

A comparison of the effects of losartan and ramipril on blood pressure, renal volume and progression in polycystic kidney disease: A 5-Year follow-up

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Abstract

Background: The major cause of hereditary renal failure is autosomal dominant polycystic kidney disease (ADPKD). Many factors affect renal progression in these patients. Among these, hypertension and an increase in renal volume are interrelated in terms of their effects on renal progression. We aimed to investigate the effects of losartan and ramipril on renal volume and progression in patients with ADPKD.

Materials and Methods: Data from 18 hypertensive patients with ADPKD were evaluated. Eleven of the 18 hypertensive patients were on losartan and 7 on ramipril treatment. Demographic parameters, use of antihypertensives and other medications, the course of blood pressure (BP), biochemical parameters, creatinine clearance (CrCL), findings at computed tomography and renal volume were recorded at baseline and at 1 and 5 years.

Results: Target BP values were maintained over 5 years. The annual decrease in CrCL was 1.33 mL/min in the losartan group compared with 6.59 mL/min in the ramipril group. There was no significant difference between the groups in terms of annual decrease in CrCL. Annual increase in renal volume was 252.04 cm³ in the losartan group and 167.36 cm³ in the ramipril group. There was no significant difference between the groups in terms of the increase in renal volumes at 1 and 5 years.

Conclusion: Our study demonstrated that losartan and ramipril provided effective BP control. In addition, the results of our study demonstrated that despite the increase in renal volume, losartan and ramipril may have regressed renal progression via other factors. Hippokratia 2012; 16 (2): 143-148

Key words: autosomal dominant polycystic kidney disease, losartan, renal volume, ramipril, renal progression

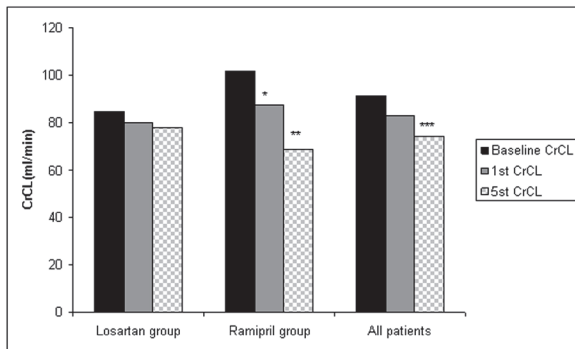
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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease causing end-stage renal failure. ADPKD has an incidence of approximately 1/500-1000 in the USA¹. The disease is characterized by continuous expansion of multiple cysts originating from renal tubules. Renal damage often cannot be identified until the third or fourth decade^{2,3}. Hypertension and an increase in renal volume are interrelated with respect to their effects on pathogenesis and renal progression. Although there is no consensus regarding the pathogenesis of hypertension in ADPKD patients, it has been suggested that the renin-angiotensin system (RAS) is activated due to the pressure induced by expanded renal cysts⁴⁻⁶. This study aimed to evaluate the effects of RAS blocking agents (losartan and ramipril) on blood pressure (BP) control, and also their clinical effects on renal volume and renal progression. We also compared the effects of losartan and ramipril on these parameters.

Materials and Methods

We obtained data for patients aged 18-70 with creatinine clearance (CrCL) levels 30 ml/min or higher from the Karadeniz Technical University Clinic of Nephrology

between 2003 and 2009. The hypertension limit before patients began treatment was $\geq 140/90$ mmHg. Patients were started on antihypertensive treatment in our clinic, initial treatment consisting of losartan or ramipril, with dose titration performed until target blood pressure was achieved. Subjects given amlodipine 5-10 mg and doxazosin 4-8 mg treatment, and regularly monitored at 3-month intervals were included in the study. Patients with diabetes mellitus, congestive heart failure, liver disease, other renal disorders or psychiatric diseases, pregnant patients, those using cigarettes, caffeine, nonsteroidal anti-inflammatory drugs, or who had had a contrast test performed or had undergone surgery over the preceding 5-year period were excluded. Biochemical parameters, including levels of blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), glucose, albumin, uric acid, calcium, phosphorous, low-density lipoprotein cholesterol (LDL-C), 24-hour urinary creatinine, protein, and hematocrit levels for patients meeting the inclusion criteria were recorded at baseline, and at 1 and 5 years. CrCL calculated using the 24-h urinary creatinine and simultaneous blood creatinine level was adjusted for a body surface area (BSA) of 1.73 m².



* Baseline versus 1 st year of Ramipril group ($p = 0,043$)
 ** Baseline versus 5 st year of Ramipril group ($p = 0,028$)
 *** Baseline versus 5 st year of All patients ($p = 0,030$)

Figure 1: Five year follow-up of CrCL in the ramipril and losartan groups and all patients.

CrCL was calculated using the formula $UV / P \times 1.73 / BSA$

U: Concentration of creatinine in urine in mg/dL

V: Volume of urine in ml divided by time of collection in minutes

P: Body surface area

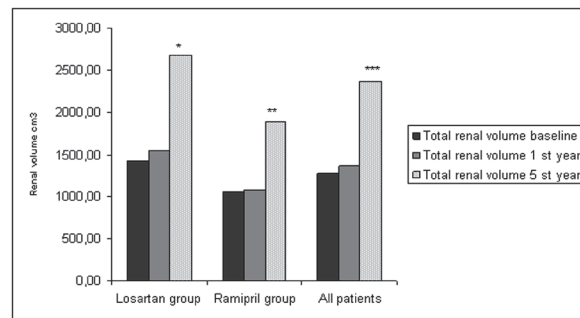
BSA was calculated using the Dubois formula:
 $BSA = [(weight \text{ in kg})^{0.425} \times (height \text{ in cm})^{0.725}] \times 0.007184$.

Biochemical parameters were measured with a Roche modular autoanalyzer using specific solutions. Patients' ages, gender, duration of hypertension, use of medications and BP course were also recorded (Table 1). Non-contrast computed abdominal tomography (Siemens Volume 700 m device) performed for various indications was re-evaluated by two independent blinded radiologists, and renal volume was computed using the method described by Breiman et al⁷. Patients were divided into losartan or ramipril groups according to their use of the antihypertensive drugs.

Eighteen patients (13 females and 5 males) with a mean age of 50.16 ± 8.95 years, and 11 receiving losartan and 7 ramipril treatment, were included in the study. In the losartan group, 7 patients were receiving losartan (100 mg), 3 patients were receiving losartan (100 mg) + amlodipine (5 mg), and 1 patient was receiving losartan (100 mg) + amlodipine (10 mg) + doxazosin (4 mg bid). In the ramipril group, 1 patient was receiving ramipril (2.5 mg), 1 patient was receiving ramipril (5 mg), 3 patients were receiving ramipril (10 mg), and 2 patients were receiving ramipril (10 mg) + amlodipine (5 mg).

Statistical Analysis

Statistical analysis was performed using SPSS 12.0. Student's t-test was used to compare mean BP, CrCL, creatinine level, and renal volumes of the losartan and ramipril groups. Comparison of the changes in these parameters from baseline to 1 and 5 years was performed using the Wilcoxon signed-ranks test. Results are expressed as mean \pm standard deviation (SD). Significance was set at $p < 0.05$.



* Baseline versus 5 st year of Losartan group ($p = 0,021$)
 ** Baseline versus 5 st year of Ramipril group ($p = 0,028$)
 *** Baseline versus 5 st year of All patients ($p = 0,001$)

Figure 2: Five year follow-up of renal volume in the ramipril and losartan groups and all patients.

Results

The effect of treatment on blood pressure

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the study population were 156.11 ± 20.33 and 97.50 ± 11.14 mmHg, respectively, at baseline. Eleven patients were on losartan and 7 on ramipril treatment. SBP and DBP were 158.18 ± 16.62 and 99.09 ± 13.75 mmHg, respectively, in the losartan group and 152.85 ± 26.27 and 95.00 ± 5.00 , respectively, in the ramipril group. There was no significant difference between the groups in terms of BP measurements at baseline (Table 1). Target BP values ($\leq 130/80$ mmHg) were achieved at the end of 1 year, and this effect was maintained at the end of 5 years in both groups. There was no significant difference between the groups in terms of BP measurements at 1 and 5 years.

The effect of treatment on renal progression

Mean CrCL in our 18 patients was 91.38 ± 46.19 mL/min at baseline, 82.98 ± 40.11 mL/min at the end of 1 year, and 74.47 ± 46.30 mL/min at the end of 5 years. While there was no significant decrease in CrCL at the end of 1 year ($p = 0.166$), a significant decrease was noted at the end of 5 years compared to the baseline ($p = 0.030$) (Figure 1), (Table 2). The mean decrease in CrCL was 8.39 mL/min at the end of 1 year, with an annual decrease in CrCL of 2.12 mL/min in the following 4 years. An annual decrease in CrCL of 3.38 mL/min was observed in the 18 patients over a 5-year period.

Mean CrCL at baseline was 84.74 ± 50.14 mL/min in the losartan group and 101.81 ± 40.59 mL/min in the ramipril group. There was no significant difference between the groups in terms of CrCL measurements at baseline (Table 1). The decrease in CrCL in the losartan group was 4.78 mL/min at the end of 1 year and 0.47 mL/min/year in the following 4 years, with an annual decrease in CrCL of 1.33 mL/min over a 5-year period (Table 3). The decrease in CrCL in the ramipril group was 14.09 mL/min at the end of 1 year and 4.72 mL/min/year in the following 4 years, with an annual CrCL decrease of 6.59 mL/min/1.73 m²

Table 1: Baseline patient characteristics.

	Losartan (n:11)	Ramipril (n:7)	All patients (n:18)	P value
Age	51.18±10.46	48.57±6.32	50.16±8.95	NS
Gender (Female/male)	9 / 2	4 / 3	13/5	
BMI	28.99±6.13	29.58±2.93	29.22±50.02	NS
BSA	1.81±0.12	1.79±0.06	1.80±0.04	NS
Hypertension year	8.40±4.70	5.20±3.40	7.19±4.51	NS
SBP (mmHg)	158.18±16.6	152.85±26.27	156.11±20.33	NS
DBP (mmHg)	99.00 ±13.70	95.00±5.00	97.50±11.14	NS
MAP (mmHg)	118.70±13.90	114.24±11.00	116.99 ±12.72	NS
Hematocrit (%)	38.60±4.50	39.90±3.60	39.05±4.20	NS
Creatinine (mg/dL)	1.19±0.54	1.15±0.48	1.17±0.50	NS
Uric acid (mg /dL)	5.46±1.60	5.90±1.14	5.65±1.46	NS
Calcium (mg/dL)	9.60±0.49	9.90±0.47	9.80±0.49	NS
Phosphor (mg/dL)	3.52±0.72	3.50±0.38	3.53±0.60	NS
Albumin (g/dL)	4.45±0.25	4.3±0.28	4.39±0.26	NS
LDL (mg/dL)	137.09±34.40	140.80±12.20	138.55±27.48	NS
CrCL (mL/min)	84.74±50.14	101.81±40.59	91.38±46.19	NS
Right renal volume (cm ³)	762.90±584.16	425±182.4	631.50±491.13	NS
Left renal volume (cm ³)	652.63±558.33	629.14±527.5	643.50±530.79	NS
Total renal volume (cm ³)	1415.54±1125.00	1054.14±684.96	1275±971.05	NS

Statistical significance was p<0.05

Data is given as mean ± SD

BMI: Body mass index, BSA: Body surface area, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, LDL: Low density lipoprotein

P value: Losartan versus Ramipril

Table 2: Five-year follow-up of All patients.

	Baseline	1st year	5 st year	P 0-1	P 0-5	P 1-5
SBP(mmHg)	156.11±20.33	117.22±8.94	122.50±16.29	< 0.0001	< 0.0001	NS
DBP(mmHg)	97.50±11.14	73.33±4.85	74.88±9.00	< 0.0001	< 0.0001	NS
Cr (mg/dL)	1.17±0.50	1.21±0.44	1.58±1.30	NS	NS	NS
CrCL (ml/min)	91.38±46.19	82.98±40.11	74.47±46.30	NS	0.030	NS
RRV (cm ³)	631.50±491.13	700.88±557.02	1188.81±638.82	0.043	< 0.0001	0.001
LRV (cm ³)	643.50±530.79	663.66±498.88	1179.76±760.15	NS	0.004	0.001
TRV (cm ³)	1275.00±971.05	1364.55±1002.75	2370.55±1313.52	NS	0.001	< 0.0001

Statistical significance was p<0.05

Data is given as mean ± SD

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CrCL: Creatinine clearance, RRV: Right renal volume, LRV: Left renal volume, TRV: Total renal volume, Cr: Creatinine,

P 0-1: Baseline versus 1st year

P 0-5: Baseline versus 5th year

P 1-5: 1st year versus 5th year

over a 5-year period (Figure 1)(Table 4). There was no significant difference between the groups in terms of the mean change in CrCL from baseline to 1 year (p=0.53) or from baseline to 5 years (p=0.06).

The effects of treatment on renal volume

The mean total renal volume in the 18 patients was

1275±971.05 cm³ at baseline (Table 1). While there was no significant increase at the end of 1 year (p=0.325), a significant increase was observed at the end of 5 years (p=0.001) (Figure 2), (Table 2).

At baseline, the total renal volumes of the losartan and ramipril groups were 1415.54±1125.00 and 1054.14±684.96 cm³, respectively (Table 1). There was no significant differ-

Table 3: 5-year follow-up of Losartan group.

	Baseline	1 st year	5 st year	P:0-1	P:0-5	P:1-5
S B P (mmHg)	158.18±16.62	115.45±8.20	120.54±12.73	0.003	0.003	NS
D B P (mmHg)	99.09±13.75	72.72±4.67	73.00±7.50	0.003	0.007	NS
Cr (mg/dL)	1.19±0.54	1.23±0.49	1.74±1.62	NS	0.011	0.015
CrCL (mL/min)	84.74±50.14	79.96±45.80	78.07±54.50	NS	NS	NS
RRV (cm³)	762.90±584.16	847.18±659.01	1369.72±704.90	NS	0.013	0.021
LRV (cm³)	652.63±558.33	701.18±518.50	1303.18±704.60	NS	0.033	0.008
TRV (cm³)	1415.54±1125.00	1548.36±1141.69	2675.74±1322.00	NS	0.021	0.008

P 0-1: Baseline vs 1st yearP 0-5: Baseline vs 5th yearP 1-5: 1st year vs 5th year**Table 4:** Five-year follow-up of Ramipril group.

	Baseline	1 st year	5 st year	P:0-1	P:0-5	P:1-5
SBP (mmHg)	152.85±26.27	120.00±10.00	111.42±15.73	0.016	0.018	NS
DBP (mmHg)	95.00±5.00	72.28±5.34	74.28±9.75	0.014	0.017	NS
Cr (mg/dL)	1.15±0.48	1.18±0.38	1.32±0.55	NS	NS	NS
CrCL (mL/min)	101.81±40.59	87.72±31.94	68.81±32.59	NS	0.022	0.013
RRV (cm³)	425±182.40	471±233.00	905.14±417.52	NS	0.018	0.018
LRV (cm³)	629.14±527.5	604.7±500.45	985.81±658.93	NS	0.043	0.018
TRV (cm³)	1054.14±684.96	1075.71±719.1	1890.95±858.93	NS	0.028	0.018

P 0-1: Baseline vs 1st yearP 0-5: Baseline vs 5th yearP 1-5: 1st year vs 5th year

ence between the groups in terms of baseline renal volumes at baseline (Table 1). While there was no significant increase in renal volume at the end of 1 year in either group, significant increases were noted at the end of 5 years. The annual total increase in renal volume was 219.11 ± 228.98 cm³ in the entire study population, 252.04 ± 271.10 cm³ in the losartan group and 167.36 ± 144.74 cm³ in the ramipril group (Figure 2), (Tables 2,3,4). There was no significant difference between the two groups in terms of the increase in renal volumes at 1 and 5 years.

No patients had proteinuria in 24-h urine collection; this parameter was therefore not included in the statistical evaluation.

Discussion

Although chronic renal failure has a diverse etiological distribution, the major cause of hereditary renal failure is ADPKD, which constitutes 7%-10% of dialysis patients in the USA^{8,9}. Hypertension, left ventricular hypertrophy and increased renal volume are interrelated in terms of

their effects on pathogenesis and renal progression⁴⁻⁶.

Hypertension is quite common in this patient group and occurs in 60% of subjects before the development of renal dysfunction¹⁰. Although the pathogenesis of hypertension in patients with ADPKD has not been fully elucidated, the most favored mechanism is activation of the RAS resulting from ischemia due to pressure induced by expanded renal cysts¹¹. Although there is no consensus as to which group of medications to select for the treatment of hypertension, several authors have advocated that hypertension observed in polycystic kidney disease is renin-dependent hypertension and that blocking this system will be effective in BP control¹⁰⁻¹⁴. In an earlier study we showed that effective blood pressure was provided with RAS blocking in hypertensive ADPKD patients¹⁵. We also observed that target BP values ($\leq 130/80$ mmHg) were achieved at the end of 1 year, and that this effect was maintained at the end of 5 years via RAS blockade induced by two different drugs in the 18 hypertensive patients with ADPKD we retrospectively evaluated in this study.

One of the important factors affecting renal progression in polycystic kidney disease is the pressure exerted on surrounding parenchymal tissues induced by expanding cysts. Expansion of cysts and the resulting increase in renal volume has a negative influence on renal progression^{16,17}. Recent studies have therefore focused on therapeutic alternatives which prevent or retard cyst expansion. These studies have evaluated the effects of sirolimus, everolimus, vasopressin and somatostatin on renal volume and renal progression in ADPKD¹⁸. Serra et al, recently evaluated the effect of sirolimus on renal volume in ADPKD patients. In that study, during the 18-month study period the median total kidney volume increased by 99 cm³ in the sirolimus group and 97 cm³ in the control group. They found no evidence that sirolimus slowed polycystic kidney growth¹⁹. Additionally, Walz et al, recently evaluated the effect of everolimus on renal volume. Mean changes in total kidney volume were 101 ml and 239 ml for the everolimus group and 157 ml and 319 ml for the placebo group at years 1 and 2, respectively. Estimated GFR decreased by 8.9 ml per min in the everolimus group and 7.7 ml per min in the placebo group over the 2-year study period²⁰. In our study of 18 patients in whom renal volume assessment was performed using non-contrast computed abdominal tomography, mean renal volume at baseline was 1275 cm³ in the entire study population, 1415.54 cm³ in the losartan group and 1054.14 cm³ in the ramipril group. Annual increase in renal volume was 219.11 cm³ in all subjects, 252.04 cm³ in the losartan group and 167.36 cm³ in the ramipril group. Despite effective BP control, the increase in renal volume was greater compared to that in these other studies^{19,20}. However, there is currently no clear-cut information about the annual increase in renal volume in patients with ADPKD. Direct comparisons among current studies are rather difficult due to methodological differences in calculation of renal volume. Ethnic group differences are also present.

Moreover, it is likely that greater renal volume increase would occur in patients without treatment; however, assessment of renal volume increase without administration of antihypertensive treatment would not be ethical. In addition, although this was not statistically significant, the greater increase in the losartan group may be ascribed to greater, albeit statistically insignificant, basal TRVs.

Several studies have evaluated the effects of various antihypertensives on renal progression in patients with polycystic kidney disease. But these have not evaluated the effects of antihypertensives on renal volume. Ecder et al⁹ compared the effects of enalapril and amlodipine in hypertensive patients with polycystic kidney disease. After 5 years of follow-up, the mean annual decrease in CrCL was reported as 3.6 mL/min. Nutahara et al¹⁰ compared the effectiveness of amlodipine and candesartan in 49 hypertensive polycystic kidney patients and determined a mean annual decrease in CrCL of 5.5 mL/min in the amlodipine group and 1.6 mL/min in the candesartan group. In the polycystic patient subgroup of the Modification of Diet in Renal Disease (MDRD) study²¹, the annual GFR decrease was 5.9 mL/min in Group A (mean GFR, 37.8 \pm 9 mL/min) and 4.4 mL/min in Group B (mean GFR, 17.4 \pm 3.2 mL/min). There is also an ongoing HALT Progression of Polycystic Kidney Disease (PKD) trial evaluating the efficacy of dual vs. single RAS blockade, activated by cyst-induced surrounding tissue pressure, on cyst growth and renal progression²². In our study, mean CrCL in our 18 patients was 91.38 mL/min at baseline; the mean decrease in CrCL was 8.39 mL/min at the end of 1 year and 2.12 mL/min/year in the following 4 years, and an annual decrease in CrCL of 3.38 mL/min was observed over the 5-year period. The rapid decrease in GFR in the first year might be attributed to the sudden decrease in filtration due to RAS blockade. The mean decrease in CrCL was 2.12 mL/min in the following years. The decrease in CrCL in our study was considerably lower than that in those in previous studies. When the CrCL results were compared between the groups, CrCL was 84.74 mL/min in the losartan group and 101.81 \pm 40 mL/min in the ramipril group at baseline in our study. Comparing the losartan and ramipril groups, the mean decrease in CrCL was 4.77 vs. 14.09 mL/min at the end of 1 year, 0.47 vs. 4.72 mL/min in the following 4 years, and 1.33 vs. 6.59 mL/min over the 5-year period. There was no statistically significant difference between the groups in terms of changes in CrCL. However, the annual decrease in CrCL in the losartan group was lower compared to that reported in previous studies^{9,10,21}. Although no statistically significant difference was determined, the increase in renal volume in the losartan group was greater than that in the ramipril group. At this point, the question arises whether losartan has an independent renoprotective effect other than renal volume, since it has no beneficial effect on renal volume increase.

This evaluation of 5-year follow-up of 18 ADPKD patients has a number of limitations. One is the low patient number involved. This was due to the long follow-

up period, groups being homogeneous and the exclusion of comorbid conditions that might affect renal progression. Another limitation is that the study is retrospective. However, the patients we enrolled had commenced treatment in our clinic and attended regularly for follow-up. Finally, we performed renal progression with 24-h urine collection and CrCL calculated on that basis. We selected this method since these patient data were available. GFR could also have been calculated with MDRD.

In conclusion, RAS blockade, either by losartan or ramipril, provides effective BP control. Although renal volume increase cannot be prevented with these treatments, it may be that both losartan and ramipril retard renal progression. It would be more appropriate to wait for the results of the HALT PKD study investigating the efficacy of these two medications in a larger patient population in order to draw more definitive conclusions.

Conflict of interest

We received no financial support for this study and have no conflict of interest to report.

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