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Beneficial Effect of Combination Therapy by Losartan and Azelnidipine on Albuminuria and Renal Function in Type 2 Diabetic Patients With Chronic Kidney Disease

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Elevated urinary albumin excretion rate（UAER）is a modifiable risk factor for renal and cardiovascular diseases in type 2 diabetes. Blockade of the renin-angiotensin system（RAS）lowers UAER. In the present study, 46 patients（male: 25, female: 21, mean age 62.8±5.9 years old）with CKD and hypertension accompanied with type 2 diabetes were enrolled, among whom there were wide ranges of blood-pressure values. Patients had been used amlodipine or nifedipine to control blood pressure between 2007 and 2009 at Nagami Clinic, Shimane Japan. However, UAER did not decrease and estimated glomerular filtration rate（eGFR）did not increase during the first 24 month follow up period. To those 46 patients, losartan which is one of angiotensin receptor blockers（ARBs）and azelnidipine which is one of calcium channel blockers（CCBs）were administered in order to examine whether combined administration of losartan and azelnidipine（Los/Azl treatment）provides superior reduction in proteinuria compared to nifedipine or amlodipine in hypertensive type 2 diabetes patients with CKD. All 46 patients received either 25 mg per day losartan, which was increased up to 50 mg per day, and 8 mg per day azelnidipine, which was increased up to 16mg per day, over 24 months. Mean systolic and diastolic pressure was controlled less than 120/80 mmHg. This present study was a 2 years'prospective cohort study. During the first 24 month follow up period, there was not a significant difference of the mean eGFR and UAER between amlodipine group and nifedipine group. However, the present changes in eGFR and UAER by Los/Azl treatment at 6, 12, 18 and 24 month showed 5.4, 7.0, 9.0, and 13.2 % for eGFR and -15.2, -24.8, -37.3, and -48.7% for UAER, respectively.

In conclusion, it was demonstrated that Los/Azl treatment should be considered for hypertensive diabetic patients with CKD.

Key words: Chronic kidney disease, Losartan, Azelnidipine, Cardiovascular diseases, and Microalbuminuria

INTRODUCTION

The increasing burden on health care providers from chronic kidney disease（CKD）is due to the escalating prevalence of obesity, hypertension and type 2 diabetes. The gradual decline in kidney function in the presence of these risk factors is also associated with increased cardiovascular disease. Excess angiotensin II production by the renin-angiotensin-system（RAS）is responsible, at least in part for the development of hypertension and for damage in the kidneys and the cardiovascular system. Pharmacological targeting of the RAS not only reduces blood pressure, but may also provide more direct renal microvascular protection. Angiotensine receptor blockers（ARBs）are better tolerated than angiotensin-converting enzyme inhibitors（ACEIs）and, thus, may be a more practical therapeutic option. Clinical studies have demonstrated the efficacy of irbesartan, losartan, telmisartan and valsartan in the management of CKD. Tight blood pressure control in the management of the patients with diabetes and hypertension is crucial［1］. A target systolic

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blood pressure (SBP) /diastolic blood pressure (DBP) <130/80 mm Hg is proposed in current guidelines when CKD is present [2, 3]. However, this target may not be sufficiently low: the findings of the Modification of Diet in Renal Disease (MDRD) study suggest that the optimal SBP/DBP is <125/75 mm Hg if urinary protein excretion rate (UPER) is >1 g/24 hours [4]. Antihypertensive agents that target the RAS; namely, ACEIs and ARBs are generally acknowledged to confer additional renal microvascular protective benefits compared with other classes of antihypertensive agents [3, 4, 5].

A large scale study-Irbesartan in Diabetic Nephropathy (IDNT) with 1715 hypertensive patients of nephropathy due to type 2 diabetes by Lewis et al [6] demonstrated that irbesartan reduced the risk of cardiovascular disease compared with amlodipine. Besides, another randomized clinical trials of the ARBs (irbesartan, losartan, telmisartan and valsartan) have been conducted predominantly in patients with type 2 diabetes and CKD of varying severity ranging from minimal renal dysfunction (urinary albumin excretion rate (UAER); 30-299 mg/24 hours) to overt nephropathy (UAER ≥300 mg/24 hours) [7]. By the way, between 2007 and 2009, amlodipine or nifedipine were used to keep normal blood pressure to the type 2 diabetes patients with CKD at Nagami Clinic, Shimane, Japan. However, such drugs could not improve renal function. After a decade of research, there is now substantial evidence to show that the use of losartan provides an efficacious treatment option for the prevention of renal disease progression in patients with hypertension. But it is difficult to reduce UAER and improve CKD diseases, because it is impossible to use losartan more than 100mg/day in Japan [8]. So it is necessary to find out the best combination therapy with use both of losartan and calcium channel blockers (CCB) in order to reduce UAER and protect renal function.

Meanwhile, accumulating experimental and clinical evidence shows that excess aldosterone not only promotes the retention of sodium and body fluid but also induces cardiac and renal injury causing cardiac hypertrophy, inflammation, fibrosis, glomerulosclerosis, renal inflammation and fibrosis [9]. Moreover, aldosterone induces oxidative stress in vascular cells through nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) activation, which has a central role in endothelial dysfunction and atherosclerotic vascular disease. Therefore, targeting aldosterone synthesis and release may be clinically important in preventing cardiovascular disease. Ca_2+inons are transported via T-type calcium channels to mitochondria, where they activate aldosterone synthesis, which in turn stimulate T-type calcium channel expression, ceasing a positive feedback loop of aldosterone biosynthesis in adrenal cells [9]. It was demonstrated that azelnidipine provided not only L-type but also T-type calcium channel blocking activity and azelnidipine was useful in protecting renal function [10]. In the present study, whether combined administration of the losartan and azelnidipine provides superior reduction in proteinuria compared to nifedipine or amlodipine in hypertensive type 2 diabetes patients with CKD was primarily examined. The secondary point observed was to examine whether this therapy could inhibit the development of cardiovascular or cerebrovascular events.

In the present study, the reason why nifedipine and amlodipine were used for the type 2 diabetic patients with CKD during the first 24 month was that Baba [11] and Kumagai et al [12] reported that nifedipine and amolodipine were effective for the hypertensive type 2 diabetic patients with CKD because of their lowering systemic blood pressure.

PATIENTS AND METHODS

The present study enrolled 46 patients (male: 25, female: 21, mean age 62.8±5.9 years old) with CKD and hypertension accompanied with type 2 diabetes, among whom there were wide ranges of blood-pressure values. Patients had been administered CCBs such as amlodipine or nifedipine to control blood pressure between 2007 and 2009 at Nagami Clinic, Shimane, Japan. All patients were followed blood pressure controlling less than 130/80 mmHg and periodically heart rate. Among 46 patients, 29 patients had been administered amlodipine to keep normal blood pressure of which the dosage was 5~10mg/day (amlodipine group). The remaining 17 patients with type 2 diabetes with CKD were administered nifedipine which daily dosage was 20~30mg/day (nifedipine group). If the blood control of the pres-

ent patients were not sufficient, other antihypertensive drug was allowed to help patients reach and maintain the target blood pressure of less than 125/80 mm Hg. There were only 5 patients who needed additional antihypertensive drugs. Those 5 patients required an administration of carvedilol with a function of α and β blocker function. All 46 patients were followed measuring blood pressure, UAER and eGFR periodically during the first 24 month follow up period. Meanwhile, the mean treatment duration of diabetic diseases of the present 46 patients was an approximately 25.6 years（from 10.8year to 32.1 year）. Medications to the diabetes mellitus of those 46 patients were glimepiride in 6 patientsa, teglinide in 4 patients, glimepiride + metoforminhydrochroride in 5 patients, glimepiride + voglibose in 6 patients, glimepride + metoforminhydrochroride + voglibose in 15 patients, glimepiride + metoforminhydrochroride + sitagliptrinphosphate hydrate in 8 patients and insulin treatment in 2 patients.

Microalbuminuria was defined as a urinary albumin-to-creatinine ratio（with albumin measured in milligrams and creatinine measured in grams）of more than 14 mg/g.cre determined by validated measurements of morning spot urine samples. There were 14 patients with microalbuminuria and 32 patients with macroalbuminuria. As an endpoint, cardiovascular diseases and cerebrovascular disease were checked during the first 24 month follow up period. And eGFR was calculated by as follows; in the case of man, eGFR = $194\times Cr^{-1.094}\times age^{-0.287}$, in the case of woman, eGFR = $194\times Cr^{-1.094}\times age^{-0.287}\times 0.739$ （ml/min/1.73m^2）. However, eGFR and UAER of all 46 patients were not improved by nifedipine or amlodipine alone. Especially, 4 patients suffered from ischemic cardiac diseases and cerebrovascular diseases in nifedipine group. And in amlodipine group, there were 2 patients with CKD related-ischemic heart diseases and cerebrovascular diseases. From this experience, combined therapy with use of losartan and azelnidipine was performed to those 46 patients from May 2009 to May 2011. Accordingly, two years'prospective study was started at May, 2009. All 46 patients were examined physical examination, vital signs such as blood pressure, heart rate, urinary analysis and blood chemical study including the number of the white blood cell, the red blood cell, the platelet. In addition, renal function, liver function and lipid analysis were examined every month during the second 24 month follow up period. The main purpose of the present study was to examine whether Los/Azl therapy could improve renal function and reduce UAER during the second 24 month follow up period. In the present study, the values of HbA1c, eGFR, UAER at 0M, 24M during the first 24 month follow up period were defined as baseline 1 and baseline 2 respectively. During the first 24 month follow up period, those values at the baseline 2 were compared to the baseline 1 both in amlodipine and nifedipine group. Furthermore, the percent changes in eGFR and in UAER of all 46 patients in amlodipine and nifedipine groups at 6M,

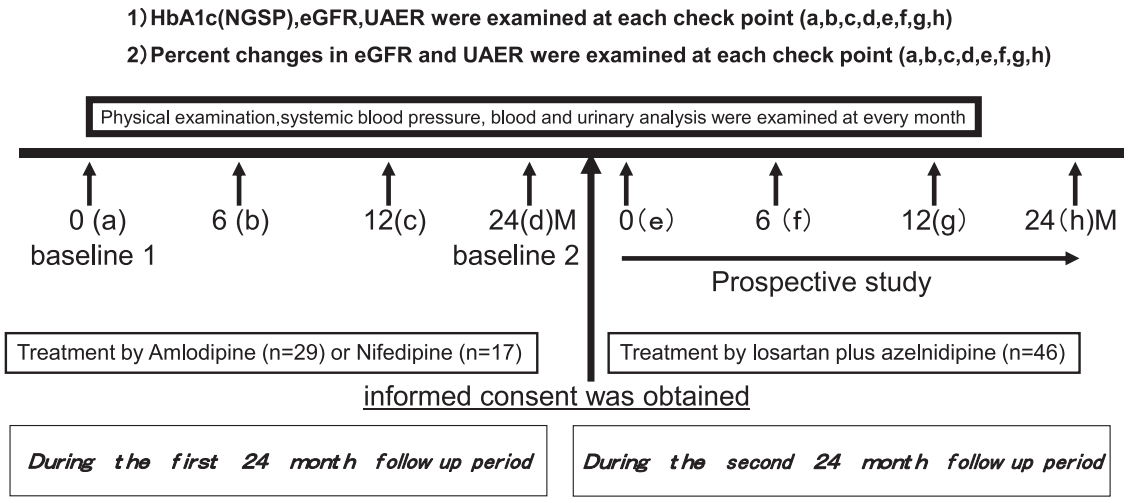

Fig. 1. This figure demonstrate a schema of the present prospective study

Table 1. Changes of systemic blood pressure during the first 24 month follow up period and during the second 24 month follow up period in the amlodipine group and nifedipine group

systolic blood pressure (mmHg)		0M	6M	12M	24M
Amlodipine Group (n=29)	first 24M period	132.8±80.8	128.9±78.9	123.9±78.8	126.8±78.0
	second 24M period	125.8±78.9	118.8±77.8	111.9±77.2	118.6±78.6
Nifedipine Group (n=17)	first 24M period	125.8±78.8	125.9±79.9	119.5±76.8	118.8±76.0
	second 24M period	122.8±72.9	120.8±67.8	117.9±75.8	119.6±74.6

12M, 18M, 24M after Los/Azl treatment were compared to the baseline 2 (Fig. 1). During the second 24 month follow up period, blood pressure was maintained less than 120/80 mmHg. If the blood pressure control was difficult, other antihypertensive drugs were additionally administered. No patients necessitated additional antihypertensive drugs. If adverse effects were occurred during the second 24 month follow up period, the patient was excluded in the present study. Fortunately, there was not a patient with exclusion by severe adverse effect both of losartan and azelnidipine. And no patient was fortunately excluded from this study because of adverse effects of losartan and azelnidipine, and other fetal diseases.

At the time of the start point of the second 24 month study, the purpose of the present study was explained to each patient and their families and informed consent was obtained. Furthermore, adequate care was taken to protect the privacy of the individuals participating in the study. Each patient was informed of the present study's intent to not use the clinical data from this study for any purpose other than for the present study.

STATISTICAL ANALYSIS

All values were expressed as the mean ± SD. The baseline characteristics of the enrolled patients were tested for comparability between the amlodipine group and niphedipine group. Comparison of the values of UAER and eGFR at baseline and that at 24 months of amlodipine group and nifedipine group were analyzed by Student's t-test. Meanwhile, changes in UAER and eGFR of the two groups after administration of Los/Azl were analyzed by paired t-test. In both of amlodipine group and nifedipine group, the values of UAER and eGFR at the point of 0 and 24 month were defined as the baseline 1 and 2, respectively. The mean percent changes of those values at each point were compared by unpaired t-test. Results throughout the text, tables, and figures are presented as mean ± SD and statistical significance was defined as $P < 0.05$.

RESULTS

Changes of blood pressure by treatment of amlodipine, nifedipine and losartan plus azelnidipine during 48 month follow up period(Table 1)

Both in amlodipine and nifedipine groups, systemic blood pressures were controlled less than 130/85 mmHg, although there were 5 patients with additional antihypertensive drugs. Those 5 patients required an administration of carvedilol. Meanwhile, systemic blood pressure was controlled less than 120/80 mmHg by Los/Azl treatment during the second 24 month follow up period. However, the mean value of blood pressure at the first 24 month in amlodipine group was significantly ($P<0.05$) higher than those in nifedipine group.

Changes of Hemoglobin A1c: HbA1c(NGSP)during total 48 month follow up priod(Fig. 2)

During the first 24 month follow up period, mean HbA1c at 24 month significantly ($P<0.01$, $P<0.05$) decreased compared to the baseline 1 both in amlodipine and nifedipine group. During the second 24 month follow up period, it was less than 6.8% in amlodipine group and less than 6.9% in nifedipine group. Furthermore, HbA1c at 18 and 24 month after Los/Azl treatment were significantly ($P<0.05$) lower compared to the baseline 2 in amlodipine group.

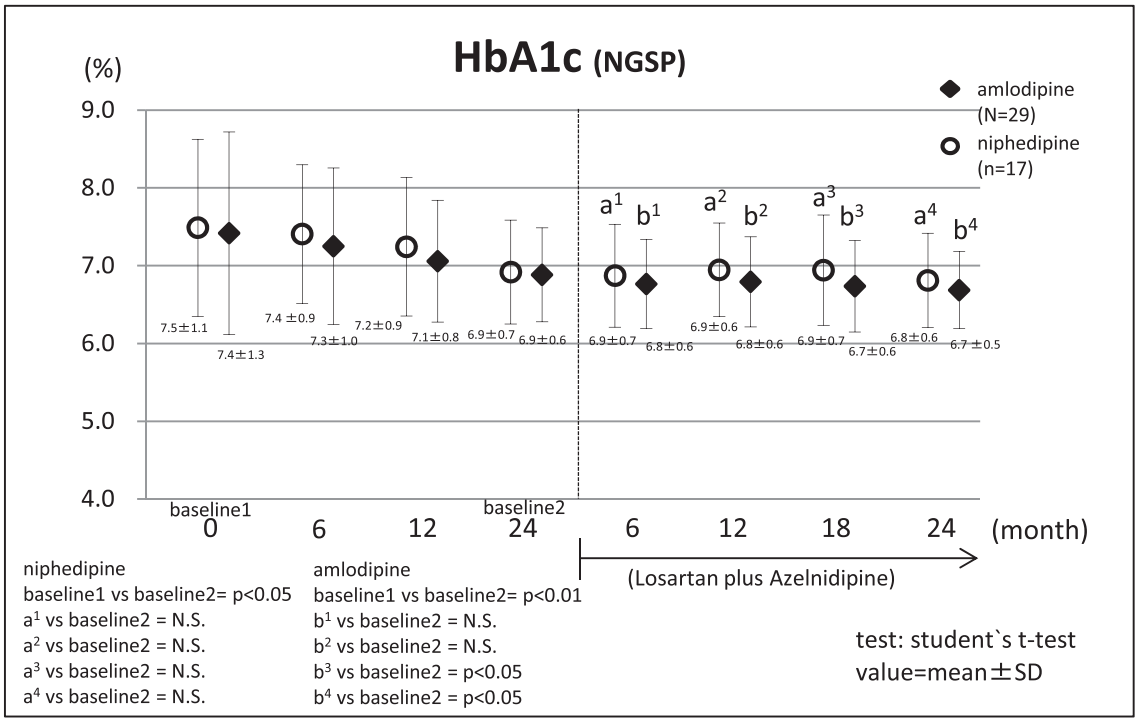

Fig. 2. Changes of HbA1c（NGSP）treated by amlodipine and nifedipine during the first 24 month follow up period and those treated by losartan plus azelnidipine during the second 24 month follow up period in the hypertensive type 2 diabetic patients with CKD

Changes of eGFR by treatment of losartan plus azelnidipine in the hypertensive type 2 diabetic patients with CKD(Fig. 3)

The mean eGFR was 55.3±15.9ml/ minute/ 1.73m^2 at baseline 1 and 54.0±15.8 ml/ minute/1.73m^2 at baseline 2 in amlodipine group（n=29）. The latter was lower compared to the former with a statistical significance（P<0.01）. Meanwhile, it was 59.9±14.7ml/ minute/ 1.73m^2 at baseline 1 and 58.5±15.4ml/ minute/ 1.73m^2 at baseline 2 in nifedipine group（n=17）. The latter was slightly lower compared to the former without a statistical significance. On the contrary, in amlodipine group, the mean eGFR increased significantly（P<0.01）from 54.0±15.8ml/ minute/ 1.73m^2 at the baseline 2 to 58.0±16.1ml/ minute/ 1.73m^2 at 6 month, 59.1±16.1 ml/ minute/ 1.73m^2 at 12 month, 60.6±15.7 ml/ minute/ 1.73m^2 at 18 month and 62.6±15.1 ml/ minute/ 1.73m^2 at 24 month during the second follow up period. And eGER at 12 month, 18 month and 24 month were significantly（P<0.01）higher compared to that at 6 month. In nifedipine group, it increased significantly（P<0.01）from 58.5±15.4ml/ minute/ 1.73m^2 at baseline 2 to 62.4±14.6ml/ minute/ 1.73m^2 at 6 month, 62.7±14.5 ml/ minute/ 1.73m^2 at 12 month, 62.7±14.5 ml/ minute/ 1.73m^2 at 18 month and 64.3±13.8 ml/ minute/ 1.73m^2 at 24 month during the second follow up period. And eGFR at 24 month was significantly（P<0.01）higher than that at 6 month during the second follow up period.

Changes of UAER by losrtan plus azelnidipine treatment in the type 2 diabetic patients with CKD(Fig. 4)

During the first 24 month period, the mean UAER was 287.6 ± 81.7mg /24hr at baseline 1 and 291.3 ± 81.9mg/24hr at the last assessment in amlodipine group（n=29）. The latter was significantly（P<0.01）higher than the former. By Los/Azl treatment, it was 208.3±57.9mg/24hr at 6 month, 184.0±58.0 mg/24hr at 12 month, 115.5±28.4 mg/24hr at 18 month and 80.8±19.2 mg/24hr at 24 month respectively. The mean UAER at the last assessment during the second 24 month follow up period was significantly（P<0.01）lower compared to that at the baseline 2. Meanwhile, in nifedipine group（n=17）, the mean UAER was 110.2±52.8 mg/24hr and 110.4±52.2 mg/24hr at baseline 1 and 2 respectively with-

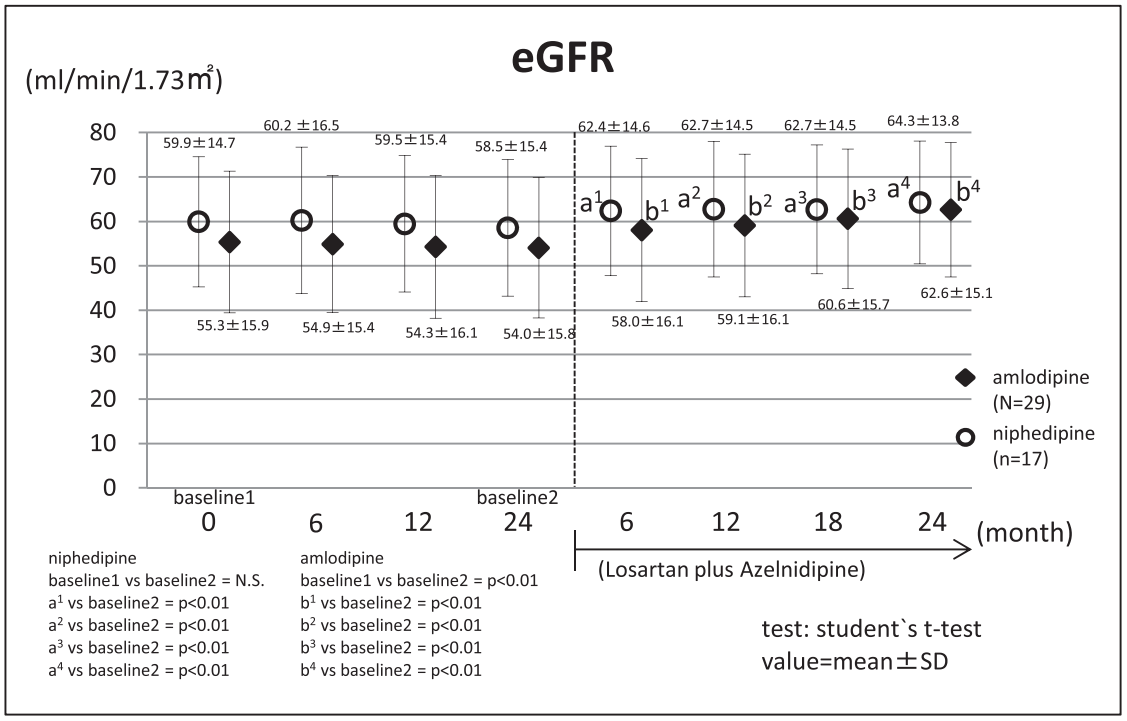

Fig. 3. Changes of eGFR treated by amlodipine and nifedipine during the first 24 month follow up period and those by treated by losartan plus azelnidipine during the second 24 month follow up period in the hypertensive type 2 diabetic patients with CKD

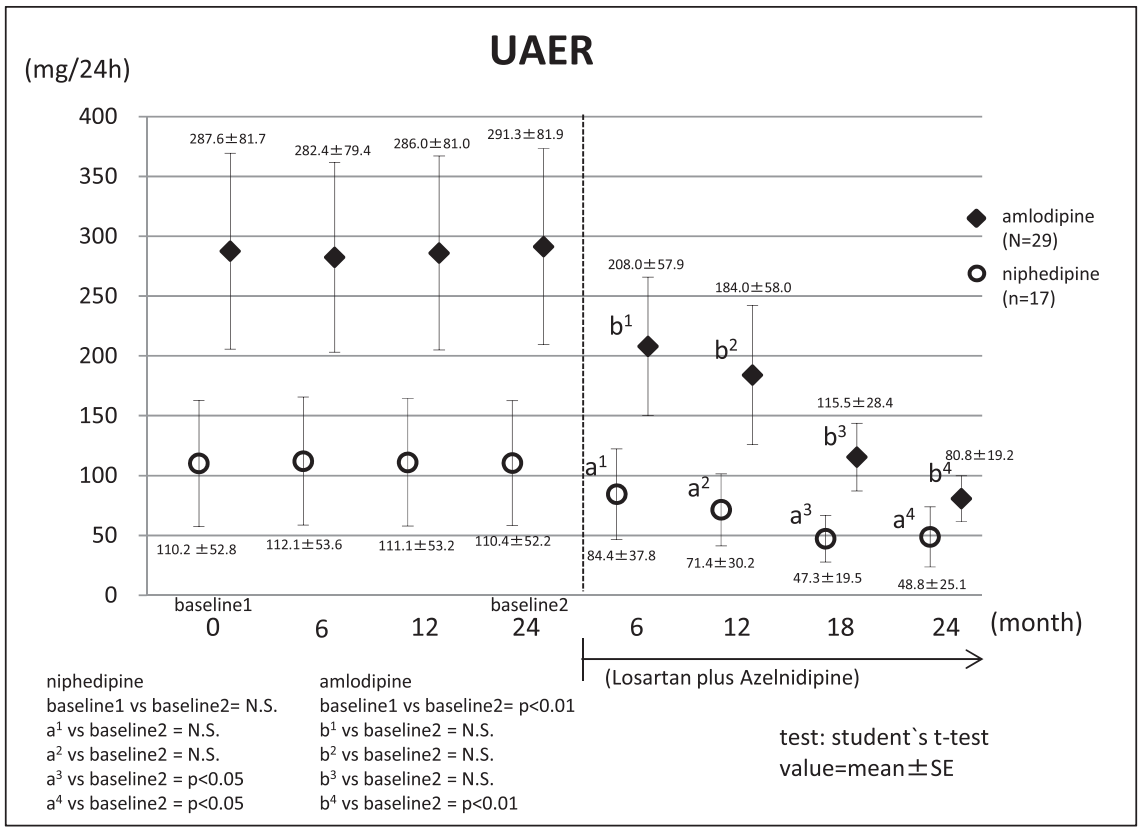

Fig. 4. Changes of UAER treated by amlodipine and nifedipine during the first 24 month follow up period and those treated by losartan plus azelnidipine during the second 24 month follow up period in the hypertensive type 2 diabetic patients with CKD

out a significant difference. During the second 24 month period, it was 84.4±37.8mg/24hr at 6 month, 71.4±30.2 mg/24hr at 12 month, 47.3±10.5 mg/24hr at 18 month and 48.8±25.1 mg/24hr at 24 month respectively. The mean UAER at 18 month and 24 month were significantly（P<0.05）lower compared to the baseline 2. The mean UAER slightly decreased during the second 24 month follow up period, although there was not a significant difference.

Percent changes in eGFR of all 46 patients before and after losartan plus azelnidipine treatment(Fig. 5)

In evaluating the percent changes in eGFR of all 46 patients in amlodipine and nifedipine groups before Los/Azl treatment, it was -0.3±4.3% at 6 month and -2.4±4.8% at 24 month with a significant difference（P<0.01）. However, after Los/Azl treatment, it was +5.4±10.9% at 6 month, +7.0±11.3% at 12 month, +9.0±12.0% at 18 month and +13.2.0±15.9% at 24 month respectively. Each value significantly（P<0.01）increased compared to the baseline 2.

Percent changes in UAER of all 46 patients before and after administration of Losartan plus Azelnidipine treatment(Fig. 6)

Of all 46 patients both in amlodipine and nifedipine groups before administration of Los/Azl, percent changes in UAER was 3.3±11.8% and 6.0±12.8% at 6 and 24 month respectively. Meanwhile, after Los/Azl treatment, it was -15.2±19.7%, -24.8±22.5%, -37.3±25.3% and -48.7±25.3% at 6, 12, 18 and 24 month respectively. Each value significantly（P<0.01）decreased compared to the baseline 2.

Cardiovascular end points

Between January in 2007 and January in 2009, 4 patients reached the composite end point of cardiovascular complications in nifedipine group. Meanwhile, ischemic cardiovascular disease was seen in 1 patient and cerebrovascular disease was recognized in 1 patient in amlodipine group. Cardio- and cerebrovascular diseases occurred in the patients who had preexisting coronary heart disease or cerebrovascular diseases. Meanwhile, there were no cases of cardio- and cerebrovascular diseases during the study period.

Adverse effect during treatment by Los/Azl

Serious adverse events were not reported in all patients treated by both of losartan and azelnidipine and drug-related adverse events such as hypotension and dizziness did not occur.

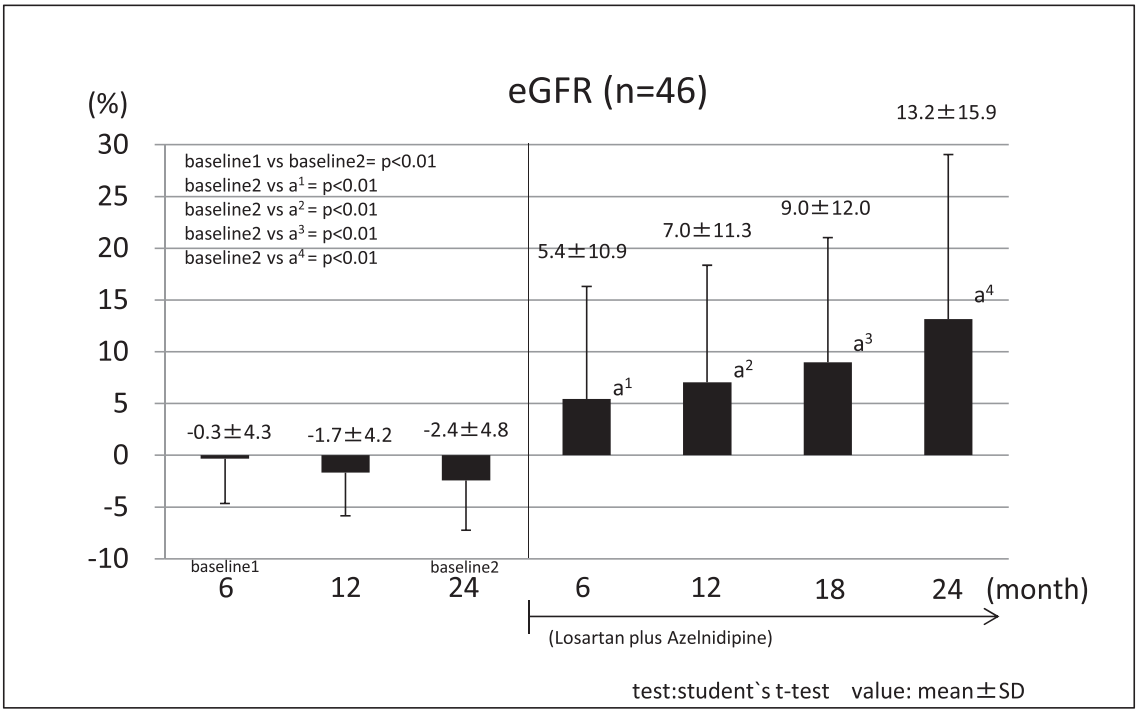

Fig. 5. Percent changes in eGFR of all 46 patients before and after Losartan plus Azelnidipine（Los/Azel）treatment

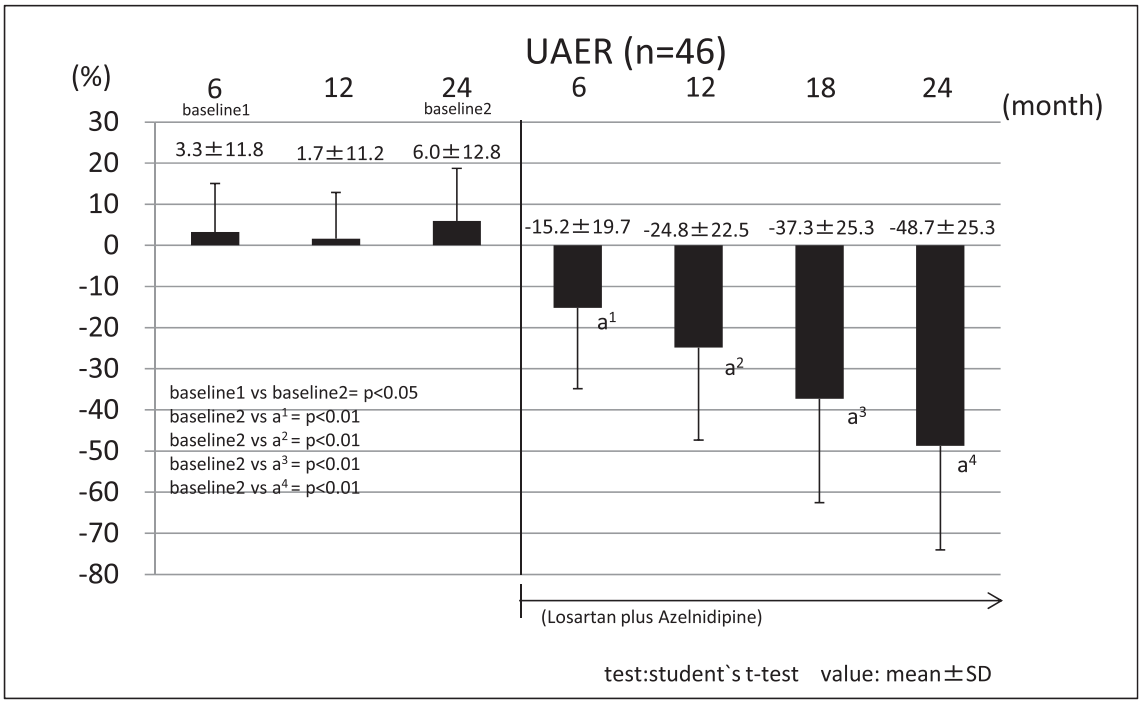

Fig. 6. Percent changes in UAER of all 46 patients before and after of Losartan plus Azelnidipine（Los/Azl）treatment

DISCUSSION

The 2007 guideline from the European Society of hypertension and the European Society of Cardiology（ESH/ESC）as well as the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure（JNC7）have recognized the following measures of CKD as risk factors for cardiovascular morbidity and mortality: the presence of microalbuminuria defined as a persistent elevation of UAER in the range 30-299mg/gl and an eGFR less than 60ml/min/m^2. Even in eGFR greater than or equal to 60ml/min/m^2, the presence of microalbuminuria may be a marker of subclinical organ damage. With the prevalence of diabetes, hypertension and obesity, the prevalence of CKD has increased up to and affected several million people worldwide［13］. The prognostic value of microalbuminuria has been shown to be superior to that of C-reactive protein. In a prospective community study, the 5-year follow-up of 626 elderly patients without cardiac or renal failure who provided serum and urine samples found that, after adjustment for age, sex, smoking, diabetes mellitus, hypertension or ischemic heart disease, total cholesterol, and serum creatinine level, the hazard ratio［95% confidence interval（CI）］for mortality for values above the 80th percentile for the UAER was 1.9（1.2-3.0）［14］. Thus, excessive urine protein including microalbunuria is important to predict cardiovascular or cerebrovascular diseases in diabetic patients with CKD.

In general, ACEIs and ARBs are possible to decrease proteinuria and retard disease progression to end stage renal disease（ESRD）［5-7］. Although the target blood pressure for patients with CKD is less than 130/80 mmHg, this target cannot be achieved in many patients by treatment with a single drug, and multidrug therapy is often required. Most clinical trials involving patients with hypertension who are at high risk for cardiovascular events have shown that treatment with multiple antihypertensive medications is necessary to attain recommended blood pressure goals. However, which combination therapy is most beneficial in terms of protection of pivotal organs remains unknown. In another study, it was pointed out that concomitant use of RAS inhibitors and CCBs reduced more effectively cardiovascular events than did concomitant use of RAS inhibitors and diuretics［15］.

There is a large body of evidence supporting improvement in renal outcomes with ARBs. Four

ARBs, namely losartan, irbesartan, valsartan and telmisartan, have shown efficacy in slowing the onset of kidney disease and/or slowing progression of CKD in hypertensive patients with and without diabetes. Among them, there are some reports which suggest that losartan is one of the ARBs to have been shown to be effective in reducing UAER and inhibiting the disease progression from microalbuminuria to macroalbuminuria [16-18]. In this point, losartan is a reasonable ARB for the hypertensive type 2 diabetic patients with CKD.

Recently it has been reported that azelnidipine is the most beneficial for organ protection in a rat model of metabolic syndrome and that azelnidipine successfully decreases radical oxidative stress (ROS) production apparently by suppressing NADPH oxidase activity inside glomeruli and endothelial cells of the thoracic aorta. This phenomenon showed azelnidipine directly suppressed activation of NADPH oxidase induced by high glucose in human glomerular endothelial cells [19]. Some CCBs have a potential to reduce cardiovascular events by improving endothelial function via an antioxidative effect on endothelial cells and in kidney [20]. Azelnidipine inhibits the RAS and inactivates sympathetic nerve and decreases insulin resistance [20].

In addition, azelnidipine inhibited endothelial cell damage induced by tumor necrosis factor alpha or angiotensin II through its antioxidative properties via suppression of NADPH [21]. The advanced glycation end products (AGE)-receptor AGE (RAGE) axis has been known to contribute to renal damage through the NADPH oxidase-derived oxidative stress generation. Azelnidipine treatment was reported to prevent glomerulosclerosis and tubulointerstitial injury in exogenously AGE-injected rats [22]. These observations suggest that azelnidipine may block the AGE-RAGE axis in the kidney and exert renal protective properties by inhibiting NADPH oxidase activity.

ACEIs are responsible for the conversion of angiotensin I to angiotensin II, as well as for the catalytic degradation of bradykinin [3]. The renal protection associated with ACEI has been shown in rats to be the result of diminished generation of angiotensin and increased bradykinin concentrations. On the contrary, renal protection of ARBs in nephropathy due to type 2 diabetes, the important pharmacologic action appears to be the restriction of intrarenal angiotensin activity. The mechanism of renal protection by agents that block the action of angiotensin II may be complex, involving hemodynamic factors that lower the intraglomerular blood pressure, the beneficial effects of diminished proteinuria, and decreased collagen formation that may be related to decreased stimulation of transforming growth factor by angiotensin II [24]. In a meta-analysis [25], an eGFR below 60ml/ minute/1.73m^2 was predictive of death from any cause and of death from cardiovascular causes, but as in the present trial, there was a little relationship between cardiovascular events and eGFR. This supports the notion that in the hypertensive type 2 diabetic patients with CKD, the observed small fall in the eGFR might be important in predicting ESRD complicated with cardiovascular and cerebrovascular diseases. In this study, the mean value of blood pressure at the first 24 month in amlodipine group was significantly higher than the in nifedipine group. Whether this significant difference of the mean blood pressure at the first 24 month between two groups influenced renal functions such as eGFR or UAER during the second 24 month is not clear. This problem must be more precisely analyzed. But it is strongly suspected that Los/Azl treatment clearly improved renal functions during the second 24 month follow up period in both groups. These results strongly demonstrated that Los/Azl treatment was an effective treatment method to the improvement of renal function of CKD without a connection of the previous treatment. And it was also suspected that the improvement of renal functions by Los/Azl was due to not only well control of systemic blood pressure but also another factors such as remodeling of renal small vessels or cytoprotective function to renal small vessels. Los/Azl treatment decreased UAER and increased eGFR significantly and did not induce any CKD-related cardiovascular and cerebrovascular complications during the second 24 month follow up period. It was possible that losartan not only decreased intraglomerular blood pressure but also protected microvasculature of the heart, vessels, and kidney by NO production and might support the preservation of cardiovascular and renal function.

In general, it has been recognized that the decrease in UAER by ARBs is due to the improvement of glomerular hyperfiltration and that the decrease in GFR as well as blood pressure is accompanied. However, in the present study, the combination therapy of Los/Azl successfully led to the improvement not only UAER but also eGFR. Although this mechanism is not clear, renoprotective effects of Los and Azl descrived above might be responsible. Further study is necessary to examinbe additive or synergistic effects of combination of Los/Azl in comparison with each single therapy.

There are some limitations in this study. First, comparing the effects of combination therapy of Los/Azl with those of each single therapy was not performed. Second, statistical significance was not achieved in cardiovascular and cerebrovascular diseases. Since the number of patients is small in this study, larger prospective study is needed to figure out the efficacy of Los/Azl therapy. Taken together, the combination therapy of Los/Azl might be clinically useful in hypertensive type 2 diabetic patients with CKD.

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