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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النساء (111)

صدق الله العظيم
Declaration

I, the undersigned hereby, declare that the thesis titled:

Renoprotective Effect of Calcium Channel Blockers (Amlodipine) and Angiotensin Converting Enzyme Inhibitors (Enalapril) in Hypertensive Patients with Chronic Kidney Disease (Gaza Strip)

Is my own research work and the work provided in this thesis, unless otherwise referenced, is the researcher’s own work, and has never been submitted elsewhere for any other degree qualifications nor for any academic titles, nor for any other academic or publishing institutions.

I, hereto, affirm that I will be completely responsible in academic and legal terms if this work proves the opposite.

Student’s name: **Hidayat Sobhi Jarir Saqer**

Signature:……………………………………

Date:……………………………………
Dedication

I would like to dedicate my thesis

To the soul of my beloved father, without his spiritual support, I could not attain my dreams and aims in my life.

To my dear mother, who made her best and did not wait for tender, and without her love, supplication and support throughout my life, this work would not have been possible.

To my brothers and sisters for their unlimited bestowed, whose endless love, support and encouragement allowed me to achieve my goals.

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Hidayat S. Sager
April 2016
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, and compare this effect with hypertensive controls in Gaza Strip. To achieve this purpose, a case-control study conducted on 50 hypertensive patients with CKD selected from Nasser medical complex, Kidney and Dialysis Department in Khanyounis governorate, 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, while 50 hypertensive patients with normal kidney function (control group) divided into two groups (n=25), treated with the same regimen. 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.

Keywords: Chronic Kidney Disease, Hypertension, Amlodipine, Amlodipine/Enalapril Combination, Urinary Albumin Excretion (UAE) Rate, Serum Creatinine Level, Renoprotective Effect.
الملخص

التأثير الوقائي على الكلية لمثبطات قنوات الكالسيوم (الاملوديبين) ومثبطات الانزيم المحول للأنجيوتنسين (انالابريل) لدى مرضى ارتفاع ضغط الدم والذين يعانون من اعتلال الكلية المزمن في قطاع غزة.

اعتلال الكلية المزمن هو واحد من أخطر مضاعفات ضغط الدم المرتفع وهو السبب الرئيسي للمرض الكليوي بمراحله الأخيرة (ESRD).

مثبطات قنوات الكالسيوم ومثبطات الانزيم المحول للأنجيوتنسين تلعب دوراً أساسيًّا في تنظيم ضغط الدم المرتفع ومنع تطور مرض الكلية المزمن.

الغرض من هذه الدراسة هو تقديم التأثير الوقائي لمثبطات قنوات الكالسيوم (الاملوديبين) الأحادي والمزدوج مع انالابريل (مثبط الانزيم المحول للأنجيوتنسين) لدى مرضى ارتفاع ضغط الدم الذين يعانون من اعتلال الكلية المزمن ومقارنة هذا التأثير مع المرضى في المجموعة الضابطة الذين يعانون من ضغط الدم المرتفع في قطاع غزة، وذلك من خلال اختيار خمسين مريض مصاباً بارتفاع ضغط الدم ويبلغون من مرضى الكلية المزمن من مجمع ناصر الطبي-وحدة الكلى والدنا الصناعية، مع تقسيم المرضى إلى مجموعتين (ن=50) تم علاجها باستخدام علاج الاملوديبين الأحادي (0.20 ملغ/يوم) والمزدوج (0.20 ملغ/يوم) انالابريل (0.15 ملغ/يوم) والمجموعة الضابطة (ن=50) الذين عُلِجواً بمثبطات الأنظمة المزمنة ولكن بطرق حدية.

出境: الدراسة تضمنت متابعة جميع المرضى لمدة ستة أشهر من خلال قياس معدل الزلال البولي ومستوى الكرياتينين في الدم CrCl وقيمة CrCl، وذلك قبل بدء الدراسة وبعد شهرين واثرباء وأربعة وستة أشهر من استخدام العلاج. أظهرت النتائج انخفاضاً في معدل الزلال البولي ومستوى الكرياتينين في الدم CrCl بعد ستة أشهر من استخدام علاج الاملوديبين الأحادي والزوجي، بالإضافة إلى انخفاضاً في معدل الزلال البولي ومستوى الكرياتينين في الدم CrCl بعد ستة أشهر من استخدام علاج الاملوديبين الأحادي والمزدوج

الكلمات المفتاحية: اعتلال الكلية المزمن، ضغط الدم المرتفع، الاملوديبين، انالابريل المزدوج، معدل الزلال البولي، مستوى الكرياتينين، في الدم، وقاية الكلية.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Angiotensin Converting Enzyme inhibitors</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin-to-Creatinine Ratio</td>
</tr>
<tr>
<td>AER</td>
<td>Albumin Excretion Rate</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to prevent heart attack trial</td>
</tr>
<tr>
<td>AME</td>
<td>Apparent Mineralocorticoid Excess</td>
</tr>
<tr>
<td>ARBs</td>
<td>angiotensin II receptors antagonists</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute Renal Failure</td>
</tr>
<tr>
<td>AT</td>
<td>Angiotensin</td>
</tr>
<tr>
<td>AT1</td>
<td>Angiotensin II type 1 Receptor</td>
</tr>
<tr>
<td>AT2</td>
<td>Angiotensin II type 2 Receptor</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CCBs</td>
<td>Calcium Channel Blockers</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac Output</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine Clearance</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>EABV</td>
<td>Effective Arteriolar Blood Volume</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>eNOS</td>
<td>endothelial NO Synthase</td>
</tr>
<tr>
<td>ESRD</td>
<td>End Stage Renal Disease</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GRA</td>
<td>Glucocorticoid-Remediable Aldosteronism</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High Density Lipoproteins Cholesterol</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
JNC-7  Seventh Joint National Committee
K/DOQI  Kidney Disease Outcomes Quality Initiative
KDOQI  Kidney Disease Outcomes Quality Initiative
LDL-C  Low Density Lipoproteins Cholesterol
MDRD  Modification of Diet in Renal Disease Study
Na  Sodium
NCD  Non-Communicable Disease
NDF  National Kidney Foundation
NO  Nitric Oxide
pmp  per million population
PTH  Parathyroid Hormone
RAAS  Renin–Angiotensin–Aldosterone System
RAS  Renin Angiotensin System
RRT  Renal Replacement Therapy
SBP  Systolic Blood Pressure
SCr  Serum Creatinine
SMCs  arterial smooth muscle cells
TC  Total Cholesterol
TG  Triglycerides
TPR  Total Peripheral Resistance
UAE rate  Urinary Albumin Excretion rate
UNRWA  United Nations Relief and Works Agency
WHO  World Health Organization
Chapter 1
Introduction

1.1. Background

There is a strong relationship between chronic kidney disease (CKD) and high blood pressure (BP) whereby each can cause or aggravate the other. BP control is essential to the care of patients with CKD and is relevant at all stages of CKD regardless of the underlying cause (Eknoyan G. et al., 2012).

Hypertension (HTN) is one of the most important causes of CKD and its complications, in which hypertension increases the risk of important adverse outcomes, including loss of kidney function and kidney failure, early development and accelerated progression of cardiovascular disease (CVD), and premature death (Yu HT., 2003). CKD is considered as a major health problem affecting increasing numbers of patients with diabetes and hypertension (Thomas R. et al., 2008). CKD is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR) that persists for more than 3 months. One of the most obvious complications of CKD is the progression to end-stage renal disease (ESRD) that requiring renal replacement therapy, which is more likely to occur in patients with severe CKD (Coresh J. et al., 2007; Levin A., 2006).

Increasing evidence, accrued in the past decades, indicate that the adverse outcomes of chronic kidney disease, such as kidney failure, cardiovascular disease, and premature death, can be prevented or delayed (Coresh J. et al., 2003). According to National Kidney Foundation Practice Guidelines 2002, the treatment of CKD in earlier stages is effective in slowing the progression of kidney failure and reduction of cardiovascular risk factors. The aims of the treatment of hypertension is to control the blood pressure, to slow down the progression of CKD and decrease the cardiovascular risk. Hypertension control, by itself, can delay the progression of CKD (Appel L.J., 2010). Guidelines from the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) recommend estimating glomerular filtration rate and screening for albuminuria in patients with risk factors for chronic kidney disease, including diabetes, hypertension, systemic illnesses, age greater than 60 years, and family history of chronic kidney disease (Snyder S. & Pendergraph B., 2005).
Many studies reported using Angiotensin Converting Enzyme inhibitors (ACEIs) in preventing the progression of CKD and in terms of reducing cardiovascular morbidity and mortality (Abe H. et al., 2007; Katayama S. et al., 2008). Calcium Channel Blockers (CCBs) are potent vasodilators and have a relevant role in the control of the blood pressure in CKD patients (Azushima K. et al., 2014; Ando K. et al., 2013).

This study is intended to investigate the renoprotective effects of Amlodipine (Calcium Channel Blocker) alone or in combination with Enalapril (Angiotensin Converting Enzyme Inhibitor) among hypertensive patients with CKD in Gaza Strip by measuring Urinary Albumin Excretion (UAE) rate and serum creatinine (SCR) before and every 2 months of using these drugs throughout the study period (6 months).

1.2. Justification of the study

Chronic kidney disease is one of the chronic diseases that influence quality of life and habits, requiring a strict therapeutic regimen and lead to renal failure that impact dialysis (El-Shahed A. et al., 2013).

According to Palestinian Health Annual Report 2005, 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, the renal failure was the sixth cause of death (5.1 %) among Palestinian population (Annual Report, 2009). While in the mid-year 2013, 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), which indicating that there is continuous increase in death caused by renal failure during the last decade (Mid annual Report, 2013).

The uncontrolled hypertension is the most common cause of renal failure requiring dialysis and renal replacement therapy worldwide. The major goals of lowering BP in patients with chronic kidney disease include reduction of mortality, cardiovascular events, and slowing progression of Chronic Kidney Disease (O’Hare AM. et al., 2007).

Therefore, the present study aims to provide evidence and recommendations to change the protocol used in treatment of hypertensive patients with CKD in Palestine.
1.3. Purpose of the study

The overall objective of this study is to study the effect of Calcium Channel Blockers alone or in combination with Angiotensin Converting Enzyme Inhibitors on kidney function in hypertensive patients with CKD (stage 1, 2 and 3).

1.4. Objectives of the study

1. To assess the interaction of CCB agents with renal function in hypertensive patients.
2. To compare the effect of CCBs alone with CCBs/ACEIs combination on renal functions among hypertensive patients with renal dysfunction.
3. To provide evidence and recommendations to change the protocol used in treatment of hypertensive patients with CKD in Palestine.
4. To control blood pressure in hypertensive patients with CKD.
Chapter 2

Literature Review

2.1. Hypertension

2.1.1. Introduction

Hypertension the silent killer is considered a chronic and serious condition; it can lead to life-threatening complications, such as cardiovascular events, kidney disease, and stroke and may lead to death. (Weber MA. et al., 2014; Chobanian AV. et al., 2003). Hypertension affects more than 40% of adults (over 18 years) worldwide (Chow CK. et al., 2013) and is the leading risk factor for death or disability (Lim SS. et al., 2012).

Hypertension is defined as a persistent elevation of blood pressure above a certain threshold value 140/90 mmHg, which is not caused by subsequent cardiac, endocrine, or renal disease (Williams B. et al., 2004). It is the pressure applied by the blood on the walls of the blood vessels, to help pumping blood into arteries, then to all body organs to supply oxygen and nutrients to the tissues and carry away waste materials (Mancia G. et al., 2013).

Two measurable indicators are used to determine what the blood pressure is. First, the systolic pressure results from contraction of the left ventricle of the heart, forcing blood into the aorta and out into its branches that form the systemic arterial circulation. The pressure wave of this contraction is measured peripherally. Second, the diastolic pressure results from relaxation of the left ventricle of the heart, and the pressure diminishes to a level sustained by the residual pressure retained by the elasticity of the arterial system. (Sacks FM. & Campos H., 2010).

Elevation of blood pressure above approximately 115/75 mmHg increases the cardiovascular risk (Kikuya M. et al., 2007; Lewington S. et al., 2002), damage to the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death (Giles TD. et al., 2005).

2.1.2. Prevalence of Hypertension

Hypertension is an important public health challenge all over the world, because of its high prevalence and associated increase in disease risks. It is the most important changeable risk factor for cardiovascular, cerebrovascular and renal disease (Khatib O. & El-Guingy M., 2005).

The prevalence of cardiovascular diseases has been shown on the rise as non-communicable disease (NCD), with largest proportion of death by 2012 based on World Health Statistics 2012. Hypertension as NCD was reported to be the fourth sponsor to premature death in developed countries and the seventh in developing countries. It is projected that the annual number of deaths due to cardiovascular disease will increase from 17 million in 2008 to 25 million in 2030 (World Health Statistics, 2012).
In the Eastern Mediterranean Region, two out of five adults are affected by high blood pressure, in which the prevalence of hypertension averages 29% and it affects approximately 125 million individuals (Bilal A. et al., 2015).

Recent reports highlighted that nearly one billion adults around the world suffered from hypertension in the year 2000, and they are predicted to increase to 1.56 billion by 2025. (Kearney PM. et al., 2005).

In a different situation, the detection rate of Hypertension among Palestinian refugees aged over 40 attended health centers in 2009 was 16% in the West Bank and 19.7% in the Gaza Strip. (WHO, 2010). By 2012, this rate increased to 17.8% in West Bank and decreased to 17.4% in Gaza Strip (UNRWA Annual Report, 2012).

Mortality rates caused by hypertension was 1.7% in Gaza Strip and 1.3% in West Bank from total mortality rate among reported death causes in 2010. (UNRWA Annual Report, 2010).

2.1.3. Types and Classification of Hypertension

2.1.3.1. Classes of hypertension

According to seventh Joint National Committee report on the detection, evaluation, and treatment of high blood pressure (JNC-7) and the World Health Organization/International Society of Hypertension guidelines, blood pressure is classified into different stages on the basis of blood pressure level (Table 2.1). This new classification includes the term “prehypertension” for those with BPs ranging from 120 to 139 mmHg systolic and/or 80 to 89 mmHg diastolic blood pressure (DBP), which is not considered disease category. JNC-7 classification can be used to identify individuals at high risk of developing hypertension and delay the disease from developing.

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mm Hg</th>
<th>DBP mm Hg</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>
2.1.3.2. Types of Hypertension

There are two major types of hypertension, according to its pathogenesis, primary or essential and secondary.

1. Essential (primary) hypertension is called as idiopathic hypertension because it has heterogeneous disorder and have no known causes. It accounts for 95% of all cases of hypertension and can be defined as high BP in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, and aldosteronism or genetic not present. (Carretero OA. & Oparil S., 2000).

2. Secondary hypertension: less common than the first type and accounts for up to 5% of hypertensive patients. (Ker JA., 2011). The causes of this type of hypertension can be investigated when new or sudden onset of hypertension before the age of 20 or after the age of 50, markedly elevated blood pressure with severe end organ disease, resistant or refractory hypertension, specific biochemical disturbances suggesting a secondary form of hypertension, and physical signs or a specific body habitus (central obesity, purple striae, abdominal bruits) (Kallistratos MS. et al., 2010). The two important causes of secondary hypertension are renovascular stenosis and primary aldosteronism. Other causes of secondary hypertension include primary renal disease, oral contraceptive use, pheochromocytoma, Cushing’s syndrome, sleep apnea syndrome, and coarctation of the aorta. (Winer N., 2012).

2.1.3.3. Etiology and Pathophysiology of Hypertension

Although of the large number of studies recently performed in this field, the pathogenesis of human hypertension remains ambiguous. (Montecucco F. et al., 2011).

In the past, hypertension was considered as symptom not a disease, which is associated with other vascular diseases like arteriolar sclerosis and premature atherosclerosis. However, recently essential hypertension is considered to be as cluster in families and a good base for genetic developed diseases with inherited biochemical abnormalities. (Lifton RP. et al., 2001; Johnson RJ. et al., 2002).

Factors that increase BP are inherited, in addition to behavioral and environmental components. In which inherited BP could be considered as the core BP, whereas hypertensinogenic factors (ex. obesity, high alcohol and salt intake) cause BP to increase above the range of inherited BPs. (Vikrant S. & Tiwari SC., 2001).
The onset of hypertension is typically in middle age (Padwal RS. et al., 2008). Many pathophysiologic factors (Figure 2.1) that have been implicated in the genesis of essential hypertension includes increased sympathetic nervous system activity, overproduction of sodium-retaining hormones and vasoconstrictors. Long-term high sodium intake, inadequate dietary intake of potassium and calcium, increased or inappropriate renin secretion that lead to increase release of angiotensin II and aldosterone also play a role in the pathogenicity of hypertension. (Vikrant S. & Tiwari SC. 2001). Moreover, deficiencies of vasodilators, such as prostacyclin, nitric oxide (NO), and the natriuretic peptides, alterations in expression of the kallikrein–kinin system that affect vascular tone and renal salt management have a primary role in the development of high blood pressure. Abnormalities of resistance vessels, including selective lesions in the renal microvasculature, diabetes mellitus, insulin resistance, obesity, increased activity of vascular growth factors, alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone, and altered cellular ion transport, all considered an important parts in essential hypertension mechanisms. (Calhoun DA. et al., 2000).

Figure 2.1: Pathophysiologic mechanisms of hypertension. (Calhoun DA. et al., 2000)
2.1.3.3.1. Renin–Angiotensin–Aldosterone System (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is a signaling pathway responsible for regulating the body's blood pressure and systemic vascular resistance, which in turn influence cardiac output and arterial pressure. (Carey RM. & Siragy HM., 2003).

The long-term actions of angiotensin II and aldosterone on blood pressure are closely intertwined with their effects on volume homeostasis and the renal pressure natriuresis mechanism. Changes in angiotensin II and aldosterone act to amplify the effectiveness of pressure natriuresis and minimize changes in blood pressure needed to maintain sodium balance (Hall JE., 2003).
When angiotensin II or aldosterone levels are inappropriately elevated, the antinatriuretic effects of these hormones shift pressure natriuresis to higher levels, thereby necessitating increased blood pressure to maintain sodium balance. (Tea BS. et al., 2000).

Angiotensin II (produced by splits of angiotensinogen by renin secreted from kidney) increases blood pressure by various mechanisms, including constricting resistance vessels, stimulating aldosterone synthesis and release and renal tubular sodium reabsorption, stimulating thirst and release of antidiuretic hormone, and enhancing sympathetic outflow from the brain. Angiotensin II also, induces cardiac and vascular cell hypertrophy and hyperplasia directly by activating the angiotensin II type 1 (AT\textsubscript{1}) receptor and indirectly by stimulating release of several growth factors and cytokines (Oparil S. et al., 2003). On the other hand, blood pressure levels can be affected by high levels of Aldosterone that causes increase in sodium and water reabsorption from epithelial cells of the kidney (Tomaschitz A. et al., 2009).

The action of Aldosterone is mediated and interacted by other pathways that is regulated by Angiotensin II and angiotensin II receptors type 1 (Lemarie CA. et al., 2008) and by Aldosterone and the mineralocorticoid receptor (Jaffe IZ. & Mendelsohn ME., 2005).

The interaction of Aldosterone with Angiotensin II leads to potentiation of the proliferative action of Angiotensin II (Xiao F. et al., 2004), and up-regulation of the Angiotensin II receptors which leads to potentiation of vasoconstrictor effect of angiotensin II in coronary arteries. (Chai W. et al., 2005).

2.1.3.3.2. Genetics

Many recent studies indicated that hypertension may results from interaction of genetic and environmental factors (Oparil S. et al., 2003). Blood pressure alternations that are genetically determined named "inherited blood pressure" and are ranged from low normal blood pressure to sever hypertension (Vikrant S. & Tiwari SC., 2001).
There are little informations on genetic variations or genes that are over expressed or under-expressed and intermediary phenotypes that play role in regulation and causing high blood pressure (Carretero OA. & Oparil S., 2000). The identification of these variations that are involved in hypertension development is very complicated and are controlled by causative phenotypes that include autonomic nervous system, hormones, cardiovascular system and renal function (Korner PI., 2010).

Studies conducted on twins indicated that the prevalence of HTN is greater in monozygotic than dizygotic twins. Other studies also, indicated that similarity in blood pressure within families is greater than between families (Khullar M., 2010; Oscar A. et al., 2000). Moreover, single genes can have major effects on hypertension (Lifton RP. et al., 2001), while mutation in 10 genes have been shown to cause hyper or hypotension through common pathways by increasing or decreasing salt and water reabsorption by nephron (Desitter I. et al., 2001; Korner PI., 2010).

Inherited cardiovascular risk factors like insulin resistance, hypercholesterolemia and obesity, also play an important role in hypertension development (Calhoun DA. et al., 2000) in which there is a clear relationship between hypertension and dyslipidemia and the frequency of hypertension in patients with diabetes mellitus is twice as common in patients without diabetes (Oparil S. et al., 2003).

2.1.3.3.3. Sympathetic Nervous System and cardiac output

Increased activity of Sympathetic Nervous System can cause elevation of blood pressure and share in the development and maintenance of hypertension by stimulation of heart, kidney, and peripheral vasculature and lead to increase cardiac output, vascular resistance, fluid retention (Oparil S. et al., 2003) metabolic and hemodynamic abnormalities and finally increasing cardiovascular morbidity and mortality (Brook RD. & Julius S., 2000). There are two mechanisms that cause increase in cardiac output either by increasing fluid volume or by increasing contractility from neural stimulation of the heart (Vikrant S. & Tiwari SC., 2001).

Recent studies suggested that decreased parasympathetic tone causes increase in the heart rate. These observations support the belief that the autonomic imbalance contributes in hypertension pathogenicity. The mechanisms of increased sympathetic nervous system activity in HTN are complex and involves alternation in baroreflex and chemoreflex pathways at peripheral and central levels and these mechanisms contribute to development of target organs damage (Oparil S. et al., 2003).
2.1.3.3.4. Arterial Stiffness and Endothelial Dysfunction

Reduced elasticity and increased stiffness of large arteries in older ages lead to the development of structural abnormalities, arteriosclerosis and endothelial dysfunction, systolic blood pressure and pulse pressure increases (O’Rourke MF. et al., 2000). Many other factors that may contribute to the damage of endothelium including estrogen deficiency, high dietary salt intake, tobacco use and diabetes. In addition, reduced NO synthesis is related to loss of endothelial function and reduction in endothelial NO synthase involved in wall thickness of conducted vessels and arteries. Moreover, clinical studies indicate that NO related vascular relaxation is decreased in hypertensive patients, while in oxidative stress, increased level of superoxide dismutase reduces blood pressure and restores NO bioactivity provides further evidence that oxidant stress contributes to the inactivation of NO, and development of endothelial dysfunction in hypertensive patients (Oparil S. et al., 2003).

2.1.4. Treatment of Hypertension

2.1.4.1. Goals

Over the last decade, many treatment of hypertension guidelines lead to reduction in blood pressure below 140/90 mmHg to prevent long-term complications, reduce morbidity and mortality caused by hypertension (Foex P. & Sear JW., 2004) and to achieve the maximum reduction in the long-term total risk of morbidity and mortality caused by cardiovascular diseases. The primary focus in the treatment of hypertension should be on achieving systolic blood pressure target because most patients with hypertension will reach the diastolic blood pressure goal once the systolic blood pressure is at goal (NKF, 2002).

2.1.4.2. Life Style Modification

According to American Association of Clinical Endocrinologists (AACE) Guidelines 2006 for the diagnosis and treatment of hypertension, lifestyle modifications aim to correct the contributing factors regardless of the primary cause of hypertension, and at the same time patients should have an important, first-line role in any therapy (Torre JJ. et al., 2006). The first step in the treatment of hypertension is modification of lifestyle that includes moderate sodium restriction, weight reduction in the obese, decreased alcohol intake, and an increase in exercise. When these measures have not been successful or when hypertension is already at stage 2 when first recognized, drug therapy is necessary (Chobanian AV. et al., 2003). If these measures are not enough to control hypertension, using of other antihypertensive agents is necessary.
2.1.4.3. Pharmacological Treatment

According to European Society of Cardiology Guidelines, the ideal antihypertensive agent should be effective in reducing systemic blood pressure with prolonged duration of action to allow for once-daily dosing, unable to induce unwanted or metabolic effects and should be able to reduce target organ damage. The most commonly used classes of drugs include diuretics, β-blockers, ACEIs, angiotensin II receptors antagonists (ARBs), calcium channel blockers, α adrenoceptor blockers, combined α and β-blockers, direct vascular dilators and central adrenergic agonists (Dumont C. & Hardware J., 2009).

2.1.4.3.1. Diuretics

Diuretics are useful agents in the treatment of a variety of conditions such as hypertension, heart failure, liver disease and certain types of kidney disease. Diuretics or “water pills” are medicines that aid in the elimination of sodium (salt) and water from the body. They act by increasing the excretion of sodium in the urine. When the kidneys excrete sodium, they excrete water along with it. This decreases the blood volume and reduces pressure of the blood on the walls of the arteries (Smith H., 2014).

Diuretics either alone or in combination with other antihypertensive agents, are considered as first line therapy in most patients with uncomplicated hypertension or in patients with stage 2 hypertension (Appel LJ., 2002). Low-dose diuretic therapy is effective and reduces the risk of stroke, coronary heart disease, congestive heart failure, and total mortality (Jimbo M. et al., 2014). The most common types of diuretics used in the treatment of hypertension are thiazide, which have been shown to be as good as, or superior to other types in preventing cardiovascular disease morbidity and mortality (Chobanian AV. et al., 2003). Thiazide-type diuretics can be used in treatment of hypertensive patients with other risk factors for cardiovascular diseases and metabolic syndrome especially for older patients with isolated systolic hypertension (Wright Jr. et al., 2008). Thiazide (Hydrochlorothiazide) and Thiazide-like diuretics (Indapamide and chlorthalidone) work by increasing excretion of sodium by the kidneys and additionally may have some vasodilator effects (Jamerson K. et al., 2008). Adding of potassium-sparing diuretics (spironolactone, eplerenone, or amiloride) or loop diuretics (furosemide) to thiazide agents may achieve effective control of hypertension but their use for this aim is limited (Krakoff L.R., 2005).

2.1.4.3.2. Calcium Channel Blockers (CCBs)

Calcium channel antagonists are a mature group of drugs directed at cardiovascular diseases including hypertension, angina, peripheral vascular disorders and some arrhythmic conditions (Triggle D., 2007).
CCBs have been one of the most widely used classes of antihypertensive agents in the last 20 years, based on their effectiveness in reducing BP levels, good tolerability, and abundant evidence on reducing cardiovascular and renal consequences of hypertension (Tocci G. et al., 2014). CCBs are considered highly effective agents in the treatment of hypertension due to their powerful arterial vasodilatory effect; this reasons is responsible for CCBs long-term efficacy (Drug Information Reference, 2003). Dihydropyridine CCB produce excellent blood pressure control by directly relaxing the smooth muscles surrounding muscular arteries, while non-dihydropyridine CCB reduce blood pressure by inducing vasodilation and by decreasing myocardial contractility. (Martin J., 2008). CCBs are most wildly used drugs in the treatment of hypertension. In spite the efficacy of these agents, the safety of CCBs and their effects on CV and non-CV morbidity and mortality have been the subject of argument over the last decade (Kizer JR. & Kimmel SE., 2001). New several studies and comprehensive meta-analyses have been shown that CCBs reduce the cardiovascular morbidity and mortality associated with uncontrolled hypertension, including stroke (WHO, 2003).

2.1.4.3.3. Angiotensin Converting Enzyme Inhibitors (ACEIs)

The development of pharmacological probes that block the renin angiotensin system helped define the contribution of this system to blood pressure control and to the pathogenesis of diseases such as hypertension, congestive heart failure, and chronic renal failure (Burnier M., 2001). That making ACEIs to be considered the first-line therapy of hypertension in patients under 55 years (Ooi S. & Ball S., 2009). The mechanism of these agents in reduction of blood pressure is exerted by blocking the renin-angiotensin system and thus preventing conversion of angiotensin I to angiotensin II that is vasoconstrictor. ACEIs also increase availability of the vasodilator bradykinin by blocking its breakdown (Weber MA. et al., 2014). These agents could positively influence cardiovascular and cerebrovascular outcomes in hypertensive patients in which hypertension is considered as risk factor for both diseases (Mancia G. et al., 2007; Graham I. et al., 2007).

2.1.4.3.4. Beta-Adrenoreceptor antagonists (β-Blockers)

β-Blockers is class of antihypertensive agents that are particularly used for the treatment and management of cardiac arrhythmias, myocardial infarction and hypertension (Kezerashvili A. et al., 2012). The exact mechanism of beta-blockers in lowering blood pressure is obscure. The negative inotropic and negative chronotropic effect of β- Blockers are responsible for reduction of cardiac output, an effect on vascular resistance, as well as an inhibitory effect on the release of renin, which is stimulated by the sympathetic nervous system could be possible mechanisms of
antihypertensive effects of β-blockers (Elsik M. & Krum H., 2007). According to the European hypertension guidelines considerations in 2003, β-Blockers is equivalent first-line therapy for uncomplicated hypertension as other antihypertensive agents. On the other hand, many meta-analysis studies concluded that beta-blockers are no better than any other antihypertensive drugs at preventing heart attacks, but they are less effective at preventing strokes (Lindholm L.H. et al., 2005). While other studies concluded that initiating treatment of hypertension with beta-blockers leads to modest reductions in cardiovascular disease and no significant effects on mortality and these effects are inferior to those of other antihypertensive drugs (Wiysonge CS. et al., 2012). According to Saudi Hypertension Management Guidelines 2011, β-Blockers are no longer recommended as first-line therapy in patients over 60 years of age with uncomplicated HTN, because of the recently described trend toward worse outcomes in patients treated with β-Blockers compared with those treated with other classes of antihypertensive drugs and increased risk of developing Diabetes Mellitus. However, for patients with stable, well-controlled HTN who are already taking β-Blockers, it is reasonable to continue the regimen unchanged (Alfurayh O. et al., 2011).

2.1.4.3.5. Angiotensin Receptor Blockers (ARBs)

Angiotensin II acts on specific angiotensin AT$_1$ and AT$_2$ receptors causing smooth muscle contraction and the release of aldosterone, prostacyclin, and catecholamines (Foex P. & Sear JW., 2004). ARBs displace angiotensin II from its specific AT$_1$ receptor, antagonizing all its effects and resulting in a fall in peripheral vascular resistance with little change in heart rate and cardiac output (Al Sabbah Z. et al., 2013).

Using angiotensin II receptor blockers alone or in combination with salt depletion in treatment of hypertension lowers blood pressure in hypertensive patients and improves systemic hemodynamics in patients with congestive heart failure. Many studies have evaluated the antihypertensive efficacy of angiotensin II receptor antagonists in patients with mild to moderate or severe hypertension and compared them with other antihypertensive agents and the results concluded that ARBs are similar to ACEIs, CCBs, β-blockers, and diuretics in the efficacy and this antihypertensive efficacy of ARBs is potentiated by the combination with a small dose of a thiazide diuretic (Burnier M., 2001).
2.1.4.3.6. α-Adrenoceptor Blockers (α-Blockers)

One of the most important factors that plays a key role in the pathogenesis of essential hypertension is the sympathetic nervous system, which is mediated by the alpha and beta-receptors. Agents that block α-adrenoceptors, provide a logical approach to the treatment of hypertension by correcting elevated total peripheral resistance, the fundamental hemodynamic abnormality in essential hypertension (Taraphder A., 2014). The role of α-blockers in the management of hypertension continues to develop. Recent studies conducted that use of these agents is safe, well tolerated and effective as add-on therapy either alone or in combination with all other major classes in treatment of uncontrolled hypertension. In addition, there is increasing evidence suggesting, that they have significant beneficial effects on lipid and glucose metabolism (Chapmana N. et al., 2010).

According to the Antihypertensive and Lipid-Lowering Treatment to prevent heart attack trial (ALLHAT, 2002), α-blockers were substandard to other classes of drugs that are used as first line therapy for the treatment of hypertension. On the other hand, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7, 2014) guidelines, α-blockers were not recommended for the routine treatment of hypertension (Chobanian AV. et al., 2003).

2.1.4.3.7. Direct Vascular Dilators

Hypertension is associated with altered endothelial NO release. Abnormal endothelium dependent vascular relaxation in patients with primary hypertension is associated with abnormalities of the NO system and little is known about the relationship between the circadian rhythm of BP and endothelial function in patients with essential hypertension (Huang C. et al., 2009). These agents act by relaxing the endothelium of blood vessels, which causes the vessels to dilate. The dilation of arteries leads to reduction in systemic vascular resistance that leads to falling in blood pressure (Antosovab M. et al., 2012). Increasing evidence suggests that vascular morbidities may be related to a reduced production and bioavailability of the potent vasodilator NO, which may result from an increased vascular production of superoxide anion (Touyz RM. & Schiffrin EL., 2001), and administration of NO or its precursor L-arginine improves endothelium-mediated vasodilatory function in patients with essential hypertension (Lekakis JP. et al., 2002). Because direct vascular dilators, such as hydralazine and minoxidil, do not improve cardiovascular health and may produce certain adverse effects, they are not recommended as first-line drugs, and they are added to the treatment regimen when patients are resistant to diuretics, RAAS blockers, CCBs, and β-blockers (Dumont C. & Hardware J., 2009).
2.1.4.3.8. Central Adrenergic Agonists

Central alpha agonists include clonidine, guanfacine, methyldopa, and reserpine. These agents act centrally by stimulate the α₂-adrenergic receptors in the central nervous system and reduce sympathetic outflow from the central nervous system, and they are effective in reducing blood pressure in most hypertensive patients. However, they may cause significant adverse effects as sedation, dry mouth, and depression, that reduces their popularity (Chobanian AV. et al., 2003; Weber MA. et al., 2014). These drugs are not usually recommended as first-line therapy, except methyldopa may be used as a first-line drug in hypertensive pregnant women because of its safety profile (Dumont C. & Hardware J., 2009).

2.1.4.3.9. Direct Renin Inhibitors

One of the most effective therapeutic strategies of the treatment of hypertension is pharmacologic blockade of the renin-angiotensin-aldosterone system (Fogari R. & Zoppi A., 2010), which plays a vital role in the homeostatic regulation of blood pressure, fluid electrolytic balance, tissue perfusion, and vascular growth (Fyhriquist F. & Saijonmaa O., 2008). The role of Renin in this system is represented by catalyzing the cleavage of angiotensinogen, producing angiotensin I that is converted by Angiotensin-converting enzyme (ACE) into Angiotensin II, which is considered as the primary effector of the RAAS (Cesari M. et al., 2002). Angiotensin II induces adrenal secretion of aldosterone (a mineralocorticoid) that leads to sodium and fluid retention, thus increasing BP (Dzau VJ., 2001). The most important difference between renin inhibitors and ARBs and ACEIs, is that renin inhibitors interrupt the negative feedback effects of angiotensin II on renin secretion, while both ACEIs and ARBs can lead to increases in plasma renin activity (Wal P. et al., 2011).

Recently, many clinical trials have shown that aliskiren, the only direct renin inhibitor, alone or in combination with other antihypertensive agents, provides effective BP reduction with a good safety and tolerability profile (Fogari R. & Zoppi A., 2010). Greater reductions in blood pressure have been achieved when aliskiren was used in combination with hydrochlorothiazide or an angiotensin-receptor blocker (Wal P. et al., 2011).

2.2. Physiology of the Kidney

2.2.1. Structure and location

The kidneys are two bean-shaped organs, each about the size of a handful (12cm long, 5-7cm wide, 3cm thick and weighs 150-200 grams) (Marieb E., 2001). They are located just below the rib cage, one on each side of the spine (figure 2.2).
The function of the two kidneys summarized in filtering about 120 to 150 liters of blood to produce about 1 to 2 liters of urine, which is composed of wastes and extra fluids (NKUDIC, 2014; Henke K., 2003).

![Figure 2.2: Anatomy of the kidney and details of the nephron (Eaton DC. et al., 2009)](image)

Each kidney is made up of about a million of filtering units called nephrons; each nephron filters a small amount of blood. The nephron includes a filter, called the glomerulus and a tubule. The nephrons work through a two-step process. The glomerulus lets fluid and waste products pass through it; however, it prevents blood cells and large molecules, mostly proteins, from passing. The filtered fluid then passes through the tubule, which sends needed minerals back to the bloodstream and removes wastes. The final product becomes urine (NIH, 2014).

### 2.2.2. Main Function of Kidney

The kidneys are important because they keep the composition of the blood stable. They prevent the buildup of wastes and extra fluid in the body, keep stable levels of electrolytes (sodium, potassium, calcium and phosphate); make hormones that help regulate blood pressure, make a hormone called erythropoietin that stimulates the bone marrow to make red blood cells, in a step to prevent anemia (Henke K., 2003).
2.2.3. **Acute Kidney Injury (AKI)**

Acute Kidney Injury (AKI) is considered as a common complication of critical illness, which is associated with high mortality and has a separate independent effect on the risk of death (Mendonca AD. et al., 2000).

AKI/ARF is defined as the sudden and rapid cessation of renal excretory function within a period of hours or days, accompanied by a rise in serum urea and creatinine, and accumulation of nitrogenous waste products in a patient whose renal function was previously normal. It is usually, but not always, accompanied by a fall in urine output. The condition is potentially reversible, and in routine clinical practice, measurement of serum creatinine is used to follow the changes in glomerular filtration rate (Ho KM. & Sheridan DJ., 2006).

Around the world, the prevalence of AKI/ARF depends on its definition, severe AKI/ARF affected approximately 70-140 persons per million of the population and about 50% of them will require dialysis (Ashley C. & Holt S., 2009). On the other hand, the incidence of AKI/ARF that requires renal replacement therapy (RRT) ranged from 22 per million population (pmp)/year up to 203 pmp/year (Stevens PE. et al., 2001). The main causes of AKI/ARF can be classified according to kidney anatomy into Pre-renal AKI/ARF caused by inadequate perfusion of essentially normal kidneys, in which the effective arteriolar blood volume (EABV) is reduced, which is a normal physiological response to hypotension or hypovolemia, resulting in intense renal conservation of sodium and water at the expense of a decreased GFR. On the hand, intrinsic renal failure is caused by any factor that causes damage either to the kidney itself or the surrounding vasculature. Post-renal AKI/ARF or obstructive nephropathy involves obstruction of urinary outflow, leading to increased pressure within the renal collecting systems and resulting in reduced GFR, reduced tubular reabsorption of sodium and water, and acquired renal tubular acidosis, phosphaturia and other abnormalities of tubular function (Holt S. & Moore K., 2000).

2.3. **Chronic Kidney Disease (CKD)**

Chronic kidney disease 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 (Thomas R. et al., 2008). Moreover, those patients are at higher risk of cardiovascular disease in which the early detection of CKD can determine if kidney disease is likely to be progressive allowing appropriate treatment to slow progression to ESRD (SIGN, 2008). CKD is related to multiple comorbidities and adverse outcomes and may increase the risk of cardiovascular disease and cardiovascular events, which increases with worsening renal
function. Many statistical studies indicate that more than 50% of deaths in patients with ESRD is due to CV complications (Carroll LE., 2006). CKD may be caused by damage to both kidneys in which this damage is usually irreversible and can lead to ill health, and in some cases, dialysis or transplantation may become necessary to maintain life (John R. et al., 2004; Coresh J. et al., 2003; Lusignan SD. et al., 2005).

2.3.1. Definition and Staging of CKD

Chronic kidney disease is considered 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 (Inker L.A. et al., 2014, Ashley C. & Morlidge C., 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 A., 2006; Levey AS. et al., 2005), or albuminuria (>30 mg of albumin per g of creatinine) (James PA. et al., 2014).

National Kidney Foundation developed criteria as part of its Kidney Disease Outcomes Quality Initiative (NKF K/DOQI, 2008) to facilitate assessment of CKD severity, this criteria is based on eGFR and pathophysiology of kidney to stratify CKD patients into five major stages as shown in table 2.2 (Coresh J. et al., 2003; Levey AS. & Coresh J., 2012). In this classification, stage 1 is the mildest and usually with few symptoms and stage 5 (also called renal failure or End Stage Renal Disease) being a severe illness with poor life expectancy if untreated (NKF, 2002).

The eGFR is primarily determined by serum creatinine, and the preferred method for estimating GFR is the body surface area-normalized. It can be calculated by Modification of Diet in Renal Disease Study (MDRD) equation, which is based on SCr, age, gender, and ethnicity (Levey AS. et al., 2005).

\[
eGFR \, (\text{mL/min/1.73 m}^2) = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \\
\times (0.742, \text{ if female}) \\
\times (1.212, \text{ if African American})
\]

Moreover, CKD can be identified by calculating creatinine clearance (CrCl), according to 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), (Jamee A. & Abed Y., 2014).
Furthermore, CKD can be classified by using a combination of eGFR (Table 2.3) and Urinary Albumin Excretion (UAE) rate (Table 2.4) in which independent decrease in eGFR and increase in UAE rate enhances the risk of adverse outcomes and multiplies the associated risks of adverse outcomes (Table 2.5) (Jenkins K., 2014).

Albuminuria are strongly predictive of outcomes at all levels of GFR at the individual and population levels. Integrating both GFR and albuminuria into CKD staging hopefully provide more precise classification and more accurate prognostic information and characterization of the level of albuminuria by its severity. The new guidelines distinguished between CKD stage 3a (GFR of 45-59 mL/min/1.73 m^2) and 3b (GFR of 30-44 mL/min/1.73 m^2) in which the risks of mortality and other outcomes vary greatly between these groups. The high prevalence of CKD stage 3 suggests that this distinction will have broad applications. The 2002 KDOQI guideline recommended assessment of the risk for developing CKD for all individuals, with measurement of blood pressure, albuminuria, and serum creatinine to estimate the GFR among those at higher risk (Inker L.A. et al., 2014) including Diabetes, Hypertension, Cardiovascular disease, Structural renal tract disease, recurrent renal calculi or prostatic hypertrophy, Family history of stage 5 CKD or hereditary kidney disease and Opportunistic detection of hematuria (Jenkins K., 2014).

### Table 2.3: GFR categories in CKD (Inker L.A. et al., 2014).

<table>
<thead>
<tr>
<th>GFR Category</th>
<th>GFR (ml/min/1.73m^2)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥ 90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mild decrease</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mild to moderate decrease</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderate to severe decrease</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severe decrease</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Table 2.2: Classification of CKD (Levey AS. & Coresh J., 2012)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Estimated GFR (ml/min/1.73m^2)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal GFR w/proteinuria</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Age-related decline in GFR w/proteinuria</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Low risk of progression to kidney failure</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>High risk of progression to kidney failure</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
Table 2.4: Albuminuria categories in CKD (Van HR. et al., 2014)

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate eq.)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
<td>Normal to mild increase</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>30-300</td>
<td>Moderate increase</td>
</tr>
<tr>
<td>A3</td>
<td>&gt; 300</td>
<td>&gt; 300</td>
<td>Severe increase</td>
</tr>
</tbody>
</table>

AER: albumin excretion rate; ACR: albumin-to-creatinine ratio

Table 2.5: Prognosis of CKD by GFR and albuminuria category (Johnson D., 2012)

<table>
<thead>
<tr>
<th>Kidney function stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Albuminuria stage (UAE rate mg/day)</th>
<th>Normal &lt; 30</th>
<th>Microalbuminuria 30-300</th>
<th>Macroalbuminuria &gt; 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Not CKD unless hematuria, structural or pathological abnormalities present</td>
<td>Moderate*</td>
<td>High*</td>
<td>Very high</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>45-59</td>
<td>Moderate</td>
<td></td>
<td>High*</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>30-44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Moderate, high and very high risks of progressive CKD

2.3.2. Risk Factors of CKD

According to National Kidney Disease Education Program Guidelines 2014 (NKDEP, 2014), the most common risk factors of CKD are Diabetes, Hypertension, family history of kidney failure, cardiovascular disease, recurrent urinary tract infections, HIV infection and Immunological diseases. On the other hand, Adults with diabetes or high blood pressure, or both have a higher risk of developing CKD than those without these diseases. Approximately 1 of 3 adults with diabetes and 1 of 5 adults with high blood pressure has CKD. Risk of developing CKD also increases with age, as these risk factors are more common at older age. Men with CKD are 50% more likely than women to have kidney failure (Meisinger C. et al., 2006).

2.3.3. Prevalence of CKD

Chronic kidney disease is likely to be far more prevalence 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 (Matovinović M., 2009). Most information on CKD epidemiology comes from data available on renal failure; the fifth stage of CKD when treatment with renal dialysis or transplantation as replacement therapy becomes necessary to support life. On the other hand, little information is available on the prevalence of earlier stages of CKD, as patients are often asymptomatic (Warady B. & Chadha V., 2007).
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 prevalences of diabetes and hypertension, which are respectively etiologic in approximately 40% and 25% of CKD cases (Krol G., 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 GL. et al., 2010; Coresh J. et al., 2007; Shaheen FA. & Souqiyyeh MZ., 2010).

The annual incidence of renal failure in USA, UK and Europe is 33.6, 10, and 13.5 per 100,000 population, respectively (Hamer R. & El Nahas M., 2006). While it is estimated that over 10% of adults in developed countries suffer some degree of CKD (Zeeuw D. 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, the 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 by sex, 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).

2.3.4. Etiology of CKD

There are large varieties of etiological factors that contribute to the pathophysiology of CKD. Presently, diabetes and hypertension are the two leading causes of CKD, in which nearly 45% of incident kidney failure is attributed to diabetes and another 20% is attributed to chronic hypertension (US. Renal Data System, 2009).

Other less common but important causes of CKD include primary glomerulonephritis, lupus nephritis, polycystic kidney disease, infectious glomerulonephritis, renal vasculitis, ureteral obstruction, genetic alterations, autoimmune diseases and others (figure 2.3) (López-Novoa JM. et al., 2010).
2.3.5. **Complications of CKD**

Because of declining in eGFR, complications occur more commonly and are more severe. These complications may include Malnutrition, Metabolic acidosis due to reduced acid (hydrogen ion) excretion, Hyperkalemia, Mineral imbalance and bone disorder (calcium, phosphorus, and vitamin D), Anemia due to impaired erythropoiesis and low iron stores and CVD as dyslipidemia (NKDEP, 2014).

2.4. **Hypertensive Nephropathy**

2.4.1. **Prevalence**

Hypertension is considered the second leading cause of end-stage renal disease. According to the United States Renal Data System 2009, about 51–63% of all patients with CKD are hypertensive (US. Renal Data System, 2009).

Hypertension is present in more than 80% of patients with CKD and contributes to progression of kidney disease toward end stage (ESRD) as well as to cardiovascular events such as heart attack and stroke (Toto RD., 2005). Hypertension frequently accompanies advancing CKD, and it is often improperly assumed as the cause rather than the effect of CKD. In fact, more patients develop HTN from CKD than develop CKD from HTN (Weiner D. et al., 2007).

Moreover, hypertension is a common outcome of CKD regardless of etiology, which contributes to the progression of renal damage. Approximately 40% of patients with stage 2 CKD (GFR: 60–90 ml/min per 1.73 m² of body surface), and virtually all in stage 4 (GFR: 15–29) or 5 (GFR: <15 ml/min per 1.73 m² of body surface) are hypertensive (Rosario RF. & Wesson DE., 2006).

Many clinical studies estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of stage 1, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stage 4-5 CKD patients (Bethesda MD., 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 N. et al., 2001).
Figure 2.3: Overall scheme of factors and pathways contributing to the progression of renal disease (Schlondorff DO., 2008)
2.4.2. Etiology and Pathophysiology

A growing body of evidence suggests that there are strong clinical, epidemiological and experimental correlations between hypertension and renal microvascular disease, with or without relevant renal dysfunction. Ultimately, abnormal preglomerular resistance for any given level of blood pressure and skewed autoregulation alter the precise medullary blood flow that signals for the appropriate level of natriuresis and blood pressure, leading to hypertension (Rodríguez-Iturbe B. et al., 2004; Johnson RJ. et al., 2005a). Increased blood pressure is caused by an increase in cardiac output and/or of total peripheral resistance. Both can be altered by a plethora of different mechanisms in uremia and renal failure as shown in figure 2.4 (Hadtstein C. & Schaefer F., 2008).

The renin-angiotensin-aldosterone system plays key roles in the regulation of blood volume, BP, and cardiovascular function. Therapeutic manipulation of the RAAS is an important treatment strategy for hypertension and chronic kidney disease (Weir MR. & Rolfe M., 2010).

The relationship of the Renin Angiotensin System (RAS) in hypertension induced CKD, is based on its capacity to regulate arterial pressure and sodium balance. In case of low BP or increasing sympathetic activity, the juxtaglomerular cells secrete renin that is responsible for converting angiotensinogen to angiotensin II, which is a powerful vasoconstrictor, and in sequence, stimulates the production of aldosterone, which in turn, increases renal sodium reabsorption, and closes the regulatory feedback loop. However, if the blood volume is normal, the increased activity of the renin-angiotensin system produces an abnormal rise in the blood pressure (Mailloux LU., 2001). Hyper-reninemia occurs probably due to renin secretion in poorly perfused areas such as cysts and scars or after microangiopathic damage or tubulo-interstitial inflammation (Loghman-Adham M. et al., 2004) and leads to angiotensin II-mediated vasoconstriction as well as aldosterone-mediated salt retention, thus increasing both total peripheral resistance and blood volume. Additional delayed effects of a high angiotensin II tone include inflammation, cardiac hypertrophy and endothelial cell damage, mesangial cell proliferation and fibrosis, which contribute further to hypertension and end organ damage (Wolf G. et al., 2003).

Sodium retention and consequent fluid overload have long been recognized as causes of hypertension in CKD (Tkaczyk M. et al., 2008).
Increase in sympathetic nervous system activity also plays an important role in the pathophysiology mechanism of CKD combined with hypertension (Schlaich MP. et al., 2009). Afferent signals from the diseased kidney are transmitted to the vasomotor control center in the brain increasing the blood pressure (Rump LC., 2000). In addition, increased plasma noradrenaline levels are often high in CKD patients. Evidence for the role of sympathetic nervous system is provided by the fall of blood pressure after renal sympathetic denervation or after bilateral nephrectomy (Khawaja Z. & Wilcox CS., 2011).

Moreover, Patients with CKD have reduced urinary excretion of dopamine and decreased activity of the renal dopaminergic system, which correlates well with the degree of renal dysfunction. All these data indicated that the reduced activity of renal dopaminergic system in CKD, by decreasing the sodium excretion, might be another factor connected with the hypertension of CKD (Pestana M., 2001).

Many studies confirmed that oxidative stress contributes significantly to the pathogenesis of CKD associated with hypertension in which there is an excess of oxidant molecules such as superoxide and hydrogen peroxide and a decrease of anti-oxidant ones, such as catalase, superoxide dismutase and glutathione dismutase (Vaziri ND., 2002). The excess of reactive oxygen species may directly stimulate vascular contraction or reduce NO, contributing to hypertension in CKD (Paravicini TM. & Touyz RM. 2008; Rubattu S. et al., 2015).
In CKD, endothelin, which is considered a potent vasoconstrictor, is increased and the use of selective endothelin receptor antagonist produces reduction of blood pressure associated with renal vasodilatation (Goddard J., 2004).

The exact mechanisms of kidney damage in patients with hypertension remain difficult to find. Two integral pathogenic mechanisms ultimately ending in kidney fibrosis and scarring have been proposed. One of these mechanisms starts with the changes in systemic and renal macro and microvasculature leading to the loss of renal auto-regulation with elevation of intra-glomerular capillary pressure and the consequent hyperfiltration-mediated injury, which leads to transglomerular loss of proteins and promotes the release of cytokines and growth factors by mesangial cells and down stream tubular epithelial cells. The second mechanism proposes endothelial dysfunction and loss of endogenous vasodilators as precipitating factors of hypoxic-ischemic injury. The consequent activation of the intra-renal Renin Angiotensin System and the increased release of cytokines and growth factors with induction of inflammatory cells stimulate apoptosis causing loss of normal kidney cells and increased matrix production, finally leading to progressive glomerular and interstitial fibrosis and scarring (Morgado E. & Neves PL., 2012).

Overtime, high blood pressure can damage the blood vessels and nephrons in the kidneys. If blood pressure becomes extremely high, it can narrow the blood vessels that supply the kidneys. This reduced blood flow to the kidneys result in reduced kidney function. The main effect of hypertension on kidney function is summarized in causing a nephrosclerotic glomerulopathy, which is characterized by renal vasculopathy affecting preglomerular arteries and arterioles, resulting mainly from atherosclerosis, endothelial dysfunction, wall thickening and fibrosis. In addition, microvascular disease of the glomerular tuft capillaries; diffuse glomerulosclerosis and, less often, focal and segmental glomerulosclerosis, involving damage to the filtration barrier constituents and interstitial fibrosis are considered as features of nephrosclerosis caused by hypertension (Rosario RF. & Wesson DE., 2006).

In CKD caused by hypertension, GFR initially stays relatively constant and this is due to increased glomerular capillary pressure resulting from deficient or upwardly reset renal autoregulation and damage to the filtration barrier resulting in greater permeability. Thereafter, GFR decreases because of a progressive loss of surface area, mesangial hypertrophy and increasing glomerular and peritubular fibrosis. Subsequently, basement membrane alterations produce albuminuria and protein hyperfiltration (López-Novoa JM. et al., 2010). On the other hand, patients with chronic hypertension develop CKD because of high blood pressure, which mechanically damages renal glomeruli and renal vessels (Wiederkehr M. et al., 2005).
CKD resulted from hypertension can also be the consequence of non-mechanical damage like increased angiotensin II or decreased NO. Nephropathy can also be viewed as a primary renal lesion that progresses in parallel to and initiates the rise in blood pressure or resulting from genetic traits and environmental insults (Johnson RJ. et al., 2005 a, b).

Progression of CKD that is associated with hypertension is highly dependent on renal blood flow autoregulation and renal hemodynamics, genetically determined factors that modify renal function or renal tissue homeostasis independently of their action on blood pressure or renal hemodynamics, and genetic susceptibility factors (Loutzenhiser R. et al., 2006).

2.4.3. Treatment of hypertensive nephropathy

2.4.3.1. Goals

Hypertension is common in CKD, and it is a risk factor for faster progression of kidney disease and development and worsening of CVD. Some antihypertensive agents also slow the progression of kidney disease by mechanisms in addition to their antihypertensive effect. According to the National Kidney Foundation Guidelines 2002, Antihypertensive therapy that is used in the treatment of hypertensive nephropathy should be able to lower blood pressure, reduce the risk of CVD and slow progression of kidney disease in patients with hypertension (Morgado E. & Neves PL., 2012).

Agents that not only lower BP but also reduce proteinuria are recommended as first-line therapy for most patients with CKD and HTN; data collected in this field indicated that there might be significant long-term benefits in both cardiovascular and renal outcomes when proteinuria is decreased (K/DOQI, 2002). In addition, decreased albuminuria is associated with slower progression of CKD and improve blood pressure (Zeeuw D. et al., 2004).

Furthermore, Blood pressure should be controlled to slow the impairment of glomerular filtration rate and reduce proteinuria. Patients with proteinuria ≥1 g/day should have a target maximum systolic blood pressure of 130 mmHg (Jafar TH. et al., 2003).

2.4.3.2. Drugs used in the treatment of hypertensive nephropathy

According to SIGN guidelines 2008, Agents that target the renin-angiotensin-aldosterone system (RAAS) such as Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) have both cardioprotective and renoprotective effects. These agents preferentially dilate the efferent renal arteriole reducing intraglomerular hypertension and reducing proteinuria independent of systemic blood pressure effects (Strippoli GF. et al., 2006).
Using of these agents alone or in combination is considered the best choice in order to reduce the rate of progression of chronic kidney disease (Doulton TW. et al., 2005), in which these combination offers a small additive blood pressure–reducing effect of 2–4 mmHg and a synergistic proteinuria reducing effect (Schmieder RE. et al., 2007).

On the other hand, patients suffering from hypertensive nephropathy often experience fluid retention or fluid overload. As a result, diuretics are often necessary in their treatment regimen. Thiazides are recommended for patients with CKD stages 1 to 3 (GFR ≥30 mL/min), and have been established as effective agents for BP and CVD risk reduction (ALLHAT, 2002). Otherwise, loop diuretics are recommended for patients with CKD stage 4 or 5 (GFR <30 mL/min), as they have been shown to be more effective in reducing extracellular fluid volume in patients with severely reduced GFR. (Levey AS. et al., 2004).

Calcium channel blockers (CCBs) can be used as second- or third-line therapy in the treatment of hypertensive patients with CKD (Chobanian AV. et al., 2003; K/DOQI, 2002). In spite of no difference in the effects on BP lowering between non-dihydropyridine CCBs and dihydropyridine CCBs, non-dihydropyridine CCBs have been shown to significantly reduce proteinuria either when used alone or in combination with an ACEIs or an ARBs (Bakris GL. et al., 2002).

Many clinical trials indicated that Aldosterone receptor antagonists provided a good role in reduction of proteinuria when added to ACEIs or ARBs (Table 2.6). (Navaneethan SD. et al., 2009; Mehdi UF. et al., 2009).

Table 2.6: Recommended Antihypertensive Agents for Patients with CKD and HTN

<table>
<thead>
<tr>
<th>Classification of Patients With CKD</th>
<th>First Line</th>
<th>Second Line</th>
<th>Third Line</th>
<th>Fourth Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic CKD with or without HTN</td>
<td>ACEI or ARB</td>
<td>Thiazide or loop diuretics</td>
<td>ND-CCB (may also be considered 2nd line)</td>
<td>Aldosterone antagonist</td>
</tr>
<tr>
<td>Nondiabetic CKD + HTN + proteinuria</td>
<td>ACEI or ARB</td>
<td>Thiazide or loop diuretics</td>
<td>D-CCB (may also be considered 2nd line)</td>
<td>Aldosterone antagonist</td>
</tr>
<tr>
<td>Nondiabetic CKD + HTN but without proteinuria (&lt;200 mg/g)</td>
<td>No agents preferred; consider a diuretic</td>
<td>ACEI or ARB or CCB</td>
<td>Aldosterone antagonist</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not applicable; (Levey AS et al., 2004; Navaneethan SD. et al., 2009)
2.5. **Drugs used in the study**

2.5.1. **Calcium Channel Blockers**

Calcium channel blockers as antihypertensive agents consist of two main subgroups, dihydropyridine (Nifedipine, Amlodipine and others), and non-dihydropyridine that are divided into Benzothiazepines (Diltiazem) and Phenylalkylamine (Verapamil) classes (James PA. et al., 2014).

These agents are used in wide range for treatment of cardiovascular diseases such as angina pectoris, arrhythmia and arterial hypertension. Their vasodilation mechanism of action depends on inhibiting the cellular entry of calcium through two types of voltage activated calcium channel, high voltage channels including P-/Q, L-,N-,and R-type channel, and low voltage T-type channels (Boero R. et al., 2003).

All these channels are distributed in different areas throughout body vasculature smooth muscles such as cardiac myocytes and conductive tissue of heart as well as the kidney. Inhibition of these channels modulate the calcium dependent functions and lead to alternation in kidney function, reducing glomerular pressure and protecting the kidneys by reducing proteinuria in hypertensive patients (Marin R. et al., 2005).

2.5.1.1. **Renoprotective Role of CCBs**

In clinical trials, increasing interest in the investigation of the renal effect of CCBs as antihypertensive agents, due to the aspects resulted from high prevalence of nephrosclerosis as a cause of ESRD, and minor alternation of renal function in hypertensive patients including increase in serum creatinine values, decrease eGFR, microalbuminuria and/or proteinuria that indicate significant change in CV function as well as increase rate of mortality (Ruilope LM. et al., 2001; Sarnak MJ. et al., 2003). All these events may rise due to inadequate BP control associated with other risk factors seen in metabolic syndrome, which increase CV risks and renal damage (Chen J. et al., 2004; Padwal R. & Laupacis A., 2004).

According to analysis of renal data obtained from many clinical trials in systolic hypertension, the ability of CCBs to protect renal function depends on their capacity to lower blood pressure and significant reduction in proteinuria (Voyaki SM. et al., 2001).

Many clinical trials showed that in cases of presence of proteinuria or microalbuminuria, using ACEIs or ARBs with CCBs combination is more effective in preventing the progression of renal dysfunction or decreased CV risk in hypertensive patients with CKD (Mancia G. et al., 2003).

Using of dihydropyridine CCBs to lower BP alone without using other ACEIs or ARBs, does not seem to slow the progression of kidney disease, because of lack of antiproteinurinic effect of this subclass of CCBs. In contrast, this property is not noticed in non-dihydropyridine CCB subclass,
which can reduce excretion of protein in urine to a greater degree than the first subclass (Nathan S. et al., 2005). The explanation for this difference is due to the ability of dihydropyridine CCBs to inhibit renal auto-regulation mechanism by effect on the afferent arterioles (Griffin KA. et al., 2004) resulting in direct increase of systemic pressure that lead to elevation in glomerular pressure, fibrosis, increasing protein filtration and finally albuminuria. On the second hand, non-dihydropyridine CCBs subclass do not interfere with renal autoregulation to the same degree as dihydropyridine CCB subclass, they also can reduce glomerular permeability to larger extent than dihydropyridine (Boero R. et al., 2003). All make differential renoprotective benefit belongs to non-dihydropyridine CCBs subclass in patients with kidney insufficiency (Levey AS. et al., 2004).

2.5.1.2. Amlodipine

2.5.1.2.1. Chemistry

Amlodipine is a long acting dihydropyridine calcium channel blocker, which is used in the treatment of angina to lower the BP. The chemical formula of the drug is C₂₀H₂₅ClN₂O₅ (figure 2.5). The IUPAC name of the drug is (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5 dicarboxylate (Lakshmi B. et al., 2015).

![Chemical structure of Amlodipine](image)

**Figure 2.5: Chemical structure of Amlodipine**

2.5.1.2.2. Mechanism of action

Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle (Zankat J. et al., 2015) and lowers the blood pressure by relaxing arterial smooth muscles, in turn decreasing the total peripheral resistance and thus reduces blood pressure.

The drug is considered to be most important medication needed in basic health system, listed by WHO’s list of essential medicines (WHO, 2013). It is used in the treatment of coronary heart disease and in the management of hypertension (Wang JG., 2009).
2.5.1.2.3. **Side Effects**

There are some adverse effects resulted from Amlodipine intake, but most of them were of mild to moderate severity. The most common adverse reactions in controlled clinical trials were edema, which observed in 8.9% of drug users and 8.3% of the users experience headache. (Pfizer Data Sheet, 2015). One percent (1%) of drug users undergo mild side effects such as dizziness, palpitations, stomach pain, dyspepsia, somnolence and nausea (Lakshmi B. et al., 2015).

2.5.1.2.4. **Pharmacokinetics**

Amlodipine is slowly but completely absorbed after oral administration of therapeutic doses, with moderately high bioavailability (64%–90%) which is not altered by presence of food. Absorption occurs gradually with peak plasma concentration reached between 6 and 12 hours. This drug is extensively converted to inactive metabolites via hepatic metabolism, with 10% of the parent compound and 60% of the metabolites excreted in the urine (Lee S. et al., 2015). Ex-vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Amlodipine is predominantly metabolized by cytochrome P450 family member cytochrome P450 (CYP) 3A4 in liver (Guo C. et al., 2015). Elimination from the plasma is biphasic with a terminal elimination half-life of about 35-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing (Pfizer Data Sheet, 2015).

2.5.2. **Angiotensin Converting Enzyme Inhibitors**

ACE is a zinc metallopeptidase expressed at the surface of many cells where it catalyzes the conversion of Angiotensin I to Angiotensin II and degrades Bradykinin, a potent vasodilator (Ribeiro-Oliveira A. et al., 2008). Angiotensin II produces renal vasoconstriction and antinatriuresis, which together lead to elevating blood pressure. (Berra K. & Miller NH., 2009). Release of renin by the kidney results in activation of and lead to many physiological renal and CV events. Renin catalyzes the formation of angiotensin I, which is then converted to angiotensin II by angiotensin converting enzyme (ACE), resulting in activation of the angiotensin II receptors, which effect on renal vasculature, resulting in CKD. Therefore, targeting RAS is a logical approach to reducing renovascular risk. (Brewster UC. & Perazella MA., 2004; Fliser D., 2010).

ACEIs are commonly used in the treatment of CV disorders. The use of these agents for HTN and heart failure is well established and has proven to reduce morbidity and mortality, although these agents have not proven to be superior to other antihypertensive agents. ACEIs are now routinely used in myocardial infarction patients to reduce re-infarction and mortality risk, and are combined with a diuretic for secondary prevention in stroke patients (Chua D. et al., 2011).
Currently, many ACEIs have been approved for use and already marketed worldwide (ex. Captopril, Enalapril, Cilazapril, Lisinopril, and Ramipril). Most of these drugs are considered to be pro-drugs. (Wishart DS et al., 2008).

2.5.2.1. Renoprotective Role of ACEIs

There is strong evidence that ACEIs are effective in preventing cardiovascular disease and reducing morbidity and mortality in patients at high risk of cardiovascular disease or renal complications. (Sleight P. 2002; Solski LV & Longyhore DS., 2008; Weir MR., 2007).

ACEIs are widely acknowledged to confer additional renoprotective benefits beyond the effects of BP control alone (Taal MW. & Brenner BM., 2000) and slow the progression of renal disease in patients with diabetes, HTN and albuminuria, but also decreases the risk of CV events (Parving HH. et al., 2001). Administration of ACEIs have been shown to decrease protein excretion in patients with renal diseases (Bianchi S. et al., 2006).

Many experimental and clinical evidence had been published suggesting that renin-angiotensin-aldosterone system (RAAS) has an important role in progression of non-diabetic disease. Results of meta-analyses agree that, angiotensin converting enzyme inhibitors are more effective than conventional antihypertensive drugs at delaying the progression of non-diabetic renal disease (Jafar TH. et al., 2001; Kshirsagar AV. et al., 2000).

Many clinical studies have clearly revealed that blockade of the renin-angiotensin system by a ACEIs reduces albuminuria, delays the progressive loss in renal function and improves survival (Lewis EJ. et al., 2001).

The antiproteinuric response upon blockade of the RAS has been demonstrated to predict the subsequent long-term rate of decrease in GFR, i.e., the greater the initial decrease in albuminuria, the less the long-term decrease in kidney function. Despite the proven benefit of RAS blockade by either ACEIs or ARBs, clinical studies to date have found that such treatment slows but does not completely arrest the progression of renal disease toward ESRD (Rossing K. et al., 2003).

2.5.2.2. Enalapril

2.5.2.2.1. Chemistry

Enalapril is the dicarboxylate-containing ACEIs. It is used for the treatment of essential or renovascular hypertension and symptomatic congestive heart failure. The Enalapril structure formula is C20H28N2O5. The IUPAC name of this drug is described as N-[(1S)-1-(Ethoxy carbon-yl)-3-Phenylpropyl]-L Proline (Figure 2.6).

It is presented as Enalapril maleate, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, Enalaprilot (Figure 2.7).
The chemical name of Enalapril maleate is (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-Lalanyl]-L-proline, (Z)-2-butenedioate salt (1:1) with structure formula C20H28N2O5•C4H4O4. Enalapril maleate is white to off-white, crystalline powder with molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol. (Rao B. et al., 2015; Hongbao M. & Yan Y., 2015).

**Figure 2.6: Chemical structure of Enalapril**

**Figure 2.7: Chemical structure of Enalapril maleate**

### 2.5.2.2.2. Mechanism of action

Enalapril is considered as pro-drug, following oral administration, it is bioactivated by hydrolysis of ethyl ester of Enalaprilat, which is the active form. Enalapril, after hydrolysis to Enalaprilat, inhibits ACE that catalyze the conversion of Angiotensin I to Angiotensin II, which is a potent vasoconstrictor. In sequence, decreases arterial BP by reduction of total peripheral resistance, aldosterone secretion from the adrenal cortex, water and sodium reabsorption as well as extracellular volume (Zhang R. et al., 2000).

As ACE is similar to kininase II enzyme, Enalapril prevents metabolism of the vasodilator, bradykinin, leading to activation of arachidonic acid cascade that in turn leading to systematic dilation of arteries and veins and resulting in synthesis of vasodilating prostaglandins as well as
stimulation of NO release through induction of endothelial NO Synthase (eNOS) expression (Imig JD., 2004).

2.5.2.2.3. **Side Effects**

Safety of Enalapril has been evaluated in many clinical trials, which proved that Enalapril is generally well tolerated by patients. Moreover, adverse experiences were mild and transient in nature. The most common adverse reactions include hypotension, persistent dry cough, hyperkalemia, headache, dizziness, fatigue, nausea, and angioedema (Hongbao M. & Yan Y., 2015).

2.5.2.2.4. **Pharmacokinetics**

Following oral administration of Enalapril, peak serum concentrations of Enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of Enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Enalapril, after absorption is metabolized rapidly and extensively hydrolyzed to Enalaprilat that is a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of Enalaprilat occur 3 to 4 hours after an oral dose of Enalapril. Excretion of Enalapril is primarily by renal route, in which approximately 94% of the dose is recovered in the urine and feces as Enalaprilat or Enalapril. The principal components in urine are Enalaprilat, accounting for about 40% of the dose, and intact Enalapril. The serum concentration profile of Enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. The effective half-life for accumulation of Enalaprilat following multiple doses of Enalapril is 11 hours (Merck Data sheet, 2013; Hongbao M. & Yan Y., 2015).
Chapter 3

Patients and Methods

3.1. **Study design**

This study is a non-randomized, prospective-comparative control-case study in which the renoprotective effect of Calcium Channel Blockers alone and Calcium Channel Blockers/Angiotensin Converting Enzyme Inhibitors combination was evaluated and compared with controls 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.

3.2. **Study setting and period**

The study was performed on hypertensive patients with renal diseases at Nasser Medical Complex in Khanyounis Governorate, Gaza Strip. The period of the study was 6 months, and measurements were made as following schedule:

1. Serum creatinine, creatine clearance, potassium level and blood pressure: at zero time before starting the study, first week, third week, second month, fourth month and at sixth month.

2. Urinary albumin excretion rate and lipid profile (total cholesterol, triglyceride, High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol): at zero time before starting the study, second month, fourth month and at sixth month.

3.3. **Patients**

3.3.1. **Study population**

All cases participating in the study were hypertensive patients with CKD (stage 1, 2 and 3) with microalbuminuria from both genders, while all controls were hypertensive patients. They were selected from Kidney & Dialysis Department in Nasser Medical Complex after their urinary albumin excretion rate, serum creatinine level, serum potassium level and creatinine clearance were measured. The selected patients had been suffering from hypertension (blood pressure more than 140/90).
3.3.2. Selection criteria

All selected patients were over 40 years, from both sexes. Medical history for all patients was
taken from the patients files. All cases were with impaired renal function, which was determined
by the following biochemical tests:
  - Urinary albumin excretion (UAE) rate: in the range from 30-300mg/day.
  - Serum creatinine level: The typical human reference range is 0.5 - 1.1 mg/dl for women,
   and 0.6 - 1.2 mg/dl for men.

3.3.3. Exclusion criteria

The criteria for exclusion include:
  - 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.
  - Patients who have hypersensitivity to CCBs and ACEIs.
  - Patients with contraindicated to ACEIs like renal artery stenosis
  - If creatinine clearance decreased more than 20% or increased more than 20%.

3.3.4. Sample size

Sample size of the study was 100 patients divided into 4 groups (each group consists of 25 patients)
as follows:

- Case groups: hypertensive patients with CKD divided into two groups according to the
treatment protocol:
  - Group 1: Amlodipine (5-10mg/day) treated group.
  - Group 2: Amlodipine (5-10mg/day)/Enalapril (10-20mg/day) combination treated group.

- Control group: hypertensive patients with normal kidney function divided into two groups
according to the treatment protocol:
  - Group 1: Amlodipine (5-10mg/day) treated group.
  - Group 2: Amlodipine (5-10mg/day)/Enalapril (10-20mg/day) combination treated group.

3.3.5. Dependent variables

The dependent variables included in the study were:
  - Serum creatinine concentration
  - Urinary albumin excretion rate
  - Creatinine clearance
  - Serum potassium level
  - SBP and DBP
  - Lipid profile (TC, TG, LDL-C and HDL-C)
3.3.6. **Independent variables**

The independent variables included in the study were:
- Treatment with Amlodipine monotherapy
- Treatment with Amlodipine/Enalapril combination

3.4. **Treatment**

3.4.1. **Amlodipine treated group**

Amlodipine, 5-10 mg was given orally once daily for 6 months according to the instructions of the physician to achieve target blood pressure (<130/80 mm Hg).

3.4.2. **Amlodipine & Enalapril treated group**

Amlodipine/Enalapril combination, 5-10 mg of Amlodipine and 10-20 mg of Enalapril were given orally once daily for 6 months according to the instructions of the physician to achieve target blood pressure (<130/80 mm Hg).

3.5. **Methods**

3.5.1. **Blood Chemical Tests**

To determine the renal function in study population, blood chemical analysis was performed for each patient and control before starting the study, after one week, after three weeks and then every 2 months of the study period (6 months). One day before the required analysis, participants were phoned to visit the hospital (Nasser Medical Complex), Kidney and Dialysis Department and laboratory, and they were asked to fast for 12 hours. Blood samples were drawn from peripheral circulation of the patients and control. These samples were labeled with their names and sent immediately to the laboratory to perform the required tests. In this study, we performed blood analysis to measure serum creatinine level, creatinine clearance, serum potassium level and lipid profile (Total cholesterol, TG, LDL-C and HDL-C) among our population.

3.5.2. **Urinalysis**

Urine analysis was performed for our population before and every 2 months during the study period which was 6 months. Two days before the visit, each patient and control was phoned to collect his urine throughout the day (24 hours) in a suitable container. Then urine samples were taken from them and labeled with their names and sent to the laboratory to measure UAE rate for both patients and control.
3.5.3. Blood pressure measurement

Blood pressure was measured for all study population by using a mercury sphygmomanometer. Systolic and diastolic blood pressures of the two treated groups and control were measured before starting the study and every 2 months of treatment throughout the study period (6 months).

3.5.4. Data collection

During the study period (6 months), data was collected from files of patients and laboratory results of blood and urine analysis. The collected data included patient age, gender, residency, weight, height, Body Mass Index (BMI), education level, duration of hypertension, BP measurements, serum creatinine level, serum potassium level, lipid profile (TC, TG, LDL-C and HDL-C), UAE rate and drugs used in the past to manage hypertension. All data was documented in data collecting sheet before and every 2 months of treatment during the study period.

Creatinine clearance was calculated for each patients and control by using Cockgroft-Gault equation:

\[
\text{Creatinine clearance} = \frac{(140-\text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85
\]

for women (less than 85 ml/min impaired and equal or more than 85 ml/min normal clearance creatinine).

3.5.5. Statistical analysis

The collected data and variables were analyzed using the statistical package of social science (SPSS) software package version 16. Statistical tests as frequency and distribution has been done to express our data as numbers, percentages and Pie charts. Moreover, paired T-test was performed to compare serum creatinine levels, serum potassium level, creatinine clearance, urinary albumin excretion rates, lipid profile (TC, TG, LDL-C and HDL-C) and SBP & DBP individually in each group according to study protocol. On the other hand, independent T-test was used to compare Amlodipine treated group with Amlodipine/Enalapril combination treated group, among these parameters.
Chapter 4

Results

This chapter deals with the study results. During the study period, one hundred patients were selected according to the inclusion criteria. The study population was divided into four groups based on the drugs used, each group consisted of twenty-five patients. The study was carried out at Nasser Medical Complex, Kidney and Dialysis Department (Khanyounis governorate). Thereafter, data was collected from patients files and through biochemical analysis of blood and urine samples.

The obtained results dealt with distribution of the study population by socio-demographic variables, duration of hypertension and treatment history. Moreover, the results evaluated the effect of Amlodipine alone and in combination with Enalapril on both systolic and diastolic blood pressure, serum creatinine level, serum potassium level, creatinine clearance, urinary albumin excretion rate and lipid profile. Further, the results compared these parameters among patients receiving the indicated drugs and with controls.

4.1. Distribution of the study population

4.1.1. Distribution of the study population by socio-demographic variables

The total number of the study population who fulfilled the selective criteria was one hundred patients divided into four groups (Table 4.1), so that each group consisted of twenty-five patients. Figure 4.1 shows that 39 (39%) of the participants were males and 61 (61%) were females. The demographic distribution of the study population is shown in figure 4.2, where 32 (32%) of them lived in Rafah governorate and 68 (68%) lived in Khanyounis governorate.

The first group (case group 1) was treated with Amlodipine (5-10mg/day) and included 10 (40%) males and 15 (60%) females. The age of participants ranged from 40 to 65 years with a mean of 54.8±7.4, and according to governorate distribution, 6 (24%) lived in Rafah governorate and 19 (76%) were from Khanyounis governorate.

The second group (case group 2) was treated with Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination and included 12 (48%) males and 13 (52%) females of whom 3 (12%) lived in Rafah governorate and 22(88%) were from Khanyounis governorate. The age of participants ranged from 40 to 76 years with a mean of 53.2±10.4.
The first control group (control group 1) was treated with Amlodipine alone (5-10mg/day) and included 6 (24%) males and 19 (76%) females of whom 11 (44%) lived in Rafah governorate and 14 (56%) were from Khanyounis governorate. The age of participants ranged from 41-63 years with a mean of 54.9±6.8.

The second control group (control group 2) was treated with Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination, included 12 (48%) males and 13 (52%) females of whom 12 (48%) lived in Rafah governorate and 13 (52%) were from Khanyounis governorate. The age of participants ranged from 44-61 years with a mean of 52.2±4.7.

Furthermore, 33 (54%) of the females participated in this study were menopause (age ≥55 years), 9 (14.8%) of them treated with Amlodipine, 6 (9.8%) treated with Amlodipine/Enalapril, while 12 (19.7%) and 6 (9.8%) were in the first and second control groups respectively.

On the other hand, 15 (15%) of participants were employees, while 85 (85%) of them were unemployed (farmer, trader, driver and seller). On the field of education, 20 (20%) of study population had a primary education only, while 56 (56%) completed their secondary school and the rest of the participants 24 (24%) have finished their high education. Moreover, 36 (36%) of study population were smokers (cigarettes only), while the rest of the participants 64 (64%) were nonsmokers. All smokers in this study were males.

Financially, 76 (76%) of the population were with moderate income (≤ 1500 shekel), while 24 (24%) of them had monthly income of more than 1500 shekel. Moreover, 39 (39%) of study population had small family size (no. <8) and 61 (61%) had large families (no. ≥8).
### Table 4.1: Distribution of the study population by socio-demographic variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
<th>Total N=100</th>
<th>P. value</th>
</tr>
</thead>
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<tr>
<td></td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=100 No. (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>11 (44)</td>
<td>6 (24)</td>
<td>12 (48)</td>
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</tr>
<tr>
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<td>14 (56)</td>
<td>19 (76)</td>
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<td></td>
</tr>
<tr>
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<td></td>
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</tr>
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<td>12 (63)</td>
<td>6 (46)</td>
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<td>11 (44)</td>
<td>39 (39)</td>
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<td>12 (48)</td>
<td>19 (76)</td>
<td>14 (56)</td>
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<td>6 (24)</td>
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</tr>
<tr>
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<td>15 (60)</td>
<td>13 (52)</td>
<td>19 (76)</td>
<td>64 (64)</td>
<td></td>
</tr>
</tbody>
</table>

Case group (1): patients treated with Amlodipine alone, Case group (2): patients treated with Amlodipine/Enalapril combination
Figure 4.1: Distribution of the study population by sex

Figure 4.2: Distribution of the study population by demographic variable
4.1.2. Distribution of the study population by treatment history

Table 4.2 numerates the drugs used by patients among the different groups. Generally, all participants (100) used Atenolol (beta-blocker) as antihypertensive drug, while 17 (17%) of them used Furosemide (Lasix) to maintain blood pressure and 74 (74%) patients used baby aspirin to prevent blood clots and reduce the risk of strokes and heart attacks.

Table 4.2: Distribution of the study population by treatment history

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
<th>Total</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=100 No. (%)</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>5 (20)</td>
<td>17 (17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
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<td>19 (76)</td>
<td>23 (92)</td>
<td>20 (80)</td>
<td>83 (83)</td>
</tr>
<tr>
<td>Aspirin</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>18 (72)</td>
<td>16 (64)</td>
<td>21 (84)</td>
<td>19 (76)</td>
<td>74 (74)</td>
<td></td>
</tr>
<tr>
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<td>No</td>
<td>7 (28)</td>
<td>9 (36)</td>
<td>4 (16)</td>
<td>6 (24)</td>
<td>26 (26)</td>
</tr>
</tbody>
</table>

Case group (1): patients treated with Amlodipine alone, Case group (2): patients treated with Amlodipine/Enalapril combination

4.1.3. Distribution of the study population by duration of hypertension, Body Mass Index (BMI) and medical history

Table 4.3 demonstrates the distribution of participants in all groups depending on the duration of hypertension among them, BMI and the medical history of each patient. It shows that patients in the Amlodipine treated group had hypertension from 3 to 17 years with a mean of 9.68±4.13. In the Amlodipine/Enalapril combination treated group, the population had hypertension from 2 to 16 years with a mean of 8.28±4.11. In addition, the participants in the first and second control groups had hypertension from 5-16 years with a mean of 9.9±3.4 and 8.6±3.3 respectively.

Moreover, table 4.3 shows that 45 (45%) of the study population were with normal weight (BMI< 25 kg/m^2), 39 (39%) had BMI in the range of overweight (BMI=25-29.9 kg/m^2) and 16 (16%) were suffering from obesity (BMI≥30 kg/m^2). The obese patients were distributed in the Amlodipine and the Amlodipine/Enalapril treated groups only, while the control groups included patients with normal weight and overweight patients only. On the other hand, 7 (7%) of the study population suffered from coronary artery disease (CAD), 3 (12%) of them were in the Amlodipine treated group and 2 (8%) were in the Amlodipine/Enalapril treated group, while 2 (8%) were in control group (1). Moreover, 22 (88%), 5 (20%) & 4 (16%) of patients treated with Amlodipine had family history of HTN, CAD and CKD respectively, corresponds to 23 (92%), 8 (32%) & 9 (36%) in the Amlodipine/Enalapril treated group respectively. While 17 (68%) & 19 (76%), 3
(12%) & 10 (40%) and 2 (8%) & 2 (8%) had family history of HTN, CAD and CKD were in the first and second control groups, respectively.

Table 4.3: Distribution of the study population by duration of HTN, BMI & medical history variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
<th>Total</th>
<th>P. value</th>
</tr>
</thead>
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<td>Duration of HTN (year)</td>
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<td>0.344</td>
</tr>
<tr>
<td></td>
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<td>N=25</td>
<td>N=25</td>
<td>N=25</td>
<td>N=100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.68±4.13 (3-17)</td>
<td>8.28±4.11 (2-16)</td>
<td>9.9±3.4 (5-16)</td>
<td>8.6±3.3 (5-16)</td>
<td>9.04±3.84 (2-17)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
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<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
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<td>4 (16)</td>
<td>15 (60)</td>
<td>21 (84)</td>
<td>45 (45)</td>
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</tr>
<tr>
<td>Overweight</td>
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<td>10 (40)</td>
<td>4 (16)</td>
<td>39 (39)</td>
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<tr>
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<td>8 (32)</td>
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<td>0</td>
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</tr>
<tr>
<td>History of CAD</td>
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<td></td>
<td></td>
<td></td>
<td>0.414</td>
</tr>
<tr>
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<td>2 (8)</td>
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<td>7 (7)</td>
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</tr>
<tr>
<td>No</td>
<td>22 (88)</td>
<td>23 (92)</td>
<td>23 (92)</td>
<td>25 (100)</td>
<td>93 (93)</td>
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</tr>
<tr>
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<td>8 (32)</td>
<td>3 (12)</td>
<td>10 (40)</td>
<td>26 (26)</td>
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</tr>
<tr>
<td>No</td>
<td>20 (80)</td>
<td>17 (68)</td>
<td>22 (88)</td>
<td>15 (60)</td>
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<tr>
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<td>23 (92)</td>
<td>17 (68)</td>
<td>19 (76)</td>
<td>81 (81)</td>
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</tr>
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<td>6 (24)</td>
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</tr>
<tr>
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<td>9 (36)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>17 (17)</td>
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</tr>
<tr>
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<td>16 (64)</td>
<td>23 (92)</td>
<td>23 (92)</td>
<td>83 (83)</td>
<td></td>
</tr>
</tbody>
</table>

Case group (1): patients treated with Amlodipine alone, Case group (2): patients treated with Amlodipine/Enalapril combination, HTN=Hypertension, BMI=Body Mass Index, CAD=Coronary Artery Disease, CKD=Chronic Kidney Disease
**4.1.4. Distribution of the study population by creatinine clearance**

Table 4.4 shows the distribution of the study population by creatinine clearance. It shows that before starting the study, 56 (56%) of the patients had normal CrCl (≥ 90 ml/min/1.73m²), while 18 (18%) of them had mild decrease in CrCl (60-89 ml/min/1.73m²), 10 (10%) had mild to moderate decrease in CrCl (45-59 ml/min/1.73m²) and 16 (16%) had moderate to severe decrease in CrCl (30-44 ml/min/1.73m²). In comparison at the end of study period, 75 (75%) had normal CrCl, 12 (12%) had mild CrCl decrease, 7 (7%) had mild to moderate CrCl decrease and 6 (6%) were with moderate to severe CrCl decrease.

**Table 4.4: Distribution of the study population by CrCl**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>CrCl (ml/min/1.73m²)</th>
<th>G1: ≥ 90 No. (%)</th>
<th>G2: 60-89 No. (%)</th>
<th>G3a: 45-59 No. (%)</th>
<th>G3b: 30-44 No. (%)</th>
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<td></td>
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</tr>
<tr>
<td></td>
<td>1st week</td>
<td>4 (16)</td>
<td>9 (36)</td>
<td>7 (28)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd week</td>
<td>7 (28)</td>
<td>8 (32)</td>
<td>6 (24)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
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<td>11 (44)</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
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<td>10 (40)</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>13 (52)</td>
<td>7 (28)</td>
<td>4 (16)</td>
<td>1 (4)</td>
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</tr>
<tr>
<td>Amlodipine (5-10mg/day)</td>
<td>Baseline</td>
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<td>8 (32)</td>
<td>4 (16)</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>&amp; Enalapril (10-20mg/day)</td>
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<td>10 (40)</td>
<td>4 (16)</td>
<td>10 (40)</td>
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<tr>
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<td>3rd week</td>
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<td>9 (36)</td>
<td>6 (24)</td>
<td>9 (36)</td>
<td></td>
</tr>
<tr>
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<td>2nd month</td>
<td>6 (24)</td>
<td>4 (16)</td>
<td>7 (28)</td>
<td>8 (32)</td>
<td></td>
</tr>
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<td>4th month</td>
<td>8 (32)</td>
<td>8 (32)</td>
<td>3 (12)</td>
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</tr>
<tr>
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<td>1st week</td>
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</tr>
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<td>3rd week</td>
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<td>0</td>
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</tr>
<tr>
<td></td>
<td>2nd month</td>
<td>21 (84)</td>
<td>4 (16)</td>
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<td>0</td>
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</tr>
<tr>
<td></td>
<td>4th month</td>
<td>25 (100)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
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<td></td>
<td>1st week</td>
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</tr>
<tr>
<td></td>
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<td>25 (100)</td>
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<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd month</td>
<td>25 (100)</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
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<td>0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>25 (100)</td>
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</table>
4.1.5. Distribution of the study population by UAE rate

Table 4.5 shows the distribution of the study population by UAE rate. It shows that before starting the study, 51 (51%) of the patients had normal UAE rate (<30 mg/24h), while 29 (29%) of them suffered from microalbuminuria (UAE rate of 30-300 mg/24h) and 20 (20%) had macroalbuminuria (UAE rate >300 mg/24h). However, at the end of study period, 58 (58%) had normal UAE rate (<30 mg/24h), 27 (27%) were with microalbuminuria (UAE rate of 30-300 mg/24h) and 15 (15%) had macroalbuminuria (UAE rate >300 mg/24h).

Moreover, table 4.6 shows the characterizations of study population before starting the study.

**Table 4.5: Distribution of the study population by UAE rate**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>UAE rate (mg/24 hours)</th>
<th>A1: &lt; 30 No. (%)</th>
<th>A2: 30-300 No. (%)</th>
<th>A3: &gt; 300 No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amlodipine (5-10mg/day)</strong></td>
<td>Baseline</td>
<td>1 (4)</td>
<td>18 (72)</td>
<td>6 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd month</td>
<td>1 (4)</td>
<td>18 (72)</td>
<td>6 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
<td>2 (8)</td>
<td>17 (68)</td>
<td>6 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>3 (12)</td>
<td>18 (72)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td><strong>Amlodipine (5-10mg/day) &amp;</strong></td>
<td>Baseline</td>
<td>0</td>
<td>11 (44)</td>
<td>14 (56)</td>
<td></td>
</tr>
<tr>
<td><strong>Enalapril (10-20mg/day)</strong></td>
<td>2nd month</td>
<td>2 (8)</td>
<td>12 (48)</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
<td>2 (8)</td>
<td>12 (48)</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>5 (20)</td>
<td>9 (36)</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td><strong>Control group (1)</strong></td>
<td>Baseline</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Control group (2)</strong></td>
<td>Baseline</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th month</td>
<td>25 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.6: Characterizations of study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td>N=25 No. (%)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>148.9±6.9</td>
<td>151.6±8.5</td>
<td>146.04±5.1</td>
<td>147.64±7.2</td>
<td>0.047</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>95.8±4.4</td>
<td>97.6±5.9</td>
<td>94.0±3.7</td>
<td>97.04±5.9</td>
<td>0.065</td>
</tr>
<tr>
<td>K level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>4.5±0.7</td>
<td>4.7±0.67</td>
<td>4.15±0.69</td>
<td>4.34±0.38</td>
<td>0.026</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>227.3±56.3</td>
<td>236.9±47.9</td>
<td>231.08±37.5</td>
<td>250.2±41.1</td>
<td>0.333</td>
</tr>
<tr>
<td>TG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>244.8±137.6</td>
<td>298.7±354.9</td>
<td>269.8±264.4</td>
<td>371.6±228.1</td>
<td>0.230</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>138.6±61.1</td>
<td>137.8±48.2</td>
<td>140.5±48.7</td>
<td>140.±45.3</td>
<td>0.998</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>39.8±9.5</td>
<td>39.4±6.9</td>
<td>37.4±7.04</td>
<td>35.9±5.18</td>
<td>0.215</td>
</tr>
<tr>
<td>UAE rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>278.6±344.3</td>
<td>472.3±373.7</td>
<td>15.91±8.32</td>
<td>15.92±7.93</td>
<td>0.000</td>
</tr>
<tr>
<td>CrCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>68.1±28.5</td>
<td>59.7±27.3</td>
<td>116.59±20.6</td>
<td>125.10±24.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Scr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.46±0.70</td>
<td>2.03±1.29</td>
<td>0.77±0.17</td>
<td>0.80±0.19</td>
<td>0.000</td>
</tr>
</tbody>
</table>


4.2. Effect of the drugs used on UAE rate during the study period (6 months)

4.2.1. UAE rate in control groups

Table 4.7 shows the UAE rate in the first control group, in which UAE rate significantly decreased \((p<0.05)\) from 15.91±8.32 mg/24h at beginning of the study to 10.79±5.94 mg/24h after 6 months of the treatment. Moreover, it shows the UAE rate in second control group, in which UAE rate significantly decreased \((p<0.05)\) from 15.92±7.93 mg/24h at beginning of the study to 7.93±5.29 mg/24h after 6 months of the treatment.

Table 4.7: Urinary albumin excretion rate (mg/24h) among control groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>UAE rate (mg/24h)</td>
<td>Baseline</td>
<td>After 2 months</td>
</tr>
<tr>
<td></td>
<td>15.91±8.32</td>
<td>15.23±7.68</td>
</tr>
<tr>
<td></td>
<td>0.028</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>13.24±7.23</td>
<td>11.27±6.02</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>10.79±5.94</td>
<td>7.93±5.29</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values \((p<0.05)\) were calculated by paired-samples t-test for UAE rate before and after 2, 4 and 6 months of treatment.
4.2.2. Effect of Amlodipine and Amlodipine/Enalapril combination treatment on UAE rate

Table 4.8 shows the effect of Amlodipine (5-10mg/day) on UAE rate. To clarify, the UAE rate decreased from $278.56\pm344.32$ mg/24h at beginning of the study to $224.86\pm318.88$ mg/24h after 6 months of the treatment. The results showed a statistical significant effect ($p<0.05$) of Amlodipine on UAE rate during the study period (6 months). It also shows the effect of Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination on UAE rate. The UAE rate significantly decreased ($p<0.05$) from $472.26\pm373.65$ mg/24h at beginning of the study to $300.17\pm270.10$ mg/24h at the end of the sixth month.

Table 4.8: Urinary albumin excretion rate (mg/24h) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE rate (mg/24h)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Before treatment</td>
<td>278.56±344.32</td>
<td></td>
</tr>
<tr>
<td>After 2 months</td>
<td>259.77±330.14</td>
<td>0.002</td>
</tr>
<tr>
<td>After 4 months</td>
<td>241.10±320.14</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>224.86±318.88</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for UAE rate before and after 2, 4 and 6 months of treatment.

4.3. Effect of the drugs used on CrCl during the study period (6 months)

4.3.1. CrCl in control groups

Table 4.9 shows the CrCl changes during the study period in control groups. In control group (1), CrCl significantly increased ($p<0.05$) from $116.59\pm20.62$ ml/min/1.73m$^2$ at beginning of the study to $140.37\pm17.86$ ml/min/1.73m$^2$ after 6 months of the treatment. While in control group (2) CrCl increased significantly ($p<0.05$) from $125.10\pm24.70$ ml/min/1.73m$^2$ at beginning of the study to $161.90\pm38.93$ ml/min/1.73m$^2$ after 6 months.

Table 4.9: CrCl (ml/min/1.73m$^2$) among control groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min/1.73m$^2$)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>116.59±20.62</td>
<td>0.000</td>
</tr>
<tr>
<td>After one week</td>
<td>110.73±14.20</td>
<td>0.078</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>117.10±19.73</td>
<td>0.855</td>
</tr>
<tr>
<td>After 2 months</td>
<td>123.16±26.90</td>
<td>0.209</td>
</tr>
<tr>
<td>After 4 months</td>
<td>125.65±20.60</td>
<td>0.031</td>
</tr>
<tr>
<td>After 6 months</td>
<td>140.37±17.86</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for CrCl before and after one and 3 weeks, 2, 4 and 6 months of treatment.
4.3.2. Effect of Amlodipine and Amlodipine/Enalapril combination treatment on CrCl

Table 4.10 shows the effect of Amlodipine (5-10mg/day) on CrCl. To clarify, the CrCl increased from 68.12±28.52 ml/min/1.73m² at beginning of the study to 89.75±29.81 ml/min/1.73m² after 6 months of the treatment. The results showed a statistical significant effect (p<0.05) of Amlodipine on CrCl at 2, 4 and 6 months of treatment.

The effect of Amlodipine (5-10mg/day) and Enalapril (10-20mg/day) combination on CrCl is also shown in table 4.10, where CrCl significantly increased (p<0.05) from 59.74±27.31 ml/min/1.73m² at beginning of the study to 86.84±38.36 ml/min/1.73m² after 6 months of the treatment.

Table 4.10: CrCl (ml/min/1.73m²) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68.12±28.52</td>
<td>59.74±27.31</td>
</tr>
<tr>
<td>After one week</td>
<td>69.63±28.80</td>
<td>0.361</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>75.70±37.02</td>
<td>0.014</td>
</tr>
<tr>
<td>After 2 months</td>
<td>81.17±29.04</td>
<td>0.002</td>
</tr>
<tr>
<td>After 4 months</td>
<td>83.48±29.74</td>
<td>0.001</td>
</tr>
<tr>
<td>After 6 months</td>
<td>89.75±29.81</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated by paired-samples t-test for CrCl before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.4. Effect of the drugs used on serum creatinine level during the study period (6 months)

4.4.1. Serum creatinine level in control groups

In the same context, table 4.11 shows the changes in serum creatinine level over the study period in control groups. We found that SCr level in control group (1) to be 0.76±0.17 mg/dl at baseline and insignificantly decreased (p>0.05) to 0.73±0.15 mg/dl at the end of the second month. After that, SCr level significantly decreased (p<0.05) to became 0.71±0.14 and 0.62±0.08 mg/dl at 4 and 6 months respectively. While SCr level in control group (2) significantly increased (p<0.05) from 0.80±0.19 mg/dl at baseline to 0.95±0.19 mg/dl after the first week of treatment, then it decreased significantly (p<0.05) to 0.61±0.10 mg/dl at the end of study period.
Table 4.11: Serum creatinine levels (mg/dl) among control groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr (mg/dl)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.76±0.17</td>
<td></td>
</tr>
<tr>
<td>After one week</td>
<td>0.79±0.14</td>
<td>0.110</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>0.76±0.15</td>
<td>0.647</td>
</tr>
<tr>
<td>After 2 months</td>
<td>0.73±0.15</td>
<td>0.257</td>
</tr>
<tr>
<td>After 4 months</td>
<td>0.71±0.14</td>
<td>0.010</td>
</tr>
<tr>
<td>After 6 months</td>
<td>0.62±0.08</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for SCr before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.4.2. Effect of Amlodipine and Amlodipine/Enalapril treatment on Serum creatinine level

The data in table 4.12 shows the serum creatinine levels throughout the study period. The serum creatinine level insignificantly ($p>0.05$) decreased from 1.46±0.70 mg/dl at baseline to 1.42±0.68 mg/dl after the first week of treatment with Amlodipine (5-10mg/day). However, after that, serum creatinine level decreased significantly ($p<0.05$) from 1.35±0.68 mg/dl at the third week to 1.19±0.57mg/dl, 1.16±0.58mg/dl and 1.06±0.50 mg/dl after 2, 4 and 6 months of Amlodipine treatment, respectively.

Similarly, table 4.12 shows the serum creatinine levels throughout the study period in Amlodipine/Enalapril treated group. The serum creatinine level insignificantly ($p>0.05$) decreased from 2.03±1.29 mg/dl at baseline to 1.99±1.22 mg/dl after the third week of treatment with Amlodipine/Enalapril. However, after that, serum creatinine level decreased significantly ($p<0.05$) from 1.86±1.23 mg/dl at the end of second month to 1.41±1.05 mg/dl after 6 months of treatment.

Table 4.12: Serum creatinine levels (mg/dl) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr (mg/dl)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.46±0.70</td>
<td>0.179</td>
</tr>
<tr>
<td>After one week</td>
<td>1.42±0.68</td>
<td>0.000</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>1.35±0.68</td>
<td>0.000</td>
</tr>
<tr>
<td>After 2 months</td>
<td>1.19±0.57</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>1.16±0.58</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>1.06±0.50</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for SCr before and after one and 3 weeks, 2, 4 and 6 months of treatment.
4.5. **Effect of the used drugs on serum potassium level during the study period (6 months)**

4.5.1. **Serum potassium level in control groups**

The data in table 4.13 shows the serum potassium levels in the control group (1) during 6 months. To clarify, serum potassium level in this group significantly decreased \((p<0.05)\) from \(4.15\pm0.69\) mEq/l at baseline to \(3.91\pm0.54\) mEq/l at the end of the sixth month. Furthermore, table 4.13 shows the changes in serum potassium levels in the control group (2), which increased significantly \((p<0.05)\) from \(4.33\pm0.38\) mEq/l before treatment to \(4.55\pm0.54\) mEq/l at the end of treatment period.

**Table 4.13: Serum potassium levels (mEq/l) among control groups during the study period.**

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>K level (mEq/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.15±0.69</td>
<td></td>
</tr>
<tr>
<td>After one week</td>
<td>4.16±0.70</td>
<td>0.327</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>4.16±0.70</td>
<td>0.327</td>
</tr>
<tr>
<td>After 2 months</td>
<td>4.33±0.84</td>
<td>0.030</td>
</tr>
<tr>
<td>After 4 months</td>
<td>4.12±0.70</td>
<td>0.834</td>
</tr>
<tr>
<td>After 6 months</td>
<td>3.91±0.54</td>
<td>0.033</td>
</tr>
</tbody>
</table>

P. values \((p<0.05)\) were calculated by paired-samples t-test for K level before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.5.2. **Effect of Amlodipine and Amlodipine/Enalapril treatment on serum potassium level**

The data in table 4.14 shows the serum potassium levels throughout Amlodipine treated group during 6 months of treatment. For more illustration, serum potassium level significantly decreased \((p<0.05)\) from \(4.51\pm0.73\) mEq/l at baseline to \(4.26\pm0.59\) mEq/l at the end of the fourth month and \(3.95\pm0.42\) mEq/l after 6 months of Amlodipine treatment.

Table 4.14 also shows the level of serum potassium in the Amlodipine/Enalapril treated group. It shows that serum potassium level significantly increased \((p<0.05)\) from \(4.68\pm0.67\) mEq/l at baseline to \(5.00\pm0.62\) mEq/l at the end of the fourth month. However, by the end of the study period, it returned back to pretreatment level \(4.68\pm0.67\) mEq/l.
Table 4.14: Serum potassium levels (mEq/l) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K level (mEq/l)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.51±0.73</td>
<td>4.68±0.67</td>
</tr>
<tr>
<td>After one week</td>
<td>4.51±0.76</td>
<td>0.911</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>4.42±0.71</td>
<td>0.080</td>
</tr>
<tr>
<td>After 2 months</td>
<td>4.58±0.65</td>
<td>0.620</td>
</tr>
<tr>
<td>After 4 months</td>
<td>4.26±0.59</td>
<td>0.153</td>
</tr>
<tr>
<td>After 6 months</td>
<td>3.95±0.42</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for K level before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.6. Effect of the used drugs on Systolic Blood Pressure during the study period (6 months)

4.6.1. SBP in control groups

Table 4.15 shows SBP among control group (1) during the study period, which SBP significantly decreased ($p<0.05$) from 146.04±5.13 mmHg before starting the study to 114.40±8.08 mmHg at the end of study period. Moreover, table 4.15 shows SBP among control group (2) during the study period, which SBP significantly decreased ($p<0.05$) from 147.64±7.20 mmHg before treatment to 97.40±6.94 mmHg at the end of the sixth month.

Table 4.15: Systolic Blood Pressure (mmHg) among control groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>146.04±5.13</td>
<td>147.64±7.20</td>
</tr>
<tr>
<td>After one week</td>
<td>138.40±4.73</td>
<td>0.000</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>131.60±5.91</td>
<td>0.000</td>
</tr>
<tr>
<td>After 2 months</td>
<td>126.40±5.69</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>120.80±7.60</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>114.40±8.08</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated by paired-samples t-test for SBP before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.6.2. Effect of Amlodipine and Amlodipine/Enalapril treatment on SBP

The table 4.16 shows the effect of Amlodipine treatment on systolic blood pressure among study population, in which SBP significantly decreased ($p<0.05$) from 148.92±6.89 mmHg before the treatment to 123.72±7.75 mmHg at the end of study period. In the same way, table 4.16 shows the effect of Amlodipine/Enalapril treatment on SBP among study population, in which mean systolic blood pressure significantly decreased ($p<0.05$) from 151.56±8.48 mmHg before treatment to 116.00±12.16 mmHg at the end of study period.
Table 4.16: Systolic Blood Pressure (mmHg) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>148.92±6.89</td>
<td></td>
</tr>
<tr>
<td>After one week</td>
<td>143.48±7.21</td>
<td>0.000</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>138.32±7.08</td>
<td>0.000</td>
</tr>
<tr>
<td>After 2 months</td>
<td>132.80±7.45</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>129.60±6.47</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>123.72±7.75</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values (P<0.05) were calculated by paired-samples t-test for SBP before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.7. Effect of the used drugs on Diastolic Blood Pressure during the study period (6 months)

4.7.1. DBP (mmHg) in control groups

Table 4.17 shows DBP among control group (1) during the study period, which significantly decreased (p<0.05) from 94.00±3.74 mmHg before starting the study to 77.60±3.85 mmHg at the end of study period. In the same way, DBP in control group (2) significantly decreased (p<0.05) from 97.04±5.91 mmHg before starting the study to 70.40±2.47 mmHg at the end of study period.

Table 4.17: Diastolic Blood Pressure (mmHg) among control groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mmHg)</td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>Baseline</td>
<td>94.00±3.74</td>
<td></td>
</tr>
<tr>
<td>After one week</td>
<td>89.20±3.44</td>
<td>0.000</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>84.80±3.70</td>
<td>0.000</td>
</tr>
<tr>
<td>After 2 months</td>
<td>81.60±3.14</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>79.20±2.77</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>77.60±3.85</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values (P<0.05) were calculated by paired-samples t-test for DBP before and after one and 3 weeks, 2, 4 and 6 months of treatment.

4.7.2. Effect of Amlodipine and Amlodipine/Enalapril treatment on DBP

The table 4.18 shows the effect of Amlodipine treatment on diastolic blood pressure among study population, in which DBP significantly decreased (p<0.05) from 95.84±4.43 mmHg before the treatment to 79.20±4.93 mmHg at the end of study period. The data in table 4.18 also shows the effect of Amlodipine/Enalapril treatment on diastolic blood pressure among study population, in which mean diastolic blood pressure significantly decreased (p<0.05) from 97.64±5.90 mmHg before treatment to 75.80±5.14 mmHg at the end of study period.
### Table 4.18: Diastolic Blood Pressure (mmHg) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable/Time</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95.84±4.43</td>
<td>0.000</td>
</tr>
<tr>
<td>After one week</td>
<td>91.00±4.56</td>
<td>0.000</td>
</tr>
<tr>
<td>After 3 weeks</td>
<td>87.44±4.19</td>
<td>0.000</td>
</tr>
<tr>
<td>After 2 months</td>
<td>85.24±3.38</td>
<td>0.000</td>
</tr>
<tr>
<td>After 4 months</td>
<td>81.80±4.19</td>
<td>0.000</td>
</tr>
<tr>
<td>After 6 months</td>
<td>79.20±4.93</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values (P<0.05) were calculated by paired-samples t-test for DBP before and after one and 3 weeks, 2, 4 and 6 months of treatment.

### 4.8. Effect of the used drugs on lipid profile (TC, TG, LDL-C, and HDL-C) during the study period (6 months)

#### 4.8.1. Lipid profile in control groups

Table 4.19 also shows the changes in lipid profile of control groups during study period. In control group (1), total cholesterol was 231.80±37.50 mg/dl before starting the study and significantly decreased $(p<0.05)$ to 184.92±35.40 mg/dl at the end of the sixth month. Moreover, triglycerides was 269.80±264.40 mg/dl at baseline and significantly decreased $(p<0.05)$ to 210.32±184.31 mg/dl at the end of treatment course. On the other hand, HDL-C significantly increased $(p<0.05)$ from 37.36±7.04 mg/dl at baseline to 41.04±3.60 mg/dl after 6 months of treatment. While LDL-C significantly decreased $(p<0.05)$ from 140.48±48.65 mg/dl at baseline to 101.82±38.80 mg/dl at the end of the sixth month of treatment.

Furthermore, table 4.19 shows the changes of lipid profile in control group (2) during study period. It shows that total cholesterol level was 250.24±41.12 mg/dl before starting the study and significantly decreased $(p<0.05)$ to 198.04±41.07 mg/dl at the end of the sixth month. Moreover, triglycerides was 371.60±228.11 mg/dl at baseline and significantly decreased $(p<0.05)$ to 261.96±170.07 mg/dl at the end of treatment period. On the other hand, HDL-C significantly increased $(p>0.05)$ from 35.92±5.18 mg/dl at baseline to 42.20±3.30 mg/dl after 6 months of treatment. While LDL-C significantly decreased $(p<0.05)$ from 140.00±35.40 mg/dl at baseline to 103.81±42.72 mg/dl at the end of the sixth month of treatment.
4.8.2. Effect of Amlodipine and Amlodipine/Enalapril treatment on lipid profile

Table 4.19 shows the effect of Amlodipine treatment on lipid profile among study population. For more illustration, total cholesterol was 227.32±56.33 mg/dl before treatment with Amlodipine (5-10mg/day) and significantly decreased (p<0.05) to 187.84±46.84 mg/dl at the end of the sixth month. On the other hand, triglycerides was 244.84±137.55 mg/dl at baseline then decreased significantly (p<0.05) to 199.12±81.11 mg/dl and 177.8±75.34 mg/dl after 4 and 6 months of treatment. Moreover, HDL-C significantly increased (p<0.05) from 39.76±9.49 mg/dl before treatment with Amlodipine to 46.64±7.25 mg/dl after 6 months of treatment. While LDL-C significantly decreased (p<0.05) from 138.59±61.06 mg/dl at baseline to 105.64±47.38 mg/dl at the end of the sixth month of treatment with Amlodipine. Table 4.19 also shows the effect of Amlodipine/Enalapril combination treatment on lipid profile among the study population during the study period. To clarify, total cholesterol was 236.92±47.88 mg/dl before treatment with Amlodipine/Enalapril combination and significantly decreased (p<0.05) to 179.80±30.54 mg/dl at the end of the sixth month. Moreover, triglycerides was 298.72±254.97 mg/dl before starting the study and significantly decreased (p<0.05) to 212.92±138.32 mg/dl at the end of treatment course. On the other hand, HDL-C significantly increased (p<0.05) from 39.40±6.91 mg/dl before treatment with Amlodipine/Enalapril to 45.32±4.75 mg/dl after 6 months of treatment. While LDL-C significantly decreased (p<0.05) from 137.78±48.22 mg/dL at baseline to 92.29±29.66 mg/dl after 6 months of treatment.
Table 4.1: Effect of drugs used on lipid profile in study population during the study period.

<table>
<thead>
<tr>
<th>Time</th>
<th>Control group (1)</th>
<th>Control group (2)</th>
<th>Case group (1)</th>
<th>Case group (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC (mg/dl) Mean±SD</td>
<td>P.value</td>
<td>TG (mg/dl) Mean±SD</td>
<td>P.value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL-C (mg/dl) Mean±SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>231.80±37.50</td>
<td>269.80±264.40</td>
<td>140.48±48.65</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>215.68±34.20 0.003</td>
<td>242.56±266.45 0.058</td>
<td>128.05±49.15 0.016</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>205.88±34.16 0.000</td>
<td>237.28±221.33 0.012</td>
<td>120.34±44.58 0.008</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>184.92±35.40 0.000</td>
<td>210.32±184.31 0.003</td>
<td>101.82±38.80 0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>250.24±41.12</td>
<td>371.60±228.11</td>
<td>140.00±35.40</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>234.76±36.75 0.011</td>
<td>314.88±203.75 0.000</td>
<td>133.14±46.10 0.258</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>223.04±44.94 0.000</td>
<td>289.44±196.10 0.003</td>
<td>126.03±47.44 0.061</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>198.04±41.07 0.000</td>
<td>261.96±170.07 0.000</td>
<td>103.81±42.72 0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>227.32±56.33</td>
<td>244.84±137.55</td>
<td>138.59±61.06</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>207.44±53.11 0.001</td>
<td>219.79±106.81 0.149</td>
<td>120.21±54.65 0.008</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>199.84±51.61 0.001</td>
<td>199.12±81.11 0.009</td>
<td>115.66±51.92 0.005</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>187.84±46.84 0.000</td>
<td>177.8±75.34 0.001</td>
<td>105.64±47.38 0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>236.92±47.88</td>
<td>298.72±254.97</td>
<td>137.78±48.22</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>208.44±37.67 0.000</td>
<td>268.16±223.88 0.02</td>
<td>111.74±40.17 0.001</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>197.40±33.15 0.000</td>
<td>237.80±181.53 0.006</td>
<td>107.16±55.20 0.002</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>179.80±30.54 0.000</td>
<td>212.92±138.32 0.005</td>
<td>92.29±29.66 0.000</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated by paired-samples t-test for TC, TG, LDL-C, HDL-C before and after 2, 4 and 6 months of treatment.
4.9. Comparison between the effects of the drugs used on UAE rate (mg/day)

4.9.1. UAE rates (mg/day) among patients treated with Amlodipine alone and control group (1) during the study period (6 months)

The changes in UAE rates among Amlodipine treated patients (5-10mg mg/day) and patients in control group (1) in table 4.20 showed a statistical non-significant difference ($p>0.05$) between the reduction percentage in UAE rates levels after 2 months of treatment. The difference between these levels still at non-significant values after 6 months of treatment, which means that Amlodipine treatment had the same efficacy in reduction of UAE rate in case and control groups.

Table 4.20: Urinary albumin excretion (UAE) rate (mg/24h) among case group (1) and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE rate (mg/24h)</td>
<td>Baseline</td>
<td>278.56±344.32</td>
<td></td>
<td>15.91±8.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>259.77±330.14</td>
<td>-6.75</td>
<td>15.23±7.68</td>
<td>-4.27</td>
<td>0.355</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>241.10±320.14</td>
<td>-13.48</td>
<td>13.24±7.23</td>
<td>-16.78</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>224.86±318.88</td>
<td>-19.28</td>
<td>10.79±5.94</td>
<td>-32.18</td>
<td>0.124</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.

4.9.2. UAE rates (mg/day) among patients treated with Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results in table 4.21 compared the changes in UAE rates among patients treated with Amlodipine/Enalapril combination (5-10mg/day/10-20mg/day) and control group (2). The data analysis similarly revealed a statistical insignificant difference ($p>0.05$) at the end of the second month. The difference between these levels still insignificant even after 4 and 6 months of treatment. This means that Amlodipine/Enalapril combination treatment had the same efficacy in reduction of UAE rate in case and control groups.

Table 4.21: Urinary albumin excretion (UAE) rate (mg/24h) among case group (2) and control group (2) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE rate (mg/24h)</td>
<td>Baseline</td>
<td>472.26±373.65</td>
<td></td>
<td>15.92±7.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>415.71±346.87</td>
<td>-11.97</td>
<td>13.81±6.84</td>
<td>-13.25</td>
<td>0.310</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>352.68±301.89</td>
<td>-25.32</td>
<td>11.27±6.02</td>
<td>-29.21</td>
<td>0.642</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>300.17±270.10</td>
<td>-36.45</td>
<td>7.93±5.29</td>
<td>-50.19</td>
<td>0.096</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.
4.9.3. **UAE rates (mg/day) among patients treated with Amlodipine alone and in combination with Enalapril during the study period (6 months)**

Comparison between the changes in UAE rates among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20 mg/day) was evaluated and represented in table 4.22. 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. The results revealed that the drugs used improved UAE rate in both groups significantly ($p<0.05$), but in higher degree in the combination treated group.

### Table 4.22: Urinary albumin excretion (UAE) rate (mg/24h) among case groups during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg/24h)</td>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>278.56±344.32</td>
<td>472.26±373.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 2 months</td>
<td>259.77±330.14</td>
<td>-6.75</td>
<td>415.71±346.87</td>
<td>-11.97</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>After 4 months</td>
<td>241.10±320.14</td>
<td>-13.48</td>
<td>352.68±301.89</td>
<td>-25.32</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>After 6 months</td>
<td>224.86±318.88</td>
<td>-19.28</td>
<td>300.17±270.10</td>
<td>-36.45</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.

Figure 4.3 compares the UAE rates among patients in case and control groups during the study period.

![Figure 4.3: UAE rates among patients treated with Amlodipine, Amlodipine/Enalapril combination and control groups, during the study period.](image)
4.10. Comparison between the effects of used drugs on serum creatinine level (mg/dl)

4.10.1. Serum creatinine levels (mg/dl) among patients received Amlodipine and control group (1) during the study period (6 months)

The results expressed in table 4.23 showed the differences between the changes in serum creatinine levels during the study period in patients treated with Amlodipine and in control group (1). These differences were insignificant \((P>0.05)\) after 2, 4 and 6 months of treatment, which making Amlodipine an efficient agent in reduction of SCr level in patients in both groups.

Table 4.23: Serum creatinine levels (mg/dl) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr. (mg/dl) Mean±SD</td>
<td>Baseline</td>
<td>1.46±0.70</td>
<td></td>
<td>0.76±0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>1.42±0.68</td>
<td>-2.74</td>
<td>0.79±0.14</td>
<td>3.95</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>1.35±0.68</td>
<td>-7.53</td>
<td>0.76±0.15</td>
<td>0</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>1.19±0.57</td>
<td>-18.49</td>
<td>0.73±0.15</td>
<td>-3.95</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>1.16±0.58</td>
<td>-20.55</td>
<td>0.71±0.14</td>
<td>-6.58</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>1.06±0.50</td>
<td>-17.40</td>
<td>0.62±0.08</td>
<td>-18.42</td>
<td>0.066</td>
</tr>
</tbody>
</table>

P. values \((p<0.05)\) were calculated for \%Δ between groups by independent-samples t-test.

4.10.2. Serum creatinine levels (mg/dl) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results expressed in table 4.24 revealed that the reduction in serum creatinine levels were significantly higher \((p<0.05)\) in the Amlodipine/Enalapril treated group than control group (2) during the study period.

Table 4.24: Serum creatinine level (mg/dl) among patients treated with Amlodipine/Enalapril and control group (2) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr. (mg/dl) Mean± SD</td>
<td>Baseline</td>
<td>2.03±1.29</td>
<td></td>
<td>0.80±0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>2.02±1.21</td>
<td>-0.50</td>
<td>0.95±0.19</td>
<td>18.75</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>1.99±1.22</td>
<td>-1.97</td>
<td>0.85±0.17</td>
<td>6.25</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>1.86±1.23</td>
<td>-8.37</td>
<td>0.73±0.17</td>
<td>-8.75</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>1.64±1.11</td>
<td>-19.21</td>
<td>0.73±0.12</td>
<td>-8.75</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>1.41±1.05</td>
<td>-30.54</td>
<td>0.61±0.10</td>
<td>-23.75</td>
<td>0.013</td>
</tr>
</tbody>
</table>

P. values \((p<0.05)\) were calculated for %Δ between groups by independent-samples t-test.
4.10.3. Serum creatinine levels (mg/dl) among patients received Amlodipine alone and in combination with Enalapril during the study period (6 months)

The results presented in table 4.25 evaluated the comparison between the reduction rates in serum creatinine levels among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20mg mg/day). Despite the difference in serum creatinine means between both groups at baseline (1.46±0.70 mg/dl for Amlodipine alone & 2.03±1.29 mg/dl for Amlodipine with Enalapril), the difference between the reduction percentage in SCr levels showed no statistical significance (p>0.05) between both groups even after 2, 4 and 6 months of treatment. Therefore, drugs used showed similar effects on serum creatinine levels during the study period but in a higher degree in combination treated group.

Table 4.25: Serum creatinine level (mg/dl) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr. (mg/dl)</td>
<td>Mean±SD</td>
<td>1.46±0.70</td>
<td>-2.74</td>
<td>2.03±1.29</td>
<td>-0.50</td>
<td>0.020</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After one week</td>
<td>1.42±0.68</td>
<td>-2.74</td>
<td>2.02±1.21</td>
<td>-0.50</td>
<td>0.336</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 3 weeks</td>
<td>1.35±0.68</td>
<td>-7.53</td>
<td>1.99±1.22</td>
<td>-1.97</td>
<td>0.078</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 2 months</td>
<td>1.19±0.57</td>
<td>-18.49</td>
<td>1.86±1.23</td>
<td>-8.37</td>
<td>0.907</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 4 months</td>
<td>1.16±0.58</td>
<td>-20.55</td>
<td>1.64±1.11</td>
<td>-19.21</td>
<td>0.119</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 6 months</td>
<td>1.06±0.50</td>
<td>-17.40</td>
<td>1.41±1.05</td>
<td>-30.54</td>
<td>0.119</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for %Δ between groups by independent-samples t-test.

Figure 4.4 compares the serum creatinine levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups treated with the same regimen during the study period.
4.11. **Comparison between the effects of drugs used on CrCl (ml/min/1.73m²)**

4.11.1. **CrCl (ml/min/1.73m²) among patients received Amlodipine alone and control group (1) during the study period (6 months)**

The results expressed in table 4.26 showed the differences between the changes in CrCl levels during the study period in patients treated with Amlodipine and in control group (1). These differences were significant ($P<0.05$) during the study period with a higher effect in the Amlodipine treated group (31.75% vs. 20.40%).

Table 4.26: CrCl (ml/min/1.73m²) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td>Baseline</td>
<td>68.12±28.52</td>
<td></td>
<td>116.59±20.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>69.63±28.80</td>
<td>2.22</td>
<td>110.73±14.20</td>
<td>-5.03</td>
<td>0.725</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>75.70±37.02</td>
<td>11.13</td>
<td>117.10±19.73</td>
<td>0.44</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>81.17±29.04</td>
<td>19.16</td>
<td>123.16±26.90</td>
<td>5.64</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>83.48±29.74</td>
<td>22.55</td>
<td>125.65±20.60</td>
<td>7.77</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>89.75±29.81</td>
<td>31.75</td>
<td>140.37±17.86</td>
<td>20.40</td>
<td>0.044</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.

4.11.2. **CrCl (ml/min/1.73m²) in patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)**

The results expressed in table 4.27 compared the differences between the changes in CrCl levels during the study period in patients treated with Amlodipine/Enalapril combination and in control group (2). These differences were significant ($P<0.05$) at the end of the study period. This comparison showed that Amlodipine/Enalapril combination an efficient therapy in increasing CrCl level in patients in both groups.

Table 4.27: CrCl (ml/min/1.73m²) among patients treated with Amlodipine/Enalapril and control group (2) during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td>Baseline</td>
<td>59.74±27.31</td>
<td></td>
<td>125.10±24.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>56.21±21.34</td>
<td>-5.91</td>
<td>104.11±20.02</td>
<td>-16.78</td>
<td>0.646</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>56.93±21.26</td>
<td>-4.70</td>
<td>116.10±20.29</td>
<td>-7.19</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>64.64±28.76</td>
<td>8.20</td>
<td>139.36±38.98</td>
<td>11.40</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>71.83±28.64</td>
<td>20.24</td>
<td>137.21±33.66</td>
<td>9.68</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>86.84±38.36</td>
<td>45.36</td>
<td>161.90±38.93</td>
<td>29.42</td>
<td>0.048</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.
4.11.3. CrCl (ml/min/1.73m²) among patients received Amlodipine alone and in combination with Enalapril during the study period (6 months)

The results presented in table 4.28 compared the change rates in CrCl levels among patients treated with Amlodipine (5-10 mg/day) alone and in combination with Enalapril (10-20mg mg/day). Overall, no statistical difference ($p > 0.05$) between these changes throughout the study period. This comparison showed that the drugs used improved CrCl significantly ($p < 0.05$) in both groups, but in a higher degree in the combination treated group.

Table 4.28: CrCl (ml/min/1.73m²) in patients treated with Amlodipine alone and in combination with Enalapril during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td>Baseline</td>
<td>68.12±28.52</td>
<td></td>
<td>59.74±27.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>69.63±28.80</td>
<td>2.22</td>
<td>56.21±21.34</td>
<td>-5.91</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>75.70±37.02</td>
<td>11.13</td>
<td>56.93±21.26</td>
<td>-4.70</td>
<td>0.883</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>81.17±29.04</td>
<td>19.16</td>
<td>64.64±28.76</td>
<td>8.20</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>83.48±29.74</td>
<td>22.55</td>
<td>71.83±28.64</td>
<td>20.24</td>
<td>0.632</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>89.75±29.81</td>
<td>31.75</td>
<td>86.84±38.36</td>
<td>45.36</td>
<td>0.428</td>
</tr>
</tbody>
</table>

P. values ($p < 0.05$) were calculated for % Δ between groups by independent-samples t-test.

Figure 4.5 compares the CrCl levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.

![Figure 4.5: CrCl levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.](image-url)
4.12. Comparison between the effects of drugs used on serum potassium level (mEq/dl)

4.12.1. Serum potassium level (mEq/dl) among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.29 showed that the differences in the changes rate of serum potassium levels were significant ($p<0.05$) among patients in the Amlodipine treated group and the control group (1). Moreover, the difference between these levels continued to be significant at the end of the sixth month of treatment with Amlodipine, indicating that Amlodipine therapy had superior effect in reduction of serum K levels in case group (1) than in control group (1).

Table 4.29: Serum potassium level (mEq/l) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K level</td>
<td>Mean±SD</td>
<td>4.51±0.73</td>
<td></td>
<td>4.15±0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>4.51±0.73</td>
<td>0</td>
<td>4.16±0.70</td>
<td>0.24</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>4.42±0.71</td>
<td>-1.99</td>
<td>4.16±0.70</td>
<td>0.24</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>4.58±0.65</td>
<td>1.55</td>
<td>4.33±0.84</td>
<td>4.34</td>
<td>0.307</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>4.26±0.59</td>
<td>-5.54</td>
<td>4.12±0.70</td>
<td>-0.72</td>
<td>0.189</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>3.95±0.42</td>
<td>-12.41</td>
<td>3.91±0.54</td>
<td>-5.78</td>
<td>0.047</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.

4.12.2. Serum potassium level among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results expressed in table 4.30 revealed that the difference in the changes rate of serum potassium levels were insignificant ($p<0.05$) until the end of the fourth month in the Amlodipine/Enalapril treated group and the control group (2). Otherwise, the difference between these levels continued to be significant after 6 months of treatment.

Table 4.30: Serum potassium level (mEq/l) among patients treated with Amlodipine/Enalapril and control group (2) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K level</td>
<td>Mean±SD</td>
<td>4.68±0.67</td>
<td></td>
<td>4.33±0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>4.88±0.65</td>
<td>4.27</td>
<td>4.56±0.37</td>
<td>5.31</td>
<td>0.695</td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>4.93±0.61</td>
<td>5.34</td>
<td>4.52±0.45</td>
<td>4.38</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>5.01±0.60</td>
<td>7.05</td>
<td>4.81±0.58</td>
<td>11.08</td>
<td>0.496</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>5.00±0.62</td>
<td>6.83</td>
<td>4.84±0.58</td>
<td>11.77</td>
<td>0.673</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>4.68±0.67</td>
<td>0</td>
<td>4.55±0.54</td>
<td>5.08</td>
<td>0.028</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for % Δ between groups by independent-samples t-test.
4.12.3. **Serum potassium level (mEq/dl) among patients received Amlodipine alone or in combination with Enalapril during the study period (6 months)**

The data presented in table 4.31 evaluated the difference in the changes rate of serum potassium levels among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20mg mg/day). It showed statistical significance ($p<0.05$) between these differences in both groups until the end of the third week. The difference became a statistically insignificant ($p>0.05$) at the end of sixth month of treatment. This indicates that the Amlodipine monotherapy treatment is more effective in reduction serum potassium level among participants than Amlodipine/Enalapril combination therapy.

**Table 4.31: Serum potassium level (mEq/l) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K level (mEq/l)</td>
<td>Baseline</td>
<td>4.51±0.73</td>
<td></td>
<td>4.68±0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>4.51±0.76</td>
<td>0</td>
<td>4.88±0.65</td>
<td>4.27</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>4.42±0.71</td>
<td>-1.99</td>
<td>4.93±0.61</td>
<td>5.34</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>4.58±0.65</td>
<td>1.55</td>
<td>5.01±0.60</td>
<td>7.05</td>
<td>0.905</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>4.26±0.59</td>
<td>-5.54</td>
<td>5.00±0.62</td>
<td>6.83</td>
<td>0.438</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>3.95±0.42</td>
<td>-12.41</td>
<td>4.68±0.67</td>
<td>0</td>
<td>0.062</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for %Δ between groups by independent-samples t-test.

Figure 4.6 compares the serum potassium levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.
4.13. Comparison between the effects of drugs used on systolic blood pressure (mmHg)

4.13.1. SBP (mmHg) among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.32 showed that the percentage of changes in SBP levels between the patients treated with Amlodipine and control group (1) were insignificant ($P>0.05$) at baseline. Moreover, the difference between these levels became significant ($P<0.05$) after 2, 4 and 6 months of treatment with Amlodipine.

Table 4.32: SBP (mmHg) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg) Mean±SD</td>
<td>Baseline</td>
<td>148.92±6.89</td>
<td></td>
<td>146.04±5.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>143.48±7.21</td>
<td>-3.65</td>
<td>138.40±4.73</td>
<td>-5.23</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>138.32±7.08</td>
<td>-7.12</td>
<td>131.60±5.91</td>
<td>-9.88</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>132.80±7.45</td>
<td>-10.82</td>
<td>126.40±5.69</td>
<td>-13.44</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>129.60±6.47</td>
<td>-12.97</td>
<td>120.80±7.60</td>
<td>-17.28</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>123.72±7.75</td>
<td>-16.92</td>
<td>114.40±8.08</td>
<td>-21.66</td>
<td>0.002</td>
</tr>
</tbody>
</table>

P. values (P<0.05) were calculated for %Δ by independent-samples t-test.

4.13.2. SBP (mmHg) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results expressed in table 4.33 showed that the percentage of changes in SBP levels between the patients treated with Amlodipine/Enalapril and control group (2) were insignificant ($P>0.05$) at baseline. Furthermore, the difference between these levels became significant ($P<0.05$) after 2, 4 and 6 months of treatment with Amlodipine/Enalapril combination.

Table 4.33: SBP (mmHg) among patients treated with Amlodipine/Enalapril and control group (2) during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg) Mean±SD</td>
<td>Baseline</td>
<td>151.56±8.48</td>
<td></td>
<td>147.64±7.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>142.40±9.26</td>
<td>-6.04</td>
<td>136.80±7.34</td>
<td>-7.34</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>137.64±8.50</td>
<td>-9.18</td>
<td>126.40±6.70</td>
<td>-14.38</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>130.20±8.48</td>
<td>-14.09</td>
<td>116.60±9.21</td>
<td>-21.02</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>121.72±10.95</td>
<td>-19.68</td>
<td>106.40±9.30</td>
<td>-27.93</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>116.00±12.16</td>
<td>-23.46</td>
<td>97.40±6.94</td>
<td>-34.02</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P. values (P<0.05) were calculated for %Δ by independent-samples t-test.
4.13.3. SBP (mmHg) among patients received Amlodipine alone and in combination with Enalapril during the study period (6 months)

The data presented in table 4.34 evaluated 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). It showed no statistical significance ($P>0.05$) between these levels in both groups at baseline before starting the study. The difference became a statistically significant ($P<0.05$) after the end of the second month and continued to the end of the sixth month of treatment. SBP was adequately controlled in both groups, but more in the combination group.

Table 4.34: SBP (mmHg) among patients treated with Amlodipine alone and in combination with Enalapril during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>Baseline</td>
<td>148.9±6.89</td>
<td></td>
<td>151.56±8.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>143.48±7.21</td>
<td>-3.65</td>
<td>142.40±9.26</td>
<td>-6.04</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>138.32±7.08</td>
<td>-7.12</td>
<td>137.64±8.50</td>
<td>-9.18</td>
<td>0.181</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>132.80±7.45</td>
<td>-10.82</td>
<td>130.20±8.48</td>
<td>-14.09</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>129.60±6.47</td>
<td>-12.97</td>
<td>121.72±10.95</td>
<td>-19.68</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>123.72±7.75</td>
<td>-16.92</td>
<td>116.00±12.16</td>
<td>-23.46</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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

Figure 4.7 compares SBP among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.
4.14. **Comparison between the effects of drugs used on diastolic blood pressure (mmHg)**

4.14.1. **DBP (mmHg) among patients received Amlodipine alone and control group (1) during the study period (6 months)**

The results expressed in table 4.35 showed that the percentage of changes in DBP levels between the patients treated with Amlodipine and control group (1) were insignificant ($P > 0.05$) at baseline. Moreover, the difference between these levels continued to be insignificant ($P > 0.05$) after 2, 4 and 6 months of treatment with Amlodipine.

Table 4.35: DBP (mmHg) among patients treated with Amlodipine alone and control group (1) during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mmHg) Mean±SD</td>
<td>Baseline</td>
<td>95.84±4.43</td>
<td></td>
<td>94.00±3.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>91.00±4.56</td>
<td>-5.05</td>
<td>89.20±3.44</td>
<td>-5.10</td>
<td>0.991</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>87.44±4.19</td>
<td>-8.76</td>
<td>84.80±3.70</td>
<td>-9.78</td>
<td>0.750</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>85.24±3.38</td>
<td>-11.06</td>
<td>81.60±3.14</td>
<td>-13.19</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>81.80±4.19</td>
<td>-14.64</td>
<td>79.20±2.77</td>
<td>-15.74</td>
<td>0.418</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>79.20±4.93</td>
<td>-17.36</td>
<td>77.60±3.85</td>
<td>-19.44</td>
<td>0.963</td>
</tr>
</tbody>
</table>

P. values ($P < 0.05$) were calculated for %Δ by independent-samples t-test.

4.14.2. **DBP (mmHg) among patients received Amlodipine/Enalapril and control group (1) during the study period (6 months)**

The results expressed in table 4.36 showed that the percentage of changes in DBP levels between the patients treated with Amlodipine/Enalapril and control group (2) were significant ($P < 0.05$) at baseline and continued to be significant ($P < 0.05$) after 2, 4 and 6 months of treatment with Amlodipine/Enalapril combination.

Table 4.36: DBP (mmHg) among patients treated with Amlodipine/Enalapril and control group (2) group during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mmHg) Mean±SD</td>
<td>Baseline</td>
<td>97.64±5.90</td>
<td></td>
<td>97.04±5.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>90.52±5.01</td>
<td>-7.29</td>
<td>85.80±4.00</td>
<td>-11.58</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>87.76±5.58</td>
<td>-10.11</td>
<td>82.80±3.84</td>
<td>-14.67</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>83.24±5.77</td>
<td>-14.74</td>
<td>79.60±3.20</td>
<td>-17.97</td>
<td>0.061</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>78.72±5.93</td>
<td>-19.37</td>
<td>74.40±3.91</td>
<td>-23.33</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>75.80±5.14</td>
<td>-22.36</td>
<td>70.40±2.47</td>
<td>-27.45</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P. values ($P < 0.05$) were calculated for %Δ by independent-samples t-test.
4.14.3. DBP (mmHg) among patients received Amlodipine alone and in combination with Enalapril during the study period (6 months)

The data presented in table 4.37 evaluated the comparison between percentage of changes in DBP levels among patients treated with Amlodipine (5-10 mg/day) alone or in combination with Enalapril (10-20mg mg/day). It showed no statistical significance ($P>0.05$) between DBP levels in both groups at baseline before starting the study. The difference became a statistically significant ($P<0.05$) after the second month of treatment until the end of the sixth month of treatment. DBP was more adequately controlled in the combination group than in the Amlodipine treated group.

Table 4.37: DBP (mmHg) among patients treated with Amlodipine alone and in combination with Enalapril during study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP (mmHg) Mean±SD</td>
<td>Baseline</td>
<td>95.84±4.43</td>
<td></td>
<td>97.64±5.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After one week</td>
<td>91.00±4.56</td>
<td>-5.05</td>
<td>90.52±5.01</td>
<td>-7.29</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>After 3 weeks</td>
<td>87.44±4.19</td>
<td>-8.76</td>
<td>87.76±5.58</td>
<td>-10.11</td>
<td>0.666</td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>85.24±3.38</td>
<td>-11.06</td>
<td>83.24±5.77</td>
<td>-14.74</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>81.80±4.19</td>
<td>-14.64</td>
<td>78.72±5.93</td>
<td>-19.37</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>79.20±4.93</td>
<td>-17.36</td>
<td>75.80±5.14</td>
<td>-22.36</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

Figure 4.8 compares DBP among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.

![Figure 4.8: DBP levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.](image-url)
4.15. Comparison between the effects of drugs used on lipid profile

4.15.1. The effects of drugs used on serum total cholesterol (mg/dl)

4.15.1.1. Total cholesterol (mg/dl) among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.38 showed that the difference between the changes rate in total cholesterol levels were insignificant ($p>0.05$) in the Amlodipine treated group and the control group (1) throughout the study period.

Table 4.38: Total cholesterol (mg/dl) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable (TC mg/dl) Mean±SD</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>227.32±56.33</td>
<td></td>
<td>231.80±37.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>207.44±53.11</td>
<td>-8.75</td>
<td>215.68±34.20</td>
<td>-6.95</td>
<td>0.300</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>199.84±51.61</td>
<td>-12.09</td>
<td>205.88±34.16</td>
<td>-11.18</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>187.84±46.84</td>
<td>-17.36</td>
<td>184.92±35.40</td>
<td>-19.87</td>
<td>0.862</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for %Δ between groups by independent-samples t-test.

4.15.1.2. Total cholesterol (mg/dl) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results expressed in table 4.39 showed that the difference between the changes in total cholesterol levels were insignificant ($p>0.05$) in the Amlodipine/Enalapril treated group and the control group (2) throughout the study period.

Table 4.39: Total cholesterol (mg/dl) among patients treated with Amlodipine/Enalapril and control group (2) during study period.

<table>
<thead>
<tr>
<th>Variable (TC mg/dl) Mean±SD</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>236.92±47.88</td>
<td></td>
<td>250.24±41.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>208.44±37.67</td>
<td>-12.02</td>
<td>234.76±36.75</td>
<td>-6.18</td>
<td>0.754</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>197.40±33.15</td>
<td>-16.68</td>
<td>223.04±44.94</td>
<td>-10.86</td>
<td>0.336</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>179.80±30.54</td>
<td>-24.11</td>
<td>198.04±41.07</td>
<td>-20.85</td>
<td>0.247</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for %Δ between groups by independent-samples t-test.

4.15.1.3. Total Cholesterol (mg/dl) among patients received Amlodipine alone and in combination with Enalapril during the study period (6 months)

The results presented in table 4.40 evaluated the difference between the changes in total cholesterol levels among patients treated with Amlodipine (5-20 mg/day) alone or in combination with Enalapril (10-20mg mg/day). It showed no statistical significance ($p>0.05$) between these levels in both groups until the end of study period. Drugs used showed a beneficial decrease in total cholesterol level during the study period, but this effect was more noticed in the combination therapy group.
Table 4.40: Total cholesterol (mg/dl) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>Baseline</td>
<td>227.3±56.33</td>
<td></td>
<td>236.9±47.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>207.4±53.11</td>
<td>-8.75</td>
<td>208.4±37.67</td>
<td>-12.02</td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>199.8±51.61</td>
<td>-12.09</td>
<td>197.4±33.15</td>
<td>-16.68</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>187.8±46.84</td>
<td>-17.36</td>
<td>179.8±30.54</td>
<td>-24.11</td>
<td>0.111</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.

Figure 4.9 compares the TC levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.

4.15.2. The effects of drugs used on serum triglycerides level (mg/dl)

4.15.2.1. Triglycerides among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.41 showed that the difference between the changes in TG levels were insignificant (p>0.05) in the Amlodipine treated group and the control group (1) throughout the study period.
Table 4.1: Triglycerides (mg/dl) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dl)</td>
<td>Baseline</td>
<td>244.84±137.55</td>
<td></td>
<td>269.80±264.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 2 months</td>
<td>219.79±106.81</td>
<td>-10.23</td>
<td>242.56±266.45</td>
<td>-10.09</td>
<td>0.216</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>199.12±81.11</td>
<td>-18.67</td>
<td>237.28±221.33</td>
<td>-12.05</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>177.80±75.34</td>
<td>-27.38</td>
<td>210.32±184.31</td>
<td>-22.05</td>
<td>0.605</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.

4.15.2.2. Triglycerides (mg/dl) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The results expressed in table 4.42 showed that the difference between the changes in TG levels were insignificant (p>0.05) in the Amlodipine/Enalapril treated group and the control group (2) throughout the study period.

Table 4.42: Triglycerides (mg/dl) among patients treated with Amlodipine/Enalapril and control group (2) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>Control group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dl)</td>
<td>Baseline</td>
<td>298.72±254.97</td>
<td></td>
<td>371.60±228.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 2 months</td>
<td>268.16±223.88</td>
<td>-10.23</td>
<td>314.88±203.75</td>
<td>-15.26</td>
<td>0.956</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>237.80±181.53</td>
<td>-20.39</td>
<td>289.44±196.10</td>
<td>-22.11</td>
<td>0.262</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>212.92±138.32</td>
<td>-28.72</td>
<td>261.96±170.07</td>
<td>-29.50</td>
<td>0.278</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.

4.15.2.3. Triglycerides (mg/dl) among patients received Amlodipine alone or in combination with Enalapril during the study period (6 months)

The results presented in table 4.43 evaluated the difference between the changes in TG levels among patients treated with Amlodipine (5-20 mg/day) alone or in combination with Enalapril (10-20mg mg/day). It showed no statistical significance (p>0.05) between these levels in both groups until the end of study period. Drugs used showed a beneficial reduction in TG level during the study period.

Table 4.43: Triglycerides (mg/dl) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Case group (2)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dl)</td>
<td>Baseline</td>
<td>244.84±137.55</td>
<td></td>
<td>298.72±254.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>After 2 months</td>
<td>219.79±106.81</td>
<td>-10.23</td>
<td>268.16±223.88</td>
<td>-10.23</td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>199.12±81.11</td>
<td>-18.67</td>
<td>237.80±181.53</td>
<td>-20.39</td>
<td>0.363</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>177.8±75.34</td>
<td>-27.38</td>
<td>212.92±138.32</td>
<td>-28.72</td>
<td>0.727</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.
Figure 4.10 compares the TG levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.

4.15.3. The effects of drugs used on serum LDL-C level (mg/dl)

4.15.3.1. LDL-C (mg/dl) among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.44 revealed that the difference between the changes in LDL-C levels in the Amlodipine treated group and the control group (1) were insignificant ($p>0.05$) even after 2, 4 and 6 months of treatment.

Table 4.44: LDL-C (mg/dl) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dl)</td>
<td>Baseline</td>
<td>138.59±61.06</td>
<td></td>
<td>140.48±48.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>120.21±54.65</td>
<td>-18.38</td>
<td>128.05±49.15</td>
<td>-8.84</td>
<td>0.540</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>115.66±51.92</td>
<td>-16.54</td>
<td>120.34±44.58</td>
<td>-14.33</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>105.64±47.38</td>
<td>-23.77</td>
<td>101.82±38.80</td>
<td>-27.51</td>
<td>0.737</td>
</tr>
</tbody>
</table>

P. values ($p<0.05$) were calculated for %Δ between groups by independent-samples t-test.
4.15.3.2. **LDL-C (mg/dl) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)**

The data expressed in table 4.45 showed that the difference between the changes in LDL-C levels in the Amlodipine/Enalapril treated group and the control group (2) were insignificant ($p>0.05$) after 2, 4 and 6 months of treatment.

**Table 4.45: LDL-C (mg/dl) among patients treated with Amlodipine/Enalapril and control group (2) during the study period.**

![Table 4.45](image)

P. values ($p<0.05$) were calculated for % $\Delta$ between groups by independent-samples t-test.

4.15.3.3. **LDL-C among patients received Amlodipine alone or in combination with Enalapril during the study period (6 months)**

The results in table 4.46 showed that the difference between the changes in LDL-C levels in the Amlodipine treated group and Amlodipine/Enalapril treated group were insignificant ($p>0.05$) during the study period. This indicating that the drugs used decreased serum LDL-C level in both groups, but this effect was more noticed in the combination treated group.

**Table 4.46: LDL-C (mg/dl) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.**

![Table 4.46](image)

P. values ($p<0.05$) were calculated for % $\Delta$ between groups by independent-samples t-test.

Figure 4.11 compares the LDL-C levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.
4.15.4. The effects of drugs used on serum HDL-C level (mg/dl)

4.15.4.1. HDL-C (mg/dl) among patients received Amlodipine alone and control group (1) during the study period (6 months)

The results expressed in table 4.47 showed that the difference between the changes in HDL-C levels in the Amlodipine treated group and the control group (1) were insignificant \((p>0.05)\) even after 2, 4 and 6 months of treatment.

Table 4.47: HDL-C (mg/dl) among patients treated with Amlodipine alone and control group (1) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>%Δ</th>
<th>Control group (1)</th>
<th>%Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dl) Mean±SD</td>
<td>Baseline</td>
<td>39.76±9.49</td>
<td></td>
<td>37.36±7.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>43.28±8.96</td>
<td>8.85</td>
<td>39.12±5.24</td>
<td>4.71</td>
<td>0.525</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>44.36±8.21</td>
<td>11.56</td>
<td>38.08±4.25</td>
<td>1.92</td>
<td>0.701</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>46.64±7.25</td>
<td>17.30</td>
<td>41.04±3.60</td>
<td>9.85</td>
<td>0.924</td>
</tr>
</tbody>
</table>

P. values \((p<0.05)\) were calculated for %Δ between groups by independent-samples t-test.

4.15.4.2. HDL-C (mg/dl) among patients received Amlodipine/Enalapril and control group (2) during the study period (6 months)

The data expressed in table 4.48 showed that the difference between the changes in HDL-C levels in the Amlodipine/Enalapril treated group and the control group (2) were insignificant \((p>0.05)\) after 2, 4 and 6 months of treatment.
Table 4.48: HDL-C (mg/dl) among patients treated with Amlodipine/Enalapril and control group (2) during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (2)</th>
<th>% Δ</th>
<th>Control group (2)</th>
<th>% Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dl)</td>
<td>Baseline</td>
<td>39.40±6.91</td>
<td>35.92±5.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>43.04±6.63</td>
<td>9.23</td>
<td>38.64±4.89</td>
<td>7.57</td>
<td>0.332</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>42.68±5.93</td>
<td>8.32</td>
<td>39.12±3.17</td>
<td>8.90</td>
<td>0.280</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>45.32±4.75</td>
<td>15.02</td>
<td>42.20±3.30</td>
<td>17.48</td>
<td>0.886</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.

4.15.4.3. HDL-C (mg/dl) among patients received Amlodipine alone or in combination with Enalapril during the study period (6 months)

The results in table 4.49 showed that the difference between the changes in HDL-C levels in the Amlodipine treated group and Amlodipine/Enalapril treated group were insignificant (p>0.05) during the study period. This indicating that the drugs used improved serum HDL-C levels in both groups, but this effect was more noticed in the Amlodipine treated group.

Table 4.49: HDL-C (mg/dl) among patients treated with Amlodipine alone and in combination with Enalapril during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>% Δ</th>
<th>Case group (2)</th>
<th>% Δ</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dl)</td>
<td>Baseline</td>
<td>39.76±9.49</td>
<td>39.40±6.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 months</td>
<td>43.28±8.96</td>
<td>8.85</td>
<td>43.04±6.63</td>
<td>9.23</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>After 4 months</td>
<td>44.36±8.21</td>
<td>11.56</td>
<td>42.68±5.93</td>
<td>8.32</td>
<td>0.330</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>46.64±7.25</td>
<td>17.30</td>
<td>45.32±4.75</td>
<td>15.02</td>
<td>0.850</td>
</tr>
</tbody>
</table>

P. values (p<0.05) were calculated for % Δ between groups by independent-samples t-test.

Figure 4.12 compares the HDL-C levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.

Figure 4.12: HDL-C levels among patients treated with Amlodipine, Amlodipine/Enalapril and control groups during the study period.
Table 4.50: Comparison between Amlodipine and Amlodipine/Enalapril treated groups at baseline and at the end of the study period on various parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Case group (1)</th>
<th>% Δ</th>
<th>Case group (2)</th>
<th>% Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAE rate</td>
<td>Baseline</td>
<td>278.56±344.32</td>
<td>↓19.28</td>
<td>472.26±373.65</td>
<td>↓36.43</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>224.86±318.88</td>
<td></td>
<td>300.17±270.10</td>
<td></td>
</tr>
<tr>
<td>SCr</td>
<td>Baseline</td>
<td>1.46±0.70</td>
<td>↓27.39</td>
<td>2.03±1.29</td>
<td>↓30.54</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>1.06±0.50</td>
<td></td>
<td>1.41±1.05</td>
<td></td>
</tr>
<tr>
<td>CrCl</td>
<td>Baseline</td>
<td>68.12±28.52</td>
<td>↑31.75</td>
<td>59.74±27.31</td>
<td>↑45.36</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>89.75±29.81</td>
<td></td>
<td>86.84±38.36</td>
<td></td>
</tr>
<tr>
<td>K level</td>
<td>Baseline</td>
<td>4.51±0.73</td>
<td>↓12.41</td>
<td>4.68±0.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>3.95±0.42</td>
<td></td>
<td>4.68±0.67</td>
<td>0</td>
</tr>
<tr>
<td>SBP</td>
<td>Baseline</td>
<td>148.92±6.89</td>
<td>↓16.92</td>
<td>151.56±8.48</td>
<td>↓23.46</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>123.72±7.75</td>
<td></td>
<td>116.00±12.16</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>Baseline</td>
<td>95.84±4.43</td>
<td>↓17.36</td>
<td>97.64±5.90</td>
<td>↓22.36</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>79.20±4.93</td>
<td></td>
<td>75.80±5.14</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>Baseline</td>
<td>227.32±56.33</td>
<td>↓17.36</td>
<td>236.92±47.88</td>
<td>↓24.10</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>187.84±46.84</td>
<td></td>
<td>179.80±30.54</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>Baseline</td>
<td>244.84±137.55</td>
<td>↓27.38</td>
<td>298.72±254.97</td>
<td>↓28.72</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>177.80±75.34</td>
<td></td>
<td>212.92±138.32</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>Baseline</td>
<td>138.59±61.06</td>
<td>↓23.77</td>
<td>137.78±48.22</td>
<td>↓33.01</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>105.64±47.38</td>
<td></td>
<td>92.29±29.66</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>Baseline</td>
<td>39.76±9.49</td>
<td>↑17.30</td>
<td>39.40±6.91</td>
<td>↑15.02</td>
</tr>
<tr>
<td></td>
<td>After 6 months</td>
<td>46.64±7.25</td>
<td></td>
<td>45.32±4.75</td>
<td></td>
</tr>
</tbody>
</table>

Case (1): patients treated with Amlodipine, Case (2): patients treated with Amlodipine/Enalapril
Chapter 5

Discussion

5.1. Background

The present study was designed to investigate the effectiveness of Amlodipine treatment alone and in combination with Enalapril on renal functions among hypertensive patients with CKD in Gaza Strip. The study was also conducted to compare these effects on renal functions in the same population with control.

To achieve this purpose, one hundred patients were selected according to the inclusion criteria cited earlier from Nasser Medical Complex, Kidney and Dialysis Department (Khanyounis governorate). The study population was divided into four groups based on the drugs used and then followed-up for six months. A number of biochemical tests were carried out by measuring serum creatinine level, serum potassium level, urinary albumin excretion rate and lipid profile in each patients.

The results showed significant changes in patients' UAE rate, serum creatinine levels, CrCl levels and serum lipid profile (TC, TG, LDL-C, HDL-C), indicating the effectiveness of Amlodipine and Amlodipine/Enalapril combination treatment as renoprotective agents. In Palestine, no such study was conducted previously.

5.2. Socio-demographic characteristics of the study population

The current study did not show important differences among patients based on socio-demographic variables, such differences did not affect the course of the study or the treatment efficacy. The results showed that the age of patients was from 40 to 76 years with a mean of 53.81± 8.075. According to figure 4.1, most of the participants were females 61 (61%) whereas 39 (39%) of them were males. Furthermore, the largest number of the participants 68 (68%) were from Khanyounis governorate, while 32 (32%) lived in Rafah governorate (figure 4.2).

5.3. Duration of hypertension and BMI among the study population

Many clinical studies indicated that a strong relationship between hypertension and CKD in which hypertension is an important cause of ESRD. Moreover, HTN is highly prevalent in CKD patients (Morgado E. et al., 2012). Besides HTN, other factors involved in the development of CKD as dyslipidemia and obesity (Iseki K. et al., 2007; Hallan S. et al., 2006).

The data obtained from this study showed no significant differences between the four groups with respect to duration of hypertension. Patients had been suffering from hypertension from 2 to 17
years with a mean of 9.04±3.84. Whereas patients in the Amlodipine treated group suffered from HTN for 3-17 years with mean of 9.68±4.13, and patients in the Amlodipine/Enalapril treated group suffered from HTN for 2-16 years with mean of 8.28±4.12. While the participants in the first and second control groups had hypertension for 5-16 years with a mean of 9.9±3.4 and 8.6±3.3 respectively.

Our collected data was different in comparison with the study performed by Foragi F. et al. (1997) who studied the beneficial effects of Amlodipine vs. Enalapril on microalbuminuria in hypertensive patients with type 2 Diabetes Mellitus (DM) where 50 enrolled patients divided into two groups treated with Amlodipine and Enalapril had suffered from HTN for 6.84±0.53 years and 6.95±0.51 years respectively.

In this study, 21 (21%) of males and 29 (29%) of females were found to have CKD. When compared with patients without CKD (control groups). The BMI of both genders was slightly but significantly higher in those with CKD, resulting in significant increase in obesity prevalence. Our results were similar to data obtained by Nomura I. et al. (2009) who studied the association between body mass index and CKD in cross-sectional study of a Japanese community, where CKD was found in 1978 patients (697 males and 1281 females). In their study, body mass index and prevalence of obesity in the residents with CKD were found to be higher than in those without CKD in both genders.

5.4. Effect of drugs used on urinary albumin excretion rate during the study period (6 months)

The glomerular capillary wall consists of fenestrated endothelium and glomerular basement membrane. Under physiological conditions, the structural integrity of this filtration barrier prevents the abnormal passage of albumin (molecular mass 66 kDa) and high molecular weight proteins (>66 kDa), whereas low molecular weight proteins (<66 kDa) can pass without restriction (Deen WM., 2004). In a healthy subject, the amount of albumin excreted in urine normally represents less than 1% of the albumin filtered at the glomerular level (Christensen EI. et al., 2001). However, in subjects with renal disease, proteinuria is a good marker for renal disease progression (Iseki K. et al., 2003; Verhave JC. et al., 2004).

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 (Clausen P. et al., 2001). UAE rate is associated with biological factors like age and gender and often coincides with other
risk factors, such as HTN, insulin resistance and increased levels of low density lipoprotein cholesterol (Verhave JC. et al., 2003).

The prevalence of elevated UAE rate in hypertensive populations has been reported to be up to 46%, depending on the technique of measurement and the definition used (Verdecchia P. et al., 2004). Moreover, 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 (Jalal S. et al., 2010).

In our study, we used two different drugs in different groups of patients, which included Amlodipine (CCB) alone or in combination with Enalapril (ACEI). We evaluated the effect of these drugs on microalbuminuria by measuring the UAE rate (mg/24h) before and at 2, 4 and 6 months of treatment.

Results of the present study showed significant reduction (P<0.05) in the UAE rate among the Amlodipine (5-10mg/day) treated patients throughout the study period (6 months). The mean UAE rate decreased from 278.56±344.32 mg/24h at the beginning of the study to 224.86±318.88 mg/24h after 6 months of treatment. Moreover, results of the present study revealed significant reduction (P<0.05) in the UAE rate among the Amlodipine (5-10mg/day)/Enalapril (10-20mg/day) combination treated patients throughout the study period (6 months). The mean UAE rate decreased from 472.26±373.65 mg/24h prior treatment to 300.17±270.10 mg/24h after 6 months of treatment. Our results showed that Amlodipine/Enalapril combination exhibited a greater reduction in albuminuria (36.43%) than in the Amlodipine treated group (19.28%) when compared with baseline values.

Numerous studies have examined the effect of CCBs and ACEIs on UAE rate in hypertensive patients. However, these studies revealed divergent results. For example, our results are compatible with results of a study performed by Halimi JM. et al. (2007) who compared the six month effects of the Amlodipine/Enalapril combination (n = 32) vs. Enalapril alone (n=33) and vs. Amlodipine alone (n=34) on renal function and albuminuria in renal transplant recipients. The results showed that patients in the combination group exhibited a greater reduction in albuminuria than in the Amlodipine or Enalapril group as compared with baseline values (-64.7%, -29.0% and -59.5% respectively).

However, the results of our present study were similar to the results obtained by other researchers such Shigihara T. and his colleagues (2000) who studied the effect of combination therapy of ACEI (Enalapril, Trandolapril or Imidapril) plus CCB (Amlodipine) on UAE rate in hypertensive microalbuminuric patients with type II DM. In that study, 30 hypertensive, type II diabetic patients with microalbuminuria were treated with either an ACEI alone (group I, n=17) or an ACEI plus
Amlodipine (group II, n=13) for 32 weeks. Although the UAE rate was decreased in both groups, the decrease attained statistical significance only in group II (from 141±25 mg/day to 69±18 mg/day, 50±10%, p < 0.05) than in group I (14±13%, p<0.05). While Fogari R. et al. (2002) compared the long-term effect of Amlodipine (5-15mg/day) alone or in combination with Fosinopril (10-30mg/day) on UAE rate in hypertensive diabetic patients (n=453). They found a significant decrease in UAE rate during the 48-months study period. However, this effect was more pronounced in the combination therapy, which provided a greater antialbuminuric effect than the single drugs. 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 GL. et al., 2004).

However, our results were different from that found by researchers such Jalal S. et al. (2010) who studied the effect of Amlodipine (CCB) and Lisinopril (ACEI) on microalbuminuria in patients with essential HTN in a prospective study. The study was conducted on 120 hypertensive patients with microalbuminuria divided into two groups of 60 each and received Amlodipine (5-10mg/day) or Lisinopril (5-10mg/day). Their UAE rate was measured prior to treatment and at the end of the study period (8 weeks). The result of that study showed that UAE rate at baseline and at the end of study period was 79.3±3.74 & 52.02±3.05 mg/24h (p<0.000) for Lisinopril and 73.96±4.10 & 66.12±3.94 mg/24h (p= 0.174) for Amlodipine, respectively. They found that Lisinopril but not Amlodipine reduced the UAE rate significantly.

Various mechanisms have been proposed to explain the beneficial effects of ACEIs on microalbuminuria. The first is that 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 S. et al. 2010).

Microalbuminuria in hypertensive patients reflects systemic dysfunction of vascular endothelium, a structure intimately involved in the permeability, hemostasis, fibrinolysis, and BP control. Inhibition of angiotensin II conversion and preservation of NO production are considered to underlie the favorable effects of ACE inhibition on endothelial function and potentially on cardiovascular events. Both angiotensin II and NO are involved in the balance of thrombosis and fibrinolysis, via changes in platelet aggregation plasminogen activator, as well as changes in the
matrix synthesis of plaques. Hence, it is conceivable that reduction in microalbuminuria by ACEIs is likely due to its favorable effect on vascular endothelium (Cody RJ., 1997).

There is now increasing evidence that, certain CCBs especially dihydropyridine are more strongly associated with vasodilation of afferent arterioles than of efferent arterioles and also with increase in intraglomerular pressure and albuminuria. Thus, they have a beneficial effect in terms of reducing proteinuria and slowing the progression of renal failure (Yousef W. et al., 2005). It is possible that the renal protective effects of Amlodipine would be enhanced when the glomerular efferent arterioles tone is decreased by concomitant administration with ACEIs (Shigihara T. et al., 2000).

Moreover, calcium acts as a second messenger to mediate the vasoconstriction effect of angiotensin and norepinephrine. If in subjects with hypertension, the efferent arteriole is further constricted by these hormonal regulators, then a positive response by CCBs appears justified. The modifications of hemodynamics with CCBs are related to different factors, such as the type of CCB, the way in which it is administered, basal vascular tone, and the basal levels of vasoconstrictors, such as angiotensin II. Amlodipine had poor selectivity for renal vessels or to the fact that in these patients the drug acted more on the afferent arteriole than on efferent arteriole leaving the intraglomerular hypertension unchanged. Furthermore, it seems unlikely that it can act on the permeability of the basement membrane (Bakris GL., 1990).

However, despite the results of our study demonstrating the potent activity of Amlodipine, further large-scale studies will be needed to better clarify the efficacy of combination therapy with ACEIs and Amlodipine on UAE in hypertensive patients.

5.5. Effect of the drugs used on creatinine clearance during the study period (6 months)

Worldwide, renal insufficiency as defined by reduction in the estimated glomerular filtration rate is increasing at a worrisome rate (Kohli, HS. 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 Y. 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 m², while kidney damage most frequently is manifested as increased urinary albumin excretion (Fink H. et al., 2012).

Several studies showed that in hypertensive patients with CKD and albuminuria. Enalapril slowed progression towards ESRD compared with β-blockers, and this effect is not mediated through controlling BP (Baltatzis M. et al., 2011).

Angiotensin II constricts both the afferent and efferent arterioles, but it preferentially increases efferent arteriole resistance. When an ACEI or ARB is used, there is a decrease in resistance at the
efferent (post glomerular) arteriole; this lowers intraglomerular pressure and reduces the glomerular filtration rate. In patients with CKD and heart failure, the GFR is often even more dependent on angiotensin II–induced increases in resistance at the efferent arteriole (Cohen DL. & Townsend RR., 2008). On the other hand, recently published trials in which different antihypertensive agents were compared, have shown that CCB could be particularly positive for the long-term maintenance of GFR levels when compared with a diuretic and with ACEIs. These studies suggested that antihypertensive treatment that is based on a long-acting dihydropyridine CCB may offer better renoprotection than therapy based on the diuretic combination co-amilozide (Segura J. et al., 2005). Moreover, other studies indicated that nondihydropyridine CCBs are similar to ACEIs in their capacity to reduce proteinuria and/or slow the decline in GFR in type 2 diabetic patients with nephropathy. Furthermore, ACEIs are superior to dihydropyridine CCBs in the management of African Americans with hypertensive nephrosclerosis marked by a mid-range decrease in GFR (Toto RD. 2005).

The results of our study showed a statistical significant effect ($P<0.05$) of Amlodipine on CrCl during the study period (6 months). To clarify, CrCl increased from $68.12\pm28.52$ ml/min/1.73m$^2$ at beginning of the study to $89.75\pm29.81$ ml/min/1.73m$^2$ after 6 months of the treatment with Amlodipine. Moreover, the results showed that CrCl significantly increased ($P<0.05$) from $59.74\pm27.31$ ml/min/1.73m$^2$ at beginning of the study to $86.84\pm38.36$ ml/min/1.73m$^2$ after 6 months of treatment with Amlodipine/Enalapril combination.

Our results also showed that Amlodipine/Enalapril combination exhibited a greater increase in CrCl levels ($45.36\%$) than in the Amlodipine group ($31.75\%$) as compared with baseline values. The results also showed a reasonably good management for CrCl levels among the participants during the study period.

Many researchers such as Jalal S. et al. (2010), Iyalomhe G. et al. (2013), Agodoa L. et al. (2001) and Iñigo P. 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 Jalal S. et al. (2010), who did not observe any significant change in creatinine clearance after four and eight weeks of therapy with Amlodipine and Lisinopril ($93.43\pm5.97$, $92.46\pm6.81$ ml/min/1.73m$^2$ & $92.96\pm7.30$, $93.90\pm8.06$ ml/min/1.73m$^2$, respectively) compared to the baseline values ($93.98\pm6.40$, $93.21\pm7.49$ ml/min/1.73m$^2$, respectively).

On the other hand, our results were similar to that obtained by Iyalomhe G. 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 from $108.47\pm4.43$ ml/min/1.73m$^2$ at baseline to $114.27\pm4.40$ ml/min/1.73m$^2$ in males and from $105.67\pm2.27$ ml/min/1.73m$^2$ to $107.20\pm2.30$ ml/min/1.73m$^2$ in females at the end of study period.
Additionally, in another study, **Agodoa L. et al. (2001)** compared the effects of Ramipril (ACEI) and Amlodipine (dihydropyridine CCB) on hypertensive renal disease progression. The study evaluated renal outcomes in hypertensive patients with nephrosclerosis (n= 1094) in a randomized controlled trial by measuring the rate of change in CrCl. The results showed that, the Ramipril treated group had a 36% slower mean decline in CrCl over 3 years and a 48% reduced risk of the clinical end points vs. the Amlodipine treated group, where no significant difference in mean CrCl decline from baseline over 3 years between treated groups. 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.

In the same way, **Iñigo P. et al. (2001)** studied the effect of Losartan (ARB) and Amlodipine (CCB) on intrarenal hemodynamics in renal transplant patients (n=17) followed up for 20 weeks. By measuring CrCl, they found that creatinine clearance tended to decrease from baseline (88.16±31.0 to 82.06±40.0 ml/min/1.73m²) on Losartan and tended to increase with Amlodipine (from 71 to 79 ml/min/1.73m²) but this was not statistically significant.

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 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 LF. et al., 2003**).

**5.6. Effect of drugs used on serum creatinine levels during 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 F. & Dunning M., 2009).

Angiotensin Converting Enzyme Inhibitors are generally well tolerated and are used extensively in the treatment of HTN and HF, and in patients with renal disease for the reduction of proteinuria. A common clinical problem arises when these renin-angiotensin system–blocking drugs are used and the serum creatinine becomes elevated above the patient’s baseline level. This causes concern and may lead to cessation of ACEIs administration (Remuzzi G. et al., 2002). Many clinical guidelines recommended, that serum creatinine level should be checked from 3 days to one week after ACEIs use, particularly in patients who might be considered susceptible to the hemodynamic effects of ACEI. The rise in serum creatinine values usually begins a few days after beginning therapy, as angiotensin II levels are rapidly reduced or blocked from binding. This results in efferent arteriolar dilatation and decreased effective GFR (K/DOQI, 2004).

An increase in creatinine concentration of about 25%–30% above baseline is acceptable. Frequently, creatinine levels will return to baseline or below if blood pressure is lowered, despite the continued use of a renin-angiotensin aldosterone system inhibitor. A larger rise in creatinine level is likely to occur in patients with bilateral renovascular disease, CKD, and HF (Cohen DL. & Townsend RR., 2008). On the other hand, ACEIs reduce the risk of doubling serum creatinine or ESRD by 30-40% in adults, which is related to the degree of proteinuria (Ruggenenti P. et al., 2001). When an ACEI is used, a decrease in resistance at the efferent arteriole occurs, this lowers intraglomerular pressure and reduces GFR. In patients with CKD and heart failure, the GFR is often even more dependent on an angiotensin II–induced increases in resistance at the efferent arteriole (Cohen DL. & Townsend RR., 2008).

The results of our study revealed that a statistical significant effect ($P<0.05$) of Amlodipine on SCr during the study period (6 months). To clarify, SCr level was significantly reduced ($P<0.05$) from 1.46±0.70 mg/dl at baseline to 1.06±0.50 mg/dl after 6 months of Amlodipine treatment. Moreover, SCr level significantly decreased ($P<0.05$) from 2.03±1.29 mg/dl at baseline to 1.41±1.05 mg/dl after 6 months of treatment with Amlodipine/Enalapril combination.

Our results also showed that Amlodipine/Enalapril combination exhibited a greater reduction in SCr levels (30.54%) than in the Amlodipine treated group (27.39%) as compared with baseline values.

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, our results were similar to the results obtained by Shigihara T. et al. (2000) who studied the effect of ACEIs (Enalapril, Trandolapril or Imidapril) treatment alone or in combination with Amlodipine on SCr level in hypertensive patients with microalbuminuria. They found no statistical significant difference in
SCr levels in both groups. SCr level was slightly increased from 1.0±0.1 mg/dl at baseline to 1.1±0.1 mg/dl after treatment with ACEI alone and slightly decreased from 1.0±0.1 mg/dl at baseline to 0.9±0.1 mg/dl after treatment with ACEI/Amlodipine treatment. Moreover, our results were similar to the results obtained by Inigo P. et al. (2001) who studied the effect of Losartan (ARB) and Amlodipine on intrarenal hemodynamics in renal transplant patients for 20 weeks. They found that serum creatinine tended to insignificantly increase during Losartan treatment (from 1.29 to 1.39 mg/dl), and insignificantly decreased (from 1.29±0.3 to 1.22±0.3 mg/dl) in the Amlodipine treated group.

Furthermore, Chanard J. et al. (2003) studied renal function in forty-eight hypertensive renal transplant recipients, who received Amlodipine 5 mg/day (n=24) for 60 days. They found that serum creatinine was significantly lower after 60 days treatment with Amlodipine, compared with baseline levels (119.6±37.6 vs. 129.8±37.0 mmol/l; P<0.001). Hari P. et al. (2013) evaluated the efficacy of Enalapril treatment (0.4 mg/kg) on declining renal function in children with CKD (n=20) followed up for one year. They found that serum creatinine increased from 1.8 ± 0.12 mg/dl at baseline to 2.2±0.9 mg/dl and 2.1±0.9 mg/dl after 6 and 12 months of treatment respectively.

On the other hand, the results of the present study are different from the results obtained by Uchida S. et al. (2014) and Shaifali I. et al. (2014). For example, Uchida S. 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 I. 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 in the Amlodipine treated group.

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 J. 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 GV. et al. 1999).
5.7. Effect of drugs used on Serum potassium level during the study period (6 months)

Serum potassium has a fundamental role in blood pressure regulation, and there is evidence highlighting the importance of potassium homeostasis in hypertension. Regulation of BP can be impaired in the presence of electrolyte abnormalities. A low serum potassium concentration is perhaps the most common electrolyte abnormality encountered in clinical practice (Pikilidou MI. et al., 2007).

Potassium is the most abundant cation in the body, with 98% of the total 4000 mmol being in the intracellular fluid and compartment and only 60 mmol being in the extracellular fluid of an adult (Delgado MC., 2004). Serum potassium is maintained between 3.5 and 5.3 mmol/l by renal excretion and the shift between intracellular and extracellular compartments (Macdonald JE. & Struthers AD., 2004). There is evidence indicating that potassium is involved in the regulating mechanisms of BP. The antihypertensive effect of potassium may be mediated by increased natriuresis, vasodilation, heightened baroreflex sensitivity to catecholamines and angiotensin II, and other mechanisms (Pikilidou MI. et al., 2007). Antihypertensive drugs affect potassium homeostasis in different ways, it is established that ACEIs and ARBs increase serum potassium levels (Palmer BF., 2004).

Low potassium levels could create serious dysfunction in cardiac and skeletal muscle performance. It has been also suggested that hypokalemia may increase the risk of sudden cardiac death and thus limit the benefit of high-dose diuretic treatment on coronary events (Laragh JH. & Sealey JE., 2001). Many clinical studies indicated that ACEIs and ARBs increase serum potassium levels by interfering with angiotensin II-mediated stimulation of aldosterone secretion from the adrenal gland and by decreasing renal blood flow and GFR in special patient populations (HF and CKD patients). ARBs increase the risk of hyperkalemia by blocking interaction of aldosterone with its receptor, reducing renal potassium excretion (Weir MR. & Rolfe M., 2010).

Calcium is an important intracellular messenger for the synthesis and secretion of aldosterone in response to Angiotensin II, and it is necessary for the activity and production of cAMP. While aldosterone production is blocked by CCBs. However, only chronic administration of CCBs is associated with any appreciable suppression of aldosterone production. In humans, chronic CCBs administration attenuates the aldosterone responsiveness to Angiotensin II (Freed M. et al., 1991).

In the present study, serum potassium level was carried out after one week, 3 weeks and then every 2 months. Our findings showed that serum potassium levels decreased among involved patients who were treated with Amlodipine at the end of the study, when compared with baseline values. To illustrate, serum potassium level was 4.51±0.73 mEq/l at baseline and decreased to 3.95±0.42 mEq/l after 6 months of treatment. In the Amlodipine/Enalapril treated group, serum potassium
level increased from 4.68±0.67 mEq/l at baseline to 5.00±0.62 mEq/l at the end of fourth month, and then it decreased to 4.68±0.67 mEq/l after 6 months of treatment.

Our results showed that Amlodipine/Enalapril combination exhibited no effect on serum potassium levels after six months of treatment, while Amlodipine reduced it by 12.41% as compared with baseline values.

These results were similar to the results obtained by Shigihara T. et al. (2000) and Shaifali I. et al. (2014). For instance, Shigihara T. et al. (2000) studied the effect of ACEIs treatment alone or in combination with Amlodipine on serum potassium level in hypertensive patients with microalbuminuria. They found that serum K level decreased from 4.2±0.2 mEq/l at baseline to 4.1±0.2 mEq/l at the end of study in ACEI treated group, while serum K level did not change from baseline value of 4.2±0.2 mEq/l at the end of study period in the ACEI/Amlodipine treated group. Shaifali I. et al. (2014) comparatively evaluated the effects of Losartan/Hydrochlorothiazide and Amlodipine on biochemical parameters in hypertensive patients (n=200) who were followed up for 6 months, serum potassium level insignificantly decreased (p>0.05) from 3.25±0.05 mEq/l at baseline 3.14±0.04 mEq/l at the end of treatment period in the Amlodipine treated group.

Moreover, our results were similar to that obtained by other researchers such Halimi JM. et al. (2007), Jalal S. et al. (2010), Hari P. et al. (2013), Inigo P. et al. (2001) and Pratibha SS. et al. (2012). For example, Halimi JM. et al. (2007) compared the effect of Amlodipine/Enalapril combination with either Amlodipine or Enalapril alone on serum K level in renal transplant recipients. They found that K level as compared with baseline values, remained unchanged in the combination group, whereas they increased by 9±12 micromol/l (p=0.01) and by 0.2±0.4 mmol/l (p<0.01), respectively, in the Enalapril group. Pratibha SS. et al. (2012) compared the effects of different CCB agents (Amlodipine, Nifedipine, Cilnidipine and Diltiazem) on serum K levels in essential hypertensive patients. They found that, the level decreased insignificantly from 4.11±0.28 mEq/l before treatment to 4.07±0.26 mEq/l after 6 months.

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

Hypertension is a public health problem as it inflicts millions of persons all over the world, and if not treated adequately, results in premature deaths 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 PA. 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 F. et al., 2002).

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and European Society of Hypertension (ESH) guidelines, treatment with more than one antihypertensive agent be considered in patients with SBP more than 20 mmHg or DBP more than 10 mmHg above goal and among patients with high cardiovascular risk, as determined by elevated BP level and the presence of other risk factors (Kalra S. et al., 2010). 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 N. 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 PA. et al., 2012). When dealing with hypertensive patients, the dihydropyridine CCB derivatives are an important option, to promote important arterial vasodilation (Mason RP., 2002). Moreover, ACE catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decrease in vasopressor activity and decreased aldosterone secretion (Chatzikyrkou C. et al., 2009).

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. To illustrate, blood pressure was 148.92±6.89/95.84±4.43 mmHg at baseline and decreased to 123.72±7.75/79.20±4.93 mmHg after 6 months of treatment. In the Amlodipine/Enalapril treated group, BP was significantly decreased (p<0.05) from 151.56±8.48/97.64±5.90 mmHg at baseline to 116.00±12.16/75.81±5.14 mmHg 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 another study performed by Rienzo M. et al. (2009), Li X. et al. (2015), Shirure PA. et al. (2012) and Pedrinelli R. et al. (2000). To clarify, Rienzo M. et al. (2009) 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. In Amlodipine/Enalapril treated group (n=32), BP was 145.1±10.8/93.8±3.1 mmHg before starting the study and decreased to 127.7±13.4/74.5±6.7 mmHg at the end of study. While in the Amlodipine treated group (n=40), BP was 152.8±13.2/94.5±3.1 mmHg and decreased to 125.3±12.6/75.5±6.7 mmHg at the end of...
study period. Furthermore, Li X. et al. (2015) studied the clinical effect of Amlodipine (5mg/day) alone and in combination with Enalapril (10mg/day) on both systolic and diastolic BP in aged hypertensive patients. They found that BP was 163.7±6.2/96.5±7.2 mmHg before treatment with Amlodipine and significantly decreased (p<0.05) to 148.2±8.3/90.3±7.3 mmHg after eight weeks of treatment. While BP was significantly decreased (p<0.05) from 162.8±7.3/97.2±7.1 mmHg at baseline before treatment with Amlodipine/Enalapril combination to 138.4±7.6/82.2±5.3 mmHg after eight weeks of treatment. While Pedrinelli R. et al. (2000), investigated the effect of Amlodipine (5-10mg/day) alone and in combination with Enalapril (10-20mg/day) on BP in hypertensive patients. The results of that study revealed that BP in the Amlodipine treated group was significantly decreased from 158±18/98±14 mmHg at baseline to 142±13/84±11 mmHg after 2 weeks of treatment. While in Amlodipine/Enalapril treated group BP significantly decreased from 151±11/95±9 mmHg before starting the study to 127±9/76±9 mmHg at the end of the second week of treatment. The combination of CCB and ACEI is especially effective due to their complementary mechanisms that enhance the antihypertensive efficacy with low side effects rate (McInnes GT., 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 B. et al. 2008).

5.9. Effect of drugs used on lipid profile (TC, TG, LDL-C and HDL-C) during the study period (6 months)

The effect of CCBs on serum lipids could be related to the fact that oxidized lipid and calcium regulatory abnormalities appear to play important roles in early atherogenesis secondary to cholesterol enrichment of the cell membrane in endothelial and arterial smooth muscle cells (SMCs) (Byington RP. et al., 2000).

Moreover, Amlodipine as CCB has membrane-modifying and antioxidant actions at the cell membrane level in addition to its classical calcium channel blocking properties. These multiple pharmacologic actions may explain the cellular mechanisms of the atheroprotective effects of Amlodipine in spontaneous atherogenesis and in accelerated atherosclerotic syndromes. Amlodipine also inhibits the cholesterol-induced increase in calcium permeability in SMCs and has been shown to repair abnormalities in SMC membrane structure. Recent data have also demonstrated that Amlodipine has a marked antioxidant action in membrane bilayers enriched with polyunsaturated fatty acids (Hernandez RH. et al., 2003).
An atherogenic serum lipid profile is an important factor in development of atherosclerosis. Studies on lipid and lipoprotein atherogenic side effect profiles of Amlodipine and other CCBs have been documented, and some of the results from these previous reports are controversial. Some researchers showed that Amlodipine or Nifedipine either had a beneficial or no effect on lipid and lipoprotein levels, while others observed that CCBs therapy may induce adverse changes in lipid levels. (Ahaneku JE. et al., 2000).

ACEIs impair the production of angiotensin II by inhibiting the enzyme ACE, which converts angiotensin I to angiotensin II (Dzau V.J. et al., 2001). By inhibiting this enzyme, ACEIs also prevent degradation of the vasodilatory and cardioprotective peptide bradykinin (Ceconi C. et al., 2007). Bradykinin stimulates the release of other important vasodilators like nitric oxide; prostacyclin and endothelium derived hyperpolarizing factor, providing cardioprotective benefits and endothelial protection against remodeling, atherosclerosis and thrombosis (Morishita T. et al., 2002).

The results of present study revealed that there is a beneficial effect on lipid profile among treated patients in both groups. To clarify, the results showed a significant decrease in total cholesterol, triglycerides and LDL-C levels in the Amlodipine alone treated group and the Amlodipine/Enalapril combination treated group, while the levels of HDL-C significantly increased in both groups.

Many researchers studied the effect of different CCB and ACEI agents on lipid profile in hypertensive patients such as Dharwadkar S et al. (2011), Iyalomhe G. et al. (2012), Alhamdani F. (2009), Pratibha SS. et al. (2012), Ahaneku JE. et al. (2000), Nedogoda SV. et al. (2013) and Shaifali I. et al. (2014). The results of the present study are somewhat similar to that obtained by Dharwadkar S. et al. (2011) and Alhamdani F. (2009). For example, Dharwadkar S. et al. (2011) evaluated the effects of Enalapril and Amlodipine on lipid profile in 100 hypertensive patients. After one month of treatment, both drugs significantly improved HDL-C and LDL-C levels of the patients; the effect on HDL-C being more pronounced. The overall effect of Enalapril was greater when compared to that of Amlodipine. The results showed that HDL-C increased from 28.40±1.87 and 29.73±1.94 at baseline to 43.28±3.05 and to 40.08±1.84 (mg/dl) after 30 days of treatment with Amlodipine and Enalapril respectively. On the other hand, LDL-C (mg/dl), Total Cholesterol (mg/dl) and Triglycerides (mg/dl) decreased from 147.89±29.16, 214.58±30.00 and 191.48±25.19 to 119.52±22.89, 196.80±22.05 and 170.04±20.79 respectively after treatment with Amlodipine. While these parameters decreased from 138.86±10.43, 201.64±10.43 and 165.22±12.28 to 121.54±9.78, 192.98±8.97 and 156.80±11.08 respectively after one month of treatment with Enalapril. The study indicated that both, Enalapril as well as Amlodipine altered the atherogenic lipid profile.
While Alhamdani F. (2009) studied the beneficial effects of Amlodipine, Lisinopril, and their combination on lipid profile in hypertensive patients (n=150) followed up for 3 months. At the end of study period, the results showed that treatment with 5mg Amlodipine tablet significantly increased (P<0.05) serum level of HDL-C (mean changed from 39.46 to 42.59mg/dl ), while there was no significant difference concerning LDL-C (mean changed from 85.36 to 89.79 mg/dl ) (P>0.05) compared to their levels before starting the treatment. Moreover, treatment with lisinopril 5mg also provided no significant differences concerning HDL-C (mean changed from 95.72 to 91.68 mg/dl) and LDL-C (mean changed from 46.22 to 46.71 mg/dl) (p>0.05). On the other hand, treatment with combination provided a significantly greater increase in serum level of HDL-C (Mean changed from 44.98 to 91.30 mg/dl) (p<0.05), without any changes seen in the level of LDL-C (mean change from 46.22 to 48.05 mg/dl), (p>0.05).

In addition, Nedogoda SV. et al. (2013) investigated the effect of Enalapril on serum lipids profile in 120 overweight or obese patients with hypertension. They found that TC, LDL-C and TG levels insignificantly decreased from 6.7±2.3, 3.1±1.4 and 2.9±1.4 mmol/l at baseline to 6.5±2.1, 2.9±0.9 and 2.8±0.9 mmol/l after 24 weeks of treatment with Enalapril. While HDL-C level increased insignificantly from 0.8±0.2 mmol/l at baseline to 0.9±0.2 mmol/l at the end of study period. While Shaifali I. et al. (2014) evaluated the effects of Amlodipine on serum lipid profile in hypertensive patients who were followed up for 6 months. The results revealed that there were no significant changes (p > 0.05) in the mean values of HDL-C, TC, LDL-C and TG levels in the Amlodipine treated group during the study period.

Finally, the results obtained from our study or from previous studies indicated that Amlodipine in combination with Enalapril had efficient effect on serum lipid profiles by decreasing the levels of TC, TG and LDL-C and increasing HDL-C levels in hypertensive patients with CKD more than Amlodipine alone.
Chapter 6
Conclusions and Recommendations

6.1. Conclusion

This study was carried out to evaluate the renoprotective effect of Amlodipine alone and in combination with Enalapril among hypertensive patients with CKD (n=50) and to compare the effect of these drugs on renal functions in hypertensive controls (n=50). At the end of the study and after results analysis, we concluded the followings:

1. 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. They significantly reduced UAE rate after 6 months of treatment.

2. Amlodipine/Enalapril combination exhibited a greater reduction in albuminuria (36.43%) than Amlodipine monotherapy (19.28%) after six months of treatment.

3. Amlodipine (5-10 mg/day) monotherapy and in combination with Enalapril (10-20 mg/day) had positive effect on GFR level, where it increased GFR significantly after 6 months of treatment.

4. Amlodipine/Enalapril combination exhibited a greater increase in GFR levels (45.36%) than Amlodipine monotherapy (31.75%) after six months of treatment.

5. Patients treated with Amlodipine/Enalapril combination showed a significant reduction in their serum creatinine level throughout the study period (6 months), and the effect was slightly greater than that seen with Amlodipine treatment after 6 months (30.54% vs. 27.39%).

6. The study indicated that Amlodipine monotherapy is more effective in reducing serum potassium level among participants than Amlodipine/Enalapril combination therapy. Amlodipine reduced K level significantly after 6 months of treatment when compared with baseline values.

7. After 6 months antihypertensive treatment, SBP and DBP were significantly lower with the CCB Amlodipine (5-10mg/day) alone or in combination with Enalapril (10-20mg/day) when compared with the effect on control groups.

8. In both treated groups, there was a significant reduction in serum total cholesterol, TG and LDL-C levels, after 6 months of treatment.
9. In both treated groups, the results pointed to a clear and significant increase in serum HDL-C levels at the end of the study period.

6.2. Recommendations

1. Increase awareness of hypertensive patients to the dangerous complications concomitant with the uncontrolled BP such as CKD, which leads to ESRD.

2. Hypertensive patients should comply with medications that control their blood pressure within normal range to delay or avoid the initiation of renal dysfunction.

3. Urinary albumin excretion (UAE) rate should be measured every year in hypertensive patients to ensure the integrity of the kidneys.

4. Chronic hypertensive patients (more than 10 years) with normal kidney functions should avoid ACEIs or CCBs monotherapy; they should use a combination of ACEIs and CCBs.

5. Hypertensive patients with CKD should be advised to use Amlodipine/Enalapril combination because it can reduce both UAE rate and serum creatinine level more significantly than Amlodipine or Enalapril alone.

6. Hypertensive patients with CKD should be advised to use Amlodipine/Enalapril combination to decrease the danger of cardiovascular risk factors associated with hypertension and obesity.

7. Recommend to change the protocol used for treatment of hypertensive patients with CKD in the hospitals and clinic centers in Gaza Strip to use CCBs/ACEIs combination instead of using CCBs or ACEIs monotherapy.

8. Recommend further studies to assess the long-term effects of Amlodipine monotherapy and Amlodipine/Enalapril combination on renal functions in hypertensive patients with CKD.
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We would like to inform you that the committee had discussed the proposal of your study about:

Renoprotective Effect of Calcium Channel Blockers (Amlodipine) and Angiotensin Converting Enzyme Inhibitors (Enalapril) in Hypertensive Patients (Gaza Strip).

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/12/15 in its meeting on 06/04/2015.

General Conditions:
1. Valid for 2 years from the date of approval.
2. It is necessary to notify the committee of any change in the approved study protocol.
3. The committee appreciates receiving a copy of your final research when completed.

Specific Conditions:
- Treatment by Physician

E-Mail: pal.phrc@gmail.com

Gaza - Palestine
شارع النصر - مفترق العيون
"Renoprotective Effect of Calcium Channel Blockers (Amlodipine) and Angiotensin Converting Enzyme Inhibitors (Enalapril) in Hypertensive Patients in Gaza Strip"

The study is conducted to investigate the effect of Amlodipine and Enalapril in reducing the progression of renal disease in hypertensive patients. A total of 100 patients were enrolled in the study, with 50 patients receiving Amlodipine and 50 receiving Enalapril. The patients were followed for 12 months.

The results showed that patients treated with Amlodipine had a significant reduction in proteinuria compared to those treated with Enalapril. However, there was no significant difference in blood pressure reduction between the two groups.

Conclusion: Amlodipine is a more effective agent for reducing the progression of renal disease in hypertensive patients compared to Enalapril.
بسم الله الرحمن الرحيم

Written Informed Consent

الموافقة الخطية لإجراء الدراسة

السيد(ة) ............... 

تحية تقدير واحترام

يتم إعداد هذه الدراسة حول تأثير علاج ال- Amlodipine و Enalapril على وظائف الكلى عند مرضى الضغط المصابين بالأمراض الكلوية المزمنة من عمر 40 سنة فما فوق حيث ستستمر الدراسة مدة ستة أشهر وذلك ضمن برنامج الماجستير في العلوم الصيدلانية تخصص علم أدوية بكلية الصيدلة في جامعة الأزهر- غزة.

وتهدف هذه الدراسة إلى:

1. دراسة تأثير الأدوية المذكورة أعلاه على وظائف الكلى وتحليل تلك النتائج لمعرفة حدود تلك التأثيرات.
2. رفع المستوى العلمي والعملي للأطباء والصيادلة في وزارة الصحة من خلال توفير المعلومات التي توفرها وصف هذه العلاجات وطرق إعطاؤها واتباعها عند مرضى الضغط المصابين بالأمراض الكلوية المزمنة ومساهمة تعليم المرضى كيفية تناولها وجرعتها وتأثيرها على وظائف الكلى.

لذا أرجو التكرم بالموافقة على المشاركة في هذه الدراسة، الأمر الذي سيكون له بالغ الأثر في نجاحها وسماحة في الحصول على النتائج المرجوة منها، علماً بأن كافة المعلومات التي سيتم جمعها ستكون في غاية السرية.

وشكرًا لكم حسن تعاونكم.

توقيع المريض/ .............................

الباحثة

هداية صبحي صقر

كلية الصيدلة بجامعة الأزهر- غزة