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RESULT OF ACE INHIBITORS ON ALBUMINURIA AND CREATININE CLEARANCE IN PATIENTS WITH DIABETIC NEPHROPATHY

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Abstract:

Aim: *The aim of this study is to determine the Effect of ACE inhibitors on Creatinine Clearance and albuminuria in diabetic nephropathy.*

Place and Duration: *In the nephrology department of Services Hospital Lahore for one-year duration from March 2019 to March 2020.*

Methods: *Thirty diabetic patients were tested for the effect of ramipril on creatinine clearance and albuminuria. They all had type 2 diabetes and were taking oral hypoglycemic drugs. They all had varying degrees of hypertension. Ramipril was taken for 3 months at a variable dose ranging from 5 to 10 mg / day. Creatinine clearance and albuminuria were determined before and after treatment. The patients were divided into 3 groups: Group 1: 10 patients with albuminuria and mild hypertension. Group 2: 10 patients with albuminuria and moderate hypertension. Group 3: 10 patients with macroalbuminuria and moderate to severe hypertension.*

Results: *In our study, Group 1 achieved the maximum benefit from ramipril in terms of a very significant reduction (P = 0.002) of creatinine clearance and albuminuria, which significantly improved (P = 0.001). Group 2 was less successful with only a significant decrease in albuminuria (P = 0.005), but with a slight decrease in creatinine clearance. Group 3 with macroalbuminuria did not benefit from the effect of ramipril on albuminuria, but there was a significant decrease in creatinine clearance below normal levels (p = 0.001).*

Conclusion: *Early and strict blood pressure control with ramipril is necessary for successful treatment of diabetic nephropathy with microalbuminuria. In our study, patients with macroalbuminuria did not benefit from treatment with ramipril.*

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INTRODUCTION:

It has now become obvious that type 2 diabetes should be taken as seriously as type 1 diabetes, partly because of kidney complications [1-2]. Moreover, some recent and encouraging evidence suggests that diabetic nephropathy and worsening of kidney function are to some extent preventable (Ritz et al., 1999) [3-4]. In diabetic nephropathy, angiotensin converting enzyme (ACE) inhibitors have a greater effect on proteinuria and a progressive decline in the glomerular filtration rate (GFR) than other antihypertensive drugs. ACE inhibitors have a beneficial effect on the permeability and size selective function of the glomeruli; these effects would lead to limited ultrafiltration of macromolecules and proteins (Ruggenenti et al., 1997). A study of the efficacy of ramipril in nephropathy (REIN) showed that in patients with chronic nephropathy and proteinuria, ramipril safely reduced the rate of decline in the glomerular filtration rate (GFR) and halved the risk of doubling serum creatinine or end-stage renal disease (ESRF) (Ruggenenti et al, 1998) [5-6]. In the Heart Outcome Prevention Evaluation (HOPE) Study Investigators, ramipril reduced the risk of overt nephropathy by 24% (Stubanus et al., 2000).

PATIENTS AND METHODS:

Thirty diabetic patients of varying duration were selected from the nephrology department of Services Hospital Lahore for one-year duration from March 2019 to March 2020. They all had albuminuria and varying degrees of hypertension.

Group 1: included 10 patients with albuminuria (<300 mg / day) and mild hypertension. Group 2: included 10 patients with albuminuria (<300 mg / day) and moderate hypertension). Group 3: comprised 10 patients with macroalbuminuria (> 300 mg / day) and moderate to severe hypertension. Complete history and clinical examination including age, duration of diabetes, degree of hypertension and degrees of lower limb edema. Abdominal ultrasound was performed in all patients. Blood chemistry, including urea and creatinine, creatinine clearance and urinary albumin, measured before treatment with ramipril and after 3 months of continuous ramipril treatment.

The dose of Ramipril was as follows:

Group 1: dose 5 mg / day. Group 2 and Group 3: variable dose from 5 to 10 mg / day depending on the case. All 30 patients were taking oral hypoglycemic drugs and had type 2 diabetes. Creatinine clearance was determined by collecting 24-hour urine and determining urine and serum creatinine and then using the equation. Urine albumin was tested by radioimmunoassay.

RESULTS:

Statistical comparisons between the different groups are made in Tables (1), (2) and (3) Hypertension (HTN) • Mild hypertension up to 139/104. • Moderate hypertension up to 199/114. • Severe hypertension up to 200/115.

Table (1) Statistical Comparison between Group (1) and Group (2) results.

Variants	**Group (1)**	**Group (2)**	**P value** N.S.
Age (years)	4 9.40 ±2.91	52.40 ± 2.91	.000 Sig
Duration of DM (years)	9.50 ± 2.01	13.40 ± 1.83	N.S.
Urea (mg/dl)	40.90 ± 10.67	48.40 ± 19.2	N.S.
Creatinine (mg)	. 67 ± . 31	.81 ± . 32	.0000 Sig
Creatinine Clearance before Ramipril (ml/md)	101.10 ± 9.0	90.31 ± 5.35	N.S.
Create, Clearance after Ramipril (ml/mm)	94.10 ± 7.88	85.80 ± 7.71	N.S.
Albumin in urine before Ramipril (mg/day)	259.50 ± 36.32	270.50 ± 38.32	N.S.
Albumin in urine after Ramipril (mg/day)	234.60 ± 43.92	293.00 ± 44.73	

In group 1, 100% of patients had mild hypertension. 2. In group 2, 100% of patients had moderate hypertension. 3. In group 3, 20% had severe hypertension and 80% had moderate hypertension. Edema of the lower limbs: Mild edema of the ankle Moderate edema Knee level Generalized severe edema (including face) There was a very significant edema of the lower limbs (P = .0001) in different groups, of which: In group 1: 70% had mild edema and 30% there was no edema. In group 2: 100% had moderate edema. In group 3: 80% had moderate edema and 20% had severe edema.

Table (2) Statistical Comparison between Group (1) and Group (3)

variants	**Group (1)**	**Group (3)**	**P value**
Age (years)	49.40 ± 2.91	50.50 ± 4.8	N.S.
Duration of DM (years)	9.50 ± 2.01	17.90 ± 2.4	.0000 Sig
Urea (mg/dl)	40.90 ± 10.67	86.30 ± 10.97	.0000 Sig
Creatinine (mg)	.67 ± .31	1.73 ± .39	.0000 Sig
Creatinine Clearance before Ramipril (ml/mn)	101.10 ± 9.0	73.2 ± 12.9	.0000 Sig
Create, Clearance after Ramipril (ml/mn)	94.10 ± 7.88	58.60 ± 14.00	.0000 Sig
Albumin in urine before Ramipril (mg/day)	259.50 ± 36.32	3930 ± 2020	.0000 Sig
Albumin in urine after Ramipril (mg/day)	234.60 ± 43.92	3770 ± 1534.81	.0000 Sig

Grade 1: Mild increase in cortical echogenicity, but less than that of the liver or spleen, with cortico-spinal differentiation. 2. Grade 2: Mild increase in cortical echogenicity equal to that of liver or spleen, but still cortico-spinal differentiation. 3. Grade 3: Loss of cortico-spinal differentiation with increased echogenicity. Highly significant (P = 0.001) presence of nephropathy of various degrees was found in three groups. In group 1: 70% had grade 1 nephropathy and 30% had grade 2 nephropathy.

Table (3) Statistical Comparison between Group (2) and Group (3)

variants	**Group (2)**	**Group (3)**	**P value**
Age (years)	52.40 ± 2.91	50.50 ± 4.8	N.S.
Duration of DM (years)	13.40 ± 1.83	17.90 ± 2.4	.0000 Sig
Urea (mg/dl)	48.40 ± 19.2	86.30 ± 10.97	.0000 Sig
Creatinine (mg)	. 81 ± .32	1.73 ± .39	.0000 Sig
Creatinine Clearance before Ramipril (ml/mn)	90.30 ± 5.35	73.2 ± 12.9	.0000 Sig
Create, Clearance after Ramipril (ml/mn)	85.80 ± 7.71	58.60 ± 14.00	.0000 Sig
Albumin in urine before Ramipril (mg/day)	270.50 ± 38.32	3930 ± 2020	.0000 Sig
Albumin in urine after Ramipril (mg/day)	293.00 ± 44.73	3770 ± 1534.81	.0000 Sig

In group 2: 80% had grade 2 nephropathy and 20% had grade 1 nephropathy. - In group 3: 70% had grade 2 nephropathy and 30% had grade 3 nephropathy. Urea, creatinine, creatinine clearance before ramipril, creatinine clearance after ramipril, urine albumin before ramipril and urine albumin after ramipril: Statistical comparisons between the results of the different groups are presented in Tables (1), (2) and (3).

Table (4) Statistical comparison between creatinine clearance before and after Ramipril treatment in every group

Group	2-tail Sig	
Group 1	.002	Highly significant
Group 2	0.120	NS
Group 3	.001	Highly significant

Group 1 made significant differences in both creatinine clearance and urinary albumin clearance before and after ramipril treatment. Group 2 showed no significant change in creatinine clearance after ramipril treatment, but there was a significant reduction in albuminuria. Group 3 showed no change in albuminuria after ramipril treatment, but there was a significant change in creatinine clearance, demonstrating a decrease in GFR.

Table (5) Statistical comparison between Albuminuria before and after Ramipril treatment in each group

Group	2-tail Sig	
Group 1	.001	Highly significant
Group 2	.005	Highly significant
Group 3	.632	NS

DISCUSSION:

The Ramipril Efficacy in Nephropathy (REIN) study showed that in patients with chronic nephropathy and proteinuria of 3 g or more over 24 hours, ramipril safely reduced the rate of decline in glomerular filtration rate (Ruggenenti et al., 1998) [7-8]. In our study, ramipril decreased creatinine clearance in patients with albuminuria and mild hypertension, with a very significant decrease (= 0.002). Patients with albuminuria and moderate hypertension did not show the same decrease, which may be due to the frequent occurrence of grade 2 nephropathy in this group [9-10]. Patients with macroalbuminuria and moderate to severe hypertension showed a very significant reduction in creatinine clearance below normal, which would burden the use of ramipril in this patient group [11-12]. The results for creatinine clearance in groups 1 and 2 were in good agreement with the HOPE study (Stubanus et al., 2000), but group 3 with macroalbuminuria and moderate to severe hypertension showed no improvement in creatinine clearance or albuminuria. The decrease in creatinine clearance in this group may be due to the initial decrease in GFR, which suggests the use of ACE inhibitors during the first 6 weeks of use[14]. In the results of the HOPE and MICRO-HOPE studies (Grestein et al., 2000), ramipril lowered the risk of overt nephropathy. In our study, groups (1) and (2) with albuminuria and mild to moderate hypertension benefited from ramipril, while a third group with macroalbuminuria did not. A study (Ruggenenti et al., 2000) showed that the progression of nephropathy was much faster in patients with type 2 diabetes than in other patients with primary glomerular disease. This applied only to group 3, there was a significant decrease (P = 0.001) of creatinine clearance below the norm, which did not apply to groups 1 and 2, may be due to structural changes accompanying macroalbuminuria [15].

CONCLUSION:

Patients with type 2 diabetes must start ramipril therapy as soon as possible, especially if microalbuminuria or hypertension is detected.

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