Renoprotective Effects of Combined Aliskiren and Valsartan in Progressive Diabetic Nephropathy in Rats

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ABSTRACT: Renin angiotensin system plays a major role in the pathology of progressive Diabetic Nephropathy. In the present study, the renoprotective effects of low dose combined novel direct renin inhibitor-aliskiren and angiotensin II type 1 receptor blocker (ARB)-valsartan were estimated and compared with monotherapy in wistar rats. Rats were divided into 5 groups: control, diabetic control, diabetic rats treated with aliskiren (10 mg/kg/day), valsartan (20 mg/kg/day) and combination of aliskiren and valsartan (5 mg/kg/day, 10mg/kg/day respectively). Clinical characteristics like proteinuria, serum creatinine and renal histopathological studies like glomerulosclerotic index, tubulointerstitial fibrosis were estimated and compared between all diabetic rats. Results showed that combination therapy of aliskiren and valsartan was more effective than the monotherapy in progressive diabetic nephropathy.

KEYWORDS: Renin-angiotensin system; Diabetic Nephropathy; Direct renin inhibitor; Aliskiren; Angiotensin II type 1 receptor blocker; Valsartan

Introduction

Diabetic Nephropathy (DN) is the major single cause of End Stage Renal Disease (ESRD) in developing countries (Stern M. 1995) and extrapolations suggest that this number will multiply in the future (Eastman R et al., 1993). End stage renal disease require dialysis; and is becoming a staggering challenge to public health care systems due to the prohibitive costs of renal replacement therapy that could become unaffordable even for developed countries (Turner R. 1998). Advance diabetic nephropathy is also the leading cause of glomerulosclerosis and end-stage renal disease worldwide (Clark CJ, Lee D, 1995 and Fore W. 1995). Between 20 to 40 % of all diabetic patients are prone to developing kidney failure, and family-based studies suggest that a significant genetic component confers risk for DN (Cudworth AG et al., 1992 and Nathan D 1994). DN manifests as a clinical syndrome that is composed of albuminuria, progressively declining GFR, and increased risk for cardiovascular disease (Remuzzi et al., 1997 and Parving et al., 2000). And it is a late complication of diabetes, occurring progressively in susceptible people only after 15 to 25 year of diabetes (Makino H.1996 and Mauer S.M. 1984).

Renin-angiotensin system (RAS) activation in diabetes mellitus is a core abnormality that leads to many complications of the disease, including hypertension, nephropathy, and renal tissue injury. Persistent proteinuria is the hallmark of diabetic nephropathy which is the leading cause of end-stage renal disease. The degree of proteinuria is closely associated with the rates of renal events. Furthermore, a reduction in proteinuria is associated with a slowing of both the decline in the glomerular filtration rate and the progression to end-stage renal disease. As a result, a reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

Although the administration of ACEI results in a fall in plasma angiotensin II levels, the efficacy of ACEI is probably limited by their inability to completely block ACE activity and the generation of angiotensin II through other enzymatic pathways. However, ACE inhibitors have other effects including interference with the breakdown of
bradykinin. Long-term ACEI use is associated with a return in circulating angiotensin II levels following a reactive rise in plasma renin and angiotensin I due to the interruption of angiotensin II feedback on renin release. On the other hand, angiotensin-receptor blockers (ARBs) do not affect bradykinin production and should theoretically block the actions of angiotensin II chronically at the AT-1 receptor level (Jennifer L Wilkinson 2001).

Clinical studies indicate that ARBs may be as effective as ACE inhibitors and have fewer side effects. ACE inhibitors can induce a very troubling cough in susceptible individuals as a result of the increase in kinins. ARBs serve as a very good substitute for such patients (Michael Azizi and Joel Menard, 2004). Valsartan has a higher affinity for the AT1 receptor than losartan, does not have an active metabolite, and has a slightly longer duration of action than losartan. Valsartan is the drug of choice if the patient has compromised liver function. With the exception of captopril and lisinopril, all of the available ACE inhibitors are pro-drugs and require liver metabolism for elimination (Charles R. Craig and Robert E. Stitzel).

Aliskiren, is the first of novel direct renin inhibitor approved for the treatment of hypertension. Aliskiren, with its 40hr half-life and ideal pharmacokinetics, can now address angiotensin production directly at its rate-limiting step. Aliskiren binds to the active site of renin, preventing angiotensinogen from binding and being cleaved to form angiotensin I, thereby inhibiting the activation of renin system at the rate-limiting step. Direct renin inhibition offers a number of advantages over ACE inhibitors and ARB. Theoretically, inhibiting the renin system at the point of activation with a direct renin inhibition will provide comprehensive angiotensin II suppression. In addition, since angiotensinogen is the only known renin substrate, direct renin inhibition should have minimal side effects. Cough would not be expected (Dominik N Muller et al., 2008). No drug interactions reported between Aliskiren and Valsartan. Compared with Valsartan, Aliskiren more strongly decreases renin activity in the circulation and reduces urinary aldosterone excretion for a longer period (Wlodzimierz B. and Justyna M. H., 2008).

In a study reported in 2000 that involved patients with type 2 diabetes, hypertension, and microalbuminuria, Mogensen et al. showed that treatment with a combination of submaximal doses of candesartan and lisinopril was more effective in reducing blood pressure (reductions in systolic pressure of approximately 10 mm Hg and in diastolic pressure of approximately 6 mm Hg) than therapy with only one agent; however, the effectiveness of the combined therapy in reducing albuminuria was not firmly established. Since then, numerous small studies, often using submaximal doses of ACE inhibitors in patients with diabetic nephropathy, have shown a significant reduction in blood pressure and albuminuria with this treatment strategy. In contrast, a large, randomized, controlled trial involving patients with type 2 diabetes, hypertension, and albuminuria who received the maximal recommended doses of ramipril and irbesartan failed to show a significant effect of combination therapy, as compared with monotherapy, on albuminuria, despite a significant reduction in systemic blood pressure. The benefit of blocking the renin–angiotensin–aldosterone system in patients with diabetes who are at risk for end-stage renal disease is now well established. However, most studies to date also show that renal disease progresses in many patients despite treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin II-receptor blockers. Consequently, alternatives that optimize the blockade of the renin–angiotensin–aldosterone system are being explored in the hope that a more complete blockade will lead to a better therapeutic outcome (Hans-Henrik Parving 2008).

It suggests that there is a need for the studies of new renoprotective strategies that include, dual blockade of the renin angiotensin aldosterone system with combined novel renin inhibitor Aliskiren and ARB (Valsartan) in progressive diabetic nephropathy. Hence, in the present study, the renoprotective effects of combined aliskiren and valsartan were estimated and compared with monotherapy in diabetic Wistar rats.

Materials and Methods

Animal Model

Female Wistar rats (200-250g) were purchased from Mahaveera enterprises (CPCSEA Reg. No. 146/1999) Hyderabad registered by the Government of India.

Drugs

Streptozotocin 45mg/kg (Sigma, St Louis, MO, USA), Aliskiren (gift from Novartis NJ, USA), Valsartan (gift from Novartis NJ, USA), Insulin (2–4 U i.p, Humulin NPH, Eli Lilly, Indianapolis, IN, USA).

Diagnostic Kits

One Touch blood glucose monitoring systems (Johnson& Johnson Medical India Ltd, Mumbai, India, Uristix (SIEMENS), Serum Creatinine (Alkaline Picrate Method), (EXCEL DIAGNOSTICS Pvt. Ltd).
Research design

Six-week-old female, Wistar rats were used in the present study. Rats were assigned to receive either 55 mg/kg of STZ diluted in 0.1 mol/l citrate buffer, pH 4.5, or citrate buffer alone (non-diabetic) by tail vein injection following an overnight fast. Rats were then randomized into five groups (n=4), receiving one of the following treatments: Control, Diabetic control, Diabetic rats treated with Aliskiren (10 mg/kg per day), Valsartan (20 mg/kg per day), combination of Aliskiren and Valsartan (5 mg/kg + 10 mg/kg per day). Treatment commenced within 24 h of STZ or citrate buffer injection. All rats had free access to normal rat chow and drinking water. They were housed in a stable environment maintained at 22±1°C (12 h light–dark cycles with lights on at 06:00 hours).

Clinical Characteristics of Animals

Each week, rats were weighed and their bloodglucose levels were measured by using One Touch blood glucose monitoring systems. Only STZ-treated animals with blood glucose >250 mg/dl were considered diabetic. Every 4 weeks, Serum Creatinine (mg/dl), Body Weight (g), Urine Volume (ml/day) of each rat was serially monitored. Proteinuria (mg/dl/day), Kidney Weight (g) was monitored on the 8th week of the study. Diabetic rats received a daily injection of insulin (2-4 U i.p) to reduce mortality and promote weight gain. Serum Creatinine was estimated by Alkaline Picrate Method. Proteinuria is estimated by Uristix. Twenty-four-hour urine samples were collected with the aid of metabolic cages. Rats were housed individually in metabolic cages equipped with drinking bottles and food cups outside the cages.

Tissue preparation

At 8 weeks post-STZ or control vehicle, rats were anaesthetized (Nembutal 60 mg/kg body weight i.p) and perfused via the abdominal aorta with 0.1 mol/l PBS, pH 7.4 (20 to 50 ml), to remove circulating blood. Simultaneously, the inferior vena cava adjacent to the renal vein was severed, allowing free flow of the perfusate. After clearance of circulating blood, 4% paraformaldehyde (wt/wt) in 0.1 mol/l phosphate buffer, pH 7.4, was perfused for a further 5 min (100 to 200 ml of fixative). Kidneys were excised and de-capsulated. The kidneys were sliced transversely, and post fixed overnight. After routine processing through graded alcohols, the kidneys were embedded in paraffin and sectioned at 3 μm (Jennifer L Wilkinson 2001).

Histopathology

Changes in kidney structure were assessed in a masked protocol in at least 25 randomly selected tissue sections from each group studied. Sections were stained with either periodic acid-Schiff’s reagent or Masson’s modified trichrome to assess glomerulosclerosis and demonstrate collagenous tubulointerstitial matrix, respectively (D.J Kelly 2007).

Glomerulosclerotic index

In 4μm kidney sections stained with periodic acid-Schiff’s reagent, 150 glomeruli from each animal were examined in a masked protocol. The extent of sclerosis in each glomerulus was subjectively graded on a scale of 0 to 4, as previously described21, with the following grades: grade 0 normal, grade 1 sclerotic area <25% (minimal), grade 2 sclerotic area 25–50% (moderate), grade 3 sclerotic area 50–75% (moderate to severe) and grade 4 sclerotic area 75–100% (severe). A glomerulosclerotic index was then calculated using the formula:

\[ GSI = \sum_{i=0}^{4} Fi (i) \]

Where GSI is glomerulosclerotic index, Fi is the % of glomeruli in the rat with a given score (i).

Quantitation of matrix deposition

The accumulation of matrix within the tubulointerstitium was assessed on Masson’s trichrome-stained sections using computer-assisted image analysis (Lehr HA et al 1997 and 1999). Briefly, ten random non-overlapping fields of each section from six rats per group were captured and digitized using a BX50 microscope (Olympus Optical, Shibuya-Ku, Tokyo, Japan) attached to a Fujix HC5000 digital camera (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Digital images were then loaded onto a Pentium IV IBM computer. An area of blue on a trichrome-stained section was selected for its color range and the proportional area of tissue with this range of color was then quantified. Calculation of the proportional area stained blue (matrix) was then determined using image analysis (Analytical Imaging Station, Indian Institute of Chemical Technology, Hyderabad, India).

Statistical Analysis

All data are expressed as the mean ± S.D. The differences in all parameters, except blood glucose levels, proteinuria between diabetic and non-diabetic rats were analyzed by a
one-way analysis of variance (ANOVA) followed by a Newman-Keuls Multiple Comparison Test using Graph Pad Prism version 5. A change was considered statistically significant if \( P<0.05 \).

**Results**

**Clinical Characteristics of Animals**

**Blood glucose levels (mg/dl):** There was significant difference in blood glucose levels (80-426 mg/dl) observed between control and diabetic rats and also significant difference in blood glucose levels (426-398.4 mg/dl) observed between the diabetic control and drug treated groups on progression of the study from 1st week to 8th week (Fig. 1). But, there was no significant difference between the blood glucose levels of diabetic rats treated with either monotherapy or combination therapy with of Aliskiren and Valsartan.

**Serum creatinine (mg/dl):** After 4th and 8th week, in comparison with control animals (0.1863, 0.1808 mg/dl), diabetic control rats, had elevated serum creatinine (0.4595, 0.4718 mg/dl), which was extremely significantly reduced in drug treatment groups with Aliskiren, Valsartan and combination of these two drugs. But after 4th week, combination of Aliskiren and Valsartan has reduced serum creatinine (0.2163 mg/dl), extremely compared to Aliskiren (0.2998 mg/dl) and Valsartan (0.3550 mg/dl) monotherapy. Whereas after 8th week, combination of Aliskiren and Valsartan has very significantly reduced serum creatinine (0.2073 mg/dl) compared to Aliskiren monotherapy (0.2720 mg/dl), but extremely reduced when compared to Valsartan monotherapy (0.3330 mg/dl) (Fig. 2).

![Fig. 1](image1.png) **Fig. 1** Blood glucose levels (mg/dl) in control and STZ induced diabetic rats treated with mono- and combination therapies of aliskiren and valsartan. \(+ P<0.001 \) vs diabetic control. Values are expressed as means ± S.D. N=4 rats/group.

![Fig. 2](image2.png) **Fig. 2** Serum creatinine (mg/dl) in control and STZ induced diabetic rats treated with mono- and combination therapies of aliskiren and valsartan. \( ***, P<0.001 \) vs combination of aliskiren and valsartan. \(+ P<0.001 \) vs diabetic control. Values are expressed as means ± S.D. N=4 rats/group.
**Body weight (g):** After 4th and 8th week, in comparison with control animals (253, 253.5 g), diabetic control rats had reduced body weight (185.8, 166 g), which was very significantly increased in drug-treated groups with Aliskiren, Valsartan and combination of Aliskiren and Valsartan. After 4th week, there was a significant increase in body weight of diabetic rats treated with combination of Aliskiren and Valsartan (248.3 g) compared with diabetic rats treated with Aliskiren monotherapy (235 g) and very significant increase in diabetic rats treated with combination of Aliskiren and Valsartan (248.3 g) compared with Valsartan monotherapy (229.3 g). But after 8th week, there was extremely significant increase in body weight of diabetic rats treated with combination of Aliskiren and Valsartan (242.5 g) compared with diabetic rats treated with Aliskiren (228.5 g) and Valsartan (225.5 g) monotherapy (Fig. 3).

**Urine volume (ml/day):** After 4th and 8th week, in comparison with control animals, diabetic control rats had elevated urine volume (33.50, 39.25 ml/day), which was very significantly reduced in drug treated groups with Aliskiren (14.25, 13.75 ml/day), Valsartan (15.75, 14.50 ml/day) and combination of Aliskiren and Valsartan (12.50, 12.00 ml/day). But, there was no significant reduction in urine volume of diabetic rats treated with combination of Aliskiren and Valsartan compared with diabetic rats treated with monotherapy using Aliskiren and Valsartan (Fig. 4).

![Fig. 3](image1.png) **Fig. 3** Body weight (g) in control and STZ induced diabetic rats treated with mono- and combination therapies of aliskiren and valsartan. ***P<0.001, **P<0.01, *P<0.05 vs combination of aliskiren and valsartan. + P<0.001 vs diabetic control. Values are expressed as means ± S.D. N=4 rats/group.

![Fig. 4](image2.png) **Fig. 4** Urine Volume (ml/day) in control and STZ induced diabetic rats treated with mono- and combination therapies of aliskiren and valsartan. + P<0.001 vs diabetic control. Values are expressed as means ± S.D. N=4 rats/group.
Proteinuria (mg/ml/day) and Kidney weight (g) : After 8th week, in comparison with control animals (<30 mg/dl/day, 1.240 g), diabetic control rats had elevated proteinuria (>30 mg/dl/day), kidney weight (2.095 g), which was extremely significantly reduced in drug treatment groups with Aliskiren, Valsartan and combination of Aliskiren and Valsartan (Table1). The combination of Aliskiren and Valsartan extremely significantly reduced kidney weight (1.27 g) compared to the monotherapy with either Aliskiren (1.465 g) or Valsartan (1.570 g) (Fig. 5).

Histopathology: In control rats, the kidney cortex appeared normal with only some glomeruli displaying thickened glomerular basement membranes (GBM) (Fig. 6, Fig. 7). In contrast, in diabetic rats treated with Aliskiren, Valsartan, or a combination of Aliskiren and Valsartan, glomerular pathology was improved (Fig. 8 and Fig. 9).

Glomerulosclerotic index (GSI): Diabetes was associated with an increase in GSI. Compared to diabetic control rats, GSI was lower in diabetic rats treated with either Aliskiren or Valsartan and the combination of Aliskiren and Valsartan. There is extremely significant reduction in the GSI of diabetic rats treated with combination of Aliskiren and Valsartan (0.05) compared with Aliskiren (0.35), Valsartan (0.435) monotherapy (Fig. 6).

Table1 Proteinuria (mg/dl/day) in control and STZ induced diabetic rats treated with mono-and combination therapies of aliskiren and valsartan.

<table>
<thead>
<tr>
<th>Group</th>
<th>&lt; 30 mg/dl</th>
<th>&gt; 30 mg/dl</th>
<th>Observation</th>
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<tbody>
<tr>
<td>Control</td>
<td>Yellow</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>Yellow – Green</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Yellow</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Yellow</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Aliskiren + Valsartan</td>
<td>Yellow</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

Fig. 5 Kidney weight (g) in control and STZ induced diabetic rats treated with mono- and combination therapies of aliskiren and valsartan. ***P<0.001 vs combination of aliskiren and valsartan. + P<0.001 vs diabetic control. Values are expressed as means ± S.D. N=4 rats/group.
Fig. 6 Representative periodic acid-Schiff’s reagent-stained section from a. control rat, only minimal glomerulosclerosis was noted, b. diabetic control rat was associated with marked glomerulosclerosis, c. Aliskiren, d. Valsartan treated diabetic rats were associated with a significant reduction in the glomerulosclerosis, e. combination of aliskiren and valsartan treated diabetic rat was associated with extremely significant reduction in the glomerulosclerosis compared with monotherapy of either.
**Quantitation of matrix deposition:** In the tubulointerstitium of kidney cortex or medulla, increased collagen and inflammatory cells were observed in diabetic control rats compared to control rats. Compared to diabetic control rats, interstitial fibrosis was lower in diabetic rats treated with Aliskiren and Valsartan monotherapy and the combination of Aliskiren and Valsartan. There was extremely significant reduction in the interstitial fibrosis of diabetic rats treated with combination of Aliskiren and Valsartan (0.215) compared with Aliskiren (0.665) and Valsartan (1.06) monotherapy. (Fig. 8 and Fig. 9)

**Discussion**

In the present study, the renoprotective effects of Aliskiren, Valsartan and combination of Aliskiren and Valsartan were compared in diabetic nephropathy in rats. Clinical characteristics like blood glucose levels, serum creatinine, urine volume, proteinuria, body weight and kidney weight were estimated in all experimental rats. In addition, kidney histopathological parameters like Glomerulosclerotic index and tubulointerstitial fibrosis were also estimated and compared.

With regard to the attenuation of the decline in renal function, combined Aliskiren and Valsartan treatment significantly reduced serum creatinine, urine volume and kidney weight in comparison with monotherapy of Aliskiren and Valsartan. Body weight of diabetic rats treated with Aliskiren and Valsartan monotherapy and combination of Aliskiren and Valsartan was significantly increased compared with diabetic control rats. By the dual blockade of RAS, with combination of Aliskiren and Valsartan at the two different important steps, the renin activation might effectively prevented progression of diabetic nephropathy to end stage renal disease.

Aliskiren acts through the direct renin inhibition which is the rate limiting step for the activation of RAS. It binds to the active sites of renin, preventing angiotensinogen from binding and being cleaved to form angiotensin I, thereby inhibiting the activation of renin system at the rate limiting step. It is possible that Aliskiren also differs from ACEIs or ARBs in other ways that might explain these results. In 2002, Nguyen et.al discovered a (pro) renin receptor that was detected in the brain, heart, liver, and kidney. Prorenin, when bound to the (pro) renin receptor, displayed enzymatic activity and activation of intracellular signaling pathways without proteolytic removal of the prosegment. Recent studies in animals with diabetes and in *in-vitro* conditions with high glucose have shown that aliskiren reduced the number of (pro) renin receptors in the kidney, mitigated profibrotic activity in the kidney, and nearly abolished the apoptotic effects on cultured podocytes. Furthermore, data from transgenic (mRen-2)27 rats with diabetes suggest that aliskiren has a greater renoprotective capacity than ACE inhibitors (Wlodzimierz Buczko and Justyna M. Hermanowicz, 2008).
Fig. 8  Representative Masson’s trichrome-stained section from a. control rat, very little collagen (blue staining) is present within the interstitium, b. diabetic control rat, extensive collagen (blue staining) is present within the interstitium indicating extensive interstitial fibrosis, c. Aliskiren, d. Valsartan treated diabetic rats, interstitial fibrosis was significantly reduced, e. Combined aliskiren and valsartan treated diabetic rat, interstitial fibrosis was extremely significantly reduced compared with monotherapy of either.
Valsartan acts by blocking the binding of angiotensin II to the AT1 receptor, thereby preventing the activation of RAS. Clinical characteristics of the diabetic control rats and diabetic rats treated with Aliskiren and Valsartan monotherapy and combination therapy clearly suggest that combination therapy is more effective than the monotherapy.

In diabetic rats, high glucose activates the RAS, providing a further mechanism for a diabetic-induced amplification of angiotensin II-mediated tissue injury. RAS plays a central role in mesangial cell proliferative signaling, angiotensin II is a major contributor to the apoptosis of proximal tubular cells either directly or via other injurious cytokines, such as transforming growth factor-beta and platelet-derived growth factor. In diabetic rats, glomerular angiotensin II levels are increased due to increase in angiotensinogen. Angiotensin II also produces deleterious effects on kidney by affecting the blood pressure and renal hemodynamics, renal tubular and glomerular hypertrophy and oxidative stress in kidney. Therefore, blockade of angiotensin II is very important factor for preventing the progress of DN. Hence, activation of RAS leads to the increased glomerular basement membrane thickness, glomerulosclerotic index, mesangial expansion and tubulointerstitial fibrosis in diabetic rat kidney. Further, these histopathological changes lead to increased kidney weight, protein synthesis, proteinuria and serum creatinine and urine volume.

In the present study, after 8th week, fewer numbers of rats were studied for renal structural damage. Combination of Aliskiren and Valsartan exerted a significant additive effect in reducing the development of severe glomerulosclerosis, tubulointerstitial fibrosis compared to Aliskiren and Valsartan monotherapy. Tubulointerstitial injury is a major feature of diabetic nephropathy and also an important predictor of renal dysfunction and the response to therapeutic interventions in both the experimental and human settings (Hans-Henrik Parving, 2008).

This difference may be due to the combined blockade of RAS, direct inhibition of renin with aliskiren and blockade of angiotensin II at its receptor level which more effectively prevents the formation and activation of angiotensin II in diabetic kidney. In Valsartan monotherapy, there are chances, for the binding of angiotensin II to AT1 receptor, when it is over expressed. In Aliskiren monotherapy, the binding of circulating angiotensin II to AT1 receptor may occur, which leads to further progression of the diabetic nephropathy. Hence, the combination of Aliskiren and Valsartan is more effective than the monotherapy of either drug in prevention of progression of diabetic nephropathy to end stage renal disease.

The present study reports that in a model of severe renal pathology in diabetic Wistar rat, low dose combination therapy of Aliskiren and Valsartan was more
efficacious than either monotherapy in improving severe diabetic glomerulosclerosis and effective at ameliorating the decline in renal function and increase in proteinuria.

Conclusion. Proteinuria, serum creatinine, kidney weight and urine volume were significantly reduced and body weight was significantly increased in diabetic rats treated with combination of Aliskiren and Valsartan compared with that of monotherapy with either or Glomerulosclerotic Aliskiren or Valsartan index and tubulointerstitial fibrosis were significantly decreased in diabetic rats treated with combination of Aliskiren and Valsartan compared with Aliskiren and Valsartan monotherapy. Hence, from the results of present study, combination of novel direct renin inhibitor-Aliskiren and ARB-Valsartan is more renoprotective compared to Aliskiren and Valsartan monotherapy in progressive diabetic nephropathy.

References


