CHAPTER ONE

1. Introduction and Literature Review

1.1 Introduction:
Hypertension or high blood pressure is cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. What that means is that the heart has to work harder than it should to pump the blood around the body. Blood pressure involves two measurements, systolic and diastolic. Normal blood pressure is 120/80 mm/Hg. The first figure is the systolic blood pressure, the pressure there is in the arteries when your heart is contracting. The second, or lower figure, is the diastolic blood pressure, which is the pressure in your arteries between heart beats. High blood pressure above 140/90 mm/Hg. Hypertension is the opposite of hypotension. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause. The remaining 5–10% of cases (Secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart or endocrine system [1].

Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment may prove necessary in patients for whom lifestyle changes prove ineffective or insufficient. In the year 2000 it was estimated that nearly one billion people or 26% of the adult population had hypertension worldwide it has common in both developed [333 million] and undeveloped [639milion] countries however rates vary markedly in different region with rate as low as 3/4% [male] and 72/5% [female] in rural India and as high 68/9% [male] and 72/5% [female] in Poland, in 1995 it estimated that 43 million people in the united states had hypertension or
were taking antihypertensive medication almost 24% of the adult population. The prevalence of hypertension in the United States is increasing and reached 29% in 2004, It more common in blacks and native in American and less in white and Mexican American rates increase with age and is greater in the southeastern united states hypertension is more prevalent in men [though menopause tends to decrease this difference and those of low socioeconomic status.\[1\]

Over 90-95percent of adult hypertension is essential hypertension one of the most common causes of secondary hypertension is primary aldosteronism. The incidence of exercise hypertension is reported to range from 1-10%.\[1\]

1.2 Rationale:

Hypertension is one of the most common worldwide diseases afflicting humans and is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. According to the American Heart Association (AHA), approximately 75 million adults in the United States are affected by hypertension, which is defined as a systolic blood pressure (SBP) of 140 mm Hg or more or a diastolic blood pressure (DBP) of 90 mm Hg or more or taking antihypertensive medication.

The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and post glomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hyper perfusion.
1.3 Literature review:
1.3.1 Blood pressure:

Blood pressure assessment is an integral part of clinical practice. Routinely, a patient’s blood pressure is obtained at every physical examination, including outpatient visits, at least daily when patients are hospitalized, and before most medical procedures. Blood pressure measurements are obtained for a wide variety of reasons, including screening for hypertension, assessing a person’s suitability for a sport or certain occupations, estimating cardiovascular risk and determining risk for various medical procedures.²

Blood pressure measurements are also obtained routinely when following a hypertensive patient to assist with tailoring of medications and treatment of hypertension. Finally, blood pressure measurements are an integral part of identifying if a patient is in potential or actual clinical deterioration.²

Two methods for measuring a blood pressure exist, the direct and indirect method. The direct method is the criterion standard and consists of using an intra-arterial catheter to obtain a measurement. This method, however, is not practical due to its invasiveness and its inability to be applied to large groups of asymptomatic individuals for hypertension screening.²

Therefore, the indirect (noninvasive) method is typically used. The indirect method involves collapsing the artery with an external cuff, providing an inexpensive and easily reproducible way to measure blood pressure. The indirect method can be performed using a manual cuff and sphygmomanometer or with an automated oscillometric device. The manual method requires auscultation of the blood pressure, whereas the automated system depends on oscillometric devices.²

With manual blood pressure measurements, both observer and methodological errors can occur. Observer errors include digit preferences, inattention, overly rapid cuff deflation, and hearing deficits, while methodological errors include not accounting for beat-to-beat variations in the pulses and sequential rather than simultaneous comparisons.³
Automated oscillometric devices remove the observer errors that can occur with manual measurements but are not without faults. The inaccuracy of the oscillometric devices has been criticized, and some concern exists that using these devices in certain populations, such as hypertensive, trauma, or cardiac arrhythmia patients, can lead to inappropriate management.\[4\]

For example, in one study, mean systolic and diastolic blood pressures were significantly greater using a mercury manometer than automated oscillometric techniques.\[5\]

These findings have important clinical implications, as the oscillometric techniques may falsely indicate that a patient treated for hypertension is now normotensive and requires no further medication adjustment. Regardless of these inaccuracies, automated oscillometric devices are used more frequently and appear to be sufficiently accurate for most clinical uses. Furthermore, automated devices may give more accurate readings in the setting of patients with the syndrome of white-coat hypertension.\[6\]

1.3.2 Hypertension:

Hypertension is one of the most common worldwide diseases afflicting humans and is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. Despite extensive research over the past several decades, the etiology of most cases of adult hypertension is still unknown, and control of blood pressure is suboptimal in the general population. Due to the associated morbidity and mortality and cost to society, preventing and treating hypertension is an important public health challenge. Fortunately, recent advances and trials in hypertension research are leading to an increased understanding of the pathophysiology of hypertension and the promise for novel pharmacologic and interventional treatments for this widespread disease.\[7\]

According to the American Heart Association (AHA), approximately 75 million adults in the United States are affected by hypertension, which is defined as a
systolic blood pressure (SBP) of 140 mm Hg or more or a diastolic blood pressure (DBP) of 90 mm Hg or more or taking antihypertensive medication.\[7\]

Substantial improvements have been made with regard to enhancing awareness and treatment of hypertension. However, a National Health Examination Survey (NHANES) spanning 2005-2006 showed that 29% of US adults 18 years of age and older were hypertensive; 7% of hypertensive adults had never been told that they had hypertension.\[7\]

Furthermore, of those with high blood pressure (BP), 78% were aware they were hypertensive, 68% were being treated with antihypertensive agents, and only 64% of treated individuals had controlled hypertension. In addition, data from NHANES 1999-2006 estimated that 30% of adults 20 years of age and older have prehypertension, defined as an untreated SBP of 120-139 mm Hg or untreated DBP of 80-89 mmHg.\[7\]

Data from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), which was released in 2003, were relatively similar to the NHANES data. The JNC 7 noted that approximately 30% of adults were unaware of their hypertension; up to 40% of people with hypertension were not receiving treatment; and, of those treated, up to 67% did not have their BP controlled to less than 140/90 mm Hg.\[7\]

Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), stroke (the third leading cause), congestive heart failure, end-stage renal disease, and peripheral vascular disease. Therefore, health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.\[7\]

Most individuals diagnosed with hypertension will have increasing blood pressure (BP) as they age. Untreated hypertension is notorious for increasing the risk of mortality and is often described as a silent killer. Mild to moderate hypertension, if
left untreated, may be associated with a risk of atherosclerotic disease in 30% of people and organ damage in 50% of people within 8-10 years after onset.\(^7\)

Death from ischemic heart disease or stroke increases progressively as BP increases. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP above 115/75 mm Hg, the mortality rate for both ischemic heart disease and stroke doubles.\(^8\)

In the Framingham Heart Study, the age-adjusted risk of congestive heart failure was 2.3 times higher in men and 3 times higher in women when the highest BP was compared to the lowest BP.\(^9\)

Multiple Risk Factor Intervention Trial (MRFIT) data showed that the relative risk for coronary artery disease mortality was 2.3 to 6.9 times higher for persons with mild to severe hypertension than it was for persons with normal BP.\(^{10}\)

The relative risk for stroke ranged from 3.6 to 19.2. The population-attributable risk percentage for coronary artery disease varied from 2.3 to 25.6%, whereas the population-attributable risk for stroke ranged from 6.8–40%.\(^{10}\)

The Framingham Heart Study found a 72% increase in the risk of all-cause death and a 57% increase in the risk of any cardiovascular event in patients with hypertension who were also diagnosed with diabetes mellitus.\(^{11}\)

Nephrosclerosis is one of the possible complications of long-standing hypertension. The risk of hypertension-induced end-stage renal disease is higher in black patients, even when blood pressure is under good control. Furthermore, patients with diabetic nephropathy who are hypertensive are also at high risk for developing end-stage renal disease.\(^{11}\)

1.3.2.1 Signs and symptoms of hypertension:

The 2013 joint European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines recommend that ambulatory blood-pressure monitoring (ABPM) be incorporated into the assessment of cardiovascular risk factors and hypertension.\(^{11}\)
Following the documentation of hypertension, which is confirmed after an elevated blood pressure (BP) on at least 3 separate occasions (based on the average of 2 or more readings taken at each of ≥2 follow-up visits after initial screening), a detailed history should extract the following information:

- Extent of end-organ damage (e.g., heart, brain, kidneys, eyes)
- Assessment of patients’ cardiovascular risk status
- Exclusion of secondary causes of hypertension

Patients may have undiagnosed hypertension for years without having had their BP checked. Therefore, a careful history of end-organ damage should be obtained. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identifies the following as targets of end-organ damage:

- Heart: left ventricular hypertrophy, angina/previous myocardial infarction, previous coronary revascularization, and heart failure
- Brain: stroke or transient ischemic attack, dementia
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

The historical and physical findings that suggest the possibility of secondary hypertension are a history of known renal disease, abdominal masses, anemia, and urochrome pigmentation. A history of sweating, labile hypertension, and palpitations suggests the diagnosis of pheochromocytoma. A history of cold or heat tolerance, sweating, lack of energy, and bradycardia or tachycardia may indicate hypothyroidism or hyperthyroidism. A history of obstructive sleep apnea may be noted. A history of weakness suggests hyperaldosteronism. Kidney stones raise the possibility of hyperparathyroidism.\(^\text{[12]}\)
1.3.2.2 Classification of Hypertension:

1.3.2.2.1 Primary Hypertension:

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure but the genetic basis of hypertension is still poorly understood. Several environmental factors influence blood pressure. Lifestyle factors that lower blood pressure include reduced dietary salt intake, increased consumption of fruits and low fat products, exercise, weight loss and reduced alcohol intake. Stress appears to play a minor role with specific relaxation techniques not supported by the evidence. The possible role of other factors such as caffeine consumption, and vitamin D deficiency are less clear cut. Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Recent studies have also implicated events in early life (for example low birth weight, maternal smoking and lack of breast feeding) as risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain obscure.\(^{[12]}\)

1.3.2.2.2 Secondary Hypertension:

Secondary hypertension results from an identifiable cause. Renal disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions as: hyperthyroidism, hypothyroidism, acromegaly, Conn's syndrome or hyperaldosteronism, hyperparathyroidism and pheochromocytoma.\(^{[12]}\)
### 1.3.2.3 Pathophysiology of Hypertension:

In most people with established essential (primary) hypertension, increased resistance to blood flow (total peripheral resistance) accounting for the high pressure while cardiac output remains normal. There is evidence that some younger people with prehypertension or 'borderline hypertension' have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension. These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age. Whether this pattern is typical of all people who ultimately develop hypertension is disputed. The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction in the number or density of capillaries may also contribute. Hypertension is also associated with decreased peripheral venous compliance which may increase venous return, increase cardiac preload and, ultimately, cause diastolic dysfunction. Whether increased active vasoconstriction plays a role in established essential hypertension is unclear.[13]

Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low a condition termed isolated systolic hypertension. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure.[14]

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either disturbances in renal salt and water handling (particularly abnormalities in the intrarenal renin-angiotensin system) and/or abnormalities of the system. These mechanisms are not
mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension.[12]

1.3.2.4 Management of Hypertension:

1.3.2.4.1 Lifestyle modifications:

The first line of treatment for hypertension is identical to the recommended preventive lifestyle changes and includes dietary changes, physical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. Their potential effectiveness is similar to using a single medication. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication.[16]

Dietary change such as a low sodium diet is beneficial. A long term (more than 4 weeks) low sodium diet in Caucasians is effective in reducing blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet, a diet rich in nuts, whole grains, fish, poultry, fruits and vegetables lowers blood pressure. A major feature of the plan is limiting intake of sodium although the diet is also rich in potassium, magnesium, calcium, as well as protein. Different programs aimed to reduce psychological stress such as bio feed, relaxation or transcendental meditation may be reasonable add-ons to other treatment to reduce hypertension. However, overall efficacy is not greater than health education, with evidence being generally of low quality.[16]

1.3.2.4.2 Medications:

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Use should take into account the person's cardiovascular risk (including risk of myocardial infarction and stroke) as well as blood pressure readings, in order to gain a more accurate picture of the
person's cardiovascular profile. Evidence in those with mild hypertension (SBP less than 160 mmHg and/or DBP less than 100 mmHg) and no other health problems does not support a reduction in the risk of death or rate of health complications from medication treatment. Medications are not recommended for people with prehypertension or high normal blood pressure.[16]

The best first line agent is disputed. The Cochrane collaboration, World Health Organization and the United States guidelines supports low dose thiazide-based diuretic as first line treatment. The UK guidelines emphasise calcium channel blockers (CCB) in preference for people over the age of 55 years or if of African or Caribbean family origin, with angiotensin converting enzyme inhibitors (ACE-I) used first line for younger people. In Japan starting with any one of six classes of medications including: CCB, ACEI/ARB, thiazide diuretics, beta-blockers, and alpha-blockers are deemed reasonable, while in Canada and Europe all of these but alpha-blockers are recommended as options.[17]

Drug combinations the majority of people require more than one drug to control their hypertension. In those with a systolic blood pressure greater than 160 mmHg or a diastolic blood pressure greater than 100 mmHg the American Heart Association recommends starting a thiazide and an ACEI, ARB or CCB. An ACEI and CCB combination can be used as well.[17]

Unacceptable combinations are non-dihydropyridine calcium blockers (such as verapamil or diltiazem) and beta-blockers, dual renin–angiotensin system blockade (e.g. angiotensin converting enzyme inhibitor + angiotensin receptor blocker), renin–angiotensin system blockers and beta-blockers, beta-blockers and centrally acting agents. Combinations of an ACE-inhibitor or angiotensin II–receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known colloquially as a "triple whammy" in the Australian health industry. Tablets containing fixed combinations of two classes of drugs are
available and while convenient for the people, may be best reserved for those who have been established on the individual components.\textsuperscript{[17]}

Elderly treating moderate to severe hypertension decreases death rates and cardiovascular morbidity and mortality in people aged 60 and older. There are limited studies of people over 80 years old but a recent review concluded that antihypertensive treatment reduced cardiovascular deaths and disease, but did not significantly reduce total death rates. The recommended BP goal is advised as $<150/90$ mm Hg with thiazide diuretic, CCB, ACEI, or ARB being the first line medication in the United States, and in the revised UK guidelines calcium-channel blockers are advocated as first line with targets of clinic readings $<150/90$, or $<145/85$ on ambulatory or home blood pressure monitoring.\textsuperscript{[18]}

Resistant hypertension is defined as hypertension that remains above goal blood pressure in spite of concurrent use of three antihypertensive agents belonging to different antihypertensive drug classes. Guidelines for it have been published in the UK and US. It has been proposed that a proportion of resistant hypertension may be the result of chronic high activity of the autonomic nervous system; this concept is known as "neurogenic hypertension".\textsuperscript{[19]}

1.3.2.5 Complications of Hypertension:
Complications of hypertension are clinical outcomes that result from persistent elevation of blood pressure. Hypertension is a risk factor for all clinical manifestations of atherosclerosis since it is a risk factor for atherosclerosis itself. It is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease and peripheral arterial disease. It is the most important risk factor for cardiovascular morbidity and mortality in industrialized countries.\textsuperscript{[20]}

1.3.2.5.1 Complications affecting the heart:
Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, diastolic dysfunction, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and micro vascular disease, and cardiac arrhythmias. Individuals with left ventricular hypertrophy are
at increased risk for stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. Left ventricular hypertrophy is seen in 25% of the hypertensive patients and can easily be diagnosed by using echocardiography. Underlying mechanisms of hypertensive left ventricular hypertrophy are of 2 types: mechanical, mainly leading to myocyte hypertrophy; neuro-hormonal, mainly resulting in a fibroblastic proliferation.\textsuperscript{[20]}

Abnormalities of diastolic function, ranging from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Patients with diastolic heart failure have a preserved ejection fraction, which is a measure of systolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia.\textsuperscript{[21]}

1.3.2.5.2 Complications affecting the brain:
Hypertension is an important risk factor for brain infarction and hemorrhage. Approximately 85% of strokes are due to infarction and the remainder is due to hemorrhage, either intracerebral hemorrhage or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years. Treatment of hypertension convincingly decreases the incidence of both ischemic and hemorrhagic strokes.\textsuperscript{[21]}

Hypertension is also associated with impaired cognition in an aging population, Hypertension-related cognitive impairment and dementia may be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.\textsuperscript{[22]}

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed auto
regulation of blood flow. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudo tumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.[22]

1.3.2.5.3 Complications affecting the eye:

Hypertensive retinopathy is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure. The retinal circulation undergoes a series of pathophysiological changes in response to elevated blood pressure. In the initial, vasoconstrictive stage, there is vasospasm and an increase in retinal arteriolar tone owing to local auto regulatory mechanisms. This stage is seen clinically as a generalized narrowing of the retinal arterioles. Persistently elevated blood pressure leads to intimal thickening, hyperplasia of the media wall, and hyaline degeneration in the subsequent, sclerotic, stage. This stage corresponds to more severe generalized and focal areas of arteriolar narrowing, widening and accentuation of the central light reflex.[23]

These changes are manifested in the retina as micro aneurysms, hemorrhages, hard exudates, and cotton-wool spots. Swelling of the optic disk may occur at this time and usually indicates severely elevated blood pressure (i.e., malignant hypertension). Because better methods for the control of blood pressure are now available in the general population, malignant hypertension is rarely seen. In contrast, other retinal vascular complications of hypertension, such as macroaneurysms and branch-vein occlusions, are not uncommon in patients with chronically elevated blood pressure. These stages of hypertensive retinopathy however, may not be sequential.[23]
1.3.2.5.4 Complications affecting the kidneys:

Hypertension is a risk factor for renal injury and ESRD. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure.\[^{23}\]

The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and post glomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in necrosis.\[^{24}\]

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio > 300 mg/g) or macroalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and for cardiovascular disease.\[^{24}\]

1.3.3 Urea:

Urea or carbamide is an organic compound with the chemical formula CO(NH2)2. The molecule has two —NH2 groups joined by a carbonyl (C=O) group. Urea serves an important role in the metabolism of nitrogen-containing compounds by animals and is the main nitrogen-containing substance in the urine of mammals. It is solid, colorless, and odorless (although the ammonia that it gives off in the presence of water, including water vapor in the air, has a strong odor). It is highly soluble in water and non-toxic. Dissolved in water, it is neither acidic nor alkaline. The body uses it in many processes, the most notable one being nitrogen excretion. Urea is widely used in fertilizers as a convenient source of nitrogen. Urea
is also an important raw material for the chemical industry. The synthesis of this organic compound by Friedrich Wöhler in 1828 from an inorganic precursor was an important milestone in the development of organic chemistry, as it showed for the first time that a molecule found in living organisms could be synthesized in the lab without biological starting materials (thus contradicting a theory widely prevalent at one time, called vitalism). The terms urea and carbamide are also used for a class of chemical compounds sharing the same functional group \( RR'N—CO—NRR' \), namely a carbonyl group attached to two organic amine residues. Examples include carbamide peroxide, allantoin, and hydration. Ureas are closely related to biurets and related in structure to amides, carbamide, carbodiimides, and thiocarbamides.[25]

1.3.3.1 Physiology of Urea:

Urea is synthesized in the body of many organisms as part of the urea cycle, either from the oxidation of amino acids or from ammonia. In this cycle, amino groups donated by ammonia and L-aspartate are converted to urea, while L-ornithine, citrulline, L-argininosuccinate, and L-arginine act as intermediates. Urea production occurs in the liver and is regulated by N-acetyl glutamate. Urea is found dissolved in blood (in the reference range of 2.5 to 6.7 mmol/liter) and is excreted by the kidney as a component of urine. In addition, a small amount of urea is excreted (along with sodium chloride and water) in sweat. Amino acids from ingested food that are not used for the synthesis of proteins and other biological substances are oxidized by the body, yielding urea and carbon dioxide, as an alternative source of energy. The oxidation pathway starts with the removal of the amino group by a transaminase; the amino group is then fed into the urea cycle. Ammonia (NH3) is another common byproduct of the metabolism of nitrogenous compounds. Ammonia is smaller, more volatile and more mobile than urea. If allowed to accumulate, ammonia
would raise the pH in cells to toxic levels. Therefore many organisms convert ammonia to urea, even though this synthesis has a net energy cost. Being practically neutral and highly soluble in water, urea is a safe vehicle for the body to transport and excrete excess nitrogen. In water, the amine groups undergo slow displacement by water molecules, producing ammonia and carbonate anion. For this reason, old, stale urine has a stronger odor than fresh urine. The handling of urea by the kidneys is a vital part of human metabolism. Besides its role as carrier of waste nitrogen, urea also plays a role in the countercurrent exchange system of the nephrons, that allows for re-absorption of water and critical ions from the excreted urine. Urea is reabsorbed in the inner medullary collecting ducts of the nephrons, thus raising the osmolarity in the medullary interstitium surrounding the thin ascending limb of the loop of Henle, which in turn causes water to be reabsorbed. By action of the urea transporter 2, some of this reabsorbed urea will eventually flow back into the thin ascending limb of the tubule, through the collecting ducts, and into the excreted urine. This mechanism, which is controlled by the antidiuretic hormone, allows the body to create hyper osmotic urine, that has a higher concentration of dissolved substances than the blood plasma. This mechanism is important to prevent the loss of water, to maintain blood pressure, and to maintain a suitable concentration of sodium ions in the blood plasmas. The equivalent nitrogen content (in gram) of urea (in mmol) can be estimated by the conversion factor 0.028 g/mmol.[7] Furthermore, 1 gram of nitrogen is roughly equivalent to 6 grams of protein, and 1 gram of protein is roughly equivalent to 4 grams of muscle tissue. In situations such as muscle wasting, 1 mmol of excessive urea in the urine (as measured by urine volume in litters multiplied by urea concentration in mmol/l) roughly corresponds to a muscle loss of 0.67 gram. In aquatic organisms the most common form of nitrogen waste
is ammonia, whereas land-dwelling organisms convert the toxic ammonia to either urea or uric acid. Urea is found in the urine of mammals and amphibians, as well as some fish. Birds and saurian reptiles have a different form of nitrogen metabolism, that requires less water and leads to nitrogen excretion in the form of uric acid. It is noteworthy that tadpoles excrete ammonia but shift to urea production during metamorphosis. Despite the generalization above, the urea pathway has been documented not only in mammals and amphibians but in many other organisms as well, including birds, invertebrates, insects, plants, yeast, fungi, and even microorganisms.[26]

1.3.4 Albumin:
The albumins (formed from Latin: albumen "(egg) white; dried egg white") are a family of globular proteins, the most common of which is serum albumin. The albumin family consists of all proteins that are water-soluble, are moderately soluble in concentrated salt solutions, and experience heat denaturation. Albumins are commonly found in blood plasma, and are unique from other blood proteins in that they are not glycosylated. Substances containing albumins, such as egg white, are called albuminoids. A number of blood transport proteins are evolutionarily related, including serum albumin, alpha-fetoprotein, vitamin D-binding protein and afamin.[27]

1.3.4.1 Functions of Albumin:
Albumin is the main protein of human blood plasma.[28] It binds water, cations (such as Ca2+, Na+ and K+), fatty acids, hormones, bilirubin, thyroxin (T4) and pharmaceuticals (including barbiturates) - its main function is to regulate the colloidal osmotic pressure of blood. Alpha-fetoprotein (alpha-fetoglobulin) is a fetal plasma protein that binds various cations, fatty acids and bilirubin. Vitamin D-binding protein binds to
vitamin D and its metabolites, as well as to fatty acids. The biological role of afamin (alpha-albumin) has not yet been characterized.\[29\]

1.3.4.2 Structure of Albumin:
The 3D structure of human serum albumin has been determined by X-ray crystallography to a resolution of 2.5 Å.\[29\]

Albumin comprises three homologous domains that assemble to form a heart-shaped molecule.\[29\] Each domain is a product of two subdomains that possess common structural motifs.\[29\] The principal regions of ligand binding to human serum albumin are located in hydrophobic cavities in subdomains IIA and IIIA, which exhibit similar chemistry. Structurally, the serum albumins are similar, each domain containing five or six internal disulfide bonds.\[29\]

1.3.4.3 Types of Albumin:
1.3.4.3 Serum albumin:
Serum albumin is the most abundant blood plasma protein and is produced in the liver and forms a large proportion of all plasma protein. The human version is human serum albumin, and it normally constitutes about 50% of human plasma protein.\[29\]

Serum albumins are important in regulating blood volume by maintaining the oncotic pressure (also known as colloid osmotic pressure) of the blood compartment.\[29\] They also serve as carriers for molecules of low water solubility this way isolating their hydrophobic nature, including lipid soluble hormones, bile salts, unconjugated bilirubin, free fatty acids (Apo protein), calcium, ions (transferrin), and some drugs like warfarin, phenobutazone, clofibrate & phenytoin. For this reason, it's sometimes referred as a molecular "taxi". Competition between drugs for albumin binding sites may cause drug interaction by increasing the free fraction of one of the drugs, thereby affecting potency.\[29\]

Specific types include:
-human serum albumin

-bovine serum albumin (cattle serum albumin) or BSA, often used in medical and molecular biology labs.\[29\]

Low albumin (hypoalbuminemia) may be caused by liver disease, nephrotic syndrome, burns, protein-losing enteropathy, malabsorption, malnutrition, late pregnancy, artefact, and malignancy.\[29\]

High albumin (hyperalbuminemia) is almost always caused by dehydration. In some cases of retinol (Vitamin A) deficiency, the albumin level can be elevated to high-normal values (e.g., 4.9 g/dL). This is because retinol causes cells to swell with water (this is also the reason too much Vitamin A is toxic).\[29\] In lab experiments it has been shown that All-trans retinoic acid down regulates human albumin production.\[29\]

Normal range of human serum albumin in adults (> 3 years old) is 3.5 to 5 g/dL. For children less than three years of age, the normal range is broader, 2.9-5.5 g/dL.\[29\]

Albumin binds to the cell surface receptor Albondin.\[29\]

Other types include the storage protein ovalbumin in egg white, and different storage albumins in the seeds of some plants.\[29\]

Note that the protein 'albumin' is spelled with an "i", while "albumen" with an "e", is the white of an egg, which contains (among other things) several dozen types of albumin (with an 'i'), mostly ovalbumin.\[29\]

1.3.4.4 Medical uses of Albumin:

For patients with low blood volume, there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as normal saline, or that albumin reduces mortality in patients with burns and low albumin levels. Therefore, the Cochrane Collaboration recommends that it not be used, except in clinical trials.\[30\]
1.3.5. Previous studies:

Bulpitt et al\textsuperscript{[31]} addressed that annual increase in plasma urea was measured in 253 hypertensive patients. On average there was a significant increase in plasma urea with time which did not depend on the sex of the patient or the type of hypertension. It did, however, depend on the initial level of plasma urea. A table giving the upper limits for expected annual increment may prove useful in clinical assessment. The relation between plasma urea and presenting blood pressure and age was examined in 1217 patients seen at the Hammersmith Hospital hypertension clinic from 1952 to 1967. The plasma urea was significantly related to both age and diastolic and systolic blood pressure. It was higher in men than in women up to 60 years of age, but not above that age, and it increased with presenting mean blood pressure in both sexes, but the increase was greater in men. There was a quadratic relation between age and plasma urea in both men and women. In both sexes the plasma urea increased between the ages of 60 and 80 years old.\textsuperscript{[31]}

Peter et al\textsuperscript{[32]} reported that increase blood urea and serum creatinine measured in 10,940 persons for 10 years in a community-based, randomized, controlled trial of treatment for hypertension. Participants were randomized to one of two treatment groups, stepped care and referred care. The primary end point of the study was all-cause mortality, with morbid events involving the heart, brain, and kidney as secondary end points. Loss of renal function, ascertained by a change in serum creatinine, was among these secondary events. Baseline serum creatinine concentration had a significant prognostic value for 8-year mortality. For persons with a serum creatinine concentration greater than or equal to 1.7 mg/dl, 8-year mortality was more than three times that of all other participants. The estimated 10-year incidence of substantial decline in renal function was 21.7/1,000 in the stepped-care group and 24.6/1,000 in
the referred-care group. Among persons with a baseline serum creatinine level between 1.5 and 1.7 mg/dl, the 10-year incidence of decline was 113.3/1,000 (stepped care) and 226.6/1,000 (referred care) (p less than 0.01). The incidence of decline in renal function was greater in men, blacks, and older adults, as well as in those with higher entry diastolic blood pressure. Among persons with a baseline serum creatinine level greater than or equal to 1.7 mg/dl, serum creatinine concentration declined by 25% or more in 28.6% of stepped-care and 25.2% of referred-care participants. Although the incidence of clinically significant hyper creatininemia in a hypertensive population is low, an elevated serum creatinine concentration is a very potent independent risk factor for mortality. The slightly lower rate of development of hyper creatininemia and the higher rate of improvement in stepped-care compared with referred-care participants is consistent with the belief that aggressive treatment of hypertension may reduce renal damage and the associated increased risk of death.\[32\\]

Dr. Nagah addressed\[33\\] Serum Creatinine and serum albumin in hypertensive patients showed significant increase over control Mean and SD (141.3 ± 39, 52.4 ± 18) and (5.06 ± 7.7, 3.70 ± 5.7). Proteinuria was found in hypertensive patients. Hypertensive individuals might be in greater risk of developing renal disease. So reduction of blood pressure is advisable.\[33\\]
1.4 Objectives:

1.4.1 General objective:
To assess plasma urea and albumin levels in Sudanese hypertensive patients.

1.4.2 Specific objectives:
- To compare plasma urea and albumin levels between hypertensive patients and non-hypertensive.
- To correlate between plasma urea and albumin with duration of hypertension.
CHAPTER TWO
Materials and Methods

2.1 Materials:

2.1.1 Study design:
This is a quantitative, descriptive, analytic, cross-sectional and hospital-based study.

2.1.2 Study area and period:
This study was conducted in Khartoum state, capital and central of Sudan country. Patients enrolled in this study were come to refer clinic of Aldesogi Specialized Hospital, during the period from March 2014 to July 2014.

2.1.3 Study population and sample size:
Population of this study was categorized into a study group of 50 hypertensive patients who attended Aldesogi Specialized hospital and a control group of 30 healthy subjects (non hypertensive).

2.1.4 Ethical consideration:
Firstly the permission of this study was obtained from Medical directors of Aldesogi Specialized Hospital, then all participants were told about the research aims and benefits during interview and all of them were agreed to participate in addition to all samples were taken from participants after their agreement and filling the questionnaire.

2.1.5 Data collection and clinical examination:
Clinical data for every patient was collected by questionnaire using refer card for patient while clinical examinations done by clinicians in above mentioned hospital.

2.1.6 Inclusion criteria:
Sudanese patients with hypertension where included as a test group and healthy subjects as control.
2.1.7 Exclusion criteria:
Patients with renal diseases.

2.1.8 Sample collection:
Blood sample 3ml were collected from subjects of study group after fulfillments of questionnaire as well as control group, using disposable syringe and sprit for sterilization the area of collection. Collected blood was drawn in heparin containers and gently mixed with anticoagulant. The sample in heparin containers was separated by centrifuged it at 3000 rpm for 5 min. Hemolized and lipamic samples were rejected and excluded from the study. Obtained plasma was tested for urea and albumin using biosystem chemical analyzer.

2.2 Methods

2.2.1 Measurement of Urea:
Enzymatic, colorimetric, endpoint-Berthelot method.

2.2.1.1 Principle:
Urea catalysis the conversion of urea to ammonia. In modified Berthelot reaction the ammonium ions react with a mixture of salicylate, hypochlorite. And nitroprusside to yield a blue –green dye (indophenols). The intensity of this dye is proportional to the concentration of urea in the sample.

2.2.1.2 Sample:
Three ml of venous blood was collected using sterile disposable syringes. Poured into heparin containers, then centrifuged at 3000 rpm for 5 minutes and obtained plasma was not need to be diluted before assaying.

2.2.1.3 Reagent content:
Reagent1 120mmol/l sodium salicylate 60mmol/l, sodium nitroprusside 5mmol/l, EDTA 1mmol/l and urease 5KU/l. Reagent2 120mmol/l sodium hydroxide 400mmol/l, sodium hypochlorite 10mmol/l. Urea standard 80mg/dl or 13.3mmol/l. The reagents and standard were ready for used.
2.2.1.4 Procedure:
The sample in heparin container was separated by centrifuged it at 3000 rpm for 5 min and the test was completed as follow:

<table>
<thead>
<tr>
<th></th>
<th>Blank</th>
<th>Standard</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample (ml)</td>
<td>_</td>
<td>_</td>
<td>0.01</td>
</tr>
<tr>
<td>Standard (80mg/dl) (ml)</td>
<td>_</td>
<td>0.01</td>
<td>_</td>
</tr>
<tr>
<td>Reagent1 (ml)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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</tbody>
</table>

Mixed and incubated for 5 minutes at 20-25°C. Or 3 minutes at 37°C

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</thead>
<tbody>
<tr>
<td>Reagent2 (ml)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Mixed and incubated for 10 min at 20-25°C or 5 min at 37°C, the absorbance of the sample and standard were measured against reagent blank at wavelength 520nm.

2.2.1.5 Calculation:

\[
\text{Urea (mg/dL)} = \frac{\text{Abs of } T}{\text{Abs of } std} \times \text{con of std}
\]

Urea (g/24 urine) = mg/dl volume of 24hr urine.

To convert mg/dl to mmol/l, divide 6.01

2.2.1.6 Reference value:

- Serum= 10-50mg/dl or 1.66-8.30mmol/l.
- Urine= 20-35g/l or 3.33-5.83mol/l.\(^{49}\)

2.2.2 Measurement of Albumin:

Bromocresol green, chemical, colorimetric-end point method.

2.2.2.1 Principle:
The assay is based on the reaction of albumin with Bromocresol green in acid medium forming complex that can be measured by spectrophotometry.

2.2.2.2 Reagent content:

Reagent (A), acetate buffer 100 mmol/l, Bromocresol green 0.27 mmol/l, detergent, PH4.1 .Reagent (S) albumin standard bovine albumin concentration 49.1 g/l.
2.2.2.3 Procedure:
The sample in heparin container was separated by centrifuged it at 3000 rpm for 5 min and the test was done as follow:
1-Assay conditions:
Wavelength………………………630nm
Cuvette…………………………….1 cm. light path
Temperature……………………….37°C
2-Adjust the instrument to zero with distilled water
3-Pepette into acuvette:

<table>
<thead>
<tr>
<th></th>
<th>Blank</th>
<th>Standard</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent (A)(ml)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>(4.91g/dl)(µl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sample(µl)</td>
<td></td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

4- Mixed thoroughly and let stand the tubes for 1 minute at room temperature
5- Read the absorbance (A) of the standard and sample against blank.

2.2.2.4 Calculation:

\[
\text{Albumin g/l} = \frac{\Delta Abs \ of \ T}{\Delta Abs \ of \ std} \times \text{con of std}
\]

2.2.2.5 Reference range of A:

Serum or plasma:
- Newborn, 2 to 4 days = 28-44 g/l
- 4 days to 14 days….. = 38-54 g/l
- Adult………………….. = 35-50 g/l
- > 60years……………..= 34-48 g/l.\cite{49}

2.3 Data analysis:
Data was analyzed by independent t-test and person correlation by the programmed computer (SPSS).
3. Results:
This study was conducted on 50 patients with hypertension as test group and 30 control groups (healthy volunteers). Age and gender of the test group was match with control group. In the present study, male account 62.5% (n=32) from the test and 73.3% (n=22) from control group, while female account 37.5% (n=18) from the test and 26.7% (n=8) from control group.
Table (3-1) showed significant difference between the mean of urea in mg/dl in study group patients and control group. (42±6.3 mg/dl) versus (28±1.0) (P=0.000 significant at ≤0.05) and also significant difference between the mean of albumin in g/dl in study group patients and control group. (4.83±0.39 g/dl) versus (3.96±0.51 g/dl) (P=0.000 significant at ≤0.05).
Figure (3-3) A scatter plot showed the moderate positive correlation between urea and duration of hypertension. (r=0.579, P=0.000)
Figure (3-4) A scatter plot showed the moderate positive correlation between albumin and duration of hypertension. (r=0.532, P=0.000)
Table (3-1): Comparison of plasma urea (mg/dl) and albumin (g/dl) between hypertensive patients and non-hypertensive.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test group (n=50)</th>
<th>Control group (n=30)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>42 ± 6.3</td>
<td>28 ± 1.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.83 ± 0.39</td>
<td>3.96 ± 0.51</td>
<td>0.000</td>
</tr>
</tbody>
</table>

- The table shows the mean ± Std. deviation and probability (P).
- Independent t-test was used for comparison.
- P-Value ≤ 0.05 is considered significant.
Fig (3-1): A scatter plot showed the relationship between urea (mg/dl) and duration of hypertension (years), ($r=0.579$, $P=0.000$).
**Fig (3-2):** A scatter plot showed the relationship between albumin (g/dl) and duration of hypertension (years), \((r=0.532, P=0.000)\).
CHAPTER FOUR
Discussion, Conclusion and Recommendations

4.1 Discussion:
In this study there is significant increase in the mean of urea level (mg/dl) of the test group when compared with control group (P= 0.000), this result agree with the result observed by Bulpitt et al$^{31}$ whom reported that there was a significant increase in plasma urea in hypertensive patients because hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and post glomerular structures.

Also there is significant increase in the mean of albumin level (g/dl) of the test group when compared with control group (P= 0.000), this result agree with the result observed by Nagah et al$^{33}$ whom reported that there was a significant increase in serum albumin Mean and SD(5.06 ± 7.7) for cases( 3.70 ± 5.7) for controls. High blood pressure also increases the stiffness of the arteries that feed the other members. There may be other consequences if deprived of such members of the oxygen and nutrients they need. The narrowing of the arteries that feed the kidneys can cause disruption in the functions of the kidneys. When less than inflow of blood to the kidneys, the body secretes a hormone called resonance, which begins to make a series of chemical reactions that make increasingly intransigent, the result is high blood pressure that leads to kidney damage, which consequently lead to more high blood pressure.

The present data demonstrated that there is a significant moderate positive correlation between urea (mg/dl) and duration of hypertension disease (r=0.579, P= 0.000), this result agree with the result observed by Peteret al$^{32}$ whom said that there was a quadratic relation between the period of hypertension and plasma urea, serum creatinine.

Also there is a significant moderate positive correlation between albumin (g/dl) and duration of hypertension (r= 0.532, P= 0.000).
4.2 Conclusion:

- Plasma levels of urea are significantly raised in hypertensive patients.
- Plasma levels of albumin are significantly raised in hypertensive patients.
- There is a significant positive correlation between urea and long duration of hypertension disease.
- There is a significant positive correlation between albumin and duration of hypertension disease.
4.3 Recommendations:

From the results of this study, it is recommended that:

- Renal function tests should be checked regularly to hypertensive patients, especially in those with prolonged period of the disease.
- Serum albumin and urine micro albumin should be checked regularly in hypertensive patients, especially in those with prolonged period of the disease.
- Health education, diet control and exercise are important factors to achieve good control of hypertension.
References:


4- Landgraf J, Wishner SH, Kloner RA. Comparison of automated oscillometric versus auscultatory blood pressure measurement. *Am J Cardiol*. Aug 1 2010; 106(3):386-8.)


18-Calhoun DA, Jones D, Textor S et al. (June 2008). "Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American


Wright AF, Rudan I, Hastie ND, Campbell H (2010) A ‘complexity’


