



MICROALBUMINURIA;

“COMPARISON OF LOSARTAN POTASSIUM AND LISINAPRIL IN TREATMENT OF PATIENTS WITH TYPE II DIABETES MELLITUS”

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ABSTRACT... Diabetes Mellitus is a rapidly increasing problem which is contributing to chronic illnesses like Cerebrovascular, Cardiovascular, Diabetic Retinopathy and End Stage Kidney Disease. These dreaded complications can be prevented if treated early. In patients with diabetes mellitus type 2, microalbuminuria is an independent and strong risk factor for cardiovascular mortality & morbidity and diabetic nephropathy. If diagnosed early, diabetic nephropathy can be treated at this stage. Angiotensin converting enzyme inhibitors (ACE Inhibitors) and Angiotensin Receptor Blockers (ARBs) are effective in prevention and treatment of microalbuminuria. **Material & Methods:** Study Design: randomized controlled trial. **Setting:** medical department, allied hospital, Faisalabad. **Duration of study:** Feb 2013 to July 2013. **Sample size:** 60 (30 in each group). **Sampling technique:** Non-probability consecutive sampling. **Results:** 60 patients were included in the study. 28(46.7%) were males and 32(53.3%) were females. Mean age of study population was 50.15 ± 7.27 years. Albumin creatinine ratio (mcg/mg) at start of study was 193 ± 67.5 in Losartan potassium group and 209.5 ± 72.00 in lisinopril group (independent sample t-test p value=0.302). Albumin creatinine ratio (mcg/mg) at 12 weeks of study was 36.33 ± 54.68 in Losartan potassium group and 72 ± 83.42 in lisinopril group (independent sample t-test p value = 0.056). Paired sample t test applied to both treatment groups and p value was found to be 0.0001 which is highly significant for both groups and shows that both drugs are effective in reducing microalbuminuria in both groups. Microalbuminuria was reduced significantly in 26 patients (86.7%) in Losartan potassium group and 20 patients (66.7%) in lisinopril group (p-value=0.067). **Conclusion:** It has been concluded from this study that lisinopril and Losartan potassium, both significantly reduce microalbuminuria in type 2 diabetes mellitus and there is no statistically significant difference in efficacy of these two drugs in reducing microalbuminuria in type 2 diabetes mellitus.

Key words: Type II diabetes mellitus, diabetic nephropathy, microalbuminuria, Lisinopril, Losartan Potassium

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INTRODUCTION

Diabetes mellitus is an rapidly growing problem that is contributing to so many chronic illnesses like Cerebrovascular, Cardiovascular (CV) diseases, Diabetic Retinopathy and End Stage Kidney Disease. These dreaded complications can be prevented if treated early. Type 2 diabetes mellitus is a common denominator of nephropathy and CV disease. In patients with type 2 diabetes, microalbuminuria is an independent and strong predictor for CV mortality and diabetic nephropathy. Diabetic nephropathy can be treated at this stage of the disease if detected early.

Microalbuminuria is abnormal urinary excretion of albumin 30 – 300 mg/24hours in a 24 hours, or an albumin to creatinine ratio (ACR ratio) greater than 30 mg/g in a 1st morning sample.¹

ACE inhibitors competitively block RAAS system decrease glomerular capillary pressure and slow progression from microalbuminuria to gross proteinuria.²

A similar effect of ARBs in slowing progression of microalbuminuria to gross proteinuria has been found in many studies.^{3,4,5}

Prevalence of microalbuminuria is 20–25% in people with type 2 diabetes mellitus.⁶ ACE inhibitors are recommended for the treatment of microalbuminuria in type I diabetes mellitus.⁷ Both ACE inhibitors and ARB's are effective in slowing progression of microalbuminuria.⁸ Losartan Potassium was found more effective for treatment of microalbuminuria in diabetes mellitus type II.

OBJECTIVE

We compared Lisinopril and Losartan Potassium in treatment of microalbuminuria in newly diagnosed Type II DM patients in terms of reduction in microalbuminuria.

OPERATIONAL DEFINITIONS

Type II Diabetes Mellitus

Diabetes Mellitus Type II was labelled as fasting blood sugar more than 126mg/dl and 2 hours after meal blood sugar more than 200mg/dl as measured by a standard laboratory on two occasions.

Newly diagnosed type II Diabetes Mellitus

Diabetes diagnosed less than 1 year ago.

Microalbuminuria

It was defined as albumin to creatinine ratio of 30–300 mcg/mg creatinine. In the early morning spot urine, albumin (mcg/L) and creatinine mg/L were measured and their ratio will be calculated.

Efficacy

Efficacy was measured in terms of 25% reduction in Albuminuria from the baseline at 12 weeks of treatment.

Null Hypothesis

There is no difference in the efficacy of between losartan potassium and lisinopril in treatment of microalbuminuria in patients of type II diabetes mellitus.

Alternate hypothesis

There is a difference in the efficacy of Losartan Potassium and Lisinopril in treatment of microalbuminuria in patients of type II diabetes mellitus.

MATERIAL AND METHODS

Study Design

Randomized Controlled Trial.

Setting

Medical Department, Allied Hospital, Faisalabad.

Duration of Study

Feb 2013 to July 2013

Sample Size

Sample size was calculated using WHO sample size calculator for two proportions (2-sided)

P1 = 87.1%

P2 = 41%

Power of study = 80%

Level of Significance = 5%

Sample size = 60 (30 in each group)

Sampling Technique

Non-Probability Consecutive Sampling.

Sample Selection

Inclusion Criteria

- Both male and female
- Age ranges from 30 to 60 years of both genders.
- Newly diagnosed type II Diabetes Mellitus with microalbuminuria
- HbA1C < 7.0% at start of study.

Exclusion Criteria

- Hypertension
- Connective tissue diseases
- Chronic heart failure
- Pregnancy
- Lactation
- Known hypersensitivity to ACE inhibitors or Angiotensin Receptor Blocker
- Pregnancy
- B. urea > 45mg/dl, creatinine > 1.1mg/dl
- Already taking nephrotoxic drugs

Data Collection Procedure

Approval from hospital ethical review committee was taken after formulation of synopsis. Informed consent was taken from each participant of the study. Patients were put on either drug regimen

randomly using computer generated random number table. Information was collected by trainee researcher and was comprise age, sex, address, and contact number, albuminuria at baseline and albuminuria at 12 weeks of treatment. 100 mg of Losartan potassium was given for 12 weeks to group A. 5 mg of Lisinopril for 12 weeks to group B. Data was collected through self-conducted interviews using a standardized Performa. There was 12 weeks interval between baseline and follow up visit. Early morning spot urine sample was collected in a standard urine container and sent to PINUM for albumin (mcg/L) to creatinine (mg/L) ratio at baseline and 12 weeks after start of treatment. Follow up was ensured by contacting the patients through telephonic contact and getting the test done at 12 weeks of treatment. Efficacy was measured in terms of 25% reduction in albumin to creatinine ratio.

Data Analysis Procedure

All the collected information transferred to SPSS version 16 and analyzed accordingly. Mean and standard deviation were calculated for all quantitative variables like age and albumin creatinine ratio at baseline and 12 weeks. Frequency and percentage were calculated for all qualitative variables like gender and efficacy of drug. Independent sample t-test was applied to compare the efficacy of Losartan Potassium and Lisinopril. Paired sample t-test was applied to determine the efficacy of Losartan potassium and Lisinopril. Chi square test was applied to compare efficacy for both groups. P value of <0.05 will be considered as significant.

RESULTS

60 patients were included in the study. 28(46.7%) weremalesand32(53.3%) werefemales (Figure-1). Patients were divided into two groups, Group A and Group B, 30 patients in each group. Group A was given Losartan potassium. 11(36.7%) were males and 19(63.3%) were female (Figure-2). Group B was given lisinopril. 17(56.7%) were males and 13(43.3%) were females (Figure-3). Mean age of study population was 50.15±7.27, 51.50±7.98 in Losartan potassium group and 48.80±6.327 in lisinopril group. Albumin creatinine ratio (mcg/

mg) at start of study was 193±67.5 in Losartan potassium group and 209.5±72.00 in lisinopril group (independent sample t-test p value=0.302) (Table-II). Albumin creatinine ratio (mcg/mg) at 12 weeks of study was 36.33±54.68 in Losartan potassium group and 72±83.42 in lisinopril group (independent sample t-test p value = 0.056) (Table-II). Paired sample t test applied to both treatment groups and p value was found to be 0.0001 which is highly significant for both groups and shows that both drugs are effective in reducing microalbuminuria in both groups. Microalbuminuria was reduced significantly in 26 patients (86.7%) in Losartan potassium group and 20 patients (66.7%) in lisinopril group (p-value=0.067) (Table-III).

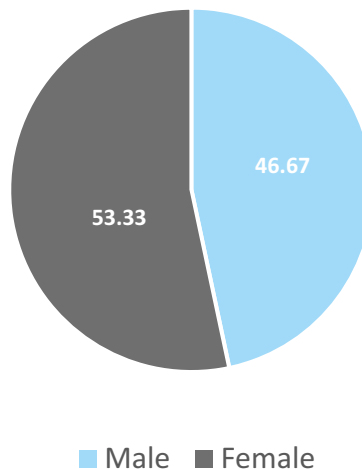


Figure-1. Whole study population Gender

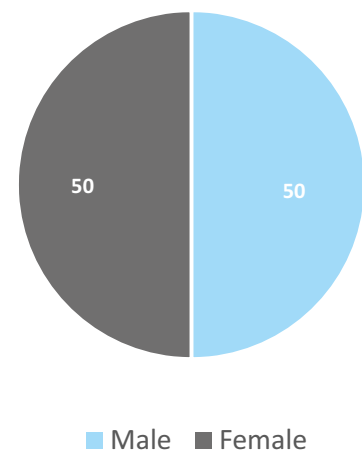
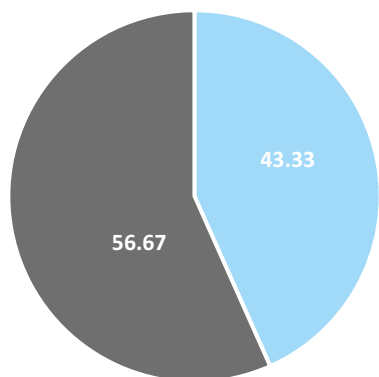


Figure-2. Gender Losartan Group



■ Male ■ Female

Figure-3. Gender Lisinopril Group

Statistics			
Age	ALL	Lisinopril	Losartan Potassium
n	60	30	30
Mean	50.15	48.80	51.50
Std. Deviation	7.272	6.327	7.986
Minimum	30	37	30
Maximum	65	60	65

Table-I. Mean Age

DISCUSSION

Diabetes Mellitus burden will be 2 times after 20 years. Diabetes mellitus Type 2 constitutes 90% of this disease burden.⁹ Diabetic nephropathy leads

to reduction in Glumerular Filtration Rate(GFR).¹⁰ A reduction in the GFR is a key determinant of end-stage renal disease(ESRD). Preventing onset of microalbuminuria is a crux of treatment for renal protection.¹¹

Microalbuminuria is reversible stage of diabetic nephropathy if adequate measures like glycemic control and ACE inhibitor / ARB are taken on time. This effect has been demonstrated in people with/without diabetes mellitus and is independent of decrease in blood pressure.¹²

ARBs also decrease blood pressure and has renal protection effect similar to ACE inhibitors. The ROAD trial demonstrated that increasing dose to maximal effect of benazepril or losartan beyond usual antihypertensive ranges did not show increased blood pressure reduction but was associated with a significant reduction in the risk of doubling of the serum creatinine concentration by 49% and 50%, respectively, at 3.7 years. This was associated with reduction in ESRD risk upto 47% with both drugs.¹³

Clinical trials suggest that inhibition of RAAS system prevents nephropathy. The analyses of the decrease in hypertension in the HOPE trial and in the Losartan Intervention for Endpoint Study, found a lower incidence of overt

	Albumin creatinine ratio (µg/mg) Group A (Losartan Potassium)	Albumin creatinine ratio (µg/mg) Group B (Lisinopril)	Independent sample t-test P value
At start of study	193±67.5	209.5±72.00	0.302
After 3 months of study	36.33±54.68	72.00±83.42	0.056
Paired sample t-test (p value)	0.0001	0.0001	

Table-II. Independent sample t-test and paired sample t-test

Efficacy * Treatment Group Crosstabulation				
Count				
		Treatment Group		Total
		Losartan potassium (A)	Lisinopril	
Efficacy	Yes	26	20	46
	No	4	10	14
Total		30	30	60
Chi Sqaure Value		3.354		
p-value		0.067		

Table-III. Chi Square Test

nephropathy in subjects with type 2 diabetes who received therapy that inhibited the Renin–Angiotensin system than in controls.¹⁴

Trials have supported the clinical equivalence of ARBs and ACE inhibitors in slowing nephropathy progression in diabetes type 2 and in conditions that place them at high risk for CV events.¹⁵

The present study is comparison of ACE inhibitor (Lisinopril) and ARBs (Losartan Potassium) in the reduction of microalbuminuria in diabetes mellitus type 2 patients.

The study has shown that both the drugs – Lisinopril and Losartan Potassium significantly reduce urinary albumin excretion. However, the difference in reduction of microalbuminuria when compared between the two groups is statistically insignificant.

The study (60 subjects) done over six months in outdoor patient setting. The two drug classes were found effective for reduction of microalbuminuria in type 2 diabetes mellitus and preventing progression to overt nephropathy. The two drug classes were found clinically equivalent in reduction of microalbuminuria.

Our data indicate that Losartan and Lisinopril has equal efficacy in providing renal protection in patients with early nephropathy in diabetes. This result supports newer data that clinical equivalence of ARBs and ACE inhibitors in numerous conditions associated with high CV risk.

Guertin and colleagues studied the cost effectiveness of ARBs and ACE Inhibitors in Canada in 2011. They observed that the use of ARBs have increased by 4000% in Canada over last few years but they found no difference between the efficacy of ACE inhibitors and ARBs in reducing albuminuria which supports the findings of our study. There was a decreased incidence of dry irritant cough in ARBs group. ARBs increased the cost burden of the

management of microalbuminuria as compared to ACE Inhibitors.¹⁶

In a study by Oguri M et al, it was found that Albumin-creatinine ratio (ACR) in urine in patients with enalapril at start of treatment and 3 month were 118.0 ± 78.7 mg/ μ g, and 119.5 ± 84.7 mg/ μ g respectively. Albumin-creatinine ratio (ACR) in urine in patients with losartan at start of treatment and 3 months were 128.1 ± 62.8 mg/ μ g and 97.0 ± 78.0 mg/ μ g respectively. The albumin-creatinine ratio (ACR) improve in patient with enalapril and losartan, though there was no significant difference. Albumin-creatinine ratio(ACR) in urine in subjects with enalapril were not significantly different from those in patients with losartan.¹⁹This supports the our results in which it is concluded that Losartan and Lisinopril both are effective equally in reducing microalbuminuria but there was no significant difference between the efficacy of these two drugs.¹⁷

Though it has been confirmed that ARBs (Losartan Potassium) and ACE Inhibitors (Lisinopril) both are effective in reducing microalbuminuria but several studies have been conducted to know the efficacy of combination therapy of ACE Inhibitors and ARBs and it was found that combination therapy has got no added advantage over the use of any single agent.

Pitfalls of my study include:

1. Small sample size
2. Non randomized sampling
3. No double blinding was done
4. No clinical correlation of side effects was made

Advantages of the study include:

1. Lisinopril and Losartan potassium are commonly used drugs
2. Cost effective treatment (both drugs are cost effective Lisinopril more than Losartan Potassium)
3. Easily available medicines(Lisinopril and Losartan Potassium)
4. No head to head comparison of Lisinopril and Losartan Potassium, was made in Pakistan before this study

Large randomized controlled trials are needed to further validate these results.

Conclusions and Recommendations

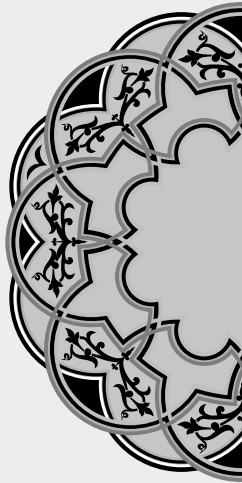
It has been concluded from this study that lisinopril and Losartan potassium, both significantly reduce microalbuminuria in diabetes mellitus type 2 and there is no statistically significant difference in efficacy of these two drugs in reducing microalbuminuria in diabetes mellitus type 2.

Both these drugs can be recommended for treatment of microalbuminuria in type 2 diabetes mellitus for prevention and regression of overt diabetic nephropathy as first line drugs until a specific indication exist for one drug over the other.

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*“Action proves who someone is.
Words just prove who they pretend to be.”*

Unknown

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