

## **Effect of ACE inhibitors on Creatinine Clearance and albuminuria in diabetic nephropathy**

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### **Abstract:**

30 diabetic female patients were studied for the effect of Ramipril on creatinine clearance and albuminuria, they all were type 2 diabetes mellitus and were on oral hypoglycemic drugs. They all had variable degrees of hypertension. Ramipril was taken for 3 months in a variable doses between 5 and 10 mg/day. Creatinine clearance and albuminuria were determined before and after treatment. 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.

In our study, Group 1 has made maximum benefit of Ramipril as regards highly significant decrease ( $P= .002$ ) of creatinine clearance and of albuminuria which improved significantly ( $P=.001$ ).

Group 2 had a lesser success with only decrease of albuminuria significantly ( $P=.005$ ) but with insignificant decrease of level of creatinine clearance.

Group 3 with macroalbuminuria did not benefit from Ramipril effect on albuminuria but there was a significant decrease in creatinine clearance below normal levels ( $P=.001$ ).

Conclusion: Early and tight control of blood pressure by Ramipril is needed to achieve a success in treating diabetic nephropathy with microalbuminuria. In our study, patients with macroalbuminuria did not benefit from Ramipril treatment.

### **Introduction**

It has now become obvious that type 2 diabetes must be taken every bit as seriously as type 1 diabetes, in part because of its renal complications. Moreover, some recent and encouraging evidence indicates that diabetic nephropathy and deterioration of renal function are to a certain extent preventable (Ritz et al., 1999).

In diabetic nephropathy, angiotensin – converting – enzyme (ACE) inhibitors have a greater effect than other antihypertensive drugs on proteinuria and the progressive decline in

glomerular filtration rate (GFR). ACE inhibitors have beneficial effects on the permeability and size-selective function of the glomerulus; these effects would lead to limited ultrafiltration of macromolecules and proteins (Ruggenenti et al., 1997).

Ramipril Efficacy in nephropathy (REIN) study found that in patients with chronic nephropathies and proteinuria, ramipril safely reduced the rate of decline of the glomerular filtration rate (GFR) and halved the risk of doubling of serum creatinine or end-

stage renal failure (ESRF) (Ruggenenti et al., 1998).

In the study of the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, Ramipril lowered the risk of overt nephropathy by 24% (Stubanus et al., 2000).

## **Patients and Methods**

30 patients with diabetes mellitus of various durations were chosen from Nephrology department, Ain Shams University Hospital. They all had albuminuria and hypertension of variable degrees.

### **They were divided into 3 groups:**

1. Group 1: comprised 10 patients with albuminuria (<300mg/day) and mild hypertension.
2. Group 2: comprised 10 patients with albuminuria (<300mg/day) and moderate hypertension.
3. Group 3: comprised 10 patients with macroalbuminuria (>300mg/day) and hypertension ranging between moderate and severe grades.

### **For all patients, the following was done:**

1. Complete history and clinical examination including age, duration of diabetes mellitus, hypertension degree and lower limb Oedema grades.
2. Abdominal Sonography .
3. Blood chemistry including urea and creatinine.
4. Creatinine clearance and albumin in urine, which were determined before Ramipril treatment and after 3 months of continuous Ramipril treatment.
5. The dose of Ramipril taken was as follows:
  - ◆ Group 1: a dose of 5 mg/day
  - ◆ Group 2 and Group 3: a varying dose of 5 to 10 mg/day according to the case.

- ◆ Group 2 and Group 3: a varying dose of 5 to 10 mg/day according to the case.

All 30 patients were on oral hypoglycemic drugs and were type 2 diabetes mellitus.

Creatinine clearance was determined by collecting 24 hours urine and determining urinary and serum creatinine, then using the equation  $\frac{\mu \text{M} \times V}{P}$ . Albumin in urine was determined by radioimmunoassay.

## **Results**

**Age and Duration:** Statistical Comparison of different groups was 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.
1. 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 while 80% had moderate hypertension.

### **Lower limb oedema:**

Mild oedema → ankle level  
moderate oedema → Knee level  
Severe oedema → generalized (including face)

There was a highly significant presence of lower limbs oedema ( $P=.0001$ ) in different groups, being:

1. In group 1 : 70% had mild oedema and 30% had no oedema.
2. In group 2 : 100% had moderate oedema.

## Effect of ACE inhibitors on Creatinine Clearance

3. In group 3: 80% had moderate oedema and 20% had Severe oedema.

### **Grades of nephropathy in ultrasound:**

1. Grade 1: Mild increase in cortex echogenicity but less than that of liver or spleen, together with corticomedullary differentiation.

2. Grade 2: Mild increase in cortex echogenicity equal to that of Liver or Spleen, but Still there is cortico-medullary differentiation.

3. Grade 3: Loss of Corticomedullary differentiation with increased echogenicity.

There was a highly Significant ( $P = .001$ ) presence of nephropathy of various grades in the three groups.

- In group 1 : 70% had grade 1 nephropathy and 30% had grade 2 nephropathy.
  - 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, Albumin in urine before Ramipril and Albumin in urine after Ramipril: Statistical comparison between results of various groups are present in table (1), (2) and (3).

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

<b>Vareints</b>	<b>Group (1)</b>	<b>Group (2)</b>	<b>Pvalue</b>
Age (years)	$49.40 \pm 2.91$	$52.40 \pm 2.91$	N.S.
Duration of DM (years)	$9.50 \pm 2.01$	$13.40 \pm 1.83$	.000 Sig
Urea (mg/dl)	$40.90 \pm 10.67$	$48.40 \pm 19.2$	N.S.
Creatinine (mg)	$.67 \pm .31$	$.81 \pm .32$	N.S.
Creat Clearance before Ramipril (ml/md)	$101.10 \pm 9.0$	$90.31 \pm 5.35$	.0000 Sig
Create, Clearance after Ramipril (ml/mm)	$94.10 \pm 7.88$	$85.80 \pm 7.71$	N.S.
Albumin in urine before Ramipril (mg/day)	$259.50 \pm 36.32$	$270.50 \pm 38.32$	N.S.
Albumin in urine after Ramipril (mg/day)	$234.60 \pm 43.92$	$293.00 \pm 44.73$	N.S.

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

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

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

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

## Effect of ACE inhibitors on Creatinine Clearance

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

Group	2-tail Sig
Group 1	.002
Group 2	0.120
Group 3	.001

**Table (5)**

Statistical comparison between Albuminuria before and after Ramipril treatment in each group

Group	2-tail Sig
Group 1	.001
Group 2	.005
Group 3	.632

From table 4 and 5:

Group 1 has made significant difference as regards both creatinine clearance and albumin in urine before and after Ramipril treatment.

Group 2 did not show significant change as regards creatinine clearance following Ramipril treatment, but there was significant decrease in albuminuria level.

Group 3 did not show change in albuminuria level following Ramipril therapy but there was a significant change in creatinine clearance showing a decrease in GFR.

## Discussion

The Ramipril Efficacy in Nephropathy (REIN) study found that in patients with chronic nephropathies and proteinuria of 3gm or more per 24 hours, Ramipril safely reduced the rate of decline of Glomerular filtration rate (Ruggenenti et al., 1998).

In our study, patients with albuminuria and mild hypertension, Ramipril has lowered the creatinine clearance, highly significant decrease ( $=.002$ ) has occurred. Patients with

albuminuria and moderate hypertension didn't show the same decrease may be because of high prevalence of grade 2 nephropathy among this group.

Patients with macroalbuminuria and moderate to severe hypertension showed a highly significant decrease in creatinine clearance below normal, which would incriminate Ramipril use in this group of patients.

The results obtained as regards creatinine clearance in groups 1 and 2 is going well with the HOPE study (Stubanis et al., 2000) but the group 3 with macroalbuminuria and moderate to severe hypertension did not show improvement as regards creatinine clearance or albuminuria. Decline in creatinine clearance in this group may be due to initial lowering of GFR suggested to be done by ACE inhibitors during the first 6 weeks of use.

In the results of HOPE study and MICRO-HOPE study, (Grestein et al., 2000), Ramipril lowered the risk of overt nephropathy. In our study, group (1) and (2) with albuminuria and mild to moderate hypertension have made benefit from Ramipril while the third

group with macroalbumuria did not benefit.

In (Ruggenenti et al., 2000) study showed that nephropathy progression was remarkably faster in patients with type 2 diabetes mellitus than in other patients with primary glomerular disease.

This was only applicable to group 3, there was a significant decrease ( $P=.001$ ) in creatinine clearance below normal, which did not apply to group 1 and 2, may be because of the structural changes that accompany macroalbuminuria.

## **Conclusion**

Patients with type 2 DM has to start treatment as early as possible with Ramipril, especially so when microalbuminuria or hypertension is detected.

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دراسة مفعول مثبطات التحول لإنزيم أنجيوتنسين على كل من  
استخلاص الكرياتينين والزلال في البول في حالات إصابة الكلي من  
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تم دراسة 30 حالة من مرضي البول السكري، كلهم من الإناث، بالنسبة لمفعول دواء الراميبيريل على كل من استخلاص الكرياتينين والزلال في البول. كل المرضى كانوا من النوع الثاني من مرض البول السكري وكلهم كانوا يستعملون الأدوية المخفضة للجلوكوز في الدم. كلهم كانوا يعانون من درجات مختلفة من ارتفاع ضغط الدم. يأخذ المرضى دواء الراميبيريل لمدة ثلاثة أشهر في جرعات مختلفة بين خمسة وعشرة ميللجرامات في اليوم. تم قياس كل من استخلاص الكرياتينين والزلال في البول قبل وبعد العلاج.

انقسم المرضى إلى الثلاث مجموعات الآتية:

مجموعة 1: - عشرة مرضى يعانون من نسبة صغرى من الزلال في البول وارتفاع بسيط في ضغط الدم.

مجموعة 2: - عشرة مرضى يعانون من نسبة صغرى من الزلال في البول وارتفاع متوسط في ضغط الدم.

مجموعة 3: - عشرة مرضى يعانون من نسبة كبيرة من الزلال في البول وارتفاع ضغط الدم يتراوح بين متوسط وشديد.

في الدراسة التي قمنا بها، المجموعة 1 كانت المجموعة التي حققت الاستفادة القصوى من دواء الراميبيريل، بالنسبة لانخفاض الملاحظ في استخلاص الكرياتينين إلى مستويات قريبة من الطبيعي وكذلك انخفاض نسبة الزلال في البول والتي تحسنت بصورة ملحوظة.

المجموعة الثانية حققت نجاحاً أقل مع انخفاض ملحوظ في نسبة زلال البول فقط، أما استخلاص الكرياتينين فلم يحقق انخفاض ملحوظ من المستويات الطبيعية.

المجموعة الثالثة التي كانت تعاني من نسبة كبيرة من زلال البول، فلم تستفد من دواء الراميبيريل بالنسبة للزلال في البول، في حين أنه كان هناك انخفاض في استخلاص الكرياتينين إلى مستويات أقل من الطبيعي.

الاستنتاج: - التدخل المبكر لضبط ضغط الدم بدواء الراميبيريل مطلوب لتحقيق نجاحاً في علاج حالات إصابة الكلي في مرضي البول السكري الذين يعانون من نسبة صغيرة في الزلال في البول.