Renoprotective Effects of Various Angiotensin II Receptor Blockers in Patients with Early-Stage Diabetic Nephropathy

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Key Words

Diabetic nephropathy • Liver-type fatty acid-binding protein • Oxidative stress • Microalbuminuria • Angiotensin receptor blocker

Abstract

Background: There is increasing evidence that inhibition of the renin-angiotensin system provides renoprotection independent of blood pressure lowering. The aim of the present study was to determine whether various angiotensin II receptor blockers (ARBs) affect urinary albumin excretion (UAE), urinary liver-type fatty acid-binding protein (L-FABP) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in early-stage diabetic nephropathy patients with microalbuminuria. **Methods:** Sixty-eight diabetic nephropathy patients with microalbuminuria were randomly allocated to 1 of 4 treatment groups: losartan 100 mg/day (group A), candesartan 12 mg/day (group B), olmesartan 40 mg/day (group C), or telmisartan 80 mg/day (group D). Treatment was continued for 12 months. UAE, L-FABP and 8-OHdG excretion, serum creatinine, and 24-hour creatinine clearance (Ccr) were measured. **Results:** The serum creatinine and 24-hour Ccr were not affected during the experimental period in any of the groups. Systolic and diastolic blood pressures, UAE, urinary L-FABP and 8-OHdG excretion were significantly reduced after 6 and

12 months compared with baseline in any of the groups. Δ L-FABP and Δ 8-OHdG were significantly greater in group D than in the other 3 groups after 12 months. **Conclusions:** ARBs have renoprotection and this effect of telmisartan appears to be more potent than that of losartan, candesartan, or olmesartan in early-stage diabetic nephropathy patients.

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Introduction

Diabetic nephropathy resulting from type 2 diabetes is the most common cause of end-stage renal disease worldwide. The molecular and cellular mechanisms responsible for diabetic nephropathy have not been fully elucidated. Although the diabetic milieu per se, hemodynamic changes, and local growth factors such as angiotensin II are considered mediators in the pathogenesis of diabetic nephropathy, the underlying pathways mediating these processes are not well understood [1]. There is increasing evidence that inhibition of the renin-angiotensin system may provide end-organ protection, independent of blood pressure lowering [2]. The angiotensin II receptor blocker (ARB) was shown to have renoprotective action in hypertensive patients with incipient diabetic nephropathy [3].

Glomerular and tubular damage resulting from type 2 diabetes occurs over several years, and it is possible that the excretion of glomerular and tubular proteins antedates the development of proteinuria and perhaps even the development of microalbuminuria [4]. In patients with diabetic nephropathy, changes in the proximal tubuli are important for the development of progressive diabetic kidney disease, and renal function and prognosis correlate better with structural lesions in the tubulointerstitium than with glomerular changes [5].

Urinary liver-type fatty acid-binding protein (L-FABP) is an important marker of tubulointerstitial changes in diabetic nephropathy [6, 7]. Oxidative stress is a pathogenetic factor in underlying diabetes complications including nephropathy. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) has been reported to serve as a sensitive biomarker of the oxidative DNA damage in vivo [8]. Urinary 8-OHdG excretion increased significantly with the severity of tubulointerstitial damage [8].

Recently, telmisartan was shown to be characterized by a potent and long-lasting antihypertensive effect that may be associated with another specific effect of this drug, the partial agonism of the peroxisome proliferator-activated receptor (PPAR)-gamma [9]. Telmisartan is effective, safe, and well tolerated while reducing microalbuminuria in hypertensive patients with diabetic nephropathy [10]. However, comparative renoprotective effects of various ARBs have not been examined.

In the present study, we compared the effect of various ARBs, i.e. losartan, candesartan, olmesartan, and telmisartan, on urinary markers of oxidative stress, renal glomerular and tubular function, and metabolic markers in early diabetic nephropathy patients.

Patients and Methods

Subjects

The study subjects comprised 68 hypertensive patients with type 2 diabetes and microalbuminuria (38 men and 30 women; mean age, 54 ± 13 years) and 68 healthy age-matched volunteers (36 men and 32 women; mean age, 50 ± 10 years). All patients were referred from other outpatient clinics as diabetes patients with microalbuminuria. Healthy subjects had normal blood pressure, normal renal function, a normal lipid profile, a normal hemoglobin (Hb) A1c level, and normal urinary albumin level, and were not receiving any medications. Type 2 diabetes was diagnosed according to the World Health Organization criteria based on clinical symptoms including chronic diabetes, increased urinary albumin excretion (UAE) and retinopathy, laboratory data and histopathological findings according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [11]. None of the patients showed serum creatinine in

excess of 1.2 mg/dl or 24-hour creatinine clearance (Ccr) <80 ml/min at the time of the study. Hypertension was defined as a systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg, despite the administration of anti-hypertensive drugs. Forty of 68 patients had not been treated for hypertension by other clinics and 28 patients had been treated by antihypertensive drugs including calcium-channel blockers and/or diuretics. None of the patients had been given an ARB and/or angiotensin-converting enzyme inhibitor (ACEI) at the time of the study. Patients had been maintaining the antihypertensive therapy that they were receiving. The doses of other antihypertensive agents, drugs for diabetes and statins were unchanged during the study periods. No patient had any malignancy, heart disease, cerebrovascular disease, liver disease, or systemic disease such as collagen disease according to the results of physical examination as well as urine and blood tests and radiography, electrocardiography, echocardiography, or X-ray computed tomography study. After an overnight fast, blood was drawn from the antecubital vein for measurement of glucose, HbA1c, creatinine, total cholesterol (T-chol) and triglyceride (TG) levels.

Measurement of Urinary Markers

Urine was centrifuged and analyzed after having been frozen. Urinary albumin was measured by immunoturbidimetric assay, and UAE was assessed as the mean of two 24-hour urine collections [12]. Microalbuminuria was defined as a median UAE of 20–200 $\mu\text{g}/\text{min}$. All patients had persistent microalbuminuria. Urinary L-FABP, urinary 8-OHdG, and 24-hour Ccr were also measured in the 24-hour collected urine. Urinary L-FABP concentrations were measured with human monoclonal antibodies, as reported previously [13, 14]. Urinary L-FABP was expressed as the ratio of the urinary L-FABP level (μg) to the urinary creatinine level (g). The L-FABP ELISA kit is now commercially available (CIMIC Co. Ltd., Tokyo, Japan). Urinary 8-OHdG levels were measured with an ELISA kit that uses a highly sensitive monoclonal antibody, as previously described (8-OHdG Check, Nikken Foods, Fukuroi, Shizuoka, Japan) [15].

Treatment

This study was approved by our local ethical committees on human research, and informed consent was obtained from each subject. The study was carried out in accordance with the Declaration of Helsinki as revised in 2000. The patients were randomly assigned in a blinded manner to 1 of 4 treatments (each group: $n = 17$): losartan 100 mg/day (group A), candesartan 12 mg/day (group B), olmesartan 40 mg/day (group C), or telmisartan 80 mg/day (group D). Other antihypertensive therapies, with the exception of ACEI, could be added if necessary to attain a target blood pressure $<130/80$ mm Hg. Treatment continued for 12 months, and there were no dropouts and no side effects. Blood and urinary data were obtained before treatment, and 6 and 12 months after treatment.

Statistical Analysis

Data are expressed as mean $\pm$ SD. All data were normally distributed. Statistical analysis was performed with the paired Student's *t* test or one-way analysis of variance followed by Bonferroni correction for multiple comparisons. $p < 0.05$ was considered statistically significant.

Table 1. Characteristics of study subjects per group upon enrollment

	Group A (n = 17)	Group B (n = 17)	Group C (n = 17)	Group D (n = 17)	Healthy subjects (n = 68)
Age, years	56 ± 12	54 ± 10	53 ± 15	53 ± 14	50 ± 10
Sex, M/F	9/8	9/8	10/7	10/7	36/32
SBP, mm Hg	160 ± 5*	157 ± 6*	158 ± 4*	160 ± 6*	118 ± 6
DBP, mm Hg	94 ± 4*	95 ± 6*	98 ± 4*	96 ± 6*	76 ± 4
s-Cr, mg/dl	0.91 ± 0.10	0.89 ± 0.12	0.90 ± 0.12	0.89 ± 0.11	0.86 ± 0.08
24-hour Ccr, ml/min	107.7 ± 11.1	109.7 ± 13.1	107.5 ± 12.2	103.9 ± 9.7	110.0 ± 13.0
UAE, µg/min	109.8 ± 42.9*	104.0 ± 42.4*	104.2 ± 45.0*	108.7 ± 32.6*	5.5 ± 2.5
L-FABP, µg/g·Cr	36.0 ± 11.2*	35.8 ± 14.2*	34.7 ± 13.0*	36.9 ± 12.4*	5.0 ± 2.2
8-OHdG, ng/mg·Cr	19.6 ± 5.1*	19.0 ± 4.3*	18.9 ± 4.4*	17.5 ± 3.4*	4.2 ± 1.5
BMI	24.5 ± 3.5	23.8 ± 3.2	23.5 ± 2.8	24.0 ± 3.0	23.3 ± 2.2
HbA1c, %	7.07 ± 0.63*	7.14 ± 0.62*	7.12 ± 0.65*	7.04 ± 0.57*	4.0 ± 0.3
T-chol, mg/dl	214 ± 25*	213 ± 21*	207 ± 22*	221 ± 18*	165 ± 10
TG, mg/dl	172 ± 23*	174 ± 24*	174 ± 23*	169 ± 19*	96 ± 10
Smokers, %	23.5	17.7	17.6	23.5	26.5
Therapy, %					
Antihypertensive					
ACEI	0	0	0	0	0
Ca blocker	41.2	35.3	41.2	35.3	0
α-Blocker	23.5	23.5	17.6	17.6	0
Diuretic	47.1	47.1	41.2	41.2	0
Other	17.6	17.6	23.5	17.6	
Antidiabetic					
Insulin	29.4	23.5	29.4	23.5	0
Pioglitazone	35.3	29.4	29.4	29.4	0
Voglibose	23.5	29.4	23.5	29.4	0
Glibenclamide	35.3	41.2	41.2	35.3	0
Antiplatelet	29.4	29.4	23.5	23.5	0
Statin	35.3	41.2	35.3	35.3	0

Data are mean ± SD. * p < 0.001 vs. healthy subjects.

Results

Characteristics of patients before treatment and normal healthy volunteers are shown in table 1. Before treatment, age, sex, SBP, DBP, body mass index, serum creatinine, HbA1c, T-chol and TG, 24-hour Ccr, urinary L-FABP, 8-OHdG, UAE, and coadministered drugs differed little between the 4 treatment groups. SBP, DBP, UAE, urinary L-FABP, urinary 8-OHdG, HbA1c, T-chol and TG levels were significantly higher in the patient groups than in the healthy volunteers ($p < 0.001$). SBP before treatment and 6 and 12 months after treatment is shown in figure 1a. SBP was significantly reduced after 6 months ($p < 0.001$ vs. before treatment) and after 12 months ($p < 0.001$ vs. before treatment) in all 4 groups. Changes in SBP are shown in figure 1b. Δ SBP was significantly greater in group D than in the other 3 ARB groups after 6

months ($p < 0.001$) and after 12 months ($p < 0.001$ vs. group B, $p < 0.005$ vs. group A, $p < 0.05$ vs. group C). Changes in DBP were similar to those in SBP (data not shown). The serum creatinine and 24-hour Ccr levels changed little during the experimental period in all 4 ARB groups. Δ serum creatinine and Δ 24-hour Ccr also differed little between treatment groups (data not shown). UAE levels are shown in figure 1c. UAE was significantly reduced after 6 and 12 months ($p < 0.001$ vs. before treatment) in all 4 ARB groups. Δ UAE is shown in figure 1d. Δ UAE was slightly greater in group D than in the other 3 groups, but the difference was not significant. Urinary L-FABP levels are shown in figure 2a. Urinary L-FABP levels were significantly reduced after 6 and 12 months ($p < 0.001$ vs. before treatment). However, Δ L-FABP was significantly greater in group D than in the other 3 ARB groups after 6 months ($p < 0.001$) and after 12 months

Fig. 1. a Systolic blood pressure (SBP) in the 4 groups before treatment and 6 and 12 months after treatment. Group A = Losartan, group B = candesartan, group C = olmesartan, group D = telmisartan, * $p < 0.001$ vs. before treatment. **b** Δ SBP in the 4 treatment groups. * $p < 0.001$, group D vs. groups A, B and C 6 months after treatment; # $p < 0.001$, group D vs. group B, ¶ $p < 0.005$, group D vs. group A, ‡ $p < 0.05$, group D vs. group C 12 months after treatment. **c** Urinary albumin excretion (UAE) in the 4 groups before treatment and 6 and 12 months after treatment. * $p < 0.001$ vs. before treatment. **d** Δ UAE in the 4 treatment groups. Differences between groups were not significant.

($p < 0.001$) (fig. 2b). Urinary 8-OHdG levels are shown in figure 2c. Urinary 8-OHdG was significantly reduced after 6 and 12 months in all 4 groups ($p < 0.001$ vs. before treatment). However, Δ urinary 8-OHdG was significantly greater in group D than in the other 3 ARB groups after 6 months ($p < 0.001$) and 12 months ($p < 0.001$ vs. group A and B, $p < 0.05$ vs. group C) (fig. 2d). Δ 8-OHdG was also significantly greater in group C than in groups A and B after 6 months ($p < 0.05$) and 12 months ($p < 0.001$ vs. group A, $p < 0.05$ vs. group B). HbA1c levels are shown in figure 3a. HbA1c levels were significantly de-

Fig. 2. a Urinary liver-type fatty acid-binding protein (L-FABP) in the 4 groups before treatment and 6 and 12 months after treatment. * $p < 0.001$ vs. before treatment. **b** Δ L-FABP in the 4 treatment groups. * $p < 0.001$ group D vs. groups A, B, and C. **c** Urinary 8-OHdG in the 4 groups before treatment and 6 and 12 months after treatment. * $p < 0.001$ vs. before treatment. **d** Δ 8-OHdG in the 4 treatment groups. * $p < 0.001$, group D vs. groups A, B and C, ¶ $p < 0.05$, group C vs. groups A and B 6 months after treatment, * $p < 0.001$, group D vs. groups A and B, ‡ $p < 0.05$, group D vs. group C, † $p < 0.001$ group C vs. group A, ‡ $p < 0.05$, group C vs. group B 12 months after treatment.

creased in group D after 6 months ($p < 0.005$ vs. before treatment) and 12 months ($p < 0.001$ vs. before treatment). HbA1c was also significantly decreased in group B after 12 months ($p < 0.05$ vs. before treatment). Δ HbA1c was significantly greater in group D than in group A after 6 months ($p < 0.05$) and in the other 3 ARB groups after 12 months ($p < 0.001$) (fig. 3b). T-chol levels are shown in figure 3c. T-chol levels were significantly reduced after 6 and 12 months of treatment in groups A, B and D ($p < 0.05$, $p < 0.05$ and $p < 0.001$, respectively, vs. before treatment). Changes in T-chol are shown in fig-

ure 3d. The Δ T-chol level in group D was significantly greater than that in group A ($p < 0.05$), group B ($p < 0.005$) and group C ($p < 0.001$) after 6 months. The Δ T-chol level in group D was also significantly greater than that in group A ($p < 0.005$), group B ($p < 0.005$) and group C ($p < 0.001$) after 12 months. Changes in TG levels were similar to those in T-chol (data not shown).

Discussion

In the present study, various ARBs were effective in reducing UAE, a glomerular and endothelial injury marker, urinary L-FABP, a tubulointerstitial injury marker and urinary 8-OHdG, an oxidative stress marker. In addition, telmisartan appeared to be more potent than losartan, candesartan, and olmesartan in protecting against renal injury associated with early-stage diabetic nephropathy.

Microalbuminuria is a marker of increased risk of cardiovascular and renal morbidity and mortality in diabetic patients. An increase in UAE during clinical follow-up is associated with greater cardiovascular and renal risks in diabetes patients [16]. Albumin resorption in the proximal tubules is disturbed in the early-stage of diabetic nephropathy. ARB has been shown to restore albumin reabsorption via amelioration of megalin expression in the proximal tubules of rats with early-stage diabetes [17]. The rate of progression of diabetic nephropathy correlates with the degree of corticointerstitial injury [18]. The epithelial cells of the proximal tubules are major players in orchestrating events in the corticointerstitium in diabetic nephropathy [18]. Early tubular injury has been observed in patients with diabetic nephropathy whose glomerular function was intact [19]. The hypoxia in early-stage diabetic nephropathy is aggravated by manifestations of chronic hyperglycemia abnormalities of red blood cells, oxidative stress and tubular apoptosis, and chronic hypoxia could have a dominant pathogenic role in diabetic nephropathy, not only in promoting progression but also during initiation of the condition [19]. Bolognani et al. [20] reported that neutrophil gelatinase-associated lipocalin (NGAL), a tubular stress protein, was already increased in diabetes patients without early signs of glomerular damage (microalbuminuric) and that NGAL measurement might be a useful and noninvasive tool for the evaluation of renal involvement in diabetes patients as well as for the early diagnosis of incipient nephropathy.

In the present study, we measured L-FABP as a novel biomarker of early-stage diabetic nephropathy. L-FABP is

Fig. 3. **a** HbA1c in the 4 groups before treatment and 6 and 12 months after treatment. # $p < 0.001$ vs. before treatment, ¶ $p < 0.005$ vs. before treatment, * $p < 0.05$ vs. before treatment. **b** Δ HbA1c in the 4 treatment groups. * $p < 0.001$, group D vs. group C, † $p < 0.005$, group D vs. group B, ‡ $p < 0.05$, group D vs. group A 6 months after treatment; ¶ $p < 0.005$, group D vs. groups B and A 12 months after treatment. **c** Total cholesterol (T-chol) in the 4 groups before treatment and 6 and 12 months after treatment. # $p < 0.001$ vs. before treatment, * $p < 0.05$ vs. before treatment. **d** Δ T-chol in the 4 groups. * $p < 0.001$, group D vs. group C, † $p < 0.005$, group D vs. group B, ‡ $p < 0.05$, group D vs. group A 6 months after treatment; ¶ $p < 0.005$, group D vs. groups A and B 12 months after treatment.

a clinical biomarker of tubulointerstitial damage, which plays an essential role in the progression of chronic kidney disease [13, 14]. We reported previously that urinary L-FABP appears to be associated with the progression of diabetic nephropathy [6, 7]. Recently, we reported that telmisartan decreased urinary L-FABP levels in a dose-dependent manner independent of its blood pressure lowering effect in patients with diabetic nephropathy with renal insufficiency [21]. However, little is known

about the effect of various ARBs, including telmisartan, on urinary L-FABP levels in patients with early-stage diabetic nephropathy. The results of the present study suggest that ARBs including telmisartan are effective in reducing urinary L-FABP excretion in such patients.

Increases in oxidative stress caused by angiotensin II may play a crucial role in the progression of diabetic nephropathy and may contribute to the progression of tubulointerstitial injury in patients with diabetic nephropathy [8, 22]. The increased urinary excretion of 8-OHdG reflects an increased systemic level of oxidative DNA damage in patients with diabetic nephropathy [23]. Ogawa et al. [22] reported that ARBs reduced oxidative stress and inflammation in patients with diabetic nephropathy independent of their effects on blood pressure. Izuhara et al. [24] reported the renoprotective properties of ARBs in diabetic rats. These effects were independent of blood pressure lowering effects, but related to decreased oxidative stress and correction of chronic hypoxia. Ono et al. [25] reported that blood pressure decreased to the same extent in the ARB and non-ARB groups in hypertensive patients, whereas the urinary 8-OHdG decreased significantly in the ARB group but not in the non-ARB group. In the present study, ARBs may reduce oxidative stress in patients with early-stage diabetic nephropathy in part, independent of their effects on blood pressure.

According to a post-hoc analysis of data from the RENAAAL trial, use of losartan aimed at improving renal outcomes in patients with diabetic nephropathy requires a dual strategy, targeting both SBP and albuminuria [26]. In a subanalysis of Japanese patients from the RENAAAL study, losartan was shown to offer renal protection and to be generally well tolerated [27]. The present study first reported that losartan is effective in reducing urinary L-FABP and urinary 8-OHdG levels in early-stage diabetic nephropathy. Candesartan cilexetil was also shown, in a prospective, multicenter, randomized, double-blind study, to be useful in reducing proteinuria in Japanese type 2 diabetes patients [28]. Low-dose candesartan can prevent early kidney damage in type 2 diabetes patients with mildly increased blood pressure, independent of its hypotensive action [29]. Rossing et al. [30] reported that the optimal dose of candesartan is 16 mg/day for renoprotection, as reflected by the short-term reduction in albuminuria in hypertensive type 2 diabetic patients with nephropathy. In Japan, however, the maximum allowable dose of candesartan is 12 mg/day. The beneficial actions of olmesartan on diabetic nephropathy are at least in part due to a decrease in proteinuria and the subsequent reduction of inflammatory changes in renal tubular cells

[31]. Increased oxidative stress in the kidneys of diabetic mice was ameliorated by olmesartan [32]. However, little is known about the clinical effect of olmesartan on urinary L-FABP levels in early-stage diabetic nephropathy.

Telmisartan can act as a PPAR- γ activator at concentrations normally achieved with therapeutic doses. Therefore, this drug is associated with a potentially beneficial metabolic profile including an improved lipid profile, increased insulin sensitivity, blood pressure reduction and amelioration of the associated pro-inflammatory and pro-atherogenesis risk factors [9]. Recently, we reported the effectiveness of telmisartan for the protection of renovascular function and its potential for amelioration of atherosclerosis in hypertensive chronic kidney disease patients [33]. Owing to its antioxidant structure and highly lipophilic character, the intracellular radical scavenging activity of telmisartan is angiotensin II receptor 1 independent, at least in part [34]. Thus, we have new insight into the beneficial mechanisms of antihypertensive agents in the treatment of renal diseases induced by oxidative stress such as diabetic nephropathy. In animal models, telmisartan has a definite renoprotective effect against renal injury in type 2 diabetic nephropathy [35, 36]. In the present study, telmisartan was shown to be more effective than losartan, candesartan and olmesartan in reducing UAE, urinary 8-OHdG, and urinary L-FABP levels in early-stage diabetic nephropathy patients. Δ SBP was significantly greater in group D than in the other 3 ARB groups, but actual blood pressure data of all the groups after 6 and 12 months were statistically not significant. We reported previously that the reduction rate of urinary L-FABP and proteinuria was more pronounced in CKD patients receiving 80 mg/day of telmisartan compared with those receiving 40 mg/day whereas blood pressure reduction rate was similar between both doses [37], suggesting that the blood pressure lowering effect is very important for renoprotection, but the additive effects of telmisartan on UAE, L-FABP and 8-OHdG may go beyond the blood pressure lowering effects.

In an open-label observational study, 3,643 hypertensive patients with type 2 diabetes received telmisartan at 40–80 mg/day and showed decreased plasma glucose and TG levels after 6 months of treatment [38]. Derosa et al. [39] reported that telmisartan at 40 mg/day resulted in a significant reduction in plasma T-chol, LDL-chol, and TG, but there was no effect on glucose metabolism. In Japanese type 2 diabetic patients, telmisartan at 40 mg/day reduced HbA1c, whereas no significant change in HbA1c was found in patients treated with telmisartan at 20 mg/day or candesartan at 8 mg/day [40]. Inoue et al.

[41] proposed to classify telmisartan as a 'metabolic sartan' because it reduces total cholesterol and low-density-lipoprotein cholesterol levels. A metabolic sartan that ameliorates insulin resistance and dyslipidemia could provide even more effective options of preventing end-organ damage including ESRD and cardiovascular disease in hypertensive diabetic patients. In the present study, telmisartan at 80 mg/day significantly reduced HbA1c, T-chol, and TG levels in patients with early diabetic nephropathy. A structural resemblance between telmisartan and the PPAR- γ ligand pioglitazone has been noted [42]. We reported previously that pioglitazone, another PPAR- γ agonist, is effective in reducing UAE, urinary podocytes, and urinary L-FABP levels [7, 43]. The PPAR- γ agonist may have a specific role in ameliorating progressive tubulointerstitial injury under the hyperglycemic state. PPAR- γ is specifically implicated in the tubulointerstitial response to renal injury [44]. PPAR- γ agonist therapy in patients with metabolic characteristics inherent in renal disease may reduce proteinuria and may delay the progression of tubulointerstitial injury by reducing the inflammatory and fibrous responses. Recently, Benson et al. [45] reported that telmisartan, but not candesartan, irbesartan or eprosartan, can significantly inhibit the proliferation of vascular smooth muscle cells (lacking angiotensin II receptor), suggesting that the antiproliferative effects of telmisartan may involve more than just angiotensin II receptor blockade or activation

of PPAR- γ . Bakris et al. [46] reported that telmisartan is superior to losartan in reducing proteinuria in hypertensive diabetic nephropathy patients. However, little is known about the comparison of renoprotection among various ARBs in hypertensive diabetic nephropathy patients.

As there were 17 patients in each treatment arm, the present sample is fairly small. A large-scaled multicenter randomized study is still needed to be undertaken. In addition, it is important to consider the equipotency of various ARBs. In the present study, we used the maximum doses of various ARBs recognized in Japan (losartan 100 mg, candesartan 12 mg, olmesartan 40 mg, and telmisartan 80 mg). Studies on the effects of various doses of each ARB still need to be carried out.

In summary, we showed that ARBs may be effective in reducing UAE, urinary 8-OHdG, and urinary L-FABP in early-stage diabetic nephropathy patients. Telmisartan, a partial PPAR agonist, may provide more potent renoprotection than losartan, candesartan, or olmesartan in these patients.

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