Original Article

Renoprotective Effect of the Addition of Losartan to Ongoing Treatment with an Angiotensin Converting Enzyme Inhibitor in Type-2 Diabetic Patients with Nephropathy

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Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) are frequently used for the treatment for glomerulonephritis and diabetic nephropathy because of their albuminuria- or proteinuria-reducing effects. To many patients who are nonresponsive to monotherapy with these agents, combination therapy appears to be a good treatment option. In the present study, we examined the effects of the addition of an ARB (losartan) followed by titration upon addition and at 3 and 6 months (*n*=14) and the addition of an ACE-I followed by titration upon addition and at 3 and 6 months (*n*=20) to the drug regimen treatment protocol in type 2 diabetic patients with nephropathy for whom more than 3-month administration of an ACE-I or the combination of an ACE-I plus a conventional antihypertensive was ineffective to achieve a blood pressure (BP) of 130/80 mmHg and to reduce urinary albumin to <30 mg/day. During the 12-month treatment, addition of losartan or addition of an ACE-I to the treatment protocol reduced systolic blood pressure (SBP) by 10% and 12%, diastolic blood pressure (DBP) by 7% and 4%, and urinary albumin excretion by 38% and 20% of the baseline value, respectively. However, the effects on both BP and urinary albumin were not significantly different between the two therapies. In conclusion, addition of losartan or an ACE-I to an ongoing treatment with an ACE-I, or addition of an ACE-I to ongoing treatment with a conventional antihypertensive were equally effective at reducing the urinary albumin excretion and BP, and provided renal protection in patients with type-2 diabetic nephropathy. (*Hypertens Res* 2007; 30: 929–935)

***Key Words*: albuminuria, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, diabetic nephropathy**

Introduction

Diabetic nephropathy affected about 1.5 million people in the year 2002 in Japan. Proteinuria, albuminuria, hypertension and hyperglycemia are strong risk factors for progression of renal dysfunction (*1–4*). Thus, the treatment must be focused on reducing both blood pressure (BP) and proteinuria or albuminuria. Although angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) are widely used to treat diabetic nephropathy and prevent progressive renal dysfunction by conferring renoprotection and

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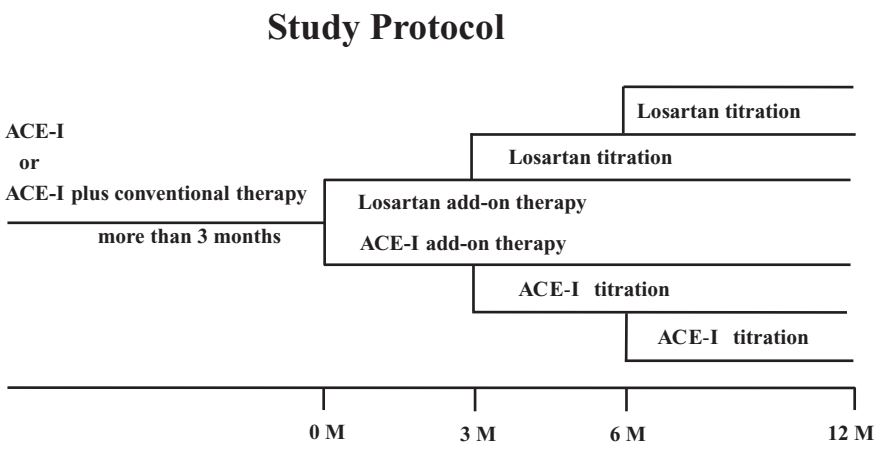

Fig. 1. *Study protocol.*

Table 1. Baseline Patient Characteristics

	Losartan add-on group (n=14)	ACE-I add-on group (n=20)	p value
Age (years)	59.5±6.5	59.8±6.7	n.s.*
Male/female	11/3	11/9	$p<0.05^{\dagger}$
BMI (kg/m^2)	23.8±2.1	23.4±3.8	n.s.*
Systolic BP (mmHg)	144±8.0	144±7.8	n.s.*
Diastolic BP (mmHg)	81±5.5	77±5.7	n.s.*
Serum creatinine (mg/dL)	1.25±0.63	1.00±0.45	n.s.*
Urinary albumin (mg/g Cr)	1,575.3±1,895.7	1,128.0±1,330.3	n.s.*

Mean±SD. *Unpaired t-test, †Fisher's exact test. BMI, body mass index; BP, blood pressure; Cr, creatinine.

Table 2. Baseline Clinical Characteristics

	Losartan add-on group (n=14)	ACE-I add-on group (n=20)
Medical history		
Retinopathy (n)	1	1
Cardiac hypertrophy (n)	1	2
Baseline treatment		
Antidiabetic drugs (n)		
Tolbutamide	4	5
Acetohexamide	0	1
Glibenclamide	5	7
Glimepride	1	2
Acarbose	3	2
Pioglitazone	0	2
Insulin	0	2
Antihypertensive drugs (n)		
Amlodipine	5	4
Barnidipine	1	2
Benidipine	0	1
Efonidipine	1	1

ACE-I, angiotensin converting enzyme inhibitor.

reducing systemic BP (*5*–*8*), the combination of an ACE-I and an ARB has recently been reported to provide greater renoprotection than monotherapy with either agent alone in patients with IgA nephropathy and type-2 diabetes mellitus (*9*–*11*). In the present study, we compared the renoprotective effects of adding an ARB (losartan) or adding an ACE-I to the drug regimen treatment protocol in type-2 diabetic patients with nephropathy for whom 3-month treatment with an ACE-I or 3-month treatment with an ACE-I plus a conventional antihypertensive drug was ineffective to reach a BP of 130/85 mmHg and reduce urinary albumin to <30 mg/day. The relatively low target BP of 130/85 mmHg was assigned because it has been recommended for hypertensive patients who have risk factors for renal disease (*12*, *13*).

Methods

Study Subjects

In this study, we recruited type-2 diabetic patients aged from 30 to 70 years who had overt nephropathy, albuminuria >30 mg/day, and BP >130/80 mmHg even after being treated with an ACE-I or the combination of an ACE-I and conventional

Table 3. Mean Dosage of Add-On ACE-I and ARB

	Losartan add-on group (n=14)		ACE-I add-on group (n=20)	
	Mean dosage	Number of patients (n (%))	Mean dosage	Number of patients (n (%))
ACE-I				
Enalapril	4.0 mg/day	9 (65)	6.1 mg/day	18 (90)
Lisinopril	5 mg/day	3 (21)	—	0 (0)
Temocapril	4 mg/day	1 (7)	—	0 (0)
Imidapril	5 mg/day	1 (7)	8 mg/day	1 (5)
Delapril	—	0 (0)	15 mg/day	1 (5)
ARB				
Losartan	42.8 mg/day	14 (100)		

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

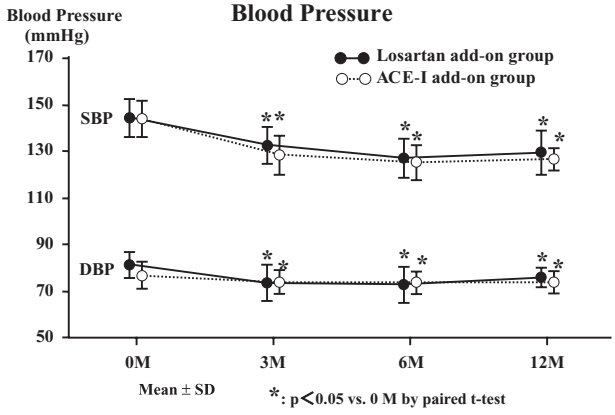

Fig. 2. *Time course of changes in systolic (SBP) and diastolic blood pressure (DBP) before and during 12-month add-on therapy.*

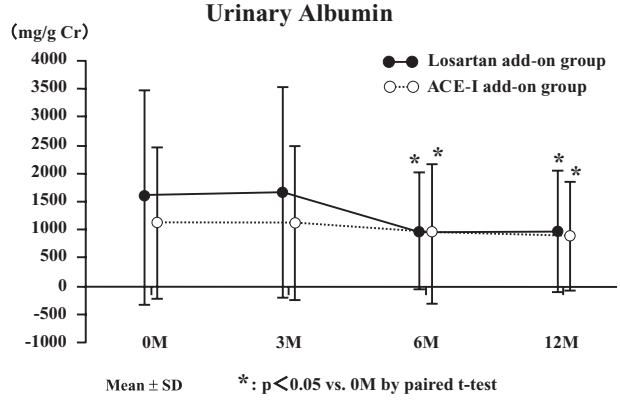

Fig. 3. *Time course of changes in urine albumin excretion corrected by urinary creatinine.*

drugs (calcium channel blacker, β-blocker or diuretics) excluding ARBs for more than 3 months. Patients were excluded if they had a diastolic BP (DBP) of more than 120 mmHg, HbA1c more than 9%, serum creatinine (Cr) more than 3.0 mg/dL, or severe hepatic dysfunction.

Study Protocol

We recruited 34 patients who visited Gifu University Hospital from March 2002 to April 2003. Patients for whom an ACE-I or the combination of an ACE-I plus a conventional antihypertensive drug was ineffective in lowering BP to 130/85 mmHg and reducing urinary albumin to <30 mg/day were allocated into two groups: the losartan add-on group (n=14) received add-on losartan (25 mg or 50 mg) at month 0, followed by titration every 3 months until their BP fell to less than 130/80 mmHg, and the ACE-I add-on group (n=20) received add-on ACE-I followed by titration every 3 months until the BP become less than 130/80 mmHg (Fig. 1). Patients took antihypertensive drugs at 7 to 8 AM. We carried out randomization using envelopes. BP was measured using a mercury sphygmomanometer with the subject in a sitting position in the morning (10 or 11 AM) at the clinic, and urinary albumin and Cr excretion were measured and blood tests were given for fasting glucose, HbA1c, uric acid, Cr and blood urea nitrogen (BUN) every 3 months. The study protocol was approved by the ethical committee of the Gifu University School of Medicine. Informed consent was obtained from each patient before the study.

Statistical Analysis

All data obtained are presented as the mean±SD. An unpaired t-test was used to compare the baseline characteristics of mean age, body mass index (BMI), systolic BP (SBP) and DBP, serum Cr, and urinary albumin between the two groups, and Fisher's exact test was used to compare the sex of patients between the two groups. Difference were analyzed in SBP, DBP, urinary albumin and Cr excretion, serum Cr value, fasting blood glucose, HbA1c, serum uric acid, BUN, and serum sodium, potassium and chloride level between two time

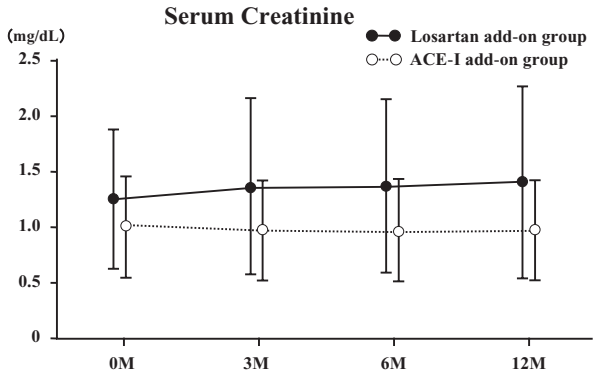

Fig. 4. *Time course of changes in serum creatinine.*

points within the group with paired *t*- test. The difference in parameters of baseline characteristics between the two groups was analyzed with unpaired *t*-test. *p* values of less than 0.05 were considered to be statistically significant. All statistical tests were two sided.

Results

As shown in Table 1, the baseline characteristics of age, BMI, SBP, DBP, serum Cr level, and urinary albumin level were similar between the two groups. However, the proportion of females was higher in the ACE-I add-on group. Table 2 shows the baseline clinical characteristics. There were no significant differences in medical history or baseline treatment between the two groups. Table 3 shows the mean dosage of add-on ACE-I and ARB.

Effect on BP

The time course of changes in BP in response to antihypertensive therapy is shown in Fig. 2. The mean baseline BP was high in both groups: 144/81.1± 8.0/5.5 mmHg in the losartan add-on group and 144/77.0±7.8/5.7 mmHg in the ACE-I add-on group. Both ARB and ACE-I add-on therapies significantly reduced mean SBP and DBP to the same extent, to 127.0±8.4 ($p<0.05$) and 125.3±7.4 ($p<0.05$) in SBP and 73.0±7.8 ($p<0.05$) and 73.6±4.6 ($p<0.05$) in DBP at month 6, and 129.1±9.5 ($p<0.05$) and 126.8±4.7 mmHg ($p<0.05$) in SBP and 75.8±4.0 ($p<0.05$) and 73.8±5.0 mmHg ($p<0.05$) in DBP at month 12 from the baseline values, respectively. The differences between the two groups in mean SBP or DBP were not significant at any of the time points.

Effect on Urinary Albumin Excretion

The time course of changes in urinary albumin excretion is shown in Fig. 3. The mean urinary albumin level was similar

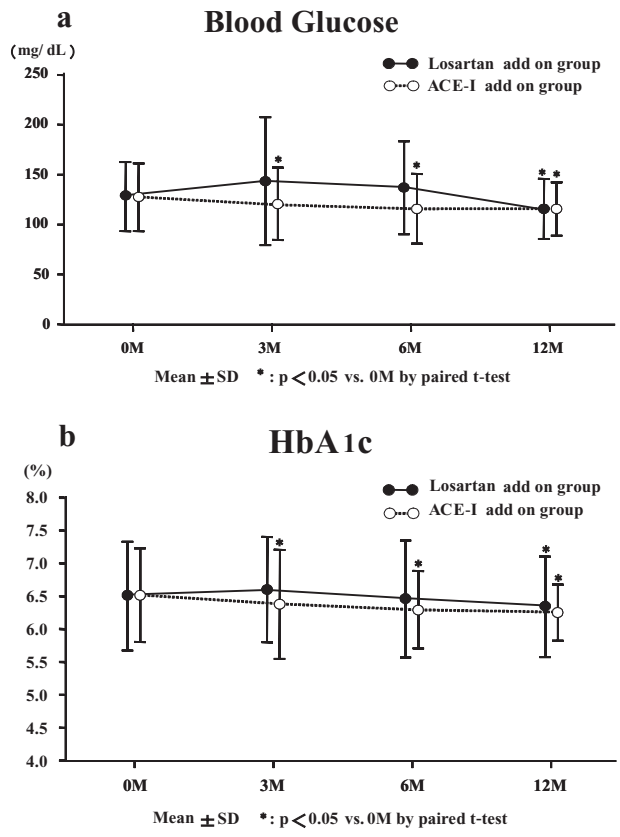

Fig. 5. *Time course of changes in fasting blood glucose (a) and HbA1c (b) levels.*

in the two groups: 1.58±1.90 g/g Cr in the losartan add-on group and 1.13±1.33 g/g Cr in the ACE-I add-on group before add-on treatment. Both the losartan add-on and ACE-I add-on therapies slightly and insignificantly increased mean urinary albumin excretion at month 3 (by 26% and 17% of the baseline values, respectively), but significantly reduced mean urinary albumin excretion at month 6 (to 0.98±1.02 g/g Cr [31%, $p<0.05$] and 0.94±1.24 g/g Cr [18%, $p<0.01$]) and at month 12 (to 0.98±1.07 g/g Cr [38%, $p<0.05$] and 0.88±0.96 g/g Cr [20%, $p<0.05$]). There was no significant difference in the reduction of urinary albumin excretion between the two groups at any of the time points.

Effect on the Urinary and Serum Cr Levels and BUN Level

The changes in serum and urinary Cr levels are shown in Fig. 4. Losartan add-on therapy significantly reduced urinary Cr levels at month 6 ($p<0.05$) and month 12 ($p<0.05$), but not serum Cr after treatment compared to the baseline values, while ACE-I add-on therapy did not reduce either urinary or serum Cr. Neither therapy had any effect on the BUN levels.

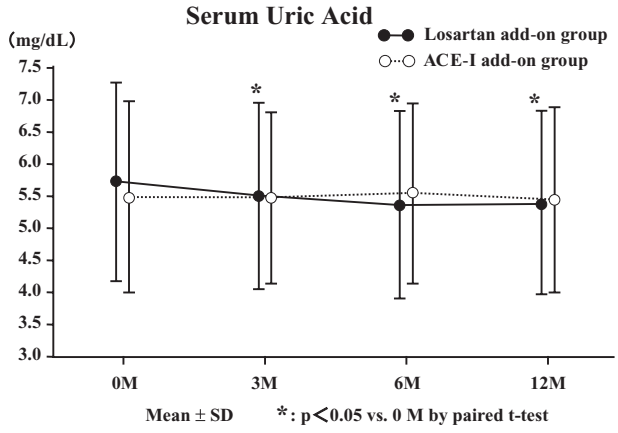

Fig. 6. *Time course of changes in serum uric acid level.*

Effects on Blood Sugar Levels and HbA1c

ACE-I add-on therapy significantly reduced both the mean fasting blood glucose (from 128±34 to 116±26 mg/dL [$p<0.05$]) and HbA1c levels (from 6.5±0.7 to 6.3±0.4% [$p<0.05$]) at month 12 compared to the baseline values, and losartan add-on therapy also significantly reduced both parameters at month 12 (from 129±34 mg/dL to 116±30 mg/dL [$p<0.05$] and from 6.5±0.82% to 6.3±0.8% [$p<0.05$], respectively). The changes during the course of treatment are shown in Fig. 5.

Effect on the Serum Uric Acid Levels

Losartan add-on therapy but not ACE-I add-on therapy significantly reduced the serum uric acid levels at the month 3, 6, and 12 (all $p<0.05$) after the treatment, as shown in Fig. 6.

Adverse Effects

No serious adverse effects such as an increased serum potassium concentration exceeding 5.5 mEq/L were observed in either group during the study periods.

Discussion

Type 2 diabetic patients with proteinuria and hypertension have a high mortality rate. For these patients, the treatment must be focused on reducing proteinuria as well as lowering BP (*14*). Many clinical studies have revealed that both ACE-Is and ARBs are effective for conferring renoprotection in patients with type 2 diabetes mellitus (*15–19*) by reducing proteinuria and BP.

Inhibition of the renin-angiotensin system (RAS) is an important element of the treatment for patients with renal disease and albuminuria. ACE-Is are commonly used for retarding the progression of renal disease by inhibiting the RAS. However, ACE-Is cannot completely inhibit the RAS, because angiotensin II is produced not only by angiotensin converting enzymes, but also by enzymes such as chymase. Thus, after the long-term use of an ACE-I, the level of circulating angiotensin II returned to the pretreatment level and ACE-I was ineffective. Numerous studies have shown that the combination of an ARB and ACE-I reinforces the blockade of the RAS and reduces urinary protein excretion (for review see Mackinnon *et al*. (*20*)). The synergism of ACE-Is and ARBs was demonstrated in a study using a combination of half doses of each monotherapy in patients with albuminuria (*21*). Although in the present study the combination therapy did not have a significant effect on albuminuria, the reduction of albumin excretion with the combination of an ARB and ACE-I tended to be somewhat greater (38%) than that with ACE-I monotherapy (20%) at the 12-month measurement.

In our study, addition of an ARB (losartan) or of an ACE-I for 12 months equally and significantly reduced the mean urinary albumin excretion in patients with diabetic nephropathy for whom the administration of an ACE-I alone or the combination of an ACE-I plus a conventional antihypertensive for more than 3 months was ineffective at reducing the BP to the target of 130/80 mmHg and urinary albumin excretion to <30 mg/day. There was no difference in the reduction of urinary albumin excretion between the two therapies. There have been many reports on the efficacy of combination therapy with ARBs and ACE-Is, and these studies have clearly shown that the combined therapy produces a more marked reduction in proteinuria as compared to monotherapy with either drug alone in patients with IgA glomerulonephritis (*9*, *10*, *22*), type-2 diabetic nephropathy (*23*) and type-1 diabetic nephropathy (*24*). Add-on therapy of the ARB losartan and add-on therapy of an ACE-I are both effective in reducing the urinary albumin excretion, suggesting that both therapies block the activity of the RAS.

We aimed to lower the BP below 130/80 mmHg with add-on therapy, because this goal has been recommended to confer protection against the development of chronic renal disease (*25*). Although not all the cases reached the target BP, both losartan add-on therapy and ACE-I add-on therapy reduced the mean SBP and DBP, and these reductions were comparable between the two therapies at 3, 6 and 12 months.

Although both ACE-Is and ARBs are considered safe drugs, hyperkalemia is a known side effect common to both. In the present study, however, no significant change in serum potassium was observed in either treatment group.

In the COOPERATE study (*26*), the incidence of hyperkalemia was 7.8% in non-diabetic renal disease patients treated with the combination of losartan 100 mg and trandolapril 3 mg, which was lower than that of trandolapril monotherapy (9.3%). It has been reported that there was no significant change in mean serum potassium level during 4-week dual blockage with the combination of 8 mg of candesartan and 20 mg of both lisinopril/enalapril in patients with

diabetic nephropathy (*27*, *28*). It has also been reported that treatment with the combination of 16 mg of candesartan and 20 mg of lisinopril for 12 months significantly increased the serum concentration of potassium by 0.30 mmol/L in patients with hypertension, microalbuminuria and non-insulin dependent diabetes, but the level was within the normal range and the increase was not considered clinically significant (*11*). Thus, many studies have demonstrated that hyperkalemia is not a significant adverse side effect but must be carefully observed in patients who receive combination therapy with ARBs and ACE-Is.

Blood glucose and HbA1c levels were significantly reduced by both the losartan and ACE-I add-on therapies after the 12-month treatment, suggesting that blockade of the RAS may improve glucose metabolism.

The addition of losartan resulted in a significant decrease in serum uric acid levels. The baseline level of uric acid was within the normal range in the study patients.

In conclusion, in patients with type-2 diabetic nephropathy who had been treated with an ACE-I or the combination of an ACE-I plus a conventional hypertensive drug and who had a BP of more than 130/80 mmHg and urinary albumin excretion >30 mg/day, add-on therapy of either an ARB (losartan) or an ACE-I was equally effective at reducing urinary albumin excretion and treating nephropathy.

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