Comparative effects of enarapril versus losartan on the prevention of diabetic nephropathy in type 2 diabetes patients with microalbuminuria

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Abstract

A prospective randomized open-labeled study was performed to compare the renoprotective effects of enarapril and losartan on the development of microalbuminuria in type 2 diabetic patients with hypertension. Diabetic patients who have hypertension and microalbuminuria at base line (n=19) were recruited. Enarapril (n=11) or losartan (n=8) was randomly chosen by envelope methods and was prescribed for one year. At the end of this study, the blood pressure of patients in these two groups decreased significantly. Urine albumin-creatinine ratio (U-ACR) also decreased in these two groups, however, U-ACR of enarapril group was not significantly different from that of losartan group at any time of this study. Body mass index, HbA1c, blood pressure, and serum lipid profiles were not significantly different between the two groups. From these results, we conclude that the effects of enarapril and losartan on the development of microalbuminuria in type 2 diabetic patients along with hypertension seem to be equivalent in terms of clinical renoprotection.

Key words: *Renoprotective effects; diabetic nephropathy; microalbuminuria; angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker*

Introduction

Diabetic nephropathy is a major cause of premature morbidity and mortality in both type 1 and type 2 diabetes mellitus.[1,2] A panel of reports have demonstrated that angiotensin converting enzyme inhibitor (ACEi) had renoproctive effects on the progression to overt proteinuria from microalbuminuria in type 1 diabetes patients[3,4] and type 2 diabetes patients.[5,6] Enarapril (ACEi) treatment has shown renoprotective effects in type 2 diabetes patients with normal blood pressure.[7,8] Recently, a line of reports have shown that angiotensin II receptor blockers (ARB) have renoprotective effects on the development of diabetic nephropathy in type 2 diabetes patients suffering from hypertension.[9] The results of RENAAL study involving the angiotensin II receptor blocker, losartan,[10] and the Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)[11] show that ARBs postpone the progression of type 2 diabetic renal disease at all stages, ranging from microalbuminuria to overt nephropathy and also End-stage renal disease (ESRD). The RENAAL study also showed that losartan improves renal outcomes in patients with type 2 diabetes mellitus and nephropathy over and above that attributable to blood pressure control alone.[10]

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It is well documented that inhibition of the renin-angiotensin system has a renoprotective effect in diabetic patients suffering from hypertension, or even in those with normal blood pressure. However, it is unclear which agent, ACEi (enapranil) or ARB (losartan) has a more beneficial effect on the development and progression of diabetic nephropathy. Recent study showed that combined therapy of ACE inhibitor and angiotensin II receptor blocker has better effects on the development of non-diabetic renal disease compared with monotherapy.[12] Thus, this study was initiated to compare the effects of an ACE inhibitor and an angiotensin II receptor blocker on the development of diabetic nephropathy in patients with type 2 diabetes with microalbuminuria. Type 2 diabetes patients suffering from hypertension were examined in a prospective randomized open-labeled study.

Patients and Methods

Subjects

In this study, elderly patients with type 2diabetes and hypertension, who showed microalbuminuria, were recruited (7 men, and 12 women). The average age was 66.0± 8.5 years. This study was approved by the Ethical Committee of Gunma University. All patients gave written informed consent. Diabetic nephropathy was diagnosed by the measurement of urinary concentration of albumin by radioimmunoassay as previously described.[13] Urine albumin creatinine ratio (UACR) (mg/g.Cr) was calculated using timed overnight urine. UACR less than 30 mg/g.Cr, UACR between 30 -300 mg/g.Cr g/min, and UACR more than 300

mg/g.Cr were classified as normo-, micro-, and macroalbuminuria, respectively.[14] To confirm the classification, the measurement of UACR was performed at least twice before the beginning of this study. Patients, who showed microalbuminuria due to other disease, such as congestive heart failure, glomerulonephritis, urinary tract infection, and other diseases, were excluded. Patients, who had short duration of diabetes (≤ 3 years) were also excluded. No patients received renal biopsy in this study. Glycemic control was assessed by glycosylated hemoglobin (HbA1c) levels every month, which were measured by high-performance liquid chromatography. Hypertension was designated as mean systolic blood pressure higher than 140 mmHg, or mean diastolic blood pressure higher than 90 mmHg at the position of sitting at the time of hospital visit. Patients on oral anti-hypertensive agents were also classified as hypertensives. All patients visited the Clinic every month and have been conventionally treated for the aim of maintaining HbA1c levels below 7.0 %, and blood pressure below 140/90 mmHg throughout the course of this study. Serum concentration of total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol were measured by standard laboratory methods. Diabetic retinopathy was assessed by ophthalmologists and graded as non-diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), and pre-proliferative diabetic retinopathy (pre-PDR) and proliferate diabetic retinopathy (PDR) according to the diagnostic classification by Davis *et al.*[15]

At the beginning of this study, patients were divided into two groups according to the envelope method by using a table of random numbers. Thus, patients were randomly prescribed with enarapril, or losartan.

Data were analyzed by using the SPSS statistical software (SPSS Inc., Chicago, IL). Data were presented as means ± SD, median (range) or prevalence (%). Comparison between groups was performed with Student's T test or the Mann-Whitney U-test. For multiple comparison, the one-way analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) test was used. Fisher's exact test and $\chi 2$ test were performed for comparison between groups of discrete variables. Probability (P) value <0.05 was considered significant.

Results

Table 1 shows the clinical characteristics of the subjects at base line. At base line, age, sex, duration of diabetes, body mass index (BMI), glycosylated hemoglobin (HbA1c) levels, systolic and diastolic pressure, serum lipid profile were not significantly different between subjects prescribed with enarapril, and those with losartan. BMI, blood glucose levels, and lipid profiles, at base line were not significantly different from those at 12 months in both subjects with enarapril and those with losartan. Systolic and diastolic blood pressure in subjects with enarapril at beginning, were 150.1 ± 4.0, and 83.6 ± 7.7, respectively. Systolic and diastolic blood pressure in subjects with enarapril at 12 months were 131.7 ± 7.6, and 75.6 ± 6.2, respectively, and they were significantly lower

Table 1: Baseline characteristics in patients using enarapril and losartan

	Enarapril	Losartan	P
Male/Female	4/7	3/5	NS
Age (Year)	67.2 ± 10.6	65.5 ± 5.0	NS
BMI	23.7 ± 4.0	21.4 ± 2.0	NS
sBP (mmHg)	150.1 ± 10.1	146.4 ± 13.8	NS
dBP (mmHg)	83.6 ± 7.7	78.9 ± 12.6	NS
BUN (mmol/l)	6.46 ± 1.75	6.18 ± 0.54	NS
Creatinine (μmol/l)	60.1 ± 23.9	64.5 ± 12.4	NS
Potassium (mmol/l)	4.46 ± 0.47	4.51 ± 0.46	NS
TC (mmol/l)	5.38 ± 1.17	5.10 ± 0.38	NS
TG (mmol/l)	1.56 ± 0.49	1.37 ± 0.62	NS
HDL (mmol/l)	1.42 ± 0.33	1.60 ± 0.46	NS
Insulin therapy (%)	27.2	37.5	NS
CCB (%)	18.2	25.0	NS

BMI= body mass index; sBP = systolic blood pressure; dBP = diastolic blood pressure; BUN = blood urea nitrogen; TC = total cholesterol; TG = triglycerides; HDL = high density lipoprotein; CCB = calcium channel blocker

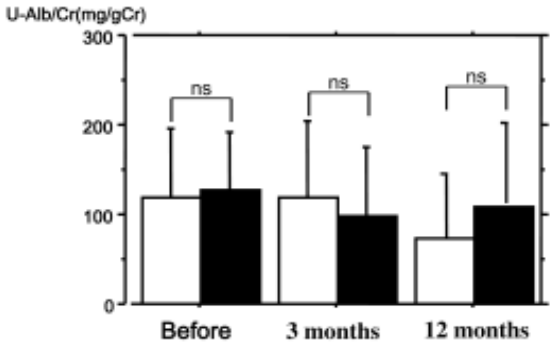

Figure 1: Urine albumin creatinine ratio in subjects with enarapril (Open square) at base line, 3 month, and 12 month, were 118.0 ± 78.7 mg/g.Cr, 119.5 ± 84.7 mg/g.Cr, and 77.6 ± 70.0 mg/g.Cr, respectively. Urine albumin creatinine ratio in subjects with losartan (Closed square) at base line, 3 month, and 12 month, were 128.1 ± 62.8 mg/g.Cr, 97.0 ± 78.0 mg/g.Cr, and 107.3 ± 94.8 mg/g.Cr, respectively. ACR in these two groups were not significantly different at any time during this study.

than those at baseline in subjects with enarapril. Whereas, systolic and diastolic blood pressure in subjects with losartan at beginning, were 146.4 ± 13.8, and 78.9 ± 12.6, respectively. Systolic and diastolic blood pressure in subjects with losartan at 12 months was 133.7± 8.3, and 77.3±3.9, respectively. Although systolic blood pressure at 12 months was significantly lower than that at base line in subjects with losartan, diastolic blood pressure at 12 months was not significantly lower than that at base line in subjects with losartan (Table 2). Urine albumin creatinine ratio in subjects with enarapril at base line, 3 month, and 12 month, were 118.0 ± 78.7 mg/g.Cr, 119.5 ± 84.7mg/g.Cr, and 77.6 ±70.0 mg/g.Cr, respectively. Urine albumin

Table 2: Systolic and diastolic blood pressures, HbA1c, BUN, creatinine and potassium at baseline and after 12 months in patients using enarapril and losartan

	Enarapril		Losartan	
	Baseline	12 Months	Baseline	12 Months
sBP (mmHg)	150.1 ± 10.1	131.7 ± 7.6*	146.4 ± 13.8	133.7 ± 8.3*
dBP (mmHg)	83.6 ± 7.7	75.6 ± 6.2*	78.9 ± 12.6	77.3 ± 3.9
HbA1c (%)	8.2 ± 2.1	7.7 ± 2.1	8.3 ± 1.7	8.3 ± 1.2
BUN (mmol/l)	6.46 ± 1.75	6.35 ± 0.96	6.18 ± 0.54	6.89 ± 0.61
Creatinine (μmol/l)	60.1 ± 23.9	66.3 ± 20.3	64.5 ± 12.4	70.7 ± 12.4
Potassium (mmol/l)	4.46 ± 0.47	4.40 ± 0.39	4.51 ± 0.46	4.47 ± 0.25

sBP = systolic blood pressure; dBP = diastolic blood pressure; BUN = blood urea nitrogen. * Signigicant

creatinine ratio in subjects with losartan at base line, 3 month, and 12 month, were 128.1 ± 62.8 mg/g.Cr, 97.0 ± 78.0 mg/g.Cr, and 107.3 ± 94.8 mg/g.Cr, respectively. The urine albumin creatinine ratio appeared to improve in subjects with enarapril, and losartan, although they were not significantly different. UACR in subjects with enarapril were not significantly different from those in subjects with losartan.

Discussion

In this one-year open-labeled, prospective study, we show that the renoprotective effect of ACE inhibitor, enalapril, is not significantly different from that of ARB, losartan, on the progression of microalbuminuria in Japanese patients with type 2 diabetes mellitus along with hypertension.

There is a clear evidence that pharmacological blockade of the renin-angiotensin system (RAS) with angiotensin converting enzyme inhibitors (ACEi)[3,4,5,6,7,8] or angiotensin receptor blockers (ARB)[11,12] reduces proteinuria and slows down the progression of renal disease in diabetic and non-diabetic nephropathies. The RENAAL study has specifically shown that a beneficial effect by ARB seems to be beyond blood pressure control.[11]

The precise mechanisms by which ACEi and/or ARB induce a protective effect on the progression of diabetes nephropathy have been documented through various points of view. An ACEi or an ARB suppresses renal expression of the p47phox component of NAD(P)H oxidase and eNOS with increased indices of systemic and renal oxidative stress, and then prevents the development of proteinuria, independent of blood pressure or blood glucose levels.[16] The ACE inhibitor, enalapril and the ARB, losartan treatment were equally effective in reducing blood pressure, urine albumin creatinine excretion as well as urine glycosaminoglycan excretion and preserving red blood cell anionic charge in hypertensive type 2 diabetic patients. ACE inhibition and ARB may have favorable effects on preserving glomerular anionic content in hypertensive diabetic patients.[17] Enalapril and losartan are equally effective in reversing NAME-induced endothelial dysfunction, the beneficial effect of enalapril on the endothelial vasodilator function in L-NAME-treated rats is mediated by bradykinin B(2)-receptor activation, and the enhanced endothelial generation of prostacyclin induced by losartan in L-NAME rats is also mediated by bradykinin B(2)-receptor activation.[18] Moreover, renin-angiotensin system blockade has been reported to prevent the increase in plasma transforming growth factor beta 1, and reduces proteinuria and kidney hypertrophy in the streptozotocin-diabetic rat.[19] These data are in accordance with our study in which enalapril and losartan are equally effective in terms of clinical renoprotection in diabetic patients with hypertension. On the other hand, differential effects of RAS inhibitors have also been demonstrated. Seki et al, reported that differential effects of ACEi and ARB was associated with ACE gene polymorphisms in type 2 diabetic nephropathy.[20] ARB significantly decreased transforming growth factor-beta1 (TGF-beta) compared to ACEi in patients with the I/I genotype but not in patients with the D/I+D/D genotype. In this study, however, we did not examine the genetic polymorphisms of ACE gene.[21]

In the clinical search of new alternatives that could improve the antiproteinuric and nephroprotective effects of RAS inhibitors, the association of ACEi and ARB might prove to be more useful than monotherapy.[12] Recently, several authors have shown a more marked antiproteinuric effect of the dual blockade of the RAS versus ACEi or ARB alone in spite of a similar effect on blood pressure.[22,23] The combination of ACE-inhibitor and ARB therapy in patients with chronic proteinuric renal disease is safe, without clinically meaningful changes in serum potassium levels or glomerular filtration rate. Combination therapy also was associated with a significant decrease in proteinuria, at least in the short-term. Furthermore, treatment with ARB as well as ACEi postpones end-stage renal disease and reduces the rate of decline in renal function in patients with type 2 diabetes and nephropathy, but until now, there is no clear evidence of a superior beneficial effect of combination therapy versus maximal recommended dose of monotherapy regarding renal progression in type 2 diabetics at an early stage of nephropathy.

In this study, we did not assess the combination therapy rather than monotherapy, because our primary goal was to compare beneficial effect of ACEi versus ARB at ordinal dose in the prevention of diabetic nephropathy. Long-term clinical trials are needed and encouraged to further establish the significance of monotherapy in renal protection particularly in early stage of diabetic nephropathy.

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