep/supine, respectively. We defined the morning BP as the average BP during the initial 2 h after awakening, as described previously.^{31–33}

Table 1 Patient baseline characteristics

Variable	Olmesartan, n = 22	Non-ARB, n = 23	P-value
Age (years); mean (s.d.)	64.7 $\pm$ 10.4	67.0 $\pm$ 7.9	0.413
Male (%)	86	87	1.000
Waist circumference (cm); mean (s.d.)	88.3 $\pm$ 7.7	90.1 $\pm$ 10.1	0.892
Diabetes (%)	41	51	0.554
CKD stage (n)			0.167
Stage 1	0	0	
Stage 2	6	1	
Stage 3	10	16	
Stage 4	3	4	
Stage 5	3	2	
Serum creatinine (mg dl ⁻¹); mean (s.d.)	1.73 $\pm$ 1.04	1.73 $\pm$ 1.10	0.742
eGFR (ml min ⁻¹ per 1.73 m ²); mean (s.d.)	43.0 $\pm$ 22.2	40.5 $\pm$ 17.9	0.751
UPCR (g per g Cr); mean (s.d.)	2.12 $\pm$ 2.58	1.58 $\pm$ 2.23	0.517
UACR (mg per g Cr); mean (s.d.)	1605.3 $\pm$ 1889.7	1182.0 $\pm$ 1614.9	0.388
hs-CRP (mg dl ⁻¹); mean (s.d.)	0.14 $\pm$ 0.17	0.07 $\pm$ 0.05	0.175
Urinary AGT (μ g per g Cr); mean (s.d.)	514.8 $\pm$ 843.3	454.3 $\pm$ 811.3	0.835
Urinary 8-OHdG (ng per mg Cr); mean (s.d.)	3.60 $\pm$ 3.53	2.65 $\pm$ 2.74	0.455
Urinary type IV collagen (μ g per g Cr); mean (s.d.)	12.70 $\pm$ 12.72	8.78 $\pm$ 8.85	0.301

Abbreviations: ARB, angiotensin II type 1 receptor blocker; AGT, angiotensinogen; CDK, chronic kidney disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity c-reactive protein; 8-OHdG, 8-hydroxydeoxyguanosine; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

Laboratory measurements

Blood and urine sampling was performed between 0800 and 1000 hours after an overnight fast. After the patients had spent 30 min at quiet rest in a recumbent position, blood samples were collected to determine laboratory parameters using routine methods in the Department of Clinical Chemistry, Yokohama City University Hospital. The urinary concentrations of type IV collagen and 8-hydroxydeoxyguanosine (8-OHdG) were determined using an enzyme immunoassay kit (SRL laboratory, Tokyo, Japan) and an ELISA kit (Japan Institute for Control of Aging, Shizuoka, Japan), respectively.³⁴ Urinary angiotensinogen (AGT) levels were measured using a sandwich ELISA, as described previously.^{35,36} Urinary type IV collagen, 8-OHdG and AGT concentrations were normalized to urinary creatinine concentration (Table 1).

Statistical analysis

The quantitative data are expressed as the mean $\pm$ s.d. To examine the effects of anti-hypertensive treatment, the values of the variables after the 16-week active treatment period were normalized to those of their respective variables at baseline and were expressed as after-treatment/baseline (A/B) ratios. For the statistical analysis of the difference between the olmesartan add-on group and non-ARB group, the Mann-Whitney *U*-test was performed for continuous variables, and the χ^2 test was performed for qualitative variables using SPSS (Statistical Package for the Social Sciences) software (Version 16.0, Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Forty-six hypertensive patients with CKD were enrolled between October 2007 and March 2010. The causes of CKD were hypertensive nephrosclerosis ($n=17$), diabetic nephropathy ($n=14$), chronic glomerulonephritis ($n=6$), polycystic kidney disease ($n=1$), other renal diseases ($n=4$) or of unknown cause ($n=4$). Patients were randomly assigned to the olmesartan add-on group ($n=23$) or the non-ARB group ($n=23$). One patient in the olmesartan add-on group was discontinued from the study; therefore, a total of 45 patients completed the study. This patient was unavailable for follow-up due to a transfer to another hospital. Table 1 shows the demographics of the study participants, including the number of participants in each CKD stage and the baseline characteristics of the participants.

The olmesartan add-on therapy was well tolerated without any significant adverse events, and the average additional dose of olmesartan was 15.9 ± 8.9 mg per day after a 16-week treatment period. The additional treatments in both groups were primarily calcium channel blockers, diuretics, ACEIs and statins; more patients in the non-ARB group were treated with ACEIs than the olmesartan add-on group during the study period (Table 2).

Table 2 Medications used during the study

Medication	Olmesartan, <i>n</i> = 22	Non-ARB, <i>n</i> = 23	<i>P</i> -value
Calcium channel blockers (%)	77	96	0.096
Diuretics (%)	36	57	0.175
ACEI (%)	14	57	0.003
Statins (%)	23	35	0.372
Oral hypoglycemic agents (%)	32	17	0.187
Insulin (%)	18	4	0.260

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker.

Although $\sim 50\%$ of patients in both groups had diabetes, there were no significant differences in the use of oral hypoglycemic agents and insulin.

Effects of olmesartan add-on therapy on the BP profile

At baseline, the mean clinical BP values were similar in the olmesartan add-on and non-ARB groups. After the 16-week active treatment period, the A/B ratios of the two groups were comparable (Table 3). With respect to the ambulatory BP profile, the baseline daytime systolic/diastolic BP levels were comparable in the olmesartan add-on and non-ARB groups, while the baseline 24-h and nighttime systolic/diastolic BP levels were significantly higher in the olmesartan add-on group (Table 4). However, compared with the non-ARB group, the 24-h diastolic BP and nighttime systolic/diastolic BP level A/B ratios in the olmesartan add-on group were significantly lower after the 16-week active treatment period (Table 4; 24-h diastolic BP, 0.92 ± 0.07 vs. 0.98 ± 0.07 , $P=0.017$; nighttime systolic BP, 0.91 ± 0.10 vs. 1.00 ± 0.08 , $P=0.001$; nighttime diastolic BP 0.90 ± 0.11 vs. 0.98 ± 0.10 , $P=0.024$), and the 24-h systolic BP A/B ratio tended to be decreased in the olmesartan add-on group (Table 4; 24-h systolic BP, 0.93 ± 0.07 vs. 0.99 ± 0.08 , $P=0.053$). However, the daytime systolic/diastolic BP A/B ratios were comparable in the olmesartan add-on group and the non-ARB group (Table 4; daytime systolic BP, 0.94 ± 0.07 vs. 0.98 ± 0.09 , $P=0.261$; daytime diastolic BP, 0.93 ± 0.07 vs. 0.97 ± 0.07 , $P=0.105$). In addition, although the differences did not reach statistical significance, there was a trend toward a decrease in morning systolic/diastolic BP A/B ratios in the olmesartan add-on group compared with the non-ARB group (Table 4).

Effects of olmesartan add-on therapy on markers of renal function

At baseline, serum creatinine, eGFR, UPCR and UACR were similar in the olmesartan add-on and non-ARB groups (Table 1). After the 16-week active treatment period, serum creatinine and eGFR A/B ratios were comparable in the two groups (Figure 1). In contrast, the UPCR and UACR A/B ratios were significantly lower in the olmesartan add-on group than in the non-ARB group (Figure 1; UPCR, 0.72 ± 0.41 vs. 1.45 ± 1.48 , $P=0.030$; UACR, 0.73 ± 0.37 vs. 1.50 ± 1.37 , $P=0.005$) after the 16-week active treatment period. Overall, the results of correlation analysis showed that there were significant positive associations between the A/B ratios of nighttime systolic BP and UPCR ($R=0.440$, $P=0.004$), and between the A/B ratios of nighttime systolic BP and UACR ($R=0.472$, $P=0.002$) in all patient groups.

Table 3 Effects of anti-hypertensive therapy on clinic BP

Variable	Olmesartan, <i>n</i> = 22	Non-ARB, <i>n</i> = 23	<i>P</i> -value
<i>Clinic BP</i>			
<i>Systolic BP</i>			
Baseline (mm Hg); mean (s.d.)	144.1 $\pm$ 13.7	144.1 $\pm$ 17.8	0.955
A/B ratio; mean (s.d.)	0.99 $\pm$ 0.12	0.96 $\pm$ 0.11	0.714
<i>Diastolic BP</i>			
Baseline (mm Hg); mean (s.d.)	79.7 $\pm$ 19.0	84.6 $\pm$ 11.5	0.474
A/B ratio; mean (s.d.)	1.36 $\pm$ 1.61	0.95 $\pm$ 0.12	0.182

Abbreviations: A/B ratio, after-treatment/baseline ratio; ARB, angiotensin II type 1 receptor blocker; BP, blood pressure.

Table 4 Effects of anti-hypertensive therapy on the ambulatory BP profile

Variable	Olmesartan, n = 22	Non-ARB, n = 23	P-value
24 h			
Systolic BP			
Baseline (mm Hg); mean (s.d.)	142.6 ± 14.4	135.0 ± 11.3	0.036
A/B ratio; mean (s.d.)	0.93 ± 0.07	0.99 ± 0.08	0.053
Diastolic BP			
Baseline (mm Hg); mean (s.d.)	83.6 ± 10.4	78.2 ± 7.5	0.045
A/B ratio; mean (s.d.)	0.92 ± 0.07	0.98 ± 0.07	0.017
Daytime			
Systolic BP			
Baseline (mm Hg); mean (s.d.)	146.6 ± 14.8	140.5 ± 11.5	0.180
A/B ratio; mean (s.d.)	0.94 ± 0.07	0.98 ± 0.09	0.261
Diastolic BP			
Baseline (mm Hg); mean (s.d.)	86.3 ± 10.8	81.5 ± 8.4	0.104
A/B ratio; mean (s.d.)	0.93 ± 0.07	0.97 ± 0.07	0.105
Nighttime			
Systolic BP			
Baseline (mm Hg); mean (s.d.)	133.4 ± 15.9	123.9 ± 13.9	0.031
A/B ratio; mean (s.d.)	0.91 ± 0.10	1.00 ± 0.08	0.001
Diastolic BP			
Baseline (mm Hg); mean (s.d.)	77.8 ± 10.7	71.8 ± 7.8	0.013
A/B ratio; mean (s.d.)	0.90 ± 0.11	0.98 ± 0.10	0.024
Morning			
Systolic BP			
Baseline (mm Hg); mean (s.d.)	144.6 ± 16.8	138.9 ± 16.9	0.107
A/B ratio; mean (s.d.)	0.95 ± 0.11	1.02 ± 0.15	0.095
Diastolic BP			
Baseline (mm Hg); mean (s.d.)	84.1 ± 12.2	80.9 ± 10.5	0.340
A/B ratio; mean (s.d.)	0.95 ± 0.12	1.03 ± 0.13	0.068

Abbreviations: BP, blood pressure; A/B ratio, after-treatment/baseline ratio.

Effects of olmesartan add-on therapy on markers of inflammation, the renal renin-angiotensin system, oxidative stress and fibrosis

At baseline, high-sensitivity C-reactive protein (hs-CRP), urinary AGT, 8-OHdG and type IV collagen levels were similar in the olmesartan add-on and non-ARB groups (Table 1). The hs-CRP and urinary 8-OHdG A/B ratios after the 16-week active treatment period were comparable in both groups (Figure 2). The urinary AGT A/B ratio after the 16-week active treatment period was lower in the olmesartan add-on group than in the non-ARB group, but the difference did not reach statistical significance (Figure 2; urinary AGT, 1.35 ± 1.59 vs. 4.43 ± 7.39 , $P = 0.172$). In contrast, the urinary type IV collagen A/B ratio following the 16-week treatment was significantly suppressed in the olmesartan add-on group compared with the non-ARB group (Figure 2; urinary type IV collagen, 0.87 ± 0.42 vs. 1.48 ± 0.87 , $P = 0.014$). The correlation analysis demonstrated that there was a significant positive relationship between the A/B ratios of nighttime systolic BP and urinary type IV collagen ($R = 0.451$, $P = 0.003$), and further revealed a trend toward a positive association between the A/B ratios of nighttime systolic BP and urinary AGT ($R = 0.332$, $P = 0.051$).

Comparison of renal function parameters between patients with and without ACEI treatment in the non-ARB group

As shown in Table 2, there was a significant difference in the percentage of patients in the olmesartan add-on group and non-ARB group that were prescribed ACEIs (14% vs. 57%, $P = 0.003$). Previous studies have shown that ACEIs exert renoprotective effects in CKD patients, and thus, ACEIs could also affect the renal function parameters measured in the present study.³⁷ Therefore, we compared the renal function parameters between patients in the non-ARB group that were either treated with ACEIs (ACEI + patients) or not treated with ACEIs (ACEI – patients). In the non-ARB group, the UPCR and UACR in the ACEI – patients both showed an increasing trend after the 16-week active treatment period, and the UPCR and UACR A/B ratios after treatment in the ACEI – patients were higher than those in the ACEI + patients (Table 5; UPCR, 2.27 ± 2.08 vs. 0.89 ± 0.37 , $P = 0.060$; UACR, 2.27 ± 1.80 vs. 0.92 ± 0.43 , $P = 0.015$). These differences were not observed between ACEI + patients and ACEI – patients when the olmesartan add-on group and all of the subjects were analyzed (data not shown). These results support the renoprotective effects of ACEIs in hypertensive CKD patients.

DISCUSSION

Accumulated evidence suggests that elevated nighttime BP levels reflect target organ injury and are a better predictor of further cardiovascular and renal risk than daytime or 24-h BP levels in hypertensive patients with diabetes and CKD.^{6,38} In addition, efficient reduction in nighttime BP by methods such as bedtime dosing, as determined by ambulatory BP monitoring, has been shown to reduce cardiovascular risk in cases of resistant hypertension and hypertension complicated by diabetes or CKD.^{39–41} The results of the present study showed that olmesartan add-on therapy exerted a significantly better BP-lowering effect than non-ARB therapy, particularly during the nighttime period; similar daytime BP lowering was observed in the olmesartan add-on group and non-ARB group.

The results of this study show that both the olmesartan add-on therapy and non-ARB anti-hypertensive therapy were well tolerated in hypertensive patients with CKD. Although the baseline clinic BP levels were similar in the olmesartan add-on and non-ARB groups, the baseline 24-h and nighttime BP levels from the ambulatory BP recording were significantly higher in the olmesartan add-on group than the non-ARB group (Table 4). Thus, to strictly compare the effects of the two treatment regimens after the 16-week active treatment period, the values of the variables, including the ambulatory BP parameters, were normalized to those of the respective variables at baseline and were expressed as A/B ratios.

In this study, although more patients were treated with ACEIs in the non-ARB group than in the olmesartan add-on group, the olmesartan add-on therapy significantly decreased urinary protein, albumin and type IV collagen excretion. Thus, these data indicate that the benefit of olmesartan add-on therapy for patients with hypertension and CKD results from inhibition of proteinuria/albuminuria and pathological renal injury, and these beneficial effects of olmesartan are exerted, at least in part, through a preferential reduction in nocturnal BP, which is an important potential therapeutic target for cardiorenal protection in hypertension with CKD.

The role of the renin-angiotensin system in promoting hypertension- and CKD-related organ damage is well established. Reducing proteinuria/albuminuria is critically important for the regression of CKD,⁴² and the evidence indicates that ARBs and ACEIs reduce cardiovascular and renal risks primarily by reducing proteinuria/albuminuria.^{13,16,43} In a recent, large-scale ORIENT clinical trial,

Figure 1 Effects of olmesartan add-on therapy on the after-treatment/baseline (A/B) ratios of (a) serum creatinine, (b) eGFR, (c) UPCR and (d) UACR. Forty-six hypertensive patients with CKD were randomly assigned to the olmesartan add-on group (ARB+) or the non-ARB group (ARB-). At baseline and after the 16-week treatment period, measurements were collected. To compare the effects of anti-hypertensive treatment in each group, the values of the variables after the 16-week active treatment period were normalized to the respective variables at baseline and were expressed as the A/B ratio. The values of the A/B ratios are expressed as the mean $\pm$ s.d.

olmesartan treatment significantly decreased clinic BP and proteinuria compared with the control anti-hypertensive treatment that included ACEIs, and there was no renal dysfunction acceleration in type 2 diabetic patients with overt nephropathy.⁴⁴ The present study included non-diabetic glomerulopathy patients as well as diabetic nephropathy patients. The results of the present study demonstrate that a preferential decrease in nighttime BP levels was accompanied by decreases in urinary protein and albumin excretion and urinary type IV collagen excretion, an important marker of renal injury in diabetic nephropathy and non-diabetic renal disease,^{45,46} without any decrease in eGFR resulting from the olmesartan add-on therapy. The results of

the ACCOMPLISH study indicated that not only a reduction of albuminuria but also long-term preservation of eGFR are important for the suppression of CKD progression and cardiovascular complications.^{17,19} Therefore, it is likely that olmesartan effectively inhibits renal deterioration through improvement in the circadian BP rhythm and maintenance of eGFR, in addition to its general BP-lowering effect in hypertensive patients with CKD.

In contrast, proteinuria/albuminuria showed an increasing trend after the treatment period in the non-ARB group. We previously showed that urinary protein excretion correlated positively with nighttime BP in hypertensive CKD patients with diabetic

Figure 2 Effects of olmesartan add-on therapy on the after-treatment/baseline (A/B) ratios of (a) hs-CRP, (b) urinary AGT, (c) urinary 8-OHdG and (d) urinary type IV collagen. Forty-six hypertensive patients with CKD were randomly assigned to the olmesartan add-on group (ARB+) or the non-ARB group (ARB-). Measurements were collected at baseline and after the 16-week treatment period. To compare the effects of anti-hypertensive treatment in each group, the values of the variables after the 16-week active treatment period were normalized to those of the respective variables at baseline and are expressed as A/B ratios. The values of the A/B ratios are expressed as the mean $\pm$ s.d.

nephropathy or non-diabetic glomerulopathy,²⁵ and a recent study reported that nocturnal BP reduction is critically important for the inhibition of CKD progression.⁴¹ Therefore, the lack of a decrease in nighttime BP may have caused the increasing trend in proteinuria/albuminuria in the non-ARB group after treatment. In addition, proteinuria/albuminuria in the ACEI- patients in the non-ARB group showed an increasing trend after the 16-week active treatment period, and urinary protein/albumin excretion after treatment was

higher in the ACEI- patients than in the ACEI+ patients (Table 5), thereby also supporting the renoprotective effects of ACEIs in hypertensive CKD patients.

What might the underlying mechanism be that is responsible for the efficient nocturnal BP-lowering effects of olmesartan? In comparison with other ARBs, olmesartan is reported to exert a long-lasting BP-lowering effect via its characteristic 'double-chain domain' structure²⁰ and to efficiently improve the altered ambulatory BP profile in

Table 5 Comparison of UPCR, UACR and urinary type IV collagen between ACEI + patients and ACEI – patients in the non-ARB group

Variable	ACEI+, n = 13	ACEI–, n = 10	P-value
UPCR			
Baseline (g per g Cr); mean (s.d.)	1.97 ± 2.18	1.09 ± 2.30	0.343
A/B ratio; mean (s.d.)	0.89 ± 0.37	2.27 ± 2.08	0.060
UACR			
Baseline (mg per g Cr); mean (s.d.)	1511 ± 1507	788 ± 1730	0.123
A/B ratio; mean (s.d.)	0.92 ± 0.43	2.27 ± 1.80	0.015
Urinary type IV collagen			
Baseline (µg per g Cr); mean (s.d.)	11.05 ± 10.33	5.83 ± 5.66	0.148
A/B ratio; mean (s.d.)	1.28 ± 0.84	1.76 ± 0.87	0.186

Abbreviations: A/B ratio, after-treatment/baseline ratio; ACEI, angiotensin-converting enzyme inhibitor; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

hypertensive patients, even if olmesartan is only administered once in the morning.²¹ In addition, sodium retention due to a reduced GFR and impaired renal sodium excretion capacity are characteristic pathophysiological states in hypertensive patients with CKD. Recent animal studies reported that activation of AT1R in the kidney mediates chronic hypertensive effects; by stimulation of the intrarenal renin-angiotensin system, sodium reabsorption from the renal tubules is promoted.^{47,48} Furthermore, previous clinical studies showed that the urinary AGT level closely reflects renal renin-angiotensin system activity in hypertension and CKD.^{36,49–51} In this regard, a recent study suggested that inhibition of renal sodium reabsorption may be an important mechanism involved in the olmesartan-mediated improvement in the circadian BP rhythm via a preferential lowering of nocturnal BP levels in CKD patients.⁵² Although the decrease in urinary AGT excretion by the olmesartan add-on therapy did not reach statistical significance in the current study, there was also a trend toward a positive relationship between nocturnal BP and urinary AGT. Therefore, olmesartan-mediated preferential reduction in nocturnal BP may be effected via the prevention of renal tubular sodium reabsorption through the inhibition of renal tubule AT1R.

The limitations of the present study include the background difference in ambulatory BP levels between the olmesartan add-on and non-ARB groups, although the clinic BP levels in these groups at baseline were comparable. To examine the effects of olmesartan add-on therapy on ambulatory BP levels, the values of the variables after the 16-week active treatment period were normalized to the respective variables at baseline and were expressed as A/B ratios. Furthermore, the sample size is relatively small, which limits our ability to determine significance.

In summary, the results of this study indicate that olmesartan add-on therapy improves the ambulatory BP profile by preferential reduction in nighttime BP and may afford protective renal effects in patients with hypertension and CKD. Further studies are needed to examine the mechanistic basis of the olmesartan-mediated therapeutic effects on ambulatory BP profiles and renal function.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by a Health and Labor Sciences Research grant and by grants from the Japanese Ministry of Education, Science, Sports and

Culture, the Salt Science Research Foundation (No. 1134), the Kidney Foundation, Japan (JKFB11-25) and the Novartis Foundation for Gerontological Research (2012). We thank Dr Boru for editing the English of this manuscript.

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