Jordan Journal of Pharmaceutical Sciences, Volume 7, No. 1, 2014

Comparative Study on Renoprotective Effect of Aliskiren-Pentoxifylline Combination, Valsartan and Enalapril Among Patients with Hypertension, Type 2 Diabetes Mellitus and Diabetic Nephropathy

Amin T. Hamed [1] ***and Mohammed M. Taha*** [2]***

[1] Associate Professor of Pharmacology, Department of Pharmacology, Faculty of Pharmacy, Al-Azhar University, Jamal Abdel Nasser Street, Gaza-Palestine.
[2] Master degree in Pharmacology, Department of Pharmacology, Faculty of Pharmacy, Al-Azhar University, Jamal Abdel Nasser Street, Gaza-Palestine.

ABSTRACT

This study was conducted to evaluate the renoprotective effect of aliskiren-pentoxifylline combination and compare it with enalapril and valsartan in patients with hypertension, type 2 diabetes mellitus and diabetic nephropathy (DN). Sixty patients with hypertension, type 2 diabetes mellitus and microalbuminurea (20-200µg/min or 30-300mg/24h) were selected from UNRWA and private clinics in Gaza Strip and divided into three groups. The first group (n=20) was treated with enalapril (10-20mg/day), the second group (n=20) was treated with valsartan (160mg/day), whereas the third group (n=20) was treated with aliskiren-pentoxifylline combination (150,400mg/day). All patients were followed-up for nine months by measuring serum creatinine level and urinary albumin excretion (UAE) rate before and at 3, 6 and 9 months of treatment. Paired T-test and independent T-test were used to analyze our results and the significance was tested at $p \leq 0.05$. The results showed a significant reduction in both UAE rate and serum creatinine level among patients who used aliskiren-pentoxifylline combination after 6 and 9 months of treatment, where the reduction was highly significant after 9 months of treatment *(p=0.001 for UAE, p=0.000 for serum creatinine level)*. In the valsartan treated group, the reduction in UAE rate was significant (*p=0.045*) after 9 months of treatment, while no significant reduction was noticed in serum creatinine level (*p=0.807*). Moreover, no significant reduction was seen in UAE rate (*p=0.125*) and serum creatinine level (*p=0.445*) among patients who were given enalapril. In conclusion, aliskiren-pentoxifylline combination showed renoprotective effect more distinct than enalapril and valsartan among patients with DN.

Keywords: Diabetic Nephropathy, Aliskiren-Pentoxifylline Combination, Valsartan, Enalapril, Renoprotective Effect, Urinary albumin excretion (UAE) rate.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism owing to defects in insulin secretion, insulin action or combination of both factors [1,2]. Diabetic nephropathy (DN) is considered as one of the major complications of DM which can develop in more than 40% of patients with DM [2-4]. It is a progressive kidney

* dr.mtaha@hotmail.com
Received on 8/5/2013 and Accepted for Publication on 17/9/2013.

disease caused by angiopathy of capillaries in the kidney glomeruli due to longstanding DM [5]. Moreover, DN is characterized by both functional and structural changes in the kidney, the structural changes include GBM thickening, glomerular and tubular hypertrophy, mesangial expansion and accumulation of extracellular matrix (ECM) proteins [6-8]. On the other hand, the functional changes include microalbuminuria, proteinuria, reduction in glomerular filtration rate and elevation in both serum creatinine and blood urea nitrogen levels, where the major functional parameter of DN is microalbuminuria [9,10]. Microalbuminuria is defined as urinary albumin excretion (UAE) rate of 20-200 µg/min (30-300 mg/24h) [11,12]. Chronic hyperglycemia is responsible for development of DN through four biochemical pathways: advanced glycation end-products (AGEs) pathway, protein kinase C (PKC) pathway, hexosamine biosynthetic pathway (HBP) and aldose reductase (AR) pathway [13,14]. Furthermore, abnormal activation of the renin-angiotensin system (RAS) by chronic hyperglycemia plays an important role in development of DN [15]. To illustrate, Angiotensin II (Ang II) which is the dominant effector of RAS, has a vital role in development of DN via its potent effects on renal structure and function [16]. It leads to mesangial expansion by stimulating the production of transforming growth factor-β1 (TGF-β1), a potent cytokine that stimulates the production of other growth factors as collagen and fibronectin [17,18]. It also increases plasminogen activator inhibitor-1 (PAI-1) synthesis and inhibits the activity of mesangial cell collagenase which results in matrix accumulation [19]. Ang II also generates oxidative stress via NADPH oxidase [20]. In addition, Ang II increases glomerular permeability of protein and impairs the size-selective function of glomerular filter by decreasing nephrin expression, a protein of the slit diaphragm implicated in pathogenesis of proteinuric conditions [21,22]. Additionally, renin which is the rate-limiting step of RAS, can also initiate DN by stimulating the production of TGF-β1, PAI-1, fibronectin and collagen through activation of the extracellular signal regulated kinases 1 and 2 (ERK1/2) pathway in mesangial cells [23, 24]. Thus, blocking RAS by angiotensin converting enzyme inhibitors (ACEIs), Ang II receptor blockers (ARBs) or direct renin inhibitors (DRIs) has many advantages with respect to renal function in patients with hypertension and type 2 DM [15]. Neither ACEIs nor ARBs can avoid the progression of DN completely, where they can decrease proteinuria by 30-35% [25, 26]. So the use of aliskiren which is the first agent that inhibits renin may have better effect on kidney functions than ACEIs or ARBs [27]. In addition, some studies have shown that inflammation plays a vital role in the development of DN [28, 29]. So drugs which have anti-inflammatory effects can be applied for treatment of DN. For example, pentoxifylline, a methylxanthine derivative with anti-inflammatory and antiproliferative properties, can moderate kidney functions by inhibiting the accumulation of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and IL-6 [30, 31].

This study was conducted to assess the renoprotective effects of aliskiren-pentoxifylline combination (DRI plus xanthine derivative) and compare it with enalapril(ACEI) and valsartan (ARB) among patients with hypertension, type 2 DM and diabetic nephropathy.

2. SUBJECTS, MATERIALS AND METHODS

2.1. Study Design

This study is a non-randomized, prospective-comparative study in which the renoprotective effect of aliskiren-pentoxifylline combination was evaluated and compared with enalapril and valsartan in patients with hypertension, type 2 DM and diabetic nephropathy.

2.2. Patients

2.2.1. Study Population and Sample Size

Participants of the study were patients with hypertension, type 2 DM and diabetic nephropathy from both genders. The sample size was sixty patients divided into three groups (each group consisted of 20 patients) according to the treatment protocol. They were selected from private clinics and UNRWA health centers in Gaza Strip.

2.2.2. Selection Criteria

Patients were considered eligible in this study upon meeting the following criteria: (1) both genders older

than 40 years. (2) have hypertension, type 2 DM and diabetic nephropathy. (3) use enalapril (10-20 mg/day) to treat hypertension. (4) urinary albumin excretion (UAE) rate should be 20-200 μg/min or 30-300mg/day [microalbuminuria stage]. (5) serum creatinine level should be ≤ 1.8 mg/dL for men and ≤ 1.5 mg/dL for women.

2.2.3. Exclusion Criteria

Exclusion criteria were as follows: (1) underlying type 2 DM without diabetic nephropathy. (2) non-diabetic kidney disease. (3) end-stage renal disease [ESRD]. (4) previous use of aliskiren, pentoxifylline or valsartan.

2.3. Treatment Protocol

Patients participating in the study (60 patients) were divided into three groups (each group consisted of 20 patients) according to the treatment protocol. The first group (n=20) continued using enalapril (10-20 mg/day), the second group (n=20) was treated with valsartan (160 mg/day) instead of enalapril, whereas the third group was treated with aliskiren-pentoxifylline combination (150, 400 mg/day) also instead of enalapril. All patients used the previous drugs protocol for 9 months. Participants were able to use any oral hypoglycemic agent or insulin therapy according to physician instructions.

2.4. Methods

2.4.1. Hematological Analysis

Hematological analysis was performed for each patient before and at 3, 6 and 9 months of treatment. One day before the required analysis, participants were phoned and asked to fast for 12 hours. Blood samples taken from patients were sent to the laboratory to perform the required tests which included serum creatinine level and fasting plasma glucose (FPG).

2.4.2. Urinalysis

Urine analysis was performed for our patients before and at 3, 6 and 9 months of treatment. Two days before the visit, patients were phoned to collect their urine throughout the day (24 hours) in a suitable container. Then urine samples were sent to the laboratory to measure UAE rate.

2.4.3. Blood Pressure Measurement

Blood pressure was measured for all patients with a mercury sphygmomanometer. Systolic and diastolic blood pressures were measured for our patients every 3 months of treatment throughout the study period (9 months). Before measuring, patients were rested for 10 min, then BP was measured three times on the left arm. Finally, the average of the three readings was recorded for each patient.

2.4.4. Statistical Analysis

The collected data was analyzed using the statistical package of social science (SPSS) software package version 16. Statistical tests as frequency and distribution were done to express our data as numbers and percentages. Moreover, paired T-test was performed to compare urinary albumin excretion rates and serum creatinine levels individually in each group before and at 3, 6 and 9 months of treatment, whereas independent T-test was used to compare aliskiren-pentoxifylline combination treated group with enalapril and valsartan treated groups for their urinary albumin excretion rates and serum creatinine levels. Significance of the association was tested at an alpha value of ≤ 0.05.

3. RESULTS

3.1. Characteristics of the Study Population

Participants included in this study were sixty patients divided into three groups according to the drug protocol used. The first group was treated with enalapril and included 13 (65%) males; 7 (35%) females. The age of participants was from 50 to 61 years with a mean of 55.5 ± 3.3 and they had type 2 DM from 9 to 16 years with a mean of 12.25 ± 2.35, while they had hypertension from 6 to 12 years with a mean of 8.9 ± 1.98 (table 1). The second group was treated with valsartan and included 12 (60%) males and 8 (40%) females and their age ranged from 51 to 60 years with a mean of 55.05 ± 2.6. Moreover, the patients had type 2 DM and hypertension from 8 to 14 years with a mean of 11.7 ± 2 and from 6 to 12 years with a mean of 9.1 ± 2, respectively (table 1). The third group was treated with aliskiren-pentoxiphylline combination and both genders were represented equally (10 males and 10 females), their age ranged from 49 to 60 years with a mean of 55.55 ± 2.9. In

addition, they had type 2 DM from 8 to 15 years with a mean of 12.05 ± 2.3, and hypertension from 7 to 13 years with a mean of 9.85 ± 2.15 (table 1).

3.2. Effect of Drugs on Urinary Albumin Excretion (UAE) Rate and Serum Creatinine Level (mg/dL)

3.2.1. Effect of Enalapril Treatment on UAE Rate (µg/min) and Serum Creatinine Level (mg/dL) in Patients before and at 3, 6 and 9 Months of Treatment

Results in table (2) show the effect of enalapril (10-20mg/day) on UAE rate and serum creatinine level. Enalapril showed no statistical significant effect (*P>0.05*) on UAE rate and serum creatinine level during the study period (9 months). The UAE rate was variable, it increased from 113 ± 10.679 µg/min at beginning of the study to 115 ± 9.862 µg/min after 3 months and then to 117.65 ± 6.761 µg/min after 6 months, however, it decreased back to 116.35 ± 6.564 µg/min after 9 months of the treatment. Regarding serum creatinine level, it insignificantly (*P>0.05*) decreased from 1.328 ± 0.052 mg/dL at baseline to 1.325 ± 0.054 mg/dL and then to 1.324 ± 0.053 mg/dL after 3 and 6 months of enalapril (10-20 mg/day) treatment, respectively. However, it increased to 1.332 ± 0.044 mg/dL after 9 months of treatment (table 2).

3.2.2. Effect of Valsartan Treatment on UAE Rate (µg/min) and Serum Creatinine Level (mg/dL) in Patients before and at 3, 6 and 9 Months of Treatment

The effect of valsartan (160 mg/day) on UAE rate and serum creatinine level is indicated in table (3). The results show that UAE rate decreased significantly (*P<0.05*) only after 9 months of valsartan treatment, where it decreased from 117.95 ± 8.075 µg/min at baseline to 115.70 ± 6.736 µg/min after 9 months of treatment. On the contrary, no significant (*P>0.05*) decrease was shown in serum creatinine levels after 9 months of valsartan (160 mg/day) use. To illustrate, the serum creatinine level decreased from 1.326 ± 0.036 mg/dL at baseline to 1.325 ± 0.038 mg/dL after 3 months. After 6 months of treatment, it returned to the same baseline value and increased after 9 months to reach a value of 1.328 ± 0.035 mg/dL.

3.2.3. Effect of Aliskiren-Pentoxiphylline Combination on UAE Rate (µg/min) and Serum Creatinine Level (mg/dL) in Patients before and at 3, 6 and 9 Months of Treatment

Data analysis revealed a highly significant (*P<0.05*) reduction in both UAE rate and serum creatinine level after 6 and 9 months of aliskiren-pentoxiphylline (150, 400 mg/day) combination when compared with baseline value. The UAE rate decreased to 111.50 ± 10.405 µg/min and then to 107.70 ± 10.780 µg/min after 6 and 9 months of treatment, respectively (table 4). Concerning the serum creatinine level, it decreased from 1.319 ± 0.035 mg/dL at baseline to 1.316 ± 0.036 mg/dL and then to 1.302 ± 0.035 after 6 and 9 months of treatment, respectively (table 4).

3.3. Drugs Effect on Urinary Albumin Excretion (UAE) Rate and Serum Creatinine Level (mg/dL) in Different Groups

3.3.1. UAE rates among Patients Treated with Enalapril, Valsartan or Aliskiren-Pentoxiphylline Combination during the Study Period

The results in table (5) as well as figure 1 compare the effect of aliskiren-pentoxiphylline (150, 400 mg/day) combination and the effect of enalapril (10-20 mg/day) and valsartan (160 mg/day) on UAE rates. There was no significant difference (*P>0.05*) neither at baseline where the levels were 113.45 ± 10.679 µg/min for enalapril, 117.95 ± 8.075 µg/min for valsartan and 113.33 ± 7.631 µg/min for aliskiren-pentoxiphylline combination, nor after 3 months of treatment, as the levels were 115 ± 9.862 µg/min, 116.95 ± 8.648 µg/min and 112.55 ± 9.517 µg/min for enalapril, valsartan and aliskiren-pentoxiphylline, respectively. However, a statistical significant difference (*P<0.05*) between the UAE rates was found after 6 and 9 months of treatment, the significance was more pronounced after 9 months (*P<0.01*). The UAE rates were 116.35 ± 6.564 µg/min for enalapril, 115.70 ± 6.736 µg/min for valsartan and 107.70 ± 10.780 µg/min for aliskiren-pentoxiphylline combination after 9 months of treatment.

3.3.2. Serum Creatinine Levels (mg/dL) among Patients Received Enalapril, Valsartan or Aliskiren-Pentoxiphylline Combination during the Study Period

The results shown in table (6) compare the effect of aliskiren-pentoxiphylline (150, 400 mg/day) combination and the effect of enalapril (10-20 mg/day) and valsartan (160 mg/day) on serum creatinine levels. Our findings showed no statistical significant difference (*P>0.05*) between the serum creatinine levels at baseline in the enalapril (1.328 ± 0.052 mg/dl), valsartan (1.326 ± 0.036 mg/dl) and aliskiren-pentoxiphylline treated patients (1.319 ± 0.035 mg/dl). Similarly, the difference in serum creatinine levels continued to be insignificant even after 3 and 6 months of treatment. In contrast, the results after 9 months of enalapril (1.332 ± 0.044 mg/dl), valsartan (1.328 ± 0.035 mg/dl) or aliskiren-pentoxiphylline (1.302 ± 0.035 mg/dl) treatment demonstrated a statistical significant difference (*P<0.05*) among the serum creatinine levels (figure 2).

4. DISCUSSION

4.1. Effect of Enalapril on Urinary Albumin Excretion (UAE) Rate and Serum Creatinine Level

Abnormal activation of RAS plays a vital role in the development of DN through Ang II that is produced from Ang I via ACE, so the use of ACEIs may improve renal function in patients with DN [15,32]. The results of our study showed insignificant reduction (P>0.05) in UAE rate and serum creatinine level among patients who used enalapril (10-20mg/day) throughout the study period (9 months). The mean UAE rate increased from 113 ± 10.679 µg/min at the beginning of the study to 116.35 ± 6.564 µg/min after 9 months of enalapril treatment. The obtained result was compatible with a study performed in Japan by Baba, 2001. In that study, the mean UAE rate in 208 patients who received enalapril (5-20 mg/day) increased from 42 mg/day at baseline to 74 mg/day after 2 years of treatment [33]. This result was explained by inability of ACEIs to produce complete suppression of Ang II, where approximately 40% of Ang II found in the kidney is generated by ACE- independent alternate pathways such as chymase pathway, therefore its level is not inhibited completely and may return to the normal level after several days [25,34]. However, some studies including Ravid et al., (1996) and Chan et al., (2000) reported a positive effect of enalapril on UAE rate [35,36]. This positive effect was probably related to the high dose of the drug used (40 mg/day in Chan et al., study) or to the long period of the study (7 years in Ravid et al., study).

In case of serum creatinine level, our study indicated that it increased from 1.328 ± 0.052 mg/dL at baseline to 1.332 ± 0.044 mg/dL at 9 months of treatment. This result was similar to the results of previous studies as Chan et al. (2000) and Baba (2001). For example, Baba (2001) showed that the serum creatinine level in 208 patients who received enalapril (20 mg/day) was 0.76 ± 0.02 mg/dL at baseline. He found no significant reduction in serum creatinine level in those patients after two years of enalapril treatment [33].

4.2. Effect of Valsartan on Urinary Albumin Excretion (UAE) Rate and Serum Creatinine Level

Although ACEIs block the conversion of Ang I to Ang II by ACE, they do not block the production of Ang II by non-ACE pathways such as chymase pathway [34]. Ang II has a vital role in the pathophysiology of DN via its interaction with the AT_1 receptor [34].

Our findings showed a statistically significant decrease in the mean UAE rate (*P<0.05*) but only after 9 months of valsartan (160 mg/day) treatment, where it decreased from 117.95 ± 8.075 µg/min at baseline to 115.70 ± 6.736 µg/min. Various studies including Suzuki et al. (2002) and Viberti et al. (2002) have evaluated the renoprotective effect of ARBs [37,38]. For instance, the results of our study were compatible to that obtained by Viberti et al. in 2002, their study was carried out to investigate the effect of valsartan on UAE rate in patients with type 2 DM and microalbuminuria. In that study, three hundred and thirty-two patients with type 2 DM and microalbuminuria were randomly assigned to 80 mg/day valsartan (n=169) or 5 mg/day amlodipine (n=163) and followed up for 6 months. Six months of valsartan therapy showed a statistical significant decrease in UAE rate, it decreased from 57.9 (33-102.3) µg/min at baseline to 33.7 (18.8-60.3) µg/min after 6 months of treatment [38].

In a different study done by Suzuki and his colleagues (2002), forty patients with type 2 DM and DN treated with 40 mg/day valsartan for 6 months and found an insignificant reduction in the UAE rate [37]. Concerning serum creatinine level, it was variable throughout the study period following valsartan use. It decreased from 1.326 ± 0.036 mg/dL at baseline to 1.325 ± 0.038 mg/dL after 3 months. After 6 months of treatment, it returned to the same baseline value, and then it increased to reach a value of 1.328 ± 0.035 mg/dL after 9 months. These findings were in agreement with the results obtained by many studies including Suzuki (2002) and Viberti et al. (2002) [37,38]. The results of those studies concluded that valsartan had no positive effect on serum creatinine level. Suzuki and his colleagues (2002), for example, found that serum creatinine level remained stable before (0.8±0.3 mg/dL) and after (0.8±0.5 mg/dL) treatment with valsartan [37].

4.3. Effect of Aliskiren-Pentoxiphylline Combination on Urinary Albumin Excretion (UAE) Rate and Serum Creatinine Level

Despite their renoprotective effect, both ACEIs and ARBs cannot prevent the progression of DN completely because they increase plasma renin level and its activity [26,39,40]. Recent studies demonstrated that renin plays a key role in the development of DN by binding to (Pro)renin Receptor [(P)RR] in glomerular mesangial cells [41,42]. The binding of renin to (P)RR stimulates the production of TGF-β, PAI-1, fibronectin, and collagen through the angiotensin-independent extracellular signal-regulated kinase 1 and 2 (ERK 1/2) pathway [23,24,43]. The results of this study indicate that aliskiren-pentoxiphylline (150, 400 mg/day) combination significantly (*P<0.05*) reduced both UAE rate and serum creatinine level after 6 and 9 months of treatment. The UAE rate decreased from 113.33 ± 7.761 µg/min at baseline to 111.50 ± 10.405 µg/min after 6 and then to 107.70 ± 10.780 µg/min after 9 months of treatment (table 4). In addition, our findings showed that aliskiren-pentoxiphylline combination had an efficient effect on renal function by decreasing the serum creatinine level significantly (*P<0.05*). To exemplify, serum creatinine level decreased from 1.319 ± 0.035 mg/dL at baseline to 1.316 ± 0.036 mg/dL, and then to 1.302 ± 0.035 mg/dL after 6 and 9 months of treatment, respectively (table 4). To date, no study had evaluated the antiproteinuric effect of aliskiren-pentoxiphylline combination. For this reason our results are not compared with the results of other studies.

Moreover, our study demonstrated that the reduction produced by the combination throughout the study period (9 months) in both UAE rate and serum creatinine level was more noticeable than the reduction produced by the other drugs used in the study. To illustrate, the significant reduction in the UAE rate occurred at the 6th month of the combination use, whereas it occurred after 9 months of valsartan use and it did not occur with enalapril over the study period (figure 1). Moreover, the difference between the mean serum creatinine levels among the three drugs was insignificant at baseline and after 3 and 6 months of therapy. After 9 months of therapy, the difference between the mean serum creatinine levels became significant in both enalapril/aliskiren-pentoxiphylline and valsartan/aliskiren-pentoxiphylline comparisons (figure 2).

The most possible explanation of these advantages for aliskiren-pentoxiphylline combination over other drugs used in the study is related to the mechanism by which both aliskiren and pentoxifylline can produce their antiproteinuric effects. The antiproteinuric effect of aliskiren was previously elucidated, while the antiproteinuric effect of pentoxifylline has been explained by three probable mechanisms. First, pentoxifylline reduces glomerular hydraulic pressure and proteinuria by decreasing the blood viscosity [44]. Second, pentoxifylline can reduce hyperfiltration and proteinuria by antagonism of adenosine (renal overproduction of adenosine is associated with hyperfiltration and proteinuria) [44]. Third, pentoxifylline reduces the production and secretion of TNF and MCP-1, which play an essential role in DN pathogenesis.

5. CONCLUSION

At the end of the study and based on the obtained results, we conclude the followings:

1. Aliskiren-pentoxifylline (150,400 mg/day) combination had renoprotective effect among patients

with hypertension, type 2 DM and diabetic nephropathy. It significantly reduced UAE rate after 6 and 9 months of treatment and the reduction produced after 9 months of treatment was more distinct.

2. Aliskiren-pentoxifylline combination (150,400 mg/day) had positive effect on serum creatinine level, where it significantly decreased after 6 and 9 months of treatment.

3. In the valsartan (160 mg/day) treated group, there was a significant reduction in UAE rate after 9 months of treatment only, while a clear increase in UAE rate at the end of the study period was found after using of enalapril (10-20mg/day).

4. The study indicated that neither enalapril nor valsartan treatment caused an efficient effect on serum creatinine level among patients in this study.

5. The use of aliskiren-pentoxifylline combination would have better and earlier renoprotective effect than enalapril or valsartan.

ACKNOWLEDGMENT

We would like to thank the director of health department at UNRWA for his recommendations and facilities provided to conduct this study.

Ethical Approval

The study was approved by Helsinki Committee of ministry of health-Palestine at 6/6/2011.

Conflict of Interest

There is no conflicts of interest**.**

Table 1. Characteristics of the study population

Variable	Enalapril Group (N=20)	Valsartan Group (N=20)	Aliskiren-Pentoxiphylline Group (N=20)
Sex	(13 males and 7 females)	(12 males and 8 females)	(10 males and 10 females)
Age (years)	55.5 ± 3.3	55.05 ± 2.6	55.55 ± 2.9
Duration of DM type 2 (years)	12.25 ± 2.35	11.7 ± 2	12.05 ± 2.3
Duration of HTN (years)	8.9 ± 1.98	9.1 ± 2	7-13 (9.85 ± 2.15)
FPG (mg/dl)			
• *Baseline*	133.55 ± 4.70	134.10 ± 2.42	133.19 ± 3.97
• *After 3 months*	130.80 ± 4.48	130.75 ± 5.52	131.45 ± 2.91
• *After 6 months*	129.95 ± 3.70	130.35 ± 4.26	129.35 ± 5.17
• *After 9 months*	130.45 ± 3.53	131.10 ± 7.05	130.80 ± 4.95
SBP (mmHg)			
• *Baseline*	135.40 ± 3.12	135.40 ± 4.98	136.69 ± 3.02
• *After 3 months*	136.05 ± 2.98	135.60 ± 1.79	136.70 ± 2.97
• *After 6 months*	134.95 ± 2.44	135.35 ± 3.49	135.45 ± 4.11
• *After 9 months*	135.70 ± 3.01	134.55 ± 3.47	135.30 ± 2.47
DBP (mmHg)			
• *Baseline*	87.50 ± 2.37	87.25 ± 2.02	85.62 ± 2.36
• *After 3 months*	85.65 ± 1.42	86.55 ± 1.64	85.80 ± 2.58
• *After 6 months*	86.20 ± 1.70	87.15 ± 1.69	85.10 ± 2.53
• *After 9 months*	86.05 ± 1.57	85.90 ± 1.58	85.40 ± 3.15

DM: Diabetes mellitus, HTN: Hypertension, FPG: Fasting plasma glucose, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. Data are expressed as mean ± S.D

Table 2. Urinary albumin excretion (UAE) rate (µg/min) and Serum creatinine levels (mg/dL) of patients before and after 3, 6 and 9 months of Enalapril (10-20 mg/day) treatment

Time	No.	UAE rate (µg/min) Mean ± S.D.	p-value §	Serum creatinine level (mg/dL) Mean ± S.D.	p-value §
Before enalapril	20	113.45 ± 10.679		1.328 ± 0.052	
After 3 months	20	115.00 ± 9.862	0.177[a]	1.325 ± 0.054	0.500[a]
After 6 months	20	117.65 ± 6.761	0.055[b]	1.324 ± 0.053	0.528[b]
After 9 months	20	116.35 ± 6.564	0.125[c]	1.332 ± 0.044	0. 445[c]

(§) p-values ($P<0.05$) are calculated by paired-samples t-test. (a) p-value for tested parameter before and after 3 months of treatment. (b) p-value for tested parameter before and after 6 months of treatment. (c) p-value for tested parameter before and after 9 months of treatment.

Table 3. Urinary albumin excretion (UAE) rate (µg/min) and Serum creatinine levels (mg/dL) of patients before and after 3, 6 and 9 months of Valsartan (160 mg/day) treatment

Time	No.	UAE rate (µg/min) Mean ± S.D.	p-value §	Serum creatinine level (mg/dL) Mean ± S.D.	p-value §
Before valsartan	20	117.95 ± 8.075		1.326 ± 0.036	
After 3 months	20	116.95 ± 8.648	0.438[a]	1.325 ± 0.038	0.913[a]
After 6 months	20	117.35 ± 6.011	0.655[b]	1.326 ± 0.036	0.956[b]
After 9 months	20	115.70 ± 6.736	0.045[c]	1.328 ± 0.035	0.807[c]

(§) p-values (P<0.05) are calculated by paired-samples t-test. (a) p-value for tested parameter before and after 3 months of treatment. (b) p-value for tested parameter before and after 6 months of treatment. (c) p-value for tested parameter before and after 9 months of treatment.

Table 4. Urinary albumin excretion (UAE) rate (µg/min) and Serum creatinine levels (mg/dL) of patients before and after 3, 6 and 9 months of Aliskiren-Pentoxiphylline (150, 400 mg/day) treatment

Time	No.	UAE rate (µg/min) Mean ± S.D.	p-value §	Serum creatinine level (mg/dL) Mean ± S.D.	p-value §
Before aliskiren-pentoxiphylline	20	113.33 ± 7.631		1.319 ± 0.035	
After 3 months	20	112.55 ± 9.517	0.077[a]	1.318 ± 0.044	0.459[a]
After 6 months	20	111.50 ± 10.405	0.020[b]	1.316 ± 0.036	0.006[b]
After 9 months	20	107.70 ± 10.780	0.001[c]	1.302 ± 0.035	0.000[c]

(§) p-values (P<0.05) are calculated by paired-samples t-test. (a) p-value for tested parameter before and after 3 months of treatment. (b) p-value for tested parameter before and after 6 months of treatment. (c) p-value for tested parameter before and after 9 months of treatment.

Table 5. Urinary albumin excretion (UAE) rate (µg/min) of patients before and after 3, 6 and 9 months of Enalapril (10-20 mg/day) Valsartan (160 mg/day) or Aliskiren-Pentoxiphylline (150, 400 mg/day) combination treatment

Time	Drug	No.	UAE rate mean ± S.D.	p-value ¥
Baseline	Enalapril	20	113.45 ± 10.679	
	Valsartan	20	117.95 ± 8.075	0.972*
	Aliskiren-Pentoxiphylline	20	113.33 ± 7.631	0.096[Δ]
After 3 months	Enalapril	20	115.00 ± 9.862	
	Valsartan	20	116.95 ± 8.648	0.429*
	Aliskiren-Pentoxiphylline	20	112.55 ± 9.517	0.134[Δ]
After 6 months	Enalapril	20	117.65 ± 6.761	

	Valsartan	20	117.35 ± 6.011	0.033*
	Aliskiren-Pentoxiphylline	20	111.50 ± 10.405	0.036$^{\Delta}$
After 9 months	Enalapril	20	116.35 ± 6.564	
	Valsartan	20	115.70 ± 6.736	0.004*
	Aliskiren-Pentoxiphylline	20	107.70 ± 10.780	0.008$^{\Delta}$

(¥) p-values (P<0.05) are calculated by independent-samples t-test.

(*) p-value of comparison between effect of Aliskiren-Pentoxiphylline and Enalapril on UAE rate. ($^{\Delta}$) p-value of comparison between effect of Aliskiren-Pentoxiphylline and Valsartan on UAE rat

Table 6. Serum creatinine level (mg/dL) of patients before and after 3, 6 and 9 months of Enalapril (10-20 mg/day) Valsartan (160 mg/day) or Aliskiren-Pentoxiphylline (150, 400 mg/day) combination treatment

Time	Drug	No.	Serum creatinine level (mg/dL) mean ± S.D.	p-value ¥
Baseline	Enalapril	20	1.328 ± 0.052	
	Valsartan	20	1.326 ± 0.036	0.532*
	Aliskiren-Pentoxiphylline	20	1.319 ± 0.035	0.522$^{\Delta}$
After 3 months	Enalapril	20	1.325 ± 0.053	
	Valsartan	20	1.325 ± 0.038	0.681*
	Aliskiren-Pentoxiphylline	20	1.318 ± 0.044	0.597$^{\Delta}$
After 6 months	Enalapril	20	1.324 ± 0.053	
	Valsartan	20	1.326 ± 0.036	0.536*
	Aliskiren-Pentoxiphylline	20	1.316 ± 0.036	0.363$^{\Delta}$
After 9 months	Enalapril	20	1.332 ± 0.044	
	Valsartan	20	1.328 ± 0.035	0.022*
	Aliskiren-Pentoxiphylline	20	1.302 ± 0.035	0.020$^{\Delta}$

(¥) p-values (P<0.05) are calculated by independent-samples t-test.

(*) p-value of comparison between effect of Aliskiren-Pentoxiphylline and Enalapril on UAE rate. ($^{\Delta}$) p-value of comparison between effect of Aliskiren-Pentoxiphylline and Valsartan on UAE rate.

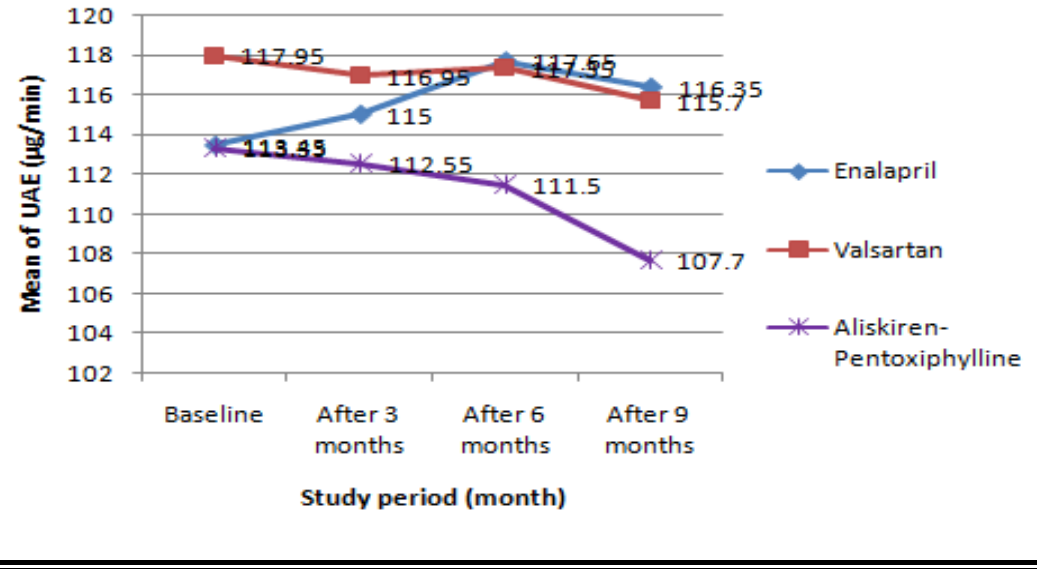

Figure 1. UAE rates (µg/min) among patients treated with Enalapril, Valsartan or Aliskiren-Pentoxiphylline combination during the study period

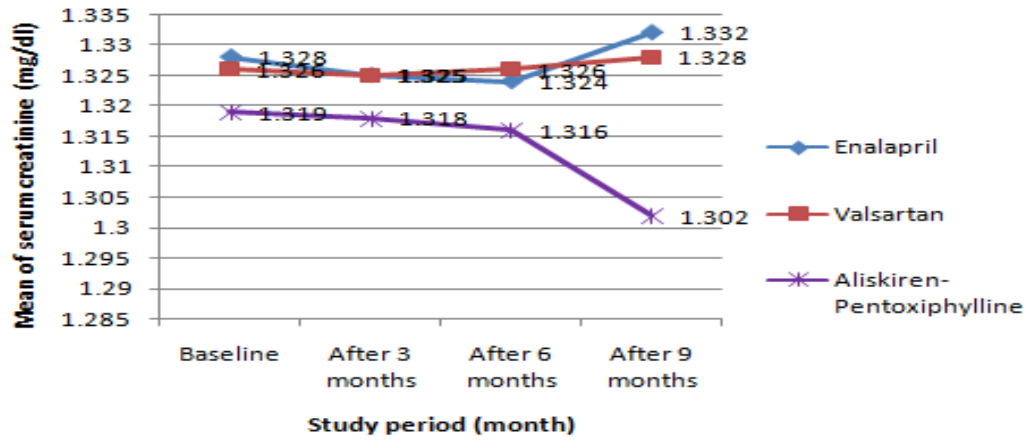

Figure 2. Serum creatinine levels (mg/dL) among patients treated with Enalapril, Valsartan or Aliskiren-Pentoxiphylline combination during the study period

REFERENCES

(1) O'Connor A. and Schelling J. Diabetes and the Kidney. Am. J. Kidney. Dis. 2005; 46(4):766-773.

(2) Balakumar P., Arora MK., Ganti SS., Reddy J. and Singh M. Recent advances in pharmacotherapy for diabetic nephropathy: Current perspectives and future directions. ***Pharmacol. Res***. 2009; 60: 24-32.

(3) Fowler M.J. Microvascular and macrovascular complications of diabetes. ***Clin. Diabetes.*** 2008; 26:77-82.

(4) Atkins RC. The changing patterns of chronic kidney disease: the need to develop strategies for prevention relevant to different regions and countries. ***Kidney Int***. 2005; 98: 83S-85S.

(5) Ritz E. and Tarng D.C. Renal disease in type 2 diabetes. Nephrol. ***Dial. Transplant***. 2001; 16(5):11-18.

(6) Hong D., Zheng T., Jia-qing S., Jian W., Zhi-hong L. and Lei-shi L. Nodular glomerular lesion: A later stage of diabetic nephropathy? *Diabetes Res. Clin. Pract.* 2007; 78:189-195.

(7) Kanwar YS., Wada J., Sun L., Xie P., Wallner EI., Chen S. et al. Diabetic nephropathy: mechanisms of renal disease progression. ***Exp. Biol. Med***. 2008; 233:4-11.

(8) Magri C. and Fava S. The role of tubular injury in diabetic nephropathy. Eur. J. Intern. Med**.** 2009; 20:551-555.

(9) Balakumar P., Chakkarwar VA., Kumar V., Jain A., Reddy J. and Singh M. Experimental models for nephropathy. ***J. Renin Angiotensin Aldosterone Syst***. 2008; 9:189-95.

(10) Chakkarwar VA., Balakumar P. and Singh M. Ameliorative effect of combination of benfotiamine and fenofibrate in diabetes-induced vascular endothelial dysfunction and nephropathy in the rat. ***Mol. Cell. Biol***. 2009; 320:149-62.

(11) Lasaridis A. and Sarafidis P. Diabetic nephropathy and antihypertensive treatment: what are the lessons from clinical trials? ***Am. J. Hypertens***. 2003; 16:689-697.

(12) Araki S., Haneda M., Koya D., Kashiwagi A., Uzu T. and Kikkawa R. Clinical impact of reducing microalbuminuria in patients with type 2 diabetes mellitus. ***Diabetes Res. Clin. Pract***. 2008; 82S:S54-S58.

(13) Kikkawa R., Koya D. and Haneda M. Progression of Diabetic Nephropathy. Am. J. Kidney. Dis**.** 2003; 41(3-1):S19-S21.

(14) Magri C. and Fava S. The role of tubular injury in diabetic nephropathy. Eur. J. Intern. Med**.** 2009; 20:551-555.

(15) Barnett A. Prevention of Loss of Renal Function Over Time in Patients with Diabetic Nephropathy. ***Am. J. Med***. 2006; 119(5A):40S-47S.

(16) Brewster U. and Perazella M. The Renin-Angiotensin-Aldosterone System and the Kidney: Effects on Kidney Disease. ***Am. J. Med***. 2004; 116 (5A):263-272.

(17) Chen S., Lee JS., Iglesias-de la Cruz MC., Wang A., Izquierdo-Lahuerta A., Gandhi NK. et al. Angiotensin II stimulates alpha3(IV) collagen production in mouse podocytes via TGF-beta and VEGF signaling: implications for diabetic glomerulopathy. ***Nephrol. Dial. Transplant***. 2005; 20:1320-1328.

(18) Raij L. The Pathophysiologic Basis for Blocking the Renin-Angiotensin System in *Hypertensive* Patients With Renal Disease. ***Am. J. Hypertens***. 2005; 18:95S-99S.

(19) Mogensen CE. ***The Kidney and Hypertension in Diabetes Mellitus***; Taylor & Francis, London. 2004, p309-354.

(20) Vasavada N. and Agarwal R. Role of Oxidative Stress in Diabetic Nephropathy. Adv. ***Chronic Kidney Dis***. 2005; 12(2):146-154.

(21) LeRoith D., Taylor S., Olefsky J. Diabetes Mellitus: A Fundamental and Clinical Text; Lippincott Williams & Wilkins, Philadelphia, 2004, p459, 1318-1324.

(22) Ziyadeh F. Different roles for TGF-b and VEGF in the pathogenesis of the cardinal features of diabetic nephropathy. *Diabetes Res.* ***Clin. Pract***. 2008; 82s:s38-s41.

(23) Huang Y., Noble NA., Zhang J., Xu C. and Border WA. Renin-stimulated TGF-beta1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. ***Kidney Int***. 2007; 72:45-52.

(24) Abassi Z., Winaver J. and Feuerstein G. The biochemical pharmacology of renin inhibitors:

Implications for translational medicine in hypertension, diabetic nephropathy and heart failure: Expectations and reality. ***Biochem. Pharmacol***. 2009; 78: 933-940.

(25) MacKinnon M., Shurraw S., Akbari A., Knoll G.A., Jaffey J., Clark H.D. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: A systematic review of the efficacy and safety data. Am. J. Kidney. Dis**.,** 2006;48(1):8-20.

(26) Tylicki L., Rutkowski P., Renke M., Larczynski W., Aleksandrowicz E., Lysiak-Szydlowska W. et al. Triple pharmacological blockade of the renin-angiotensin-aldosterone system in nondiabetic CKD: An open-label crossover randomized controlled trial. ***Am. J. Kidney. Dis***. 2008; 52(3):486-493.

(27) Wiggins K. and Kelly D. Aliskiren: a novel renoprotective agent or simply an alternative to ACE inhibitors? ***Kidney Int***. 2009; 76:23-31.

(28) Tuttle K.R. Linking metabolism and inflammation and immunology: diabetic nephropathy is an inflammatory disease**.** ***J. Am. Soc. Nephrol***. 2004; 16:1537-1538.

(29) Mora C. and Navarro JF. Inflammation and pathogenesis of diabetic nephropathy. ***Metabolism***. 2004; 53:265-266.

(30) Lin S.L., Chen Y.M., Chien C.T., Chiang W.C., Tsai C.C. and Tsai T.J. Pentoxifylline attenuated renal disease progression in rats with remnant kidney. ***J. Am. Soc. Nephrol***. 2002; 13:2916-2929.

(31) DiPetrillo K. and Gesek F.A. Pentoxifylline ameliorates renal tumor necrosis factor expression, sodium retention, and renal hypertrophy in diabetic rats. ***Am. J. Nephrol.*** 2004; 24:352-359.

(32) Preston R. Renoprotective effects of antihypertensive drugs. ***Am. J. Hypertens***. 1999; 12:19S-32S.

(33) Baba S. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. ***Diabetes Res. Clin. Pract***. 2001; 54:191-201.

(34) Thurman J. and Schrier R. Comparative Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Blood Pressure and the Kidney. ***Am. J. Med***. 2003; 114:588-600.

(35) Ravid M., Lang R., Rachmani R. and Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. ***Arch. Intern. Med***. 1996; 156:286-289.

(36) Chan J.C., Ko G.T., Leung D.H., Cheung RC., Cheung M.Y., So W.Y. et al. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. ***Kidney Int***. 2000; 57:590-600.

(37) Suzuki K., Souda S., Ikarashi T., Kaneko S., Nakagawa O. and Aizawa Y. Renoprotective effects of low-dose valsartan in type 2 diabetic patients with diabetic nephropathy. ***Diabetes Res. Clin. Pract***. 2002; 57:179-183.

(38) Viberti G. and Wheeldom N.M. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure independent effect. ***Circulation***. 2002; 106:672-678.

(39) Berman N. and Hostetter T. In the literature: Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension. Am. J. Kidney. Dis. 2008; 51(3):370-372.

(40) Cheng J. Aliskiren: Renin Inhibitor for Hypertension Management. ***Clin. Ther***. 2008; 30(1):31-47.

(41) Nistala R., Wel Y., Sowers J. and Whaley-Connell A. Renin-angiotensin-aldosterone system-mediated redox effects in chronic kidney disease. ***Transl Res***. 2008; 153(3):102-113.

(42) Carey R. and Padia S.: ***In: Textbook of Nephro-Endocrinology***. Singh A. and Williams G. (Eds).; Elsevier Inc., San Diego, USA, 2009; 1st edition, Chapter 12, pp147-165.

(43) Gradman A. and Kad R. Renin Inhibition in Hypertension. J. Am. Coll. Cardiol**.** 2008; 51(5):519-528.

(44) Navarro J., Mora C., Muros M., Macia M. and Garca ***J***. Effects of Pentoxifylline Administration on Urinary N-Acetyl-β-Glucosaminidase Excretion in Type 2 Diabetic Patients: A Short-Term, Prospective, Randomized Study. Am. J. Kidney. Dis**.** 2003; 42(2):264-270.

دراسة مقارنة على التأثير الوقائي لعلاج الألسكيرين والبنتوكسيفيلين المزدوج والفالزارتان والأنالابريل لدى مرضى ارتفاع ضغط الدم والسكري النوع الثاني الذين يعانون من اعتلال الكلية السكري

أمين توفيق حمد[1]، محمد محمود طه[2]

[1] أستاذ مشارك فى علم الأدوية، قسم علم الأدوية، كلية الصيدلة – جامعة الأزهر، غزة – فلسطين.
[2] محاضر فى علم الأدوية، قسم علم الأدوية، كلية الصيدلة – جامعة الأزهر، غزة – فلسطين

ملخص

أجريت هذه الدراسة لتقييم التأثير الوقائي على الكلية لعلاج الألسكيرين والبنتوكسيفيلين المزدوج ومقارنتها مع الفالزارتان والأنالابريل لدى مرضى ارتفاع ضغط الدم والسكري النوع الثاني الذين يعانون من اعتلال الكلية السكري، وذلك من خلال اختيار ستين مريضا من عيادات وكالة الغوث والعيادات الخاصة المنتشرة في قطاع غزة وتقسيمهم إلى ثلاث مجموعات، هي: المجموعة الأولى (ن =20) تم علاجها باستخدام الاينالابريل (10–20 ملغم/يوم)، والمجموعة الثانية (ن =20) استخدمت علاج الفالزارتان (160ملغم/يوم)، بينما المجموعة الثالثة تم علاجها باستخدام الألسكيرين والبنتوكسيفيلين المزدوج (150،400 ملغم/يوم). وقد تمت متابعة المرضى جميعهم مدة تسعة أشهر من خلال قياس مستوى الكرياتينين في الدم ومعدل الزلال البولي، وذلك قبل البدء بالعلاج وبعد ثلاثة، وستة وتسعة أشهر من استخدام العلاج، وتم تحليل البيانات باستخدام اختبار (ت) للعينات الزوجية والعينات المزدوجة. أظهرت النتائج انخفاضا ذا دلالة إحصائية في معدل الزلال البولي ($p=0.001$) ومستوى الكرياتينين في الدم ($p=0.000$) لدى المرضى الذين استخدموا علاج الألسكيرين والبنتوكسيفيلين المزدوج بعد ستة وتسعة أشهر من استخدام العلاج، وقد كان الانخفاض أكثر وضوحا بعد تسعة أشهر. بالنسبة للمجموعة التي استخدمت علاج الفالزارتان كان هناك انخفاض ذو دلالة إحصائية في معدل الزلال البولي بعد تسعة أشهر من استخدام العلاج ($p=0.045$)، بينما لم يلحظ أي انخفاض ذي دلالة إحصائية في مستوى الكرياتينين في الدم ($p=0.807$)، بالإضافة إلى ذلك لم يلحظ أي انخفاض ذو دلالة إحصائية في معدل الزلال البولي ($p=0.125$) ومستوى الكرياتينين في الدم ($p=0.445$) عند المرضى الذين استخدموا علاج الاينالابريل. وتخلص الدراسة الى أن التأثير الوقائي على الكلية لعلاج الألسكيرين والبنتوكسيفيلين المزدوج كان أكثر وضوحا من تأثير كل من الأنالابريل والفالزارتان لدى المرضى الذين يعانون من اعتلال الكلية السكري.

الكلمات الدالة: اعتلال الكلية السكري، الألسكيرين والبنتوكسيفيلين المزدوج، الفالزارتان ،الأنالابريل ،معدل الزلال البولي، مستوى الكرياتينين في الدم.

تاريخ استلام البحث 2013/5/8 وتاريخ قبوله للنشر 2013/9/17.