ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (RAMIPRIL) AND ANGIOTENSIN RECEPTOR BLOCKER (LOSARTAN) ON MICROALBUMINURIA IN DIABETES MELLITUS TYPE-II

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ABSTRACT:
All the patients included in the study were divided into three groups. Group A patients received Angiotensin converting enzyme inhibitor (Ramipril) for a period of six months, the urinary albumin decreased in them by 34.89% while group B patients received Angiotensin receptor blockers (Losartan) for the same period and urinary albumin decreased by 39.73%. The resistant cases of both the groups were included in group C and this group was given a combination of Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers i.e., Ramipril and Losartan in these resistant cases the urinary albumin decreased by 35.8%.

Conclusion: Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers and combination of both are effective in reducing the excretion of albumin in diabetic patients having microalbuminuria. These drugs beneficially influence the altered glomerular haemodynamics in patients with diabetes mellitus the measurement of albuminuria can prevent the renal damage and that it is a modifiable risk factor.

Keyword: ACEIs (Angiotensin converting enzyme inhibitors), ARBs (Angiotensin receptor blockers), Diabetes Mellitus Type-II Microalbuminuria, Kidney.

INTRODUCTION
It have been estimated that 190 million people world wide have Diabetes mellitus and it is likely that this may increase to 342 million by the year 2025 (Zimmet et al., 2005). Main risk factors for the development of complication of Diabetes mellitus include poor control of hypertension; serum lipids, body weight and smoking. Adequate control on levels of these factors decrease the risk of cardiovascular and renal damage. Diabetes mellitus is associated with a marked increase in risk of atherosclerotic vascular disorders (macro vascular and microvascular) complications including coronary, cerebrovascular and peripheral artery disease; these are responsible for 70% of deaths in patients with Type-II diabetes mellitus (Yamagishi et al 2007). Albuminuria is an early indication of renal damage but can also predict increase risk for cardiovascular disease (de Zeeuw et al., 2005. The use of anti-hypertension having synergistic action of controlling the albuminuria and blood pressure has been studied vastly. Various studies suggest to combine the drugs which inhibits RAAS i.e. (Renin Angiotensin Aldosterone System) these are ACEIs, ARBs, Aldosterone antagonists and renin inhibitors but most tested are ACEIs and ARBs (Jacobson PK 1993). ACEIs and ARBs reduce albuminuria without producing hypotension, greater the reduction of albuminuria effective is renal protection (Lewis EJ and GISEN et al). ACEIs inhibitors slow diabetic glomerulopathy, K+ levels are elevated in patients on NSAIDs β-blockers and K+ sparing diuretics (Fier FB and Fisher, 2006). It takes approximately four weeks before the maximum anti-proteinuric effect of ACEIs and ARBs effect is reached (Gansevoort et al., 1993).
Loss of > 300 mg/day of albumin usually indicates severe renal damage i.e., ERSD (End Stage Renal Disease) (Maschio et al., 2009) and this is also predictive of adverse cardiovascular event. Microalbuminuria has its importance in identifying progress of kidney damage, as increased microalbuminuria correlates with increased level of BP and increased cholesterol and hence increase the risk of CVD even in absence of renal failure. Several groups of anti-hypertensive control the hypertension and reduce albuminuria, these include ACEIs (Angiotensin converting enzyme inhibitors), ARBs (Angiotensin receptor blocker) and recent addition is Renin inhibitor. (Remikiren) (Parving et al., 2001).

So a study was conducted to compare the effects of ACEIs Tritace (Ramipril) and ARBs Losartan (cozaar) on microalbuminuria in patients suffering from diabetes mellitus Type II and the resistant patients were given combination of Ramipril and Losartan.

**Inclusion Criteria:**
1. Males and Females with Type-II diabetes mellitus
2. Microalbuminuria i.e. >30mg/day but <300 mg/day
3. Serum creatinine < 1.5 mg/dl

**Exclusion Criteria:**
1. Type-I Diabetes Mellitus
2. Gestational Diabetes Mellitus
3. Hypertension
4. Congenital malformation of kidney
5. Nephrotic syndrome
6. Patients of connective tissue disorder i.e., Rheumatoid arthritis and SLE on penicillamine
7. Impaired kidney function due to non diabetic renal disease
8. Women taking oral contraceptives

**MATERIAL AND METHODS**

Patients attending the Diabetes OPD at Government Hospital were included, a written consent was taken, the study was approved by the Ethical Committee, Demographic details regarding age, sex and social status was recorded. The preliminary examinations at base line level were Blood CP, Urine DR, Fasting and Random blood sugar levels, HbA1c, Serum Cholesterol and 24 hours urine sample for albuminuria.

**Methodology**

Between January 2009 and November 2009, 785 diabetic were screened for the study, 150 patients were randomly include in study according to the inclusion criteria, a written consent was taken, these patients were randomly divided into two groups Group A received Ramipril 1.25 mg daily. Group B received Losartan 50 mg daily. 114 patients completed the study, 36 were lost in follow up.

All the patients received the drug for a period of 6 months. The blood glucose levels were controlled with various groups of oral hypoglycemic agents as prescribed by the physician. The patients were examined monthly for routine checkup and every two months for microalbuminuria.

This study lasted 6 months, pre treatment measurement were compared with results at the end of 6 months. Out of these 29 patients did not show decrease in albuminuria, so the group was named as group C and were given a combination of Ramipril and Losartan and were then evaluated after three months.

**RESULTS**

Out of hundred fourteen patients 29 were female and 36 males in group A and in group B there were 25 females and 34 males and group C comprised of 13 females and 16 males. The number of smokers and non smokers was 30/28 and 18/11 in group A B and C respectively. The age range was 55 ±3.4 years, 51± 6.2 and 57±4.1 years in A, B and C groups respectively.

The average weight was 75±15.5 and 78±14.7 for the group A, B whereas group C comprised of obese patients having a weight of 85±12.5 kg.
The systolic blood pressure in patients of group A was 131±10.5 mm of Hg and for group B was 129±11.5 mm of Hg whereas for group C the SBP was 135±11.78 mm of Hg. The DBP for these groups was 82±7.5 mm of Hg, 85±7.1 mm of Hg and 87±6.9 mm of Hg respectively. Groups C patients had both SBP and DBP greater than the other two groups.

Serum Cholesterol was 218±40.1 mg/dl and 240±37.8 mg/dl for the two groups A and B, whereas group C had level of 251±38.8 mg/dl, slightly elevated than the rest of two groups.

HbA1c was 7.5±1.1% and 7.8±1.3% and 8.3±2.3% for group A, B and C respectively. Serum creatinine in groups A, B and C was 1.45±0.3 mg/dl, 1.5±0.29 mg/dl and 1.5±0.7 mg/dl respectively.

Urinary albumin level at base line was 212±10.6 mg/dl, 257±11.7 mg/dl and 1.5±0.7 mg/dl respectively.

After treatment the following change was observed SBP was 108±10.56 mm of Hg, 112±11.09 mm of Hg and 121±12.17 mm of Hg in groups A, B and C respectively, whereas the change in DBP was 78±4.5 mm of Hg, 80±4.8 mm of Hg and 85±6.5 mm of Hg for groups A, B and C respectively. Serum cholesterol, HbA1C% and serum creatinine were not significantly altered. (Table-2) from the base line level in all three groups. Albuminuria decreased in both groups A and B and in group A the excretion of albumin decreased from 212±10.6 mg/dl to 138±11.52 mg/dl, i.e., 34.89%, in group B, excretion was decreased from 257±11.7 mg/dl to 154±12.01 mg/dl i.e., 39.73% in A and B groups respectively. Twenty nine patients amongst the two groups failed to show the response, these patients were grouped into C group and were given a combination of Ramipril and Losartan out of these 14 were refractory to treatment and albuminuria persisted (Table-2).

**DISCUSSION**

Out study shows that both ACEIs and ARBs are effective in controlling albuminuria, this is also reported by Geuseff et al (Pieter et al., 2000) and that they prevent the progression from microalbuminuria to proteinuria and that this effect is independent of BP control (Ravid and Viberti et al.). ACEIs effect is mediated by decreasing arterial blood pressure by dilating renal efferent arterioles. ACEIs increase the permeability selectively of filtering membrane, thereby diminishing exposure of the mesangium to proteinaceous factors. ACEIs treatment reduced the progression to established proteinuria by 69% regardless of whether the BP was elevated or not. Recent studies have now demonstrated that onset and course of diabetic nephropathy can be ameliorated to a very significant degree but these interventions have their greatest impact if instituted earlier in the course of development of this complication. The earliest evidence of nephropathy is microalbuminuria. Without specific intervention 20-40% of type 2 diabetic progress to overt nephropathy, in addition to its being earliest manifestation of nephropathy, albuminuria is a maker of CV morbidity and mortality. In our study the reduction of albuminuria in Group A was 34.89% with ACEIs and with ARBs it was 39.73% and those cases who were refractory to either showed response in 35.9% of case, a study by Kaene et al reports average reduction of albuminuria with ACEIs and ARBs as 50% in both microalbuminuria and macroalbuminuria and patients showing poor or no response usually end up in ESRD. RENAAL study (Reduction of End point in NIDDM with Angiotsin-II antagonist Losartan) gives a clear reason to measure and target not only blood pressure but also albuminuria in diabetes mellitus. Eijkelkamp reports lowering in 60% for both microalbuminuria and blood pressure and 40% showed no change, our values are
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low probably due to inadequate control of dietary salt, it was further reported that such patients need a diuretic and low sodium diet or benefit by increasing the dose of ARBs or adding a renin inhibitors and aldosterone antagonist. The RAAS drugs have proven to be associated with about 50% reduction in albuminuria in both microalbuminuria and macroalbuminuria patients, it was further found that the effect can be enhanced by doubling the dose as was seen with irbesartan, microalbuminuria in type-II diabetes study subject showed that 300 mg of irbesartan was significantly more efficient that 150 mg as far as the transition of micro-albuminuria to macroalbuminuria was concerned (Zimmet, et al., 2005).

CONCLUSION

Our results support that ACEIs and ARBs slow the progression of diabetic nephropathy and can beneficially influence the altered glomerular hemodynamics in patients with diabetes mellitus, their use can thus delay dialysis, transplantation and death. Suppressing albuminuria should be a goal therapy in patients of diabetes mellitus. Controlling blood glucose and monitoring blood pressure must be accompanied by measurement of microalbuminuria in urine.

Our study shows that as it is easy and cheap to measure the albuminuria as compared with other investigational procedures, this measurement can prevent the prognosis of renal damage and risk of nephropathy, suppressing albuminuria should be a goal of therapy in individuals with type-2 diabetes mellitus

REFERENCES

dezeeuw, D., Remuzzi, G., Parving, H. et al. (2009). Albuminuria, a Therapeutics target for cardiovascular protection in