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Anti-Albuminuric Effect of Losartan Versus Amlodipine in Hypertensive Japanese Patients with Type 2 Diabetes Mellitus: A Prospective, Open-Label, Randomized, Comparative Study

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ABSTRACT

Background: The antiproteinuric effect of the angiotensin II receptor-antagonist losartan has been observed in patients with type 2 diabetes mellitus (T2DM). Proteinuria is considered to be a predictor of the progression of kidney disease.

Objective: The aims of the present study were to compare and examine the ability of losartan and amlodipine to ameliorate albuminuria in hypertensive Japanese patients (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) with T2DM and whether the change in albuminuria was associated with a change in glomerular filtration rate (GFR).

Methods: This prospective, open-label, randomized, comparative study was conducted over 3 months at the Kinki University School of Medicine, Osaka-Sayama, Japan. Hypertensive patients with T2DM were enrolled and randomly assigned to 1 of 2 study groups receiving either losartan (25–100 mg/d) or the calcium channel-blocker amlodipine (2.5–5 mg/d). Urinary albumin excretion (UAE), creatinine clearance, and GFR were recorded at study initiation (baseline) and study end (month 3). The GFR was measured from the fractional renal accumulation of ^{99m}Tc-diethylenetriaminepentaacetic acid. Adverse events (AEs) were monitored by a clinical research nurse during the examination.

Results: Fifty patients were asked to enroll and 38 returned the informed written consent. Thirty-five Japanese patients were included in the final study analysis. Seventeen patients were assigned to the losartan group (male sex, 10 [58.8%]; mean [SD] age, 58.1 [8.2] years) and 18 were assigned to the amlodipine group (male sex, 10 [55.6%]; mean [SD] age, 57.4 [8.9] years); no significant between-group difference in demographics was observed. A significant decrease from baseline to month 3 of mean (SD) UAE was observed in the losartan group (352.5 [556.6] mg/d vs 275.7 [466.1] mg/d; $P = 0.048$). No significant difference in

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mean (SD) UAE was observed in the amlodipine group for the same time period (298.2 [416.6] mg/d vs 322.7 [415.4] mg/d). There was a statistically significant difference found in the mean (SD) percent change of UAE from baseline to month 3 in the losartan group compared with the amlodipine group (–23.52 [28.42] vs +27.90 [63.51]; $P = 0.004$). Neither group was associated with a significant change in GFR during the course of the study. No patient discontinued the study due to AEs that were considered, by the investigator, to be possibly or probably associated with study treatment.

Conclusions: Treatment with losartan, but not amlodipine, was associated with a reduction in albuminuria in these hypertensive Japanese patients with T2DM within a period as short as 3 months. Neither drug was associated with a significant change in GFR. Therefore, the reduction of UAE was independent of a change in the GFR. (*Curr Ther Res Clin Exp*. 2007;68:94–106)

Key words: albuminuria, hypertension, glomerular filtration rate, losartan, amlodipine.

INTRODUCTION

Of the many factors involved in the pathophysiology of proteinuric kidney diseases (eg, diabetic nephropathy), angiotensin II influences functional and morphologic deterioration of the kidney via a renal hemodynamic effect and nonhemodynamic cellular responses.[1] In the case of patients with hypertension and chronic kidney disease, hypertension plays an adverse role by influencing the progression of kidney diseases. Once the permselectivity of the glomerular membrane is impaired, glomerular hypertension becomes a catalyst for excessive filtering of proteins through glomerular capillaries.[2] Therefore, proteinuria is considered as a possible predictor of the progression of kidney disease. Strong arguments have also been made[3–5] that proteinuria is an underlying factor for the mechanisms of progression of kidney diseases. In the case of diabetic nephropathy, there is concern that glycosylated albumin might be nephrotoxic, inciting an inflammatory response leading to glomerular and interstitial damage.[6] Indeed, abnormal amounts of filtered protein might contribute directly to the pathogenesis of progressive renal injury.[1]

The inhibitive effect on the renin-angiotensin system (RAS) by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor-antagonists (AIIAs) for the prevention of progressive kidney disease and proteinuria has been demonstrated.[7–9] However, it is not fully understood whether the antiproteinuric effect of RAS inhibition is associated with an improvement in the glomerular filtration rate (GFR). A reduction in GFR might be associated with an apparent reduction in proteinuria. However, if the antiproteinuric effect is the consequence of a decreased GFR, the effect would not provide patients with a total restoration of normal renal function.

In Japan, the AIIA losartan has only been on the market since 1998. The antiproteinuric effect of AIIA losartan has been observed in patients with type 2 diabetes mellitus (T2DM). The aims of the present study were to compare and examine the ability of losartan and amlodipine to ameliorate albuminuria in hypertensive Japanese patients with type 2 diabetes mellitus (T2DM), and to compare and examine whether the change in albuminuria was associated with a change in GFR. At the time this trial was initiated, verification of renal function in Japanese patients had not been carried out.

PATIENTS AND METHODS

Patients and Study Design

This prospective, open-label, randomized, comparative study examined the antialbuminuric effect of losartan, in comparison with the efficacy of the calcium channel-blocker, amlodipine, for 3 months in patients with T2DM and hypertension. Male and female outpatients of the Department of Endocrinology, Metabolism and Diabetes, Kinki University School of Medicine, Osaka-Sayama, Japan, aged 20 to ≤74 years were eligible for the study. Patients were enrolled if they satisfied all of the following criteria during the 8-week screening period: (1) T2DM as determined by fasting plasma glucose level ≥126 mg/dL, or the result of glucose tolerance test (75 g) at 2 hours ≥200 mg/dL, and glycosylated hemoglobin <8.0%; (2) hypertension as determined by systolic blood pressure (SBP) ≥140 mm Hg and diastolic blood pressure (DBP) ≥90 mm Hg recorded in a sitting position at ≥2 visits (recorded after the discontinuation of antihypertensives); and (3) albuminuria as determined by urinary albumin excretion (UAE) of ≥30 mg/d.

The study protocol was reviewed and approved by the institutional review board of the Kinki University School of Medicine. Written informed consent was obtained from the patients enrolled.

All antihypertensive drugs were discontinued during the pretreatment-screening period. An overview of the study design is shown in **Figure 1**. After enrollment, patients were randomly assigned (via minimizing method) to 1 of 2 treatment groups: 1 group was treated with losartan; the other group was treated with amlodipine. In Japan, approved daily doses of losartan and amlodipine are 25 to 100 mg and 2.5 to 5 mg, respectively. The group of patients assigned to receive losartan was started on 25 mg QD. The group assigned to receive amlodipine was started on 2.5 mg QD. In cases where the patient's compliance was judged (from the existence of the hypotensive anamnesis by hypertension treatment in the past) by investigator(s) to be suitable to receive higher doses, either 50 mg of losartan or 5 mg of amlodipine was adopted as the starting dose. The target goal of SBP/DBP was <130/<85 mm Hg, and if SBP/DBP did not reach the target within 1 month, the daily dose of losartan and amlodipine was increased, up to 100 and 5 mg, respectively.

Exclusion criteria were as follows: DBP ≥120 mm Hg; renovascular hypertension and/or endocrine hypertension; BP control via ACE inhibitors or AIIAs; any case

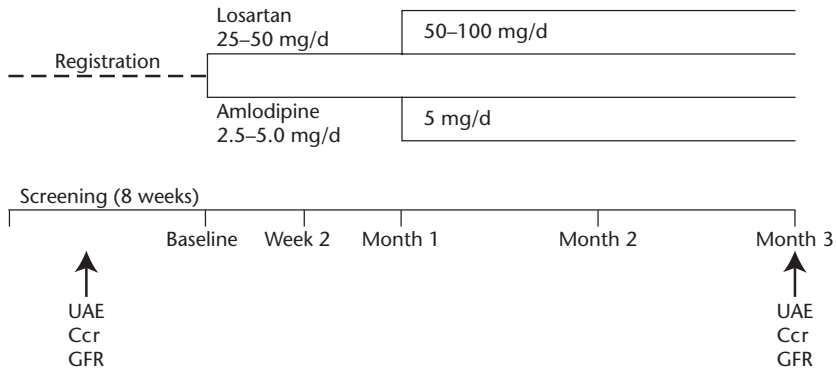

Figure 1. Study design for treatment of Japanese patients with type 2 diabetes mellitus and hypertension for 3 months. The starting dose was continued for ≥1 month, and dose escalation was allowed from the beginning of month 2 if systolic blood pressure/diastolic blood pressure did not reach target (<130/<85 mm Hg). UAE = urinary albumin excretion; Ccr = creatinine clearance; GFR = glomerular filtration rate.

in which other antihypertensive drugs could not be discontinued; serum creatinine (Scr) ≥2.5 mg/dL; renal disease(s) caused by anything other than T2DM; and pregnancy, possibility of pregnancy, or breastfeeding.

Patients were required to return to the clinic at 2 weeks and 1, 2, and 3 months after study initiation. BP in a sitting position was measured at all visits to the clinic. A KZ-620 sphygmomanometer (Kenzmedico Co., Ltd., Honjo City, Japan) was used to take BP measurements. A 24-hour urine collection was performed on the first day of treatment to obtain baseline measurements of urine volume, UAE level, and urinary creatinine excretion (Ucr) level. This process was repeated at the end of the study (month 3). Urinary albumin was determined with a turbidimetric immunoassay kit (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan). Creatinine clearance (Ccr), in mL/min, was calculated by the following formula[10]:

$$Ccr = Ucr \times (V/Scr) \times (1.73/A)$$

where V was urine volume (mL/min), and A was body surface area (cm^2).

The GFR was measured from the fractional renal accumulation of ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), calculated from computed renograms with a gamma camera, according to the method described by Gates.[11] A clinical research nurse determined each patient's compliance via interview. Patients were asked about the frequency of administration of the study medication. A report of ≥95% was considered good; all patients who participated in this study reported good compliance. Adverse events (AEs) were monitored by a clinical research nurse at the time of examination.

Statistical Analysis

All values are expressed as mean (SD). The baseline characteristics of the losartan group and the amlodipine group were compared using an unpaired Student *t* test or the Fisher exact test. The difference in SBP and DBP changes between the 2 groups was determined by an unpaired Student *t* test. Intragroup changes in UAE and GFR from baseline to 3 months were analyzed by a paired Student *t* test. The relationship between GFR and Ccr was analyzed using the Pearson correlation coefficient. A P value <0.05 was considered statistically significant. The calculation of sample size for this trial was based on the report of Fernández-Andrade et al.[12] The sample size calculations are based on an estimated efficacy of the albumin urine reduction; 40% for losartan and 10% for amlodipine at month 3. With an α level of 0.05 and a test power of 80%, the resulting sample size was 36 patients for both treatment groups. A risk of patients lost to follow-up of 10% was assumed. We estimated the required number of the minimum cases at 40 samples.

RESULTS

We asked 50 patients to participate in this trial and received written informed consent from 38 patients. We allocated 19 patients to the losartan group and 19 patients to the amlodipine group. However, 1 patient in the losartan group discontinued the study in month 3 as the result of acute heart failure. One patient in the amlodipine group discontinued the study at month 1 as the result of a stroke. The chief investigator (Y.O.) decided that these 2 cases were not associated with study drug treatments. One patient in the losartan group was fitted with a loop diuretic because of insufficient BP control and the data from this patient were eliminated from the end point analysis. Losartan 100 and 50 mg were administered to 11 and 6 patients, respectively. The mean dose of losartan was 82.4 mg/d at the end of the trial. All patients in the amlodipine group (n = 18) were receiving 5 mg from the start to the end of the trial. No patients who were started at 5 mg of amlodipine reached <130/<85 mm Hg within 1 month. The **table** summarizes the baseline demographic and clinical characteristics of the patients who completed the study.

The BP change in each group is illustrated in **Figure 2**. There was a significant change in SBP at week 4 between the losartan group and the amlodipine group. No other significant changes in BP were observed. **Figure 3A** shows UAE at baseline and at month 3 in the losartan and amlodipine groups. Losartan was associated with a significant decrease in mean (SD) UAE from 352.5 (556.6) mg/d at baseline to 275.7 (466.1) mg/d at month 3 (P = 0.048). However, there was no significant difference observed in the amlodipine group in the mean (SD) UAE values between baseline and month 3 (298.2 [416.6] mg/d vs 322.7 [415.4] mg/d, respectively). **Figure 3B** shows the percent change of UAE in the losartan group and the amlodipine group. There was a statistically significant difference in the percent change of mean (SD) UAE from baseline to

Table. Baseline demographic and clinical characteristics of hypertensive Japanese patients with type 2 diabetes mellitus (T2DM) assigned to receive either losartan or amlodipine. Values are presented as mean (SD), except where otherwise noted.

Characteristic	Group*	
	Losartan (n = 17)	Amlodipine (n = 18)
Sex, no. (%)		
Male	10 (58.8)	10 (55.6)
Female	7 (41.2)	8 (44.4)
Age, y	58.1 (8.2)	57.4 (8.9)
BMI, kg/m^2	24.4 (3.9)	26.5 (4.4)
SBP, mm Hg	158.5 (9.2)	160.6 (15.7)
DBP, mm Hg	83.9 (12.0)	86.8 (10.3)
FPG, mg/dL	133.0 (31.1)	145.4 (42.6)
HbA_{1c},%	6.8 (0.7)	6.8 (0.8)
UAE, mg/d	352.2 (556.6)	298.2 (416.6)
GFR, mL/min	81.9 (19.0)	73.9 (18.9)
T2DM duration, y	8.1 (5.2)	10.3 (6.3)
Hypertension duration, y	6.2 (3.9)	3.8 (3.9)

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; UAE = urinary albumin excretion; GFR = glomerular filtration rate.
*No significant between-group differences were found.

month 3 between the 2 groups (losartan, –23.52 [28.42] vs amlodipine, +27.90 [63.51]; $P = 0.004$). Change in UAE from baseline to month 3, when stratified by patients with macroalbuminuria (>300 mg/d; n = 4) and microalbuminuria (≤300 mg/d; n = 13), was significantly greater in those patients with microalbuminuria ($P = 0.019$) (**Figure 4**). The GFR determined at baseline and at month 3 in the losartan group and in the amlodipine group is shown in **Figure 5**. There was no statistically significant change observed in GFR in the 2 groups. **Figure 6** shows regression lines for correlation between the GFR and Ccr, determined at baseline and at month 3. At both time points, the GFR and Ccr were significantly correlated (baseline, $r = 0.68$; month 3, $r = 0.66$).

Adverse Events

Both treatment regimens were well tolerated. No patient discontinued the study due to AEs that were considered by the investigator to be possibly or probably associated with study treatment. However, 2 AEs (increased serum potassium and leukocytosis) experienced by 2 patients in the losartan group and 6 AEs (palpitations, unsteadiness, face flushing, increased serum potas-

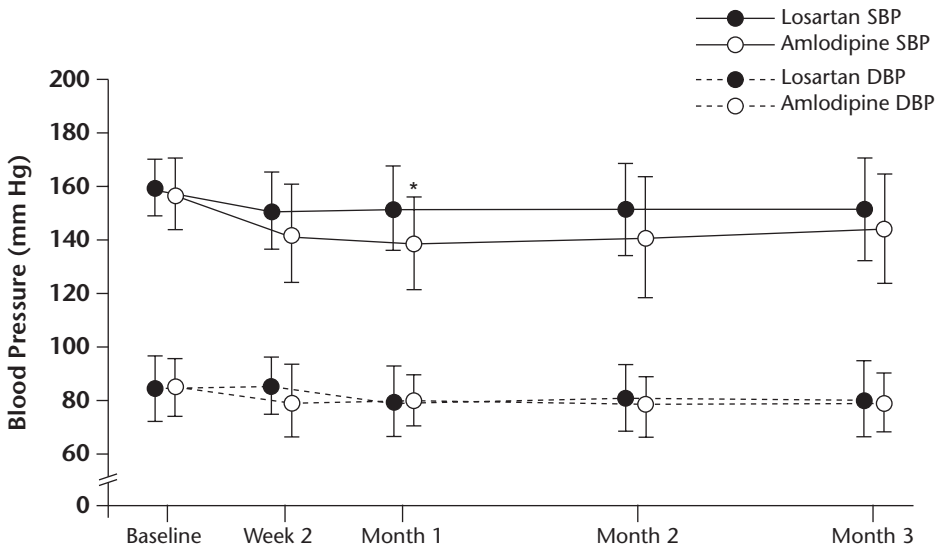

Figure 2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients of the losartan group (n = 17) and the amlodipine group (n = 18) during 3 months of study. Values are presented as mean (SD). *P = 0.040 versus losartan.

sium, increased albuminuria, positive albuminuria) experienced by 3 patients in the amlodipine group were reported as mild subjective and objective symptoms and as mild changes observed by laboratory chemistry. Although there was a case of acute heart failure in the losartan group, there was no sign of a connection to the study drug. Therefore, the investigator judged that losartan did not cause the acute heart failure. Similarly, the investigator judged that the cerebral infarction in the amlodipine group was not caused by the use of amlodipine.

DISCUSSION

In our present study, treatment of patients with losartan was associated with a significant reduction of UAE from baseline levels. A significant change in UAE was not observed in patients treated with amlodipine. The reduction of UAE associated with losartan achieved statistical significance in patients with microalbuminuria. The overall reduction in UAE in patients with macroalbuminuria was not statistically significant, and may be related to a small number of patients and large standard deviations.

Evidence is available with respect to the effect of inhibition of angiotensin II for reduction of proteinuria. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study[13] reported the renoprotective efficacy

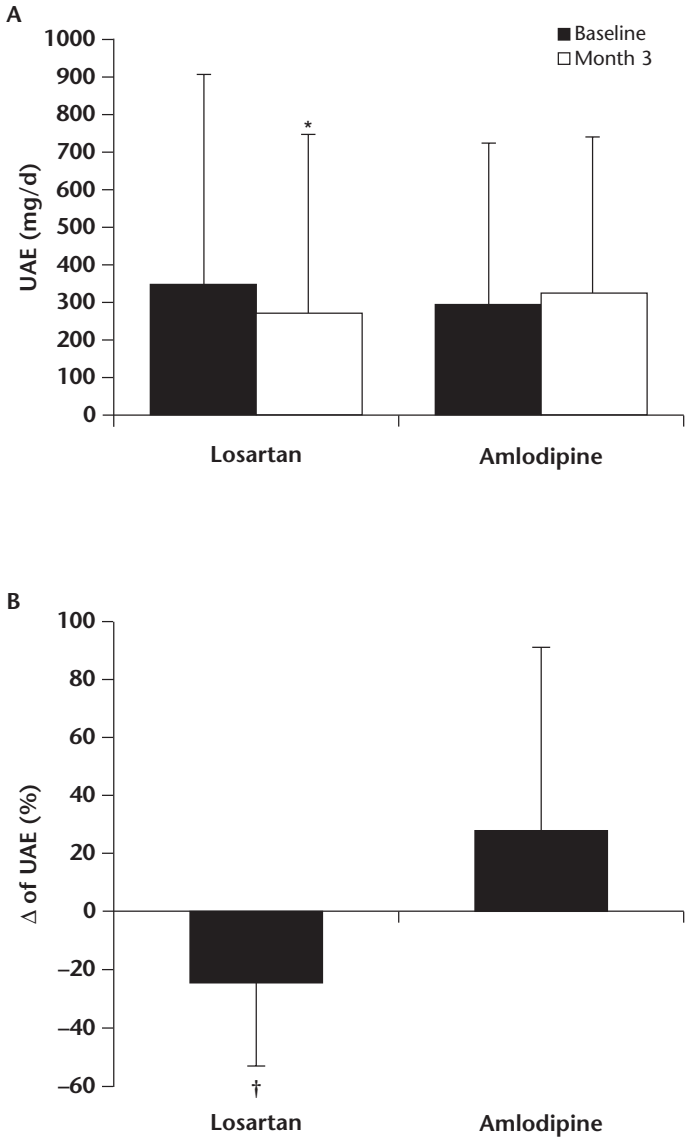

Figure 3. **(A) Urinary albumin excretion (UAE) at baseline and at month 3 in the losartan group and the amlodipine group. (B) Percent change from baseline to month 3 of UAE in the losartan and amlodipine groups. All values are presented as mean (SD). *$P = 0.048$ versus baseline; †$P = 0.004$ versus amlodipine.**

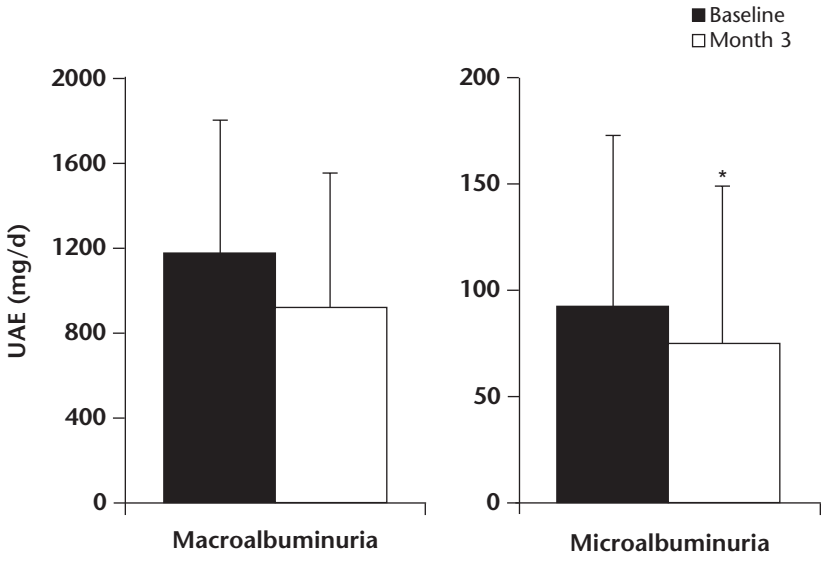

Figure 4. Urinary albumin excretion (UAE) at baseline and at month 3 in the losartan group, stratified into subgroups of macroalbuminuria (>300 mg/d; n = 4) and microalbuminuria (<300 mg/d; n = 13). Values are presented as mean (SD). *P = 0.019 versus baseline.

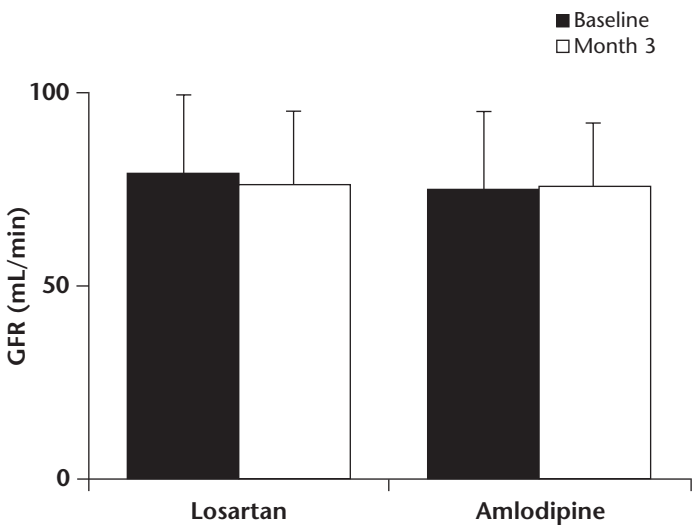

Figure 5. Glomerular filtration rate (GFR) at baseline and at month 3 in the losartan (n = 17) and amlodipine (n = 18) groups. No significant changes were observed. Values are presented as mean (SD).

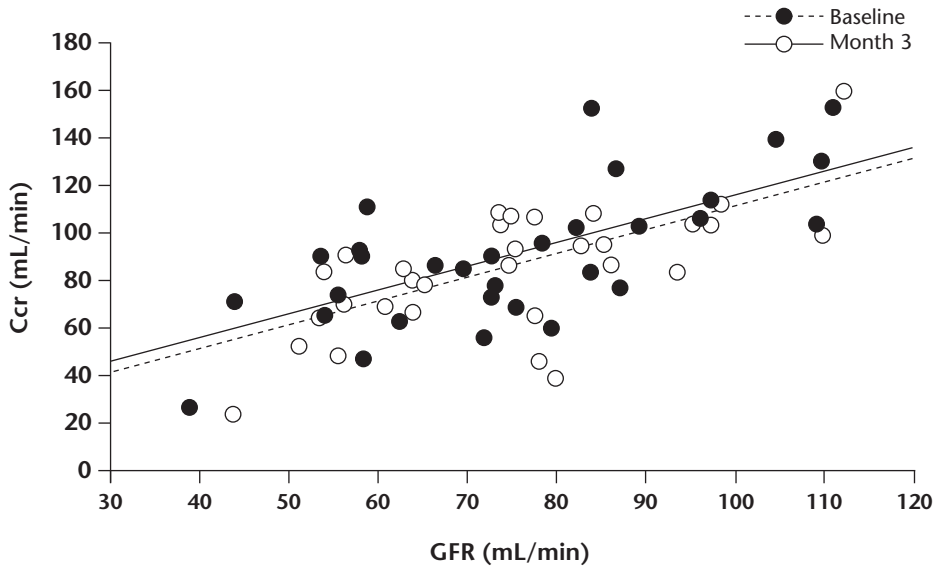

Figure 6. Regression analysis for correlation between the glomerular filtration rate (GFR) and creatinine clearance (Ccr) in Japanese patients (n = 35) with type 2 diabetes mellitus and hypertension treated with losartan or amlodipine. Values and regression lines were from determinations in all patients at baseline (r = 0.68) and at month 3 (r = 0.66).

of losartan in 1513 patients with type 2 diabetes, associated with a significant reduction in proteinuria in patients with a median urinary albumin-to-creatinine ratio of 1237 at baseline. In the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients study,[14] significant reduction of urinary protein excretion associated with the use of losartan was independent of its BP-lowering effect in 93 patients with chronic kidney disease and hypertension. This was in contrast to the effect associated with the use of amlodipine, in which there was no statistically significant reduction in urinary protein excretion. In a prospective study[15] in 117 patients with chronic nondiabetic nephropathies, treatment with dihydropyridine calcium channel-blockers resulted in a significantly higher level of proteinuria than the level in patients treated with other antihypertensive drugs (P = 0.015), although the control of BP and the severity of underlying renal disease were similar. The use of valsartan in 332 patients with type 2 diabetes was also associated with lowered BP and an antiproteinuric effect.[16] Therefore, the present study results are comparable with previously published reports, in regard to the positive antialbuminuric effect associated with the blockade of angiotensin II receptors.

In the losartan group and the amlodipine group, there was no statistically significant change in GFR as measured by renogram with ^{99m}Tc-DTPA. Although Ccr is a useful parameter to assess renal glomerular function, on the basis of

the widely accepted concept that it mimics the GFR, it is true also that Ccr does not always reflect the GFR correctly. In cases of renal failure,[17] the value of Ccr has been about twice that of the GFR value determined by inulin clearance. Measurement of the GFR by renogram with the radioactive compound ^{99m}Tc-DTPA has thus been introduced. Because the diagnosis of patients by the renogram is not common in clinical practice, we measured GFR only twice, at baseline and at month 3. Our results demonstrated that there was no change in the GFR from baseline to month 3 in the losartan group or in the amlodipine group. As is shown in **Figure 6**, because the GFR and Ccr were significantly correlated, Ccr appeared to reflect the GFR. This suggested that, in our present study, although an antiproteinuric effect was associated with losartan, renal hemodynamics and glomerular functions were not altered.

Angiotensin II constricts the efferent arterioles to a greater extent than the afferent arterioles, resulting in an increase in glomerular capillary filtration pressure.[17] The elevated filtration pressure and increased SBP caused by angiotensin II might lead to an increase in the GFR. The multinational, randomized, double-blind, placebo-controlled Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study[18] examined the effect of the AIIA irbesartan in 590 patients with type 2 diabetes. A significant decline in Ccr was not observed in a 3- to 24-month period in either the irbesartan group or the placebo group, although a significant reduction in UAE associated with irbesartan was observed from 3 months. There is concern that pharmacologic interference of the RAS reduces the GFR and the glomerular filtration fraction.[19] Therefore, in treating patients with hypertension and kidney disease, the pharmacotherapy is required to reduce BP to the target value, and concomitantly to maintain the GFR or, hopefully, to increase the GFR if it is below the normal level. The use of losartan might be beneficial, in terms of maintaining the GFR with concomitant effectiveness in reducing UAE. The single-blind, randomized, placebo-controlled study by Gansevoort et al[20] reported that losartan was associated with changes in BP and proteinuria similar to those associated with ACE-inhibition in patients with nondiabetic kidney disease. In a randomized, double-blind, crossover trial, Andersen et al[21] also reported that, in 16 patients with type 1 diabetic nephropathy, treatments with losartan and enalapril for 2 months were associated with significantly reduced urinary protein excretion, whereas no significant change in GFR, as measured by determination of the radioactivity of ^{51}Cr-ethylenediaminetetraacetic acid,[22,23] was observed. Therefore, based on the results of our study, it is our opinion that the observed reduction of UAE in patients with diabetic nephropathy and hypertension associated with losartan appears to occur without a change in the GFR. In our study, the onset of the antialbuminuric effect was seen at the first measurement within 3 months of study initiation. Because the reduction in UAE is one of the targets of treatment for renoprotection, and an early effect is expected, the early onset of the antialbuminuric effect with no substantial change in the GFR in this period might be highly beneficial, although longer treatment remains to be

investigated. As a result, we carried out a number of examples using the comparison data of albuminuria since we did not have any comparison data of amlodipine and losartan regarding GFR. Because this trial was of a small size and the trial period was short, the possible conclusions from this trial outcome are limited. It will be necessary to examine a much higher number of cases in a longer-term trial in the future.

CONCLUSIONS

Treatment with losartan, but not amlodipine, was associated with a reduction in albuminuria in these hypertensive Japanese patients with T2DM within a period as short as 3 months. Neither drug was associated with a significant change in GFR. Therefore, the reduction of UAE was independent of a change in the GFR.

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