# Role of ACE Inhibitor on Glycaemic Control in Type II Diabetes with Hypertension.

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**This study was carried out at medical department Mayo hospital to evaluate the role of ACE inhibitor on glycaemic control in type II diabetes with hypertension. The result of this study showed that ACE inhibitor Quinapril improves glycaemic control.**
**Key words: ACE inhibitor, Quinapril, glycaemic control**

Over the recent years there is an alarming increase worldwide in the incidence and prevalence of diabetes mellitus and hypertension. Constellation of type II diabetes, hypertension, ischaemic heart disease, obesity and dyslipidaemia is called syndrome X. It is proposed that insulin resistance is the main culprit in this syndrome. [1] Adequate control of hypertension is important in type II diabetes because it retards the progression of several complications. [2] Pharmacological agents used to treat hypertension in diabetes can affect glycaemic control. [3] Therefore drugs that can adversely affect glycaemic control should be avoided. [4], while drugs that have role in improving glycaemic control should be preferred in treating hypertensive diabetic patients. In addition to their anti-hypertensive effects, ACE inhibitors have shown considerable promise in ameliorating insulin resistance thereby improving glycaemic control. Though the role of ACE inhibitors in improving glycaemic control in patients with diabetes has been extensively reviewed in studies abroad there is, as yet little work done in this respect in Pakistan. The purpose of this study is to evaluate the effect of ACE inhibitors on glycaemic control in patients with type II diabetes with hypertension.

## Materials and methods

*Study design*

This was a prospective randomized drug control study, which was carried out in West Medical Ward, Mayo Hospital, Lahore from August 1998 to July 1999.

*Selection of Patients*

For the purpose of this study a cohort of 100 patients was established. All of these patients were suffering from type II diabetes and hypertension. These patients were selected from medical outpatient department and diabetic clinic of Mayo Hospital, Lahore.

Patients were explained about the purpose of the study and an informed written consent was obtained. Patients included in this study had type II diabetes with mild to moderate hypertension. Patients who were suffering from, type I diabetes, secondary hypertension, renal dysfunction, liver dysfunction, acute medical stress, decompensated heart failure, unstable angina, acute myocardial infarction, accelerated and malignant hypertension, cerebro-vascular accident thyroid, pituitary, adrenal dysfunction and patients on beta blockers, steroids, thiazide diuretics, loop diuretics or having fasting plasma glucose greater than 250mg/dl were excluded from the study.

*Control*: Drug Control.

**Method**

Patients included in this study were randomly divided into two groups of 50 patients. These groups were designated title A and B. Patients were put on standard diabetic diet for a period of three week. During this period they received their routine oral hypoglycaemic agents. After a period of three weeks, patients were advised for follow up in the morning, under fasting condition. They were allowed to rest for half an hour, during which smoking was not allowed. Their upper arm Blood Pressure (BP) was measured by standard mercury sphygmomano-meter. Korotkoff I & V were noted for systolic and diastolic BP. Both supine and three minutes after standing BP was checked. Height and weight of these patients were recorded and body mass index was calculated. A blood sample was drawn to note:

1. Blood glucose fasting
2. Serum Fructosamine
3. $HbA_{IC}$
4. LFTs
5. Blood urea/creatinine
6. Urine complete examination
7. Blood complete examination

Serum Fructosamine was done by ketoamine linkage using nitroblue tetrazolium as described by Ravel J. [5] Serum $HbA_{IC}$ was assayed by the method using boronic acid resin that reacts only with stable glycated haemoglobin, by the method described by Ravel J. [5]

Before breakfast, patients were allowed to receive their oral hypoglycaemic agents. Patients were then advised to have a breakfast with standard nutritional value that contained 75 grams of carbohydrates. After a period of two hours blood samples were again drawn from these patients to note postprandial blood glucose.

Group A patients were advised Quinapril for the control of their hypertension whereas group B patients were advised Methyldopa. Dosage advised for Quinapril was titrated between 5-10 mg o.d. For Methyldopa the

dosage was titrated between 500 to 1000mg daily. Patients were advised once weekly follow-up for 12 weeks. During follow-up blood pressure of the patients were noted in supine and standing position. Patients were also monitored for development of any adverse effect or development of any morbid complication. Adjustments were made in the dosage of anti-hypertensive medication but no adjustment was made in the dosage of oral hypoglycaemic agent. After a period of 12 weeks these patients were again recalled at medical out patient department of Mayo Hospital in the morning under fasting condition. They were allowed to rest for half an hour. Their supine and standing BP was recorded, they were weighed and body mass index was again calculated. Blood samples were drawn for:

1. Blood glucose fasting
2. Serum Fructosamine
3. $HbA_{IC}$
4. LFTs
5. Blood urea/creatinine
6. Urine complete examination
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Before breakfast patients were allowed to receive their oral hypoglycaemic agent. Patients were then advised to have a breakfast with standard nutritional value that contained 75 grams of carbohydrates. After a period of two hours blood sample were again drawn from these patients to note postprandial blood glucose.

Data collected was transferred to the spreadsheet of standard statistical package "SPSS" (ver 8). All categorical variables were described as percentages and continuous variables as mean ± SDs. Effect of the two drugs (before and after treatment), on various continuous variables was compared by paired sample t-test. Statistical significance was defined as $p \leq 0.05$.

**Results**

Of the fifty patients treated with ACE inhibitor six patients developed mild cough or feeling of irritation in the throat that did not affect quality of life and these side effects subsided on its own and the patients completed the study.

The baseline characteristics of patients put on ACE inhibitor and Methyldopa are projected in Table 1. The analysis obtained from baseline characteristics showed that both the groups were reasonably matched.

Primary end point of our study is summarized in Table 2. As can be observed from the effect of Quinapril and Methyldopa on glycaemic control, there is significant improvement in levels of blood glucose fasting ($p<0.001$), blood glucose post prandial ($p<0.002$), $HbA_{IC}$ ($p<0.001$) and serum Fructosamine ($p<0.001$), at the end of study in patients treated with Quinapril as compared to that treated with Methyldopa. The improvement seen in ACE inhibitor treated group is statistically significant. On the other hand, Methyldopa treated cases failed to show statistically significant improvement in glycaemic control.

Table 1. Comparison of basic characteristics of the patients in the study

| Variable | ACE inhibitor group | | Methyldopa group | |
|---|---|---|---|---|
| | Mean | ± SD | Mean | ± SD |
| Age of patients in years | 56.5 | 6.77 | 55.1 | 6.06 |
| Duration of hypertension in years | 6.38 | 4.08 | 6.02 | 3.63 |
| Duration of diabetes mellitus in years | 8.26 | 3.93 | 8.98 | 4.02 |
| Height (cm) | 163.94 | 7.39 | 164.3 | 7.08 |
| Weight (kg) | 72.02 | 8.44 | 69.1 | 6.4 |
| Body mass index ($kg/m^2$) | 26.94 | 3.01 | 27.02 | 3.1 |

Table 2 Comparison of parameters of glycaemic control.

| | ACE Inhibitor Group | | Methyldopa Group | |
|---|---|---|---|---|
| Variable | Mean | P Value | Mean | P Value |
| Blood glucose mg/dl (f) before * | 168.34 | .001 | 158.24 | 0.438 |
| Blood glucose mg/dl (f) after † | 142.70 | | 152.6 | |
| Blood glucose mg/dl (2hr pp) before* * | 247.74 | .002 | 299.54 | 0.275 |
| Blood glucose mg/dl (2hr pp) after † | 199.12 | | 220.92 | |
| Serum Fructosamine before* | 330.44 | 0.001 | 324.64 | 0.433 |
| Serum Fructosamine after† | 307.62 | | 319.82 | |
| $HbA_{IC}$ (%) before* | 8.20 | 0.001 | 8.41 | 0.09 |
| $HbA_{IC}$ (%) after † | 7.50 | | 8.25 | |

**Before beginning of study*
*† At the end of treatment*

Table 3 summarizes secondary end points in our study. It can be seen from the table that both Quinapril and Methyldopa treated patients showed reduction in both systolic and diastolic blood pressure that was statistically significant.

Table 3 Comparison of blood pressure control

| | ACE Inhibitor Group | | Methyldopa Group | |
|---|---|---|---|---|
| Blood Pressure ** | Mean | P Value | Mean | p Value |
| Diastolic BP supine(b) * | 100.5 | .001 | 102.5 | 0.001 |
| Diastolic BP supine(a) † | 89 | | 93 | |
| Systolic BP supine(b) * | 171.4 | .001 | 167.4 | 0.001 |
| Systolic BP supine(a) † | 147 | | 148 | |
| Diastolic BP standing(b) * | 98 | 0.002 | 96 | 0.002 |
| Diastolic BP standing (a) † | 88 | | 88 | |
| Systolic BP standing(b) * | 164.2 | 0.001 | 156.2 | .001 |
| Systolic BP standing (a) † | 143.5 | | 138.5 | |

*** in mm Hg*
**(b) Before beginning of study*
*† (a) At the end of treatment*

**Discussion**

There is frequent association of hypertension with type-II diabetes. The current status is still not clear regarding the underlying aetiological relationship between these two disease processes. The picture is further complicated by the fact that certain antihypertensive agents can worsen the insulin resistance thereby adversely affecting glycaemic control in diabetes.

Extensive review of local literature shows lack of any previous study evaluating effect of ACE inhibition on glycaemic control, therefore our study can only be partially compared with other studies done abroad showing improvement in insulin resistance with ACE inhibitor or showing any other effect on glycaemic control

We have used Fructosamine to check the short term glycaemic control. Serum Fructosamine is derived from glycosylation of serum proteins and has been described as excellent parameter for monitoring short term glycaemic control. Ueno N and colleagues in their study evaluated improvement in glycaemic control by using this parameter[6]

In order to judge long term improvement in glycaemic control we have used $HbA_{IC}$ as used by Alkharouf J. et al in their study[7]. The results in our study showed that ACE inhibitors have a beneficial effect in improving glycaemic control, as can be seen by statistically significant decrease in serum Fructosamine, $HbA_{IC}$ and blood glucose levels in patients treated with ACE inhibitor. The exact mechanism governing this change is still not known.

Study done by Weidmann P. has demonstrated that ACE inhibitors decrease insulin resistance in hypertensive patients[8]. The improvement in glycaemic control in our study could be due to this decrease in insulin resistance. Ideally insulin levels should have been measured to check the improvement in insulin resistance by using gold standard method of insulin clamp technique, but again this test is very expensive and is still not widely available in Pakistan. Therefore we were unable to use this technique.

There is statistically significant improvement in HbAic in patients treated with ACE inhibitor in our study. These results are consistent with observation made by Alkharouf J et al. in their study[7].

The result of our study regarding improvement of glycaemic control with ACE inhibitors is not consistent with the study of Petrie J. et al.that has shown no improvement of glycaemic control and insulin resistance with ACE inhibitors[9]. The ACE inhibitor used in their study was Terandopril, while we used Quinapril, so it could be one factor leading to different results.. The number of patients in their study was 18 as against 50 patients in our study who received ACE inhibitor. While the cohort in our study had sex wise relatively equal distribution (26 male vs. 24 females), the population in the study of Petrie J. et al that received treatment consisted mainly of male sex (15 males vs. 1 female). The mean age in their study was almost equal and comparable with our study (58 yrs ± 10.6 yrs vs. 56.5 yrs ± 6.77 yrs). Body mass index in our study population was lower as compared to their study ($26.94kg/m^2$ ± $3kg/m^2$ vs. $30kg/m^2$ ± $5.41kg/m^2$).

The observation made in our study were consistent with the observation made by Velasquez-MT. et al., who reviewed recent data on role of ACE inhibitor in glucose metabolism and found that this group of drugs has beneficial effect on glycaemic control[10]. No significant hypoglycaemic effect requiring hospitalization was seen with ACE inhibitor treated cases in our study, which is not consistent with the observation made by Morris AD et al[11].

Older age group patients showed greater improvement in glycaemic control with ACE inhibitor treatment in our study. This observation is consistent with the observation made by Paolisso G et al., who also noticed improvement of insulin sensitivity in aged patients with ACE inhibition[12].

## Conclusion

The results of our study showed that:

1. ACE inhibitor Quinapril improved glycaemic control in type-II diabetic patients with hypertension.
2. Methyldopa has got no detrimental effect on glycaemic control in type-II diabetic patients with hypertension.

Keeping in view the results of our study, it is suggested that further research should be done, in order to evaluate the role of ACE inhibitors in glycaemic control in Pakistani diabetic hypertensive patients.

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