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RESEARCH ARTICLE

RENOPROTECTIVE EFFECT OF CALCIUM CHANNEL BLOCKERS (AMLODIPINE) AND ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ENALAPRIL) IN HYPERTENSIVE PATIENTS WITH CHRONIC KIDNEY DISEASE (GAZA STRIP)

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ABSTRACT

Chronic Kidney Disease (CKD) is one of the most serious complications of hypertension and is the leading cause of end-stage renal disease (ESRD). Angiotensin Converting Enzyme inhibitors (ACEIs) and Calcium Channel Blockers (CCBs) play relevant role in the control of the blood pressure and in preventing progression of CKD. The purpose of this study was to evaluate the renoprotective effect of Amlodipine (calcium channel blocker) monotherapy and in combination with Enalapril (angiotensin converting enzyme inhibitor) in hypertensive patients with CKD in Gaza Strip. To achieve this purpose, this study was conducted on 50 hypertensive patients with CKD selected from Nasser medical complex, Kidney and Dialysis Department, divided into two groups. The first group (n=25) was treated with Amlodipine (5-10 mg/day) and the second group (n=25) was treated with Amlodipine (5-10 mg/day) and Enalapril (10-20 mg/day) combination. All patients were followed-up for six months by measuring urinary albumin excretion (UAE) rate, serum creatinine level and CrCl before and after 2, 4 and 6 months of treatment. The results showed a significant reduction in UAE rate among patients who used Amlodipine and Amlodipine/Enalapril combination after 6 months of treatment. In addition, the results also showed a significant reduction in serum creatinine level after 6 months of Amlodipine alone and in combination treatment. On the other hand, a significant increase in CrCl level among patients in both groups was observed during the study period (6 months). The study revealed that the use of Amlodipine/Enalapril combination had more pronounced renoprotective effect than Amlodipine monotherapy among hypertensive patients with CKD.

INTRODUCTION

Chronic kidney disease (CKD) is known as a progressive disease and is considered a major health problem affecting large number of population all over the world. Numbers of CKD affected patients is expected to continue to rise because of the growing elderly population and increasing numbers of patients with diabetes and hypertension (R. Thomas *et al*, 2008). Those patients are at higher risk of cardiovascular disease in which the early detection of CKD can determine if kidney disease is likely to progress allowing appropriate treatment to slow progression to End Stage Renal Disease (ESRD) (SIGN, 2008). CKD is related to multiple co-morbidities and adverse outcomes and may increase the risk of cardiovascular disease and cardiovascular events, which increases with worsening renal function (L.E. Carroll, 2006).

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CKD may be caused by damage to both kidneys that is usually irreversible and can lead to ill health, and in some cases, dialysis or transplantation may become necessary to maintain life (R. John *et al,* 2004; J. Coresh *et al*, 2003; S.D. Lusignan *et al*, 2005). CKD is defined as progressive irreversible loss of kidney function over several months to years, which is characterized by gradual replacement of normal kidney architecture with interstitial fibrosis (L.A. Inker *et al*, 2014; C. Ashley & C. Morlidge, 2008). CKD is also defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (eGFR) that persists for more than 3 months (Levin, 2006; Levey *et al*, 2005). Hypertension is considered the second leading cause of ESRD and a common outcome of CKD regardless of etiology, which contributes to the progression of renal damage. According to the United States Renal Data System 2009, about 51–63% of all patients with CKD are hypertensive (Bethesda, 2010). pproximately 40% of patients with stage 2 CKD (GFR:

60–90 ml/min per 1.73 m^2 of body surface), and virtually all in stage 4 (GFR: 15–29 ml/min per 1.73 m^2) or 5 (GFR: <15 ml/min per 1.73 m^2 of body surface) are hypertensive (R.F. Rosario & D.E. Wesson, 2006). Many clinical studies estimated that hypertension occurs in 23.3% of individuals without CKD (Bethesda, 2010). The prevalence of hypertension also varies with the cause of CKD; strong association with hypertension was reported in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%), (Ridao *et al*, 2001). CKD is likely to be far more prevalent worldwide than was previously assumed; it affects about 10 - 15% of the adult population in the western countries, many of whom require costly treatments or renal replacement therapy (M. Matovinović, 2009). Patients with CKD have recorded significantly higher rates of morbidity, mortality, hospitalizations and healthcare utilization. The prevalence of CKD Stages 2–5 has continued to increase since 1988 as have the prevalence of diabetes and hypertension, which are respectively etiologic in approximately 40% and 25% of CKD cases (Krol, 2011). Many recent studies indicate that the prevalence of CKD around the world increases from less than 5% to more than 45% from age 20 years to age 70 years and older, respectively (Bakris *et al*, 2010; Coresh *et al*, 2007; Shaheen & Souqiyyeh, 2010). The annual incidence of renal failure in USA, UK and Europe is 33.6, 10, and 13.5 per 100,000 population, respectively (R. Hamer & M. El Nahas, 2006). While it is estimated that over 10% of adults in developed countries suffer some degree of CKD (Zeeuw *et al*, 2005). According to Palestinian Health Annual Reports, there is a strong evidence indicating continuous increase in the rate of death caused by renal failure during the last decade (Annual Reports, 2005, 2009 and mid 2013). Renal failure was the tenth cause of death (4%) in Palestine in 2005. The death rate among patients aged 20-59 years due to renal failure in Palestine 2005 (proportional of total deaths) was 4.8% (West Bank 6.1% Vs. Gaza Strip 3.1%) and 5.1% in patients aged 60 years and above (Annual Report, 2005). In 2009, renal failure was the sixth cause of death (5.1 %) among Palestinian population (Annual Report, 2009). Distribution of reported causes of death among age group 20 - 59 years, Palestinian mid-year 2013 health report showed that renal failure was the fourth cause of death among Palestinian population (5% among patients aged 20-59 years and 5.8% among patients aged 60 and above in West Bank) (Mid annual Report, 2013).

MATERIALS AND METHODS

Study Design

This study was a non-randomized, prospective-comparative study in which the renoprotective effect of Amlodipine alone and in combination with Enalapril was evaluated in hypertensive patients with renal dysfunction over 6 months. All patients were asked to sign a written informed consent to the study and guidelines of good clinical practice was given to them.

Inclusion Criteria

All selected patients were over 40 years, from both sexes. All cases were hypertensive (BP≥ 140/90 mmHg) with impaired renal function (CKD stages I, II and III), which was determined by the CrCl ≥30 ml/min and/or UAE rate >30mg/day.

Exclusion criteria

Patients who had DM, cancer or any life-threatening disease, end-stage renal disease or dialysis, secondary hypertension or heart failure; Patients who were previously treated with CCBs and ACEIs; or have hypersensitivity to CCBs and ACEIs. Patients with contraindication to ACEIs like renal artery stenosis and if creatinine clearance decreased or increased more than 20% during the treatment course.

Patients and Methods

After approval of the study by the research and ethics committee in Palestine (Helsinki), this observational study recruited 50 hypertensive patients with the diagnosis of CKD who visited Kidney and Dialysis Department at Nasser Medical Complex in Gaza. Diagnosis of CKD was done by nephrologists based on clinical history, physical examination and biochemical analysis. Data was collected from patient`s hospital files. We identified demographic and clinical variables, including gender, age, Body mass index (BMI). The study variables also included cigarette smoking, family history of CAD, CKD or HTN, Socio economic variables, as (occupation, income, education, family size), medication used before starting the study, history of Coronary Artery Disease (CAD) and duration of HTN. Before starting the study, laboratory tests (Serum potassium and creatinine level, Urinary Albumin Excretion Rate (UAE rate)) and blood pressure measurement (SBP and DBP) were performed for each patient. Patients participated in the study were divided into two groups according to the treatment protocol, group I (n=25) treated with Amlodipine monotherapy (5-10mg/day) and group II (n=25) treated with Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination. Laboratory tests (Serum potassium and creatinine level, Urinary Albumin Excretion Rate (UAE rate)) and blood pressure measurement (SBP and DBP) were repeated for each patient every 2 months for a period of 6 months. Creatinine clearance for each patient was calculated by using Cockgroft-Gault equation, that is based on weight, age, serum creatinine and gender. Creatinine clearance = (140-age) × weight (kg)/ 72 x serum creatinine (mg/dl) multiplied by 0.85 for women (less than 85 ml/min impaired and equal or more than 85 ml/min normal creatinine clearance), (A. Jamee & Y. Abed, 2014). Categorical variables are presented as counts and percents and were compared using paired t test and sample t test for statistical significance. Continuous variables are presented as means. Data was analyzed by SPSS version 20.0, and the criterion for significance was 0.05.

RESULTS

During a follow up of 50 patients (21 males (42%) and 29 females (58%)) with CKD. The age of patients in group I who were treated with Amlodipine (5-10mg/day) ranged from 40 to 65 years with a mean of 54.8±7.4, while the age of patients in group II who were treated with Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination ranged from 40 to 76 years with a mean of 53.2±10.4. General characteristics of the study population are presented in Table 1, we noted that the

prevalence of men and women in Amlodipine monotherapy treated group were 40% and 60% respectively, while in Amlodipine/Enalapril combination treated group, the percentages were 48%, 52% without significant difference regarding the sex between two group (P= 0.78).

Similarly no significant difference was observed between the two groups regarding their job (p=0.55). We noted that 82% of study population were unemployed and 72% with monthly income less than 1500 Shekels. On the other hand, 36% of the study population were cigarette smokers, all smokers in this

Table 1. Socio demographic characteristics of the study population

Characteristics	All		Group I		Group II		P. value
Age (Mean±SD)	53.98±8.9		54.8±7.4		53.2±10.4		0.524
Gender							
Male	21	42	10	40	11	44	0.500
Female	29	58	15	60	14	56	
Menopause							
Yes	15	51.72	9	60	6	42.85	0.627
No	14	48.27	6	40	8	57.14	
Education status							
Primary school	8	16	3	12	5	20	0.493
Secondary school	30	60	17	68	13	52	
High school	12	24	5	20	7	28	
Occupation							
employee	9	18	3	12	6	24	0.532
unemployed	41	82	22	88	19	76	
Income							
≤ 1500 Shekels	36	72	20	80	16	64	0.343
>1500 Shekels	14	28	5	20	9	36	
Family size							
<8	22	44	9	36	13	52	0.099
≥8	28	56	16	64	12	48	
Smoking status							
Yes	18	36	8	72	10	40	0.384
No	32	64	17	28	15	60	

Table 2. Medical history and clinical characteristic of study population

Characteristics	All		Group I		Group II		P. value
Duration of HTN	8.89±4.13		9.68±4.13		8.28±4.11		0.89
BMI							
Normal	9	18	5	20	4	16	0.83
Over weight	25	50	12	48	13	52	
Obese	16	32	8	32	8	32	
History of CAD							
Yes	5	10	3	12	2	8	0.50
No	45	90	22	88	23	92	
Family history of CAD							
Yes	14	28	5	20	8	32	0.26
No	37	72	20	80	17	68	
Family history of HTN							
Yes	45	90	22	88	23	92	0.50
No	5	10	3	12	2	8	
Family history of CKD							
Yes	13	26	4	16	9	36	0.09
No	37	74	21	84	16	64	
Medical history							
Diuretics							
Yes	10	20	4	16	6	24	0.36
No	40	80	21	84	19	76	
Aspirin							
Yes	34	68	18	72	16	64	0.38
No	16	32	7	28	9	36	

HTN=Hypertension, CAD=Coronary Artery Disease, CKD= Chronic Kidney Disease

Table 3. Vital signs and laboratory characteristic of study population

Characteristics	All	Group I	Group II	P. value
Blood pressure mean				
SBP (mmHg)	150.24±7.76	148.9±6.9	151.6±8.5	0.233
DBP(mmHg)	96.74±5.24	95.8±4.4	97.6±5.9	0.229
Lab tests mean				
Serum Creatinine (mg/dl)	1.75±1.07	1.46±0.70	2.13±1.29	0.059
Creatinine Clearance (ml/min/1.73m^2)	63.92±27.96	68.1±28.5	59.7± 27.3	0.294
Potassium (K+) (mEq/l)	4.59±0.70	4.5±0.70	4.7±0.67	0.412
UAE rate (mg/day)	375.45±368.81	278.6±344.3	472.3±373.7	0.063

SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure, UAE rate= Urinary Albumin Excretion rate

study were males. On the field of education, 16% of study population had a primary education only, while 60% completed their secondary school, and the rest of the participants 24% finished their high education. The main clinical characteristics are listed in Table 2. Patients in group I who treated with Amlodipine had hypertension from 3 to 17 years. In the Amlodipine/Enalapril combination treated group, the population had hypertension from 2 to 16 years. Moreover, Table 2 shows that 18% of the study population were with normal weight (BMI< 25 kg/m2), 50% had BMI in the range of overweight (BMI=25-29.9 kg/m2) and 32% were suffering from obesity (BMI≥30 kg/m2).

Effect of Amlodipine and Amlodipine/Enalapril combination treatment on UAE rate

The results showed in Table 4 indicate that there was a statistical significant effect ($p<0.05$) of Amlodipine alone and in combination with Enalapril on UAE rate during the study period (6 months). The data showed a statistical significant difference ($p<0.05$) between the reduction rates in patients treated with Amlodipine alone and in combination with Enalapril after 2, 4 and 6 months of therapy. This indicates that drugs used improved UAE rate in both groups significantly ($p<0.05$).

Table 4. Effect of Amlodipine and Amlodipine/Enalapril combination on tested parameters

Variable	Group	Before treatment	After treatment					P.value*
			1st week	3rd week	2nd month	4th month	6th month	
UAE rate (mg/24h)	Group I	278.56±344.32	---------	---------	259.77±330.14	241.11±320.14	224.86±318.88	0.000
	Group II	472.26±373.65	---------	---------	415.71±346.87	352.68±301.89	300.17±270.10	0.000
CrCl (ml/min/1.73m^2)	Group I	68.12±28.52	69.63±28.80	75.70±37.02	81.17±29.04	83.48±29.74	89.75±29.81	0.000
	Group II	59.74± 27.31	56.21±21.34	56.93±21.26	64.64±28.76	71.83±28.64	86.84±38.36	0.000
SCr (mg/dl)	Group I	1.46±0.70	1.42±0.68	1.35±0.68	1.19±0.57	1.16±0.58	1.06±0.50	0.000
	Group II	2.03±1.29	2.02±1.21	1.99±1.22	1.86±1.23	1.64±1.11	1.41±1.05	0.000
K^+ level (mEq/dl)	Group I	4.51±0.73	4.51±0.76	4.42±0.71	4.58±0.65	4.26±0.59	3.95±0.42	0.000
	Group II	4.68±0.67	4.88±0.65	4.93±0.61	5.01±0.60	5.00±0.62	4.68±0.67	0.264
SBP (mmHg)	Group I	148.92±6.89	143.48±7.21	138.32±7.08	132.80±7.45	129.60±6.47	123.72±7.75	0.000
	Group II	151.56±8.48	142.40±9.26	137.64±8.50	130.20±8.48	121.72±10.95	116.00±12.16	0.000
DBP (mmHg)	Group I	95.84±4.43	91.00±4.56	87.44±4.19	85.24±3.38	81.80±4.19	79.20±4.93	0.000
	Group II	97.64±5.90	90.52±5.01	87.76±5.58	83.24±5.77	78.72±5.93	75.80±5.14	0.000

*P. values (p<0.05) were calculated by paired-samples t-test for all variables after 6 months of treatment.
UAE rate: Urinary Albumin Excretion Rate, CrCl: Creatinine Clearance, SCr: Serum Creatinine, K+: Potassium, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table 5. Comparison between Amlodipine and Amlodipine/Enalapril treated groups after 6 months of treatment on tested parameters

Variable	Time	Group I	% Δ	Group II	% Δ	P. value*
UAE rate	Baseline	278.56±344.32	↓19.28	472.26±373.65	↓36.43	0.000
	After 6 months	224.86±318.88		300.17±270.10		
SCr	Baseline	1.46±0.70	↓27.39	2.03±1.29	↓30.54	0.119
	After 6 months	1.06±0.50		1.41±1.05		
CrCl	Baseline	68.12±28.52	↑31.75	59.74± 27.31	↑45.36	0.428
	After 6 months	89.75±29.81		86.84± 38.36		
K level	Baseline	4.51±0.73	↓12.41	4.68±0.67	0	0.062
	After 6 months	3.95±0.42		4.68±0.67		
SBP	Baseline	148.92±6.89	↓16.92	151.56±8.48	↓23.46	0.001
	After 6 months	123.72±7.75		116.00±12.16		
DBP	Baseline	95.84±4.43	↓17.36	97.64±5.90	↓22.36	0.002
	After 6 months	79.20±4.93		75.80±5.14		

*P. values (P<0.05) were calculated for %Δ by independent-samples t-test, SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure, UAE rate= Urinary Albumin Excretion rate, SCr= Serum Creatinine, CrCl= Creatinine Clearance, K= Potassium.

On the other hand, 10% of the study population suffered from coronary artery disease (CAD), 26% had family history of CAD, 90% had family history of HTN and 26% had family history of CKD. Table 2 also numerates the drugs used by patients among the different groups. Generally, all participants used Atenolol (beta-blocker) as antihypertensive drug, while 20% of them used Furosemide (Lasix) to maintain blood pressure and 68% patients used baby aspirin to prevent blood clots and reduce the risk of strokes and heart attacks. Table 3 shows the characterizations of study population before starting the study. The effect of used drugs on UAE rate, CrCl, SCr, potassium level, SBP and DBP and comparison between the changes in these parameters among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20 mg/day) are represented in Table 4 and 5, and evaluated as follows.

However, Amlodipine/Enalapril combination exhibited a greater reduction in albuminuria (36.43%) than Amlodipine alone (19.28%) when compared with baseline values

Effect of Amlodipine and Amlodipine/Enalapril combination treatment on Creatinine Clearance (CrCl) level

The results showed a statistical significant effect of used drugs on CrCl after 6 months of treatment, where it significantly increased (p<0.05) after 6 months of the treatment with Amlodipine alone and in combination with Enalapril. Overall, no statistical difference *(p>0.05)* between the changes in CrCl rates throughout the study period between both treated groups. This comparison showed that the drugs used improved CrCl significantly *(p<0.05)* in both groups, where Amlodipine/Enalapril combination exhibited a greater increase

in CrCl levels (45.36%) than Amlodipine alone (31.75%) when compared with baseline values. The results also showed a reasonably good management of CrCl levels among the participants during the study period.

Effect of Amlodipine and Amlodipine/Enalapril combination treatment on Serum creatinine (SCr) level

The serum creatinine level decreased following the first week of treatment with Amlodipine (5-10mg/day). However, the decrease in serum creatinine level was significant ($p<0.05$) at the third week, and then after 2, 4 and 6 months of Amlodipine treatment. While serum creatinine level decreased insignificantly ($p>0.05$) from its baseline value after the third week of treatment with Amlodipine/Enalapril. However, it decreased significantly ($p<0.05$) after 6 months of treatment. Despite the difference in serum creatinine means between both groups at baseline, the difference between the reduction percentage in SCr levels showed no statistical significance ($p>0.05$) between both groups even after 6 months of treatment. Therefore, drugs used showed similar effects on serum creatinine levels during the study period, but the reduction was higher in the combination treated group when compared with baseline values (-27.39% in the Amlodipine treated group vs. -30.54% in the Amlodipine/Enalapril combination treated group) .

Effect of Amlodipine and Amlodipine/Enalapril combination treatment on SBP and DBP

The results obtained from this study showed that SBP significantly decreased *($p<0.05$)* at the end of treatment period of 6 months with either Amlodipine alone treatment or in combination with Enalapril. The comparison between the percentage of changes in SBP levels among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20mg mg/day) showed a statistical significance ($P<0.05$) difference between these levels in both groups at the end of the sixth month of treatment period. SBP was adequately controlled in both groups, but more in the combination group (-16.92% in Amlodipine treated group vs. -23.46% in Amlodipine/Enalapril treated group). In addition, DBP significantly decreased *($p<0.05$)* at the end of treatment period (6 months) with either Amlodipine alone treatment or in combination with Enalapril. The changes in DBP levels among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20mg mg/day) showed a statistical significance ($P<0.05$) in both groups at the end of the sixth month of treatment (-17.36% in Amlodipine treated group and -22.36% in Amlodipine/Enalapril treated group). DBP was more adequately controlled in the drug combination treated group when compared with the Amlodipine treated group.

DISCUSSION

Effect of drugs used on urinary albumin excretion (UAE) rate throughout the study period (6 months)

In hypertensive and diabetic patients, albumin leakage is more often considered a reflection of generalized endothelial or vascular dysfunction, in which the damaged endothelium may lead to increased leakage of plasma albumin making microalbuminuria. In addition, increased intraglomerular pressure can also cause local renal leakage of albumin (P. Clausen *et al*, 2001). Microalbuminuria is present in 25-100% of patients with essential HTN and is associated with increased incidence of CV events. Therapeutic intervention of microalbuminuria is considered a primary objective in HTN management because it can reverse the proteinuria and prevent progression to ESRD (S. Jalal *et al*, 2010). Numerous studies performed by different researchers like J.M. Halimi *et al*. (2007), Shigihara *et al*. (2000), Fogari *et al*. (2002), Jalal *et al*. (2010) and Yousef *et al*. (2005) have examined the effect of CCBs and ACEIs on UAE rate in hypertensive patients. However, these studies revealed divergent results. The mechanisms underlying this varied effect on proteinuria may include preferential afferent arteriolar dilatation with dihydropyridine CCBs, which allows more of the aortic pressure to be transmitted to the glomerulus, and ability of the dihydropyridine CCBs to alter renal autoregulation and the permeability of the glomerulus (Bakris *et al*, 2004). On the other hand, various mechanisms have been proposed to explain the beneficial effects of ACEIs on microalbuminuria. At first, this phenomenon might be due to the improvement in intrarenal hemodynamics, in which ACEIs reduce proteinuria, renal filtration fraction and the intraglomerular pressure. The second mechanism is that ACEIs can reduce the permeability of the basement membrane of the glomerulus. Furthermore, since angiotensin II increases the tone of the efferent arteriole, the intraglomerular pressure and the proteinuria, it is conceivable that ACEIs can reduce the proteinuria by inhibiting the effect of angiotensin II in renal microcirculation. (Jalal *et al*, 2010).

Effect of the drugs used on creatinine clearance (CrCl) throughout the study period (6 months)

Worldwide, renal insufficiency is defined as reduction in the estimated glomerular filtration rate is increasing at a worrisome rate (Kohli *et al*, 2006). On the other hand, longevity increases the risk of developing diseases, such as DM and HTN that have direct adverse effects on kidney function (Ostchega *et al*, 2007). CKD has been defined as decreased kidney function and/or kidney damage persistent for at least three months. Kidney dysfunction is indicated by a glomerular filtration rate of less than 60 ml/min/1.73 m^2, while kidney damage most frequently is manifested as increased urinary albumin excretion (Fink *et al*, 2012). Many researchers such as Jalal *et al*. (2010), Iyalomhe *et al*. (2013), Agodoa *et al*. (2001) and Iñigo *et al*. (2001) investigated the effect of CCB and ACEI alone or in combination on CrCl. For example, our results are different from the results obtained by S. Jalal *et al*. (2010), who did not observe any significant change in creatinine clearance after four and eight weeks of therapy with Amlodipine and Lisinopril compared to the baseline values. On the other hand, our results were similar to that obtained by Iyalomhe *et al*. (2013) who studied the long-term effects of Amlodipine monotherapy on creatinine clearance in hypertensive Nigerians for 48 weeks. The results of that study showed that CrCl increased significantly at the end of study period from baseline values.

These differences are related to the fact that increases in CrCl observed after initiation of Amlodipine treatment produce an acute rise in CrCl by causing afferent arteriolar vasodilation

and loss of renal autoregulation. Therefore, intraglomerular pressure typically rises, even when systemic arterial pressure falls. In contrast, ACEIs generally reduce intraglomerular pressure and do not interfere with autoregulation. Moreover, the differences between these results are related to the fact that reduced glomerular capillary pressure protects against the onset and progression of renal injury; it is well known that the afferent and efferent arteriolar resistances affect this pressure. Any substance that not only reduces systemic vascular resistances, but also induces preferential dilatation of the efferent arteriole, could thus cause a reduction in glomerular capillary pressure and in the incidence of glomerular sclerosis. It is well known that ACEIs such as Enalapril can slow the progression of the renal damage by reducing efferent arteriolar resistances and intraglomerular pressure. The intrarenal hemodynamic effects of dihydropyridine CCBs, as their vasodilatory effect on the efferent arteriole may vary according to the drug used. In particular, the results of some studies suggest that Amlodipine does not significantly reduce post glomerular resistances, whereas others have shown that Amlodipine, induce hemodynamic variations suggesting a mainly efferent vasodilatory effect (Morrone *et al*, 2003).

Effect of drugs used on serum creatinine (SCr) levels throughout the study period (6 months)

Creatinine is considered a byproduct generated from muscle metabolism. It is produced at a constant rate from creatine, a compound that is made primarily in the liver and then transported to the muscles for energy production. Production of creatinine depends on the muscle mass; therefore, it is constant as long as muscle mass remains constant. Because it is removed from the body by the kidneys and they maintain its level in a normal range, creatinine has been found to be a reliable indicator of kidney function. Therefore, when the kidneys become impaired for any reason, the serum creatinine level will rise (Fischbach and Dunning, 2009). Many clinical studies investigated the effect of different CCB and ACEI drugs on SCr levels in hypertensive patients who suffered from renal dysfunction. For example, Uchida *et al*. (2014) assessed renal function in 70 hypertensive patients with CKD and microalbuminuria under the treatment of Amlodipine (2.5-10 mg/day). After three months of switching to Cilnidipine, serum creatinine level increased significantly from 0.89±0.41 mg/dl to 0.94±0.42 mg/dl (P<.001) at the end of the study (3 months).

While Shaifali *et al*. (2014) comparatively evaluated the effects of Losartan/Hydrochlorothiazide combination and Amlodipine on biochemical parameters in hypertensive patients (n=200) who were followed up for 6 months. Both treated groups showed significant increase in serum creatinine levels at the end of study period ($p<0.05$), where it increased from 0.674±0.01 mg/dl at baseline to 0.732±0.01 mg/dl at the end of treatment period with Amlodipine. The efficacy of Amlodipine in reducing serum creatinine levels in the present study may be due to the increase in GFR occurred after Amlodipine therapy and consequently, the clearance rate of creatinine, and due to the increase in fluid output from the proximal tubules (Chanard *et al*, 2003). Furthermore, this may be due to reduction in tubular reabsorption of creatinine or an increase in tubular secretion of creatinine caused by Amlodipine treatment (Raman *et al*, 1999).

Effect of drugs used on blood pressure (SBP and DBP) throughout the study period (6 months)

Hypertension is a public health problem as it inflects millions of persons all over the world, and if not treated adequately, results in premature death and disability from stroke, heart failure, renal failure and myocardial infarction. The goal of hypertension management is to detect and control high blood pressure in patients (Shirure *et al*, 2012). Some antihypertensive agents such as ACEIs, ARBs and CCBs also may be capable of reducing CKD progression because they stop some of the pathogenetic mechanisms involved in renal damage. The possibility that combination treatment with ACEIs and CCBs may confer additive or even synergistic renoprotective effects other than BP control is not only interesting but also particularly important because multidrug antihypertensive regimens are required to obtain adequate BP in the majority of patients with CKD (Locatelli *et al*, 2002). The CCBs and the ACEIs are among the preferred antihypertensive drugs for the treatment of arterial hypertension because they protect the target organs with low incidence of adverse reactions (Poulter *et al*, 2005). Employment of low dose combinations of two antihypertensive agents, with different mode of action has gained acceptance worldwide for the treatment of mild to moderate hypertension (Shirure *et al*, 2012).

In the present study, Amlodipine decreased both SBP and DBP and when combined with Enalapril, BP dropped additively. For more illustration, our findings showed that BP significantly decreased ($p<0.05$) among involved patients who were treated with Amlodipine at the end of the study when compared with baseline values. In the Amlodipine/Enalapril treated group, BP was significantly decreased *($p<0.05$)* at the end of the sixth month of treatment. Our results indicated that the used drugs decreased BP to the target value and maintained it during the study period (6 months). These findings were similar to the results of other studies performed by M. Rienzo *et al*. (2009), Li *et al*. (2015) and Shirure *et al*. (2012). To clarify, Rienzo *et al*. (2009) for example studied the efficacy in the normalization of the blood pressure of the fixed combination of Amlodipine (2.5mg/day)/Enalapril (10mg/day) and compared it with Amlodipine (2.5mg/day) treatment in hypertensive patients with CAD. The decreases in SBP and DBP were significant ($p< 0.01$), but with no difference between the groups. The combination of CCB and ACEI was especially effective due to their complementary mechanisms that enhance the antihypertensive efficacy with low side effects rate (McInnes, 2007). CCBs are potent vasodilators that induce reflex activation of the sympathetic system and RAAS. As a result, the use of an ACEI may buffer this excessive activation. Moreover, since CCBs promote a negative sodium balance and an increase of angiotensin II levels, this may reinforce the antihypertensive effect of ACEIs (Gojanovic *et al*, 2008).

Conclusion

In conclusion, in hypertensive patients with CKD, both Amlodipine (5-10 mg/day) monotherapy and Amlodipine/Enalapril (5-10, 10-20 mg/day) combination showed renoprotective effect among hypertensive patients with CKD. Their use significantly reduced UAE rate, increased GFR and reduced serum creatinine level with a

greater degree in the combination group. Moreover, SBP and DBP were significantly lower with the CCB Amlodipine (5-10mg/day) alone or in combination with Enalapril (10-20mg/day).

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