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Research Article

COMPARATIVE EVALUATION OF RENOPROTECTION BY VALSARTAN VS TRANDOLAPRIL IN STREPTOZOTOCIN INDUCED DIABETIC NEPHROPATHY

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ABSTRACT

The aim of this study is to evaluate comparative effects of valsartan vs trandolapril in STZ induced diabetic nephropathy in rats. Albino rats (250-300 g) of either sex were used. Diabetic Nephropathy (DN) was induced by injecting STZ (50 mg/kg, I.V.) single dose. Animals were divided into 5 groups of 10 each. Group I-control, Group II-diabetic (STZ), Group III-valsartan (5 mg/kg, p.o.) daily, 5 days prior to STZ and continued for 12 weeks + STZ, Group IV- trandolapril (0.5 mg/kg, p.o.) daily, 5 days prior to STZ and continued for 12 weeks + STZ, Group V- insulin (5U/day, S.C.) + STZ. Blood and urine tests (blood sugar, serum creatinine, urine volume, urine protein and urine creatinine) were performed every month for 3 months. Marked hyperglycaemia, polyuria, proteinuria, and elevated serum creatinine level was observed in STZ diabetic rats. Valsartan as well as trandolapril pre-treated animals showed a significant ($p < 0.01$) reduction in serum creatinine, and urinary protein excretion. However, valsartan was more potent than trandolapril in this regard. Both valsartan and trandolapril prevents progressive diabetic nephropathic changes in rats, however, valsartan was more potent than trandolapril.

Keywords: ACE-inhibitors, AT-II antagonists, Diabetic nephropathy, Trandolapril, Valsartan, Streptozotocin

INTRODUCTION

Diabetes Mellitus is the most common metabolic disorder. It is characterized by metabolic abnormalities and long-term complications including retinopathy, nephropathy, neuropathy and dermopathy etc. Despite recent advances in the management of the disease, Diabetic nephropathy (DN) is the most frequent cause of end stage renal failure.[1] Diabetic nephropathy is characterized by persistent pathological albuminuria and abnormal renal function as recognized by an abnormal plasma creatinine (PCr) level, Glomerular Filtration Rate (GFR) or calculated creatinine clearance.[1] In diabetic patient protein-urea, the initial insult to the kidney is usually followed by a progressive decline in GFR. This decline has been thought to be due to changes in renal hemodynamics initiated by the loss of nephrons.[2]

The pathophysiological and the clinical manifestations of kidney damage are duration related. They appear according to a described sequence beginning with glomerular hyperfiltration and reversible proteinuria, progressive to fixed massive proteinuria (nephrotic syndrome) and ending with renal insufficiency. The pathogenesis of progressive renal damage is multifactorial and the mechanism by which hyperglycemia causes microangiopathy in diabetic glomeruli is still poorly understood. Renal damage may be triggered and sustained by a combination of hemodynamic (increased glomerular pressure flow), metabolic (hyperglycemia, dyslipidemia and hyperphosphatemia), humoral (angiotensin II, endothelin I) and immunological mechanism.[3]

Drug therapy that focuses on tight glycemic control and blood pressure control reduces the progression of nephropathy and cardiovascular complications.[2] Since many factors may contribute to the development of such tissue damage, strict control of blood glucose levels has not been shown to reverse progressive kidney and eye diseases in humans.[4] Inhibitors of Angiotensin Converting Enzyme (ACE) are the current gold standard treatment for hypertension in patients with type I diabetes in addition to their BP lowering ability, they are thought to oppose the increased intraglomerular pressure that is mediated in part by angiotensin II.[5] Angiotensin II receptor antagonists, a more recently developed class of antihypertensive agents appear to be as effective as ACE inhibitors in delaying the progression of renal injury in animal models of diabetes.[6] Primary effector of the RAAS is the peptide hormone angiotensin II which is formed from angiotensin I by the ACE. ACE inhibitors block the formation of angiotensin II. RAAS blockade has proven to be effective in reducing albuminuria and alleviating the deterioration of Diabetic nephropathy.[7] Additionally, there are alternative pathways of angiotensin formation that may be stimulated during the administration of ACE inhibitors, so that little or no reduction in Angiotensin II occurs.[8] Type I angiotensin II antagonists were developed to block angiotensin receptors.[6]

Recently Valsartan (Angiotensin II receptor antagonist) has been shown to be effective in the treatment of acute myocardial infarction in addition to its antihypertensive activity.[9] Trandolapril an ACE inhibitor has been approved for its antihypertensive activity.[10] Therefore, the present study will be undertaken to evaluate comparative effect of Valsartan

(angiotensin II receptor antagonist) and Trandolapril (ACE inhibitor) on kidney functions such as effect on creatinine clearance and to observe effects on Total urinary protein excretion in Streptozotocin (STZ) induced diabetes in rats.

Purpose: To evaluate comparative effects of valsartan vs trandolapril in STZ induced diabetic nephropathy in rats.

MATERIAL AND METHODS

Albino rats of either sex, weighing between 250-300 g, were maintained on standard diet (pellets) and used for the study. Food and water were made available *ad libitum*. Present study was approved by Institutional Animal Ethical Committee vide letter no. SGTU/IAEC/2018/05 dated 06/08/2018.

Induction of Diabetic Nephropathy

Animals were made diabetic with a single intravenous injection of streptozotocin (STZ) (Sigma, USA) at a dose of 50 mg/kg body weight.[5] Samples for blood glucose monitoring were obtained from the tail vein and rats with blood glucose level of more than 250 mg/dl were labeled as diabetics. Each rat was housed individually in a metabolic cage and its urine volume was measured for 6 hours. Their urine samples were analyzed for total proteins, after 4, 8 and 12 weeks, to confirm proteinuria as a result of diabetic nephropathy

Outline of the study

Rats were divided into 5 groups of 10 each.

Group I: Normal rats- These were the nondiabetic controls.
Group II: Rats were given STZ (50 mg/kg, I.V.) and served as diabetic controls.
Group III: Rats were given STZ (as in Group II) followed by Valsartan (5 mg/kg/day, p.o.) 5 days prior to STZ for 12 weeks.
Group IV: Rats were given STZ (as in Group II) followed by Trandolapril (0.5 mg/kg/ day, p.o.) 5 days prior to STZ for 12 weeks.
Group V: Rats were given STZ (as in Group II) followed by appropriate doses of insulin, subcutaneously daily, for 12 weeks, to make the rat euglycemic.

Tests for blood sugar, serum creatinine, urine volume, urinary proteins and urine creatinine were performed every month, for three months. Blood glucose was estimated by glucose-oxidase/ peroxidase method.[11] Estimation of serum creatinine and urine creatinine by Modified Jaffe's Reaction.[12] Estimation of urine protein using Biuret Reagent after protein precipitation.[13] To measure the urine volume each rat of different group was kept in metabolic cage for 6 hours. The urine was collected and then measured for the total volume.

For statistical analysis mean, standard deviation and standard error of mean were calculated. Results were statistically analyzed by student's 't' test.

RESULT AND DISCUSSION

Effect on Blood Glucose

There was a significant ($p < 0.01$) and sustained increase in blood glucose levels in animals treated with STZ. In valsartan + STZ pre-treated group and trandolapril + STZ pre-treated group blood glucose levels were significantly different from that of diabetic rats. Valsartan pre-treatment decreased the blood glucose levels in STZ induced diabetic rats. Trandolapril pre-treated rats also decreased the blood glucose levels in STZ induced diabetic rats. However, valsartan + STZ pre-treated group showed significantly decreased blood glucose levels as compared to trandolapril + STZ pre-treated animals.

On the other hand, insulin pre-treatment prevented the development of STZ induced hyperglycaemia in rats. The effect of valsartan and trandolapril were compared with insulin + STZ induced diabetic rats. The mean values in the valsartan and trandolapril pre-treated groups were comparable with STZ and were significantly higher as compared with insulin ($p < 0.01$) as mentioned in Table 1.

Effect on serum creatinine

The mean serum creatinine level in control group was 0.7 ± 0.04 mg/dl at 0 week. There was a significant ($p < 0.01$) and sustained increase in serum creatinine levels in animals treated with STZ at 8 and 12 weeks. In STZ diabetic rats, initial (0 week) mean creatinine levels were 0.7 ± 0.04 mg/dl as compared to 0.9 ± 0.05 mg/dl, 1.9 ± 0.06 mg/dl, 2.5 ± 0.03 mg/dl at 4, 8 and 12 weeks respectively.

Valsartan pre-treatment significantly decreased ($p < 0.001$) the serum creatinine levels in STZ diabetic rats at 8 and 12 weeks. The initial serum creatinine level in valsartan + STZ pre-treated group at 0 week was 0.7 ± 0.04 mg/dl while values were 0.8 ± 0.03, 0.9 ± 0.04 and 1.1 ± 0.05 mg/dl at 4, 8 and 12 weeks respectively.

Trandolapril pre-treatment significantly decreased ($p < 0.001$) the serum creatinine levels in STZ diabetic rats at 8 and 12 weeks. The initial serum creatinine level in trandolapril + STZ pre-treated group at 0 week was 0.7 ± 0.03 mg/dl while values were 0.8 ± 0.04, 1.0 ± 0.04 and 1.2 ± 0.04 mg/dl at 4, 8 and 12 weeks respectively.

Valsartan pre-treatment showed more decreased serum creatinine levels as compared to the trandolapril pre-treatment, though the difference was not significant.

Insulin pre-treatment also reduced the STZ induced increase in serum creatinine levels. In insulin pre-treated rats, serum creatinine values were almost normal and comparable to that of control animals. At 0-week mean serum creatinine level in this group was 0.7 ± 0.04 mg/dl, while these values were mean 0.8 ± 0.04, 0.9 ± 0.03, and 0.8 ± 0.03 mg/dl at 4, 8 and 12 weeks respectively.

Valsartan and trandolapril on the other hand were found to be equally effective to that of insulin as the mean values of serum creatinine in all the three groups were comparable ($p < 0.05$).

Effect on Urine Creatinine

The urine samples taken from control group when compared with STZ showed that there was a significant and sustained decrease ($p < 0.01$) in urinary creatinine excretion. The initial (0 week) urine creatinine excretion in STZ - diabetic rats was mean 60.6 ± 1.00 mg/dl, while it was mean 56.8 ± 1.29, 45.5 ± 0.54 and 25.5 ± 0.34 mg/dl at 4, 8 and 12 weeks respectively.

Urinary creatinine excretion was found to be significantly increased 8 weeks onwards in valsartan pre-treated group as compared to STZ group. The excretion at 0 week in valsartan pre-treated group was mean 60.5 ± 1.05 mg/dl, while these values were mean 57.1 ± 0.86, 54.1 ± 1.23, and 44.9 ± 0.74 mg/dl at 4, 8 and 12 weeks respectively.

Table 1: Effect of Valsartan (5 mg/kg, p.o.) and Trandolapril (0.5 mg/kg, p.o.) pre-treatment on blood glucose levels in rats with STZ induced Diabetic Nephropathy (values are mean ± se for 10 animals in each group)

Groups /drugs	Blood glucose levels (mg/dl)			
	0 week	4 weeks	8 weeks	12 weeks
Control	89.8 ± 1.54	86.2 ± 1.07	88.5 ± 1.32	90.0 ± 0.96
STZ	90.5 ± 0.92	274.8 ± 1.76#	284.6 ± 1.44#	293.0 ± 1.27#
Valsartan +STZ	88.7 ± 0.93	260.8 ± 0.79*	275.5 ± 0.81*	280.6 ± 0.98*
Trandolapril + STZ	87.2 ± 0.94	265.0 ± 0.52*@	280.2 ± 0.84*@	285.7 ± 1.17*@
Insulin + STZ	88.6 ± 1.37	112.0 ± 1.45*@$	111.8 ± 2.64*@$	112.8 ± 1.82*@$

# $p < 0.01$ when compared with control, * $p < 0.01$ when compared with STZ
@ $p < 0.01$ when compared with Valsartan + STZ, $ $p < 0.01$ when compared with Trandolapril + STZ

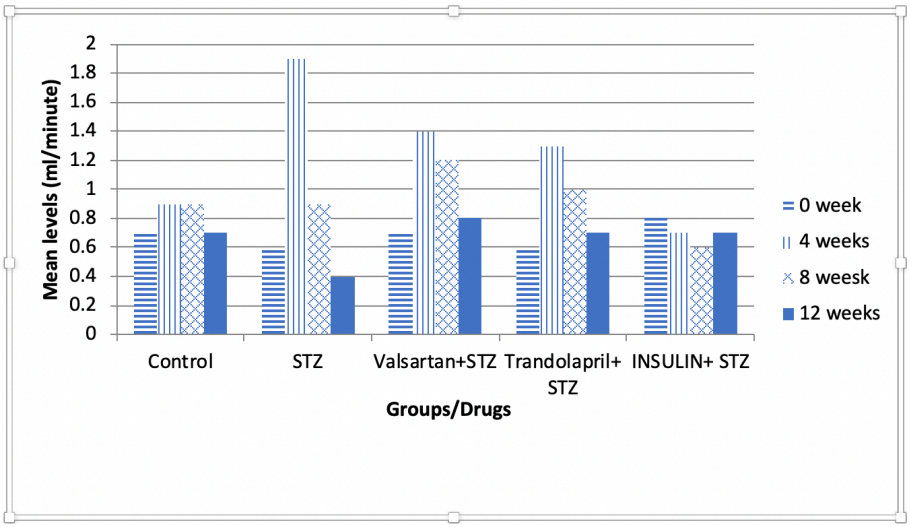

Figure 1: Effect of valsartan and trandolapril pre-treatment on creatinine clearance

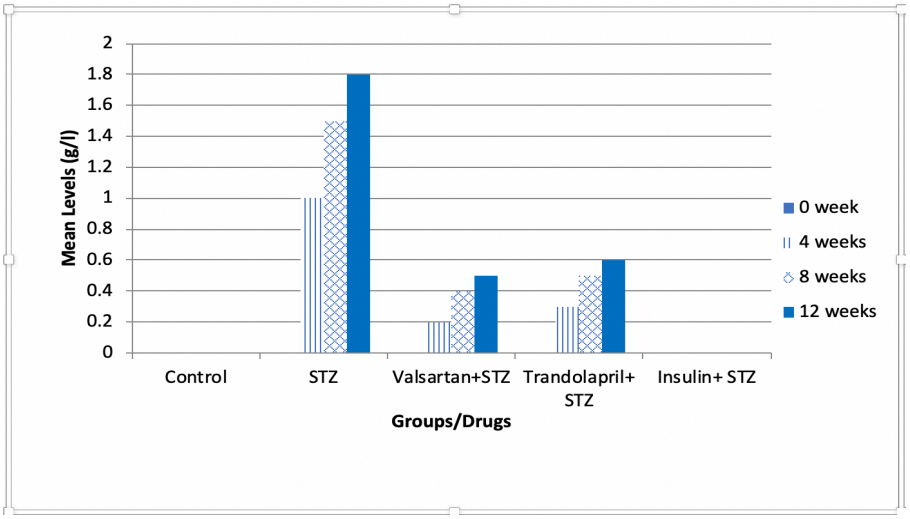

Figure 2: Effect of valsartan and trandolapril pre-treatment on urinary protein excretion

Urinary creatinine excretion was found to be significantly increased at 12 weeks in trandolapril pre-treated group as compared to STZ group. The excretion at 0 week in trandolapril pre-treated group was mean 59.7 ± 1.05 mg/dl, while these values were mean 53.3 ± 1.05, 46.3 ± 0.60, and 41.8 ± 0.42 mg/dl at 4, 8, and 12 weeks respectively.

Urinary creatinine excretion in valsartan pre-treated group was found to be significantly increased at 8 weeks onwards as compared to trandolapril pre-treated group.

When compared with insulin group, these values were significantly different ($p < 0.01$) from 8 week onwards. The mean urine creatinine level in insulin + STZ treated group at 0 week was 60.8 ± 1.19 mg/dl, while these values were mean 55.0 ± 0.42, 58.0 ± 0.42, and 58.0 ± 0.42 mg/dl at 4, 8 and 12 weeks respectively.

Effect on Urine Volume

Urinary output (ml/6 hours) was recorded using metabolic cage in normal, diabetic and study groups. In control (normal) rats the mean value of urine output was in the range of 3.0 ± 0.10 to 4.0 ±

0.07 ml/6 hours, when observed at 0, 4, 8 and 12 weeks. On the other hand, a marked and sustained increase in urine volume was observed in all the diabetic animals throughout the experimental period. The initial urine volume in diabetic rats of STZ group at 0 week was mean 3.0 ± 0.09 ml as compared to mean 12.2 ± 0.33, 14.3 ± 0.33 and 13.5 ± 0.34 ml at 4, 8, and 12 weeks respectively. The increase in urine volume was significant ($p < 0.01$) when compared to control values. However, the increase in urine volume was more marked in the early weeks of diabetes as compared to 12th week. Actually, there was a gradual decline in polyuria in the late weeks of diabetes.

Valsartan pre-treatment reduced the STZ induced diuresis in rats. The mean urine volume in valsartan + STZ pre-treated group at 0 week was 3.1 ± 0.09 ml, while it was 7.7 ± 0.09, 8.8 ± 0.09, and 8.0 ± 0.16 ml at 4, 8 and 12 weeks respectively.

Trandolapril pre-treatment also reduced the STZ induced diuresis in rats. The mean urine volume in trandolapril + STZ pre-treated group at 0 week was 3.0 ± 0.09 ml, while it was 8.6 ± 0.10, 9.0 ± 0.21, and 9.5 ± 0.16 ml at 4, 8 and 12 weeks respectively.

The mean urine volume in valsartan pre-treated group was decreased as compared to the trandolapril pre-treated group.

Insulin pre-treatment also prevented STZ induced osmotic diuresis. The urine volume in insulin pre-treated diabetic group was comparable to that of control group.

Effect on Creatinine Clearance

Creatinine clearance was taken as a parameter to assess GFR in control, diabetic and drug pre-treated (valsartan, trandolapril and insulin) groups. In the early weeks of diabetes, there is significant ($p < 0.01$) increase in creatinine clearance which gradually decreased in the later weeks. Creatinine clearance was mean 0.7 ± 0.05 ml/min in controls at 0 week. On the other hand, STZ group showed an increase in initial weeks. Mean values for creatinine clearance were 0.6 ± 0.04 ml/min at 0 week, while these were 1.9 ± 0.14, 0.9 ± 0.03, and 0.4 ± 0.01 ml/min at 4, 8 and 12 weeks respectively after STZ administration.

Initial creatinine clearance in Valsartan + STZ treated group at 0 week was mean 0.7 ± 0.05 while these values were mean 1.4 ± 0.05, 1.2 ± 0.07, and 0.8 ± 0.03 ml/min at 4, 8 and 12 weeks respectively. Creatinine clearance was improved significantly in diabetic rats after pre-treatment with valsartan.

Initial creatinine clearance in Trandolapril + STZ treated group at 0 week was mean 0.6 ± 0.03 while these values were mean 1.3 ± 0.05, 1.0 ± 0.05 and 0.7 ± 0.02 ml/min at 4, 8 and 12 weeks respectively. Creatinine clearance showed slight improvement in diabetic rats after pre-treatment with trandolapril; however the values were not significant.

Valsartan pre-treated group showed more improvement in creatinine clearance as compared to the trandolapril pre-treated group, although the difference was not significant.

In insulin pre-treated diabetic rats, values of creatinine clearance were comparable to that of control group. Valsartan and Trandolapril was found to be more effective than insulin in earlier weeks, the mean value was significantly higher ($p < 0.01$). However, at 12 weeks, the rise in creatinine clearance in the all three groups was comparable ($p < 0.05$). The results are shown in Figure 1.

Effect on Urinary Proteins

Urinary protein was not observed in any rat from control group. However, there was a significant ($p < 0.01$) and sustained increase in urinary protein excretion in animals treated with STZ. Mean values of urinary protein in diabetic animals were 1.0 ± 0.05, 1.5 ± 0.06 and 1.8 ± 0.05 g/l at 4, 8 and 12 weeks respectively.

The mean urine protein levels in Valsartan + STZ pre-treated group were 0.2 ± 0.03, 0.4 ± 0.06 and 0.5 ± 0.06 g/l at 4, 8 and 12 weeks respectively. Valsartan pre-treatment in STZ diabetic rats significantly ($p < 0.01$) reduced the excretion of proteins in urine. The mean urine protein levels in Trandolapril + STZ pre-treated group were 0.2 ± 0.05, 0.5 ± 0.06 and 0.6 ± 0.05 g/l at 4, 8 and 12 weeks respectively. Trandolapril pre-treatment in STZ diabetic rats significantly ($p < 0.01$) reduced the excretion of proteins in urine.
The mean urine protein levels in Valsartan + STZ pre-treatment group was decreased as compared to Trandolapril + STZ pre-treatment group, although the difference was not significant. Insulin pre-treatment on the other hand prevented proteinuria in STZ diabetic rats. The results are shown in Figure 2.

In the present study, rats were made diabetic with STZ administration. STZ has been shown to result in the formation of single strand breaks in DNA of pancreatic β-cells. These breaks in turn activate nuclear poly (ADP-ribose) synthetase and deplete the cell of its substrate.[14]

The result of present study confirms that the administration of STZ causes hyperglycemia, proteinuria and polyuria, along with other biochemical derangements. It is known that the metabolic derangements of diabetes are due to relative or absolute deficiency of insulin. The catabolic metabolism is initiated by a fall in plasma insulin concentration. Due to the increased catabolic state in diabetes, processes like glycogenolysis, gluconeogenesis, proteolysis; lipolysis and ketogenesis are activated leading to increased concentration of glucose as well as of other metabolites like creatinine. The peripheral utilization of glucose is also hampered which further leads to hyperglycemia.

Lapinski *et al*[15] explained that the angiotensin II via increase in glomerular capillary pressure. They suggested that a vicious cycle is established in which the changes in renal hemodynamics due to the loss of nephrons lead to proteinuria which is then followed by the loss of more nephrons. The results of the present study demonstrate that insulin pre-treatment prevents proteinuria in STZ diabetic rats. Valsartan pre-treatment also shows a significant decrease in the protein excretion. It is known that in addition to the favorable impact of angiotensin-II (ANG II) blockade on blood pressure and renal hemodynamics, the blockade of the growth promoting, profibrotic and non-hemodynamic actions of ANG II may also be important for the renoprotection.[16] The ANG II type I receptor antagonists represent a new pharmacological class of drugs that are specifically designed to displace ANG II from its receptors. These drugs (e.g.valsartan, irbesartan, losartan etc.) antagonize ANG II induced biological actions and aldosterone release.

In present study, creatinine clearance is taken as a parameter to assess the GFR. In STZ induced diabetic rats there is sustained fall in GFR with time. Insulin pre-treatment did not show any significant fall in GFR with time. On the other hand, valsartan pre-treatment shows a slow and sustained fall, the changes however were significantly different when compared with STZ group. The slower decline in valsartan treated group could be due to its antagonistic, vasodilatory effect on ANG II. Results of the present study demonstrate that insulin pre-treatment resulted in

antidiuresis. The valsartan treated group also resulted in antidiuretic effect, but the observations were not comparable with insulin treated group. A slower decline of GFR in the valsartan group reflects the beneficial effect on the progression of nephropathy. A persistent decline in proteinuria and the serum creatinine levels favor the reno-protective effect of this drug. Valsartan has been used in a number of animal and human studies to evaluate its reno-protective role. Most of the studies have shown the constant antiproteinuric effect. A similar effect was seen in the present study with no significant effect on the blood glucose levels.[17]

Results of the study review that in STZ diabetic rat trandolapril treatment reduced the urinary albumin excretion as well as the elevated serum levels of creatinine. Creatinine clearance taken to access GFR was found to be increased following trandolapril treated diabetic rats. Beneficial effect of trandolapril in STZ induced DN may be due to reduction in glomerular capillary pressure, direct effect on glomerular basement permeability, improving vascular functions, increased production of intrarenal vasodilatory bradykinins and prostaglandins, preventing progressive tubule-intestinal fibrosis, antioxidant and other metabolic actions.

Inhibition of ACE by trandolapril results in reduced conversion of angiotensin I to angiotensin II. Angiotensin II plays a central role in several of the processes involved in chronic renal injury. Angiotensin II, a vasoconstrictor substance modulates glomerular filtration by constricting afferent and efferent arteriolar blood vessels. Ang II also influences cell growth proliferation and apoptosis via cyclin dependent kinase inhibitors, prosclerotic cytokines, TGF-β, nuclear factor Kappa B, nuclear transcription factor and protein kinase C.[18] Blockade of Ang II pathway by trandolapril is beneficial in Diabetic nephropathy.

Rubio and coworkers[19] demonstrated antiproteinuric effects of trandolapril in glomerulopathies including Diabetic nephropathy in human beings. These workers concluded that reno-protective effect of trandolapril was not due exclusively to its systemic antihypertensive action and trandolapril had the greatest benefit in experimental studies which have pathological involvement of RAS. Antiproteinuric effect of long term trandolapril was also reported in normotensive patients with type I diabetes.

Wolf *et al*[20] demonstrated that renal hypertrophy, thickening of basement membrane, expansion of glomerular mesangium and accumulation of extracellular matrix occurs within a week of onset of type I diabetes. These workers suggest that increased glomerular expression of cyclin dependent kinase (P27, Ki PI) inhibitor and ACE inhibitor attenuate the glomerular expression of cyclin dependent kinase inhibitors suggesting a molecular mechanism of how ACE inhibitors present renal hypertrophy in diabetes. Metabolic effects of ACE inhibitors also contribute in reducing the complications of diabetes. ACE inhibitors have been shown to improve insulin sensitivity.

CONCLUSION

Study with valsartan and trandolapril reveals that the drugs do not influence blood glucose levels significantly. Biochemical parameters like serum creatinine show a significant fall ($p < 0.01$) in both the groups. However, when compared with insulin the changes in the two groups are comparable ($p < 0.05$). Pre-treatment with valsartan and trandolapril both shows a significant reduction ($p < 0.01$) in the urine proteins from 4 weeks onwards. The sustained but slower decline in creatinine clearance reflects the beneficial effect of the drugs in diabetic nephropathy.

From the results of the present study it can be concluded that valsartan and trandolapril both can be reno-protective. The effects, however, are more marked in the valsartan group as compared to the trandolapril group.

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