HYPERURICEMIA AMONG PATIENTS WITH HYPERTENSION AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

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A thesis submitted in part fulfillment for the award of the degree of Master of Medicine in Internal Medicine of Moi University

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Declaration

Declaration by the Candidate

This thesis is my original work and has not been presented for a degree or any academic credit in any other University or examining body. No part of this thesis may be reproduced without the prior written permission of the author or Moi University.

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Dedication

I dedicate this work to my dear parents Mr. and Mrs. Japheth Mibey for their immense effort and dedication in educating me; to my husband Barry for his love and support and to our sons George and Renley for they are a gift of joy in my life. Finally to all my teachers who over the years have molded me to become a better person and doctor.

Abstract

Hyperuricemia among Patients with Hypertension at Moi Teaching and Referral Hospital, Eldoret, Kenya.

Background: Hypertension contributes to 9.4 million of the 17 million global cardiovascular diseases annually. Uric acid, a mediator of high blood pressure is an inexpensive easy-to-obtain indicator of cardiovascular risk (stoke, myocardial infarction and renal disease). Clinical characteristics associated with hyperuricemia include: Diabetes, dyslipidemia, hypertension, renal failure, obesity, age, gender and diuretic use. This study was conducted to determine the prevalence and risk factors of hyperuricemia among patients with hypertension in Moi teaching and Referral Hospital.

Objective: To determine the prevalence of hyperuricemia and associated clinical characteristics among patients with hypertension at Moi Teaching and Referral Hospital.

Methods: This cross sectional study conducted at MTRH medical outpatients' clinic enrolled randomly patients with hypertension. Clinical (age, gender, stroke, body mass index, antihypertensive drugs and duration of illness) and laboratory (fasting lipid profile, blood sugar, uric acid and serum creatinine) data were collected. Data were keyed into Microsoft excel database and analyzed using STATA version 13 special edition, where descriptive statistics were summarized in tables and graphs. Significance tests such as the two-sample t-test for comparison of two normally distributed continuous variables, two-sample Wilcoxon rank sum test for non-Gaussian distributed continuous variables, and Pearson's Chi Square test for categorical variables were used.

Results: A total of 275 patients were enrolled; 182 (66% female). Mean age 54±12.5 years; mean Body Mass index 28.9±4.9 Kg/m^2 and median duration of illness 6months. Prevalence of hyperuricemia was 44 %(121/275): Males had a prevalence of 37.6 % (35/93) and females of 47.3 %(86/182): A history of stroke were 29 (10.6%) and 42 (15.3%) had a history of diabetes. Most patients were on treatment for hypertension, 143 (52.4%) on diuretics, 154 (56.1%) were on calcium channel blockers, eighty four 30.6%, were using enalapril, 18.2% were on losartan. Thirty eight (13.8%), were on treatment for diabetes mellitus and 23 (8.4%) were on statins. Most patients had poor blood pressure control with more than 70% with Systolic Blood Pressure > 140 mm Hg, and > 50% had Diastolic Blood pressure>90 mm Hg. Dyslipidemia was prevalent among 248(90.2%), with majority 207 (75.3%) having elevated total cholesterol, 125 (45.5%) with elevated Low Density Lipoprotein. The median Glomerular Filtration Rate was 110.5 (IQR: 88.7, 122.7) ml/min per $1.73m^2$.There was a positive association between, high Body Mass Index (P=0.036), low Glomerular Filtration Rate (P<0.0001), dyslipidemia (p<0.0001) and hyperuricemia while use of calcium channel blocker and losartan was negatively associated.

Conclusion: There is a high prevalence of hyperuricemia among patients with hypertension. The risk factors associated with hyperuricemia were high Body Mass Index, dyslipidemia, low Glomerular Filtration Rate and use of losartan.

Recommendation: Screening for hyperuricemia should be done on patients with hypertension

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List of Abbreviations

ATP	Adenosine Triphosphate
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic Acid
EHT	Essential hypertension
HBP	High Blood Pressure
MTRH	Moi Teaching and Referral Hospital
RNA	Ribonucleic Acid
SBP	Systolic blood pressure
SPSS	Statistical Package for Social Science
UA	Uric Acid
URAT	Uric Acid Transporter
WHO	World Health Organization

Operational Definition of Terms

Systolic blood pressure:

This is the pressure in the arteries as the heart contracts and pumps blood forward into the arteries.

Diastolic blood pressure:

This is the arterial pressure during relaxation and dilatation of the ventricles of the heart when the ventricles fill with blood.

Hypertension

Based on the Eighth Joint National Committee (JNC 7) guidelines, any blood pressure measurement of ≥140/90 mmHg was considered uncontrolled blood pressure.

Known hypertensive patient

A known hypertensive patient was someone who reported history of hypertension, which was also confirmed from the patient's file.

Hyperuricemia

Defined as a plasma (or serum) urate concentration >405 umol/L (6.8 mg/dl).

Females>320umol/L (5.7mg/dl) and males >420umol/L (7mg/dl)

Lipid profile

The following figures were considered deranged, as per the current lipids management guidelines: Low Density Lipoprotein (LDL) >2.6mmol/l; Triglycerides >1.7mmol/l; Total Cholesterol >5.17mmol/l and HDL <1.29mmol/l for female, and <1.03mmol/l for male patients.

Body Mass Index (BMI)

This was calculated as weight in kg divided by height in m^2. The degree of obesity was classified based on National Institute of Health (NIH) cut offs as follows;

Underweight (BMI of<18.5); Normal (BMI of 18.5-25.0); Overweight (BMI of 25-30); Obese (BMI of >30)

Estimated Glomerular Filtration Rate (eGFR)

This was calculated using chronic kidney disease -Epidemiology Collaboration (CKD-EPI) formula which was preferred based on a local study done in MTRH that showed that it was superior to other equations for estimating eGFR. Although the patients were only classified as eGFR above 60ml/min/1.73m^2; 30-60ml/min/1.73m^2 and <30ml/min/1.73m^2, mean eGFR of >90 ml/min/1.73m^2 was considered high.

Chapter One: Introduction

1.1 Background information

Hypertension is currently the most common cardiovascular problem in Africa, and it is estimated that more than 20 million people are affected. In sub-Saharan Africa hypertensive end organ damage is a major cause of morbidity and mortality(WHO, 2013). The increasing prevalence is well reflected in the increase in cardiovascular disease mortalities, especially in developing countries where the rates of illiteracy are high and there is a drastic shift from increase in communicable diseases to non-communicable diseases(Alwan, 2011). Hypertension is a primary cause of haemorrhagic and atherothrombotic stroke, hypertensive heart disease, hypertensive nephrosclerosis, coronary artery disease(WHO, 2002).The reported prevalence of hypertension in Africa ranges from 25% to 35% in adults aged 25 to 64 years and increases with advancing age(WHO, 2013). In Kenya the prevalence of hypertension is 21%(Joshi et al., 2014)

Uric acid is the end product of the metabolism of purine compounds. With a (functional) pKa of about 5.75 in blood (5.35 in urine), the reaction; Uric acid <—> Urate- + H+, is shifted far to the right at the normal arterial pH of 7.40. As a result, most uric acid circulates as the urate anion. Thus, normal humans have serum urate concentrations approaching the theoretical limit of solubility of urate in serum (6.8 mg/dL) and regularly excrete urine that is supersaturated with respect to uric acid.UA is not typically ingested; it is produced in the liver from the degradation of dietary and endogenously synthesized purine compounds. Dietary intake appears to provide a significant source of urate precursors, as a purine-free formula diet reduces urinary excretion of uric acid by approximately 40 percent. The concept that uric acid (UA) may be involved in hypertension is not a new one. In fact, in a paper published in 1879 that originally described essential hypertension, Frederick Akbar Mohamed noted that many of his

subjects came from families with a history of gout. He hypothesized that the UA might be integral to the development of essential hypertension(Mahomed, 1879).Ten years later, this hypothesis reemerged when Haig proposed low-purine diets as a means to prevent hypertension and vascular disease(Haig, 1889).

The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption((Messerli, 1980). Hypertension also results in micro vascular disease, and this can lead to local tissue ischemia (Puig et al, 1999). In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis(Friedl, 1991)With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation. The finding that ischemia results in an increase in uric acid levels may also account for why uric acid is increased in preeclampsia(Many, 1996)and congestive heart failure.(Leyva et al., 1997) Other factors may also contribute to why uric acid is associated with hypertension, including alcohol abuse,(Ramsay, 1979)lead intoxication,(Sanchez-Fructuoso et al., 1996)obesity and insulin resistance,(Galvan et al., 1995)and diuretic use.

A Japanese study showed association between serum uric acid and incident hypertension and progressive increase in blood pressure even with normal range of serum uric acid. Their results indicated that SUA level is closely associated with an increased risk for hypertension and impaired fasting glucose or Type II diabetes(Nakanishi et al., 2003).

Evidence from a number of studies suggests that uric acid be added to the list of conventional risk factors of hypertension like obesity, age, renal disease, and diabetes mellitus (Brand et al.,1985(Brand, 1985; Chaves et al., 2007; Doring et al., 2008;

Forman, 2007); Hediger (2004); (Iu, 1990; Lee et al., 2006; Selby, 1990; Syamala, 2007; Taniguchi et al., 2001; Vitart et al., 2008)

Recent epidemiological studies support a link between uric acid and the onset of hypertension (Johnson, 2007). Researchers have been debating over the possible causal association of uric acid (UA) in cardiovascular diseases and vascular dysfunction. While some believe that elevated levels of UA act only as a prognostic marker, reflecting existing cardiovascular and metabolic conditions such as hypertension, insulin resistance, and type 2 diabetes, others consider it a causative factor, leading to cardiovascular diseases such as hypertension and atherosclerosis(Culleton, 1999).

Increase uric acid level can result from decrease in renal function. Children with chronic kidney disease and end stage renal disease (ESRD) may have a higher serum uric acid .Furthermore; up to 15% of the uric acid clearance is through the gastrointestinal tract. Bowel disease can increase serum uric acid(Daniel I Feig & Johnson, 2003). Medical products that can alter normal glomerular filtration rate such as loop and thiazide diuretics can cause hyperuricemia(Franse et al., 2000). Impairment of the efficiency of purine disposal pathway, poor purine recycling metabolism or excessive recycling pathway with excessive cell death or cell turn over will increase serum uric acid(Feig; Daniel I Feig, 2012).

Elevated SUA lowers endothelial nitric oxide levels, reducing neuronal nitric oxide synthase in the macula densa of the kidney and stimulates the rennin-angiotensin system. This mechanism was demonstrated in animal studies where rats developed high blood pressure in about 3 to 5 weeks after raised uric acid levels was induced by the administration of oxonic acid which is an inhibitor of Uricase (Mazzali et al., 2001)

Hyperuricemia is one of the important risk factor for CAD in patients with hypertension, it was significantly associated with cardiovascular events and mortality in these patients(Gustafsson & Unwin, 2013).

Uric acid was also associated with the presence of target organ damage in these patients(Francesca Viazzi et al., 2005) observed that patients with target organ damage demonstrated by left ventricular hypertrophy, carotid atherosclerosis and microalbuminaemia had significantly higher levels of SUA as compared with those without target organ damage regardless of other known cardiovascular risk factors(Alderman, 1999). Hypertension has adverse effects on various target organs, thus increasing the risk of stroke, coronary heart disease, and heart failure. This leads to high morbidity and mortality in many cases. Elevated blood pressure (BP) is also associated with an accelerated rate of decline in cognitive and renal function.(Prepared, 2005)

A study done in Nigeria shows that SUA level is elevated in most patients with essential hypertension irrespective of the sex. They also noted a positive correlation between the SUA level and both the diastolic and systolic BP(Emokpae & Abdu, 2013). In a study in Cameroon on the relationship between Uric Acid and hypertension in adults in Fako Division, SW Region observed a significant positive association between uric acid with both systolic and diastolic blood pressure after controlling for confounding factors. The association was most evident in people with hypertension. They also observed a significant negative association between uric acid and age on hypertension. (Nguedia et al, 2014).

In Egypt a study done among elderly patients showed that there was an independent association between hyperuricemia and metabolic syndrome(Rahman, 2014).In Mali (Oumar1 et al., 2015) noted that hyperuricemia is a cardiovascular risk factor, a very high proportion of hypertensive patients had hyperuricemia.

In Kenya, the prevalence of hyperuricemia among patients with hypertension is an area that minimal research has been done. The last such study was done by Mwongera F. K., undertaken in 1981 at the Kenyatta National Hospital where the incidence of

hyperuricemia in untreated patients with essential hypertension was found to be 27.5% and among those on treatment it was 58%(Mwongera, 1981)

Research is required to clarify the relationship between lifestyles, individual behaviors, health and illness (Bosu, 2010).On this basis, this study seeks to estimate the serum uric acid levels and associated risk factors among hypertensive patients at the Moi Teaching and Referral Hospital.

1.2 Problem Statement

The increasing prevalence of hypertension in Africa coupled with the forecast that by the year 2020, non-communicable diseases such as cardiovascular diseases will be the major causes of morbidity and mortality in developing countries. In Kenya the prevalence of hypertension is rising and those on treatment are poorly controlled. Uric acid (UA) has been implicated in hypertension through the probable role it is thought to play in mediating hypertension and its complications.

In the Framingham Heart Study, each increase in SUA by 1.3 mg/dl was associated to the development of HT with an odd ratio of 1.17(Sundström, 2005). In the Multiple Risk Factor Intervention (MRFIT) study, in normotensive men with the SUA level greater than 7 mg/dl there was an 80% increased risk for the development of hypertension (Eswar, 2007). In the First National Health and Nutrition Study (NHANES I) study, for every 1.01 mg/dl increase in the SUA level, the hazard ratio for total mortality and for cardiovascular mortality were 1.09 and 1.19 for men and 1.26 and 1.3 for women, respectively(Lehto,1998)

Patients with hypertension have a higher risk of hyperuricemia because of associated comorbidities such as obesity, dyslipidemia, diabetes and use of diuretics such as

furosemide and hydrochlorothiazide, therefore increasing their overall cardiovascular risk.

1.3 Research Questions

1. What is the prevalence of hyperuricemia among patients with hypertension at MTRH?
2. What is the association of hyperuricemia and socio- demographic, clinical and laboratory characteristics of patients with hypertension?

1.4 Justification of the Study

Hypertension has adverse effects on various target organs, thus increasing the risk of stroke, coronary heart disease and heart failure this leads to high morbidity and mortality in many cases. This warrant that emphasis be assigned to the individual risk factors of hypertension and the existence of any possible interaction between them as this will improve the efficiency of management strategies. UA is a risk factor for the development of cardiovascular disease, and the European Society of cardiology guidelines recommend performing routine laboratory testing for serum UA (SUA) in patients with hypertension.

In clinical practice in limited-resource settings, it may not be practical to screen every patient with hypertension individual for subclinical TOD due to limited access to facilities for echocardiography and microalbuminuria; therefore, identification of a relatively inexpensive risk marker, like UA, may help to identify patients who are at higher risk, thereby directing further evaluation.(Whitworth,2007:Salako,2007)

In Kenya, there is paucity of data on prevalence of hyperuricemia among patients with hypertension. The last such study was done by Mwongera F. K., undertaken in 1981 at the Kenyatta National Hospital where the incidence of hyperuricemia in untreated

patients with essential hypertension was found to be 27.5% and among those on treatment it was 58%(Mwongera, 1981).

1.5 Objectives of the Study

1.5.1 Board objective

To determine the prevalence of hyperuricemia among patients with hypertension and its association with socio demographic, clinical and laboratory characteristics.

1.5.2 Specific objectives

1. To determine the prevalence of hyperuricemia among patients with hypertension and hyperuricemia.
2. To describe the socio-demographic, clinical and laboratory characteristics of patients with hyperuricemia.
3. To determine the association of hyperuricemia and socio-demographic, clinical &laboratory characteristics of patients with hypertension

Chapter Two: Literature review

2.1 Hypertension

2.1.1 Overview

Hypertension is defined as a systolic blood pressure equal to or above 140 mm Hg and/or diastolic blood pressure equal to or above 90 mm Hg. Normal levels of both systolic and diastolic blood pressure are particularly important for the efficient function of vital organs such as the heart, brain and kidneys and for overall health and wellbeing (WHO, 2013). Hypertension has become a major public health problem over the world because it may cause serious damage to body organs and induce cerebrovascular accident, coronary heart disease, heart failure, renal failure and other complications (Qiao et al., 2013)

Hypertension is grouped into two main categories: primary and secondary hypertension. Primary hypertension is also known as essential hypertension which affects 95% of persons suffering from the disease. Causes of hypertension are not yet known, however, factors such as age, high salt intake, low potassium diet, sedentary lifestyle, stress as well as genes have been found as contributors of hypertension(Eslami, 2004). High blood pressure occurring as a result to a consequence of another disorder or a side effect of medication is referred to as secondary hypertension. Such disorders include renal failure or renovascular disease. This type of blood pressure is evident in about 5% to 10% of cases presenting with hypertension(Carretero, 2000).

Most devices for measuring blood pressure are dependent on one common feature, namely, occluding the artery of an extremity (arm, wrist, finger, or leg) with an inflatable cuff to measure blood pressure either oscillometrically, or detection of korotk off sounds. Other techniques, which are not dependent on the limb occlusion, such as pulse-waveform analysis, can also be used, but these have little application in the clinical practice. The array of techniques available today owe the origins to the conventional

technique of auscultatory blood pressure measurement. This technique, blood pressure is measured indirectly by sphygmomanometry. Supine and erect measurements should be obtained to provide an assessment of baroreceptor function. A cuff of at least 40% the arm circumference in width is attached to a mercury or aneroid manometer and inflated around the extended arm. Auscultation over the brachial artery reveals five phases of *Korotkoff sounds* as the cuff is deflated. Phase 5 provides a better measure of diastolic blood pressure than phase 4, not only because it corresponds more closely with directly measured diastolic pressure, but also because its identification is less subjective. Nevertheless, in those conditions where Korotkoff sounds remain audible despite complete deflation of the cuff (aortic regurgitation, arteriovenous fistula, pregnancy) phase 4 must be used for the diastolic measurement(O'Brien et al., 2003).

2.1.2 Prevalence of hyperuricemia and hypertension

Globally, cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total (James et al., 2014). Of these, complications of hypertension account for 9.4 million deaths worldwide every year (Lim et al., 2013). In 2008, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008. The prevalence of hypertension is highest in the African Region at 46% for adults aged 25 and above, while the lowest prevalence of 35% is found in the USA. Overall, high-income countries have a lower prevalence of hypertension (35%) than other groups who have 40% (WHO, 2009).

In Kenya, hypertension and diabetes mellitus are considered common problems but there are few studies reporting the prevalence of these diseases or replicable screening strategies. The available data on the burden of hypertension or diabetes suggests

prevalence rates of 12% and 6.6%, respectively (Mathenge, 2010),hypertension in 2014 by M. Joshi et al was 21%. However, low awareness of chronic diseases, poverty, and health system factors, among other issues, may lead to underestimates of the true prevalence (Addo, 2007)

Essential hypertension is the most prevalent type of hypertension and affects 90-95% of hypertensive patients (WHO, 2009). Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, stress, visceral obesity, obesity in which more than 85% of cases occur in those with a body mass index greater than 25, salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension (Lackland & Egan, 2007; Stabouli, 2011; WHO, 2013; Wofford & Hall, 2004). Risk also increases with aging, some inherited genetic mutations, and having a family history of hypertension (Segura, 2007; Tuohimaa, 2009). An elevation of renin, an enzyme secreted by the kidney, is another risk factor, as is sympathetic nervous system over activity. Consuming foods that contain high fructose corn syrup may increase one's risk of developing hypertension (Hwang, 1987; Segura, 2007)

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it is treated differently than essential hypertension, by treating the underlying cause of the elevated BP. hypertension results compromise or imbalance of the pathophysiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension. Some are common and well-recognized secondary causes such as Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol (Dodt et al 2009). In addition, hypertension is caused by other conditions that cause hormone changes such as hyperthyroidism, hypothyroidism, and adrenal gland cancer. Other common causes of secondary hypertension include kidney disease, obesity/metabolic disorder, pre-eclampsia during pregnancy, the congenital

defect known as coarctation of the aorta, and certain prescription of illegal drugs (Lloyd-Jones et al., 2009).

According to data from a study conducted in the North-West Province of South Africa, up to 34.8 % of the African population had a systolic blood pressure above 140 mmHg, while 26.9 % had a diastolic blood pressure above 80 mmHg. The study notes that hypertension on its own is a serious health risk, but in Africa it is often associated with obesity(van Rooyen et al., 2000)**.** At the same time the treatment of hypertension in developing countries is unaffordable for the average worker. This is due to the fact that, the lowest treatment pharmacologically is recorded to be 7.5-12% of the monthly income of the average worker(van Rooyen et al., 2000) In effect, it is impossible for a better treatment pharmacologically. Thus, the need for understanding the disease and controlling it with preventive measures is the key to the reduction of high prevalence in Africa.

Uric acid is usually considered for its role in the pathogenesis of gout (i.e. one form of arthritis promoted by hyperuricemia, and urate crystals deposited in joints and other tissues, nephrolithiasis, and nephropathy). However, unrelated to crystallization, an elevated serum uric acid concentration has also been associated with a number of cardiovascular and renal diseases including hypertension, atherosclerosis, dyslipidemias, exogenous obesity, insulin resistance and even aging process. Studies have established that there is an increase in serum uric acid among hypertensive patients. Up to 50-70% of hypertensive patients have increased serum acid(Ouppatham et al, 2008)compared to the general population, hypertensive subjects in Taiwan had a higher prevalence (mean 35% in males, 43% in females) of hyperuricemia; this prevalence being 1.5- and 1.7-fold higher in males and females respectively(Lin et al.)

Mellen et al reported that there is a strong association between hyperuricemia and pathogenesis of hypertension(Mellen et al.).

In a Nigerian study, 62% and 59% of female and males hypertensive patients, respectively, had hyperuricemia of above 340 umol/l. A positive correlation was also found between serum uric acid and systolic blood pressure $r=0.192$; $p<0.001$. There was statistical difference observed when serum uric acid, urea, creatinine and LDL cholesterol of patients with hyperuricemia and those without(Emokpae & Abdu, 2013).

Hyperuricemia is also associated with the presence of target organ damage in hypertensive patients. Viazzi *et al.* observed that patients with target organ damage demonstrated by left ventricular hypertrophy, carotid atherosclerosis and microalbuminemia had significantly higher levels of SUA as compared with those without target organ damage regardless of other known cardiovascular risk factors.(F. Viazzi et al.)

Recent evidence suggests that serum uric acid (SUA) can be an inexpensive and easy-to-obtain indicator of cardiovascular risk (CR)(Gagliardi, 2009). This is especially important in low resource countries with high prevalence of cardiovascular disease.

2.2 Uric Acid

Uric acid is the final oxidation product of purine catabolism formed from the breakdown of adenosine and guanine. It is a waste product resulting from the biological oxidation of purines, including adenine and guanine–components of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and adenosine triphosphate (ATP**)** (Maesaka & Fishbane, 1998**).**

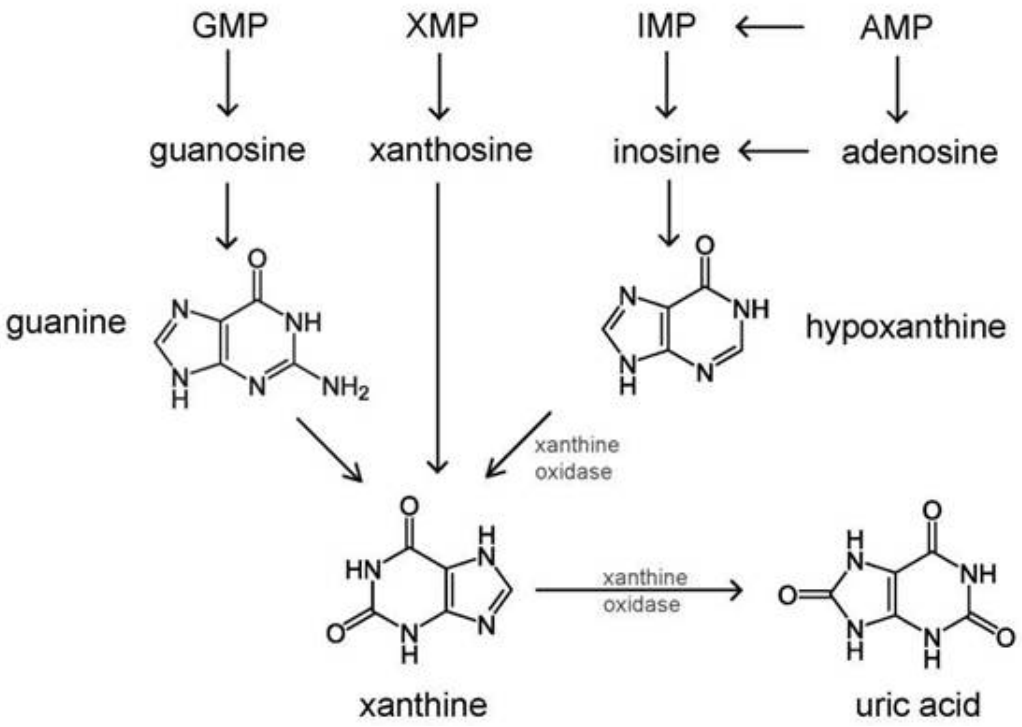

Figure 1: Uric acid production pathway

The vast majority of mammalian species have extremely low serum urate levels (about 1 mg/dL; 60 micromol) because uric acid is converted to allantoin, a highly soluble excretory product. By contrast, uric acid is the end product of purine metabolism in

humans, because the human homolog of the mammalian uricase gene is structurally modified to an unexpressed (pseudogene) state.UA is mainly produced in the liver and then secreted into the bloodstream. Mutations on the Uricase gene render it nonfunctional in humans and as a result humans are unable to degrade UA further to allantoin (Watanabe et al., 2002)**.**

Under normal physiological circumstances, the renal handling of UA involves four pathways, namely; filtration, reabsorption, secretion and post secretory reabsorption. The kidneys excrete approximately 70% of the daily production of UA and the rest undergoes intestinal elimination (Mazzali et al., 2002; Watanabe et al., 2002). The urate production process (purine degradation) involves the breakdown of the purine mononucleotides, guanylic acid (GMP), inosinic acid (IMP), and adenylic acid (AMP), ultimately into the purine bases, guanine and hypoxanthine. These latter two compounds are then metabolized to xanthine. In the final step of the xanthine oxidase reaction, xanthine is irreversibly oxidized to produce uric acid.

In conjunction with genetic or environmental factors, uric acid can cause significant health problems, leading to kidney stones when it builds up in the kidneys and to gout when crystals accumulate in the joints. The levels of uric acid in the blood must be tightly controlled to minimize these detrimental effects. Normally, the body eliminates enough uric acid in the kidney, and in part also through the intestines, to keep its concentration at a healthy level in the blood (approximately 300 microM). In patients with gout or kidney stone disease, however, the body either produces excessive amounts of uric acid or its ability to eliminate uric acid is disturbed in some way. In the kidney, uric acid is reabsorbed via the uric acid transporter URAT1(Hediger, 2004).

2.3 Risk factors for hyperuricemia

Many studies have documented the involvement of high serum uric acid in pathogenesis of cardiovascular morbidity and renal disease progression in hypertensive population (Kang, 2012)(Barker et al, 1989; Daniel I Feig et al., 2004)(Lee et al., 2006)(Taniguchi et al., 2001). Elevated serum uric acid is an independent risk factor for hypertension and renal disease, all others factors held constant.(Brenner et al, 1988)

The development of HBP at an early age has long been recorded as higher in Black Americans than the White Americans. Individuals with family history of high blood pressure, stroke and other cardiovascular diseases are always at risk of developing it. In recent studies, hereditary was referred to as participants with one or more first-degree biological family members diagnosed of HBP to identify risk groups. Results from these studies showed the high prevalence of HBP in Black Americans than the White even though there were other factors as stress, poverty, lack of access to health care and racial discrimination associated with the high prevalence (Lloyd-Jones et al., 2009).

Although significant epidemiological evidence supported the hypothesis that uric acid may be associated with hypertension, it was not until the experiments of Johnson and colleagues in 2001, established plausible mechanism. Using a rat model of pharmacologically induced hyperuricemia, they showed that increased serum uric acid level results in hypertension within 2weeks.(Mazzali et al., 2001)

Hyperuricemia leads to hypertension in a stepwise fashion. Uric acid affects the blood vessels in two phases .The first phase is direct, uric acid-dependent activation of the renin–angiotensin system and down regulation of the nitric oxide production, leading to

vasoconstriction. At this stage, uric acid reduction results in vascular relaxation and improved blood pressure. The second phase, which develops over time, is uric acid-mediated arteriolosclerosis. Uric acid is taken up into vascular smooth muscle cells which causes the activation and elaboration of production of growth factors and monocyte chemotattractant protein-1. This results in the autocrine stimulation of vascular smooth muscle cell proliferation, vascular wall thickening, loss of vascular compliance, and a shift in pressure natriuresis. This process is not reversed by the late reduction of uric acid and causes permanent sodium-sensitive hypertension.(Mazzali et al., 2002)

Studies of uric acid levels and the development of hypertension have generally been consistent, continuous, and of similar magnitude. Hyperuricemia is also common among adults with prehypertension, especially when microalbuminuria is present (Lee et al., 2006; Syamala, 2007). Many reveal that an elevated UA level consistently predicts the development of hypertension. An elevated UA level is observed in 25-60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset(Verdecchia et al., 2000)

In one study of rats with hyperuricemia, when the uricase inhibitor was stopped after renal microvascular disease and interstitial inflammation had become pronounced, blood pressure would improve only if the rats remained on a low-salt diet. Treating these rats with xanthine oxidase inhibitors, including allopurinol or febuxostat, lowered uric acid levels and partially prevented these changes (Mazzali et al., 2001).

In adults, hyperuricemia is also common among those with prehypertension, especially when microalbuminuria is present(Lee et al., 2006) The observation that hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension per se. Only one study involving subjects in whom hypertension had developed after the age of 60 has not predicted the development of hypertension(Forman, 2007). It is important to note that the strength of the relationship between uric acid level

and hypertension decreases with increasing patient age and duration of hypertension, suggesting that uric acid may be most important in younger subjects with early-onset hypertension (Daniel I. Feig , 2012).

It is also possible that genetic polymorphisms of transporters or enzymes involved in uric acid metabolism affect blood pressure, especially in younger subjects. For example, hypertension has been associated with polymorphisms of xanthine oxidoreductase(Chaves et al., 2007). Solute carrier family 2, member 9 (SLC2A9) is a newly identified fructose and uric acid transporter in which several genetic polymorphisms have been identified that are associated with an increased risk of gout (Doring et al., 2008; Vitart et al., 2008). Nevertheless, these polymorphisms were not observed to be associated with hypertension (Doring et al., 2008).This result may indicate that uric acid is not a direct causal risk factor for hypertension, or it might reflect the fact that polymorphisms in *SLC2A9* account for only a small fraction of the variance in serum uric acid, meaning that it may be difficult to detect an effect (Doring et al., 2008; Vitart et al., 2008).

Hyperuricemia is also more common in primary hypertension than in secondary hypertension, at least in adolescents (Daniel I Feig & Johnson, 2003).Several studies reveal a close association between elevated serum uric acid level and the onset of essential hypertension. In Russia, the Moscow Children's Hypertension Study found hyperuricemia (.8.0 mg/dl) in 9.5% of children with normal blood pressure, 49% of children with borderline hypertension, and 73% of children with moderate and severe hypertension (Iu, 1990). In Hungary, a study that on 17,624 children born in Budapest in 1964 for 13 years, found that significant risk factors for the development of hypertension were elevated heart rate, early sexual maturity, and hyperuricemia(Selby, 1990)

Gruskin undertook study comparing children aged 13 to 18 years with essential hypertension with age matched healthy control subjects with normal blood pressures.

The study revealed that hypertensive children had both elevated serum uric acid level (mean,.6.5 mg/dl) and higher peripheral renin activity(Gruskin, 1985)

In a racially diverse population referred for the evaluation of hypertension, Feig and Johnson observed that the mean serum uric acid level amongst those with white coat hypertension was slightly higher in secondary hypertension and significantly elevated in those with primary hypertension (Daniel I Feig & Johnson, 2003).There was a tight linear correlation between the serum uric acid levels and the SBPs and DBPs in the population referred for evaluation of hypertension (SBP and DBP). Each 1-mg/dL increase in serum uric acid was associated with an average increase of 14 mm Hg in SBP and 7 mm Hg in DBP. Among patients referred for evaluation of hypertension, a serum uric acid level .5.5 mg/dL had an 89% positive predictive value for essential hypertension, whereas a serum uric acid level ,5.0 mg/dL had a 96% negative predictive value for essential hypertension(Daniel I. Feig, 2012).

There is evidence that uric acid may directly contribute to the onset of hypertension in some humans. Five children, aged 14 to 17 years, with newly diagnosed and as yet untreated essential hypertension(Essential hypertension is defined as high BP in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or mendelian forms (monogenic) are not present) were treated for 1 month with allopurinol as a solitary pharmacological agent. All 5 children had a decrease in blood pressure by both casual and ambulatory monitoring, and 4 of the 5 were normotensive at the end of 1 month(Soletsky et al, 2008) .

A relationship between hyperuricemia and stroke has been shown in patients with or without chronic kidney disease, arterial hypertension and diabetes mellitus (Lehto, 1998; Milionis et al., 2005). Treatment with atorvastatin improves renal function and reduces serum uric acid levels(Athyros et al., 2007). A 20 years' experience study involving 7978

mild to moderate patients with hypertension on treatment program found that serum uric acid level increased during the treatment and were significantly associated with cardiovascular diseases independent of diuretics use and other cardiovascular risk factors(Alderman, 1999)Another study has found that the higher levels of serum uric acid has greater effect on vascular events rates in the presence of diabetes mellitus irrespective of other diagnostic measures(Weir et al, 2003)

Kanbay et al. treated 48 hyperuricemic patients with allopurinol 300 mg/day for 3 months and reported a significant reduction in systolic and diastolic blood pressures(Kanbay et al.)

There are few randomized controlled studies to date assessing the efficacy of allopurinol treatment in hypertensive individuals; Feig et al treated newly diagnosed hypertensive adolescents with allopurinol 200 mg twice daily for 8 weeks, using a crossover design. Compared with placebo treatment, allopurinol treatment was associated with significant ambulatory and casual systolic and diastolic blood pressure reductions(D. I. Feig et al., 2008).

Along with allopurinol treatment, the use of low-protein and low-purine diet enhances the effectiveness of drug therapy for hyperuricemia. Limitation of protein-rich and purine-rich foods such as turkey, mackerel, sardines, shellfish, beef, lamb, goat, pork, deer, elk, and cricket nymphs, could prevent the high protein load and formation of purine products which directly affects the serum uric acid levels (Kedar, 2002)

In another recent RCT, Soletsky and Feig (Soletsky & Feig, 2012)treated prehypertensive obese adolescents with allopurinol,probenecid, or placebo. Allopurinol reduced systolic and diastolic blood pressures significantly compared with placebo-treated patients. One of the important results of this study was that probenecid therapy was associated with similar decreases in blood pressure as allopurinol therapy, a result that is in line with previous experimental studies and strongly suggests that lowering

serum uric acid level independent of the xanthine oxidoreductase system may have favorable blood pressure effects (Chaves et al., 2007)

From the foregoing literature review there is a significant role of uric acid in development of hypertension and its complications. Hyperuricemia is also common among adults with prehypertension and microalbuminuria. Hyperuricemia precedes the development of hypertension but it is not simply the cause of hypertension per se. some studies involving patients with hypertension aged over 60 has shown no link with hypertension (Forman, 2007). It seems that the strength of the relationship between uric acid level and hypertension decreases with increasing age and duration of hypertension; UA has a key role in inducing hypertension and insulin resistance itself, in particular during early life; thereafter, when these metabolic derangements are already established, the association between serum UA levels and cardiovascular risk profile could become no longer statistically detectable(Daniel I Feig et al, 2008). The level at which serum UA should be considered harmful varies,several observations have shown a relationship between serum UA and cardiovascular disease even at concentrations lower than the usual cutoff levels of 6 mg/dL for women and 7 mg/dL for men. Hence, it has been suggested that the above limits could be kept as far as the risk of gout and urolithiasis is concerned, but a concentration of 5.2 mg/dL to 5.5 mg/dL in both sexes may be the preferred cutoff level in the evaluation of cardiovascular risk(Daniel I Feig et al., 2008).

The prevalence and associated risk factors of hyperuricemia among patients with hypertension is an area where minimal research has been in Kenya. This study will focus on the prevalence of hyperuricemia among hypertensive patients at MTRH.

Chapter Three: Methodology

3.1 study site and setting

This study was done in the medical outpatient clinics at Moi Teaching and Referral Hospital (MTRH). The Hospital is located in Eldoret town, which is 350 Kilometers northwest of the Kenyan capital, Nairobi. MTRH is a tertiary (level 6) health facility serving as a teaching hospital for Moi University School of Medicine, Public Health, Nursing and Dentistry. Others include Kenya Medical Training Center (KMTC), Eldoret and University of Eastern Africa Baraton School of Nursing. MTRH is also a training center for medical, clinical and nursing officer interns. It is the referral hospital for the western part of Kenya and North rift valley and has a catchment population of approximately 13 million people

The hospital has various specialist clinics, including medical outpatient clinics where patients with hypertension are seen twice weekly.

3.2 Study Population.

The study population included patients with hypertension aged over 18 years attending the medical outpatient clinics at MTRH. Subjects were screened for detection of hypertension which was defined as values >140 mmHg SBP and/or >90mmHg DBP, or taking antihypertensive medication.

Those found to be have hypertension were the target population for screening for hyperuricemia.

3.3 Study design

This study was a cross sectional descriptive study.

3.4 Sampling and recruitment

3.4.1 Sampling technique

Patients who met the study inclusion criteria were recruited through simple random sampling after initial screening of all patients with hypertension who presented to the medical outpatient clinics.

We used the register at records department to determine the number of patients booked for clinic, approximately (50 to 70) then we assigned numbers, we used computer generated random numbers to select the patients.

Our target was to recruit the patients within 3months, therefore to achieve our target (275), we recruited 25 patients per week (MOPC days-Tuesday-10, Thursday-10 and Friday-5).

3.4.2 Eligibility criteria

3.4.2.1 Inclusion Criteria

1. All patients aged 18 years and above.

2. Patient with hypertension -BP >140/90 mm/Hg for more than 2 readings.

2. Patient with hypertension already on treatment for less than 2 years, so as to target the patients to those with a shorter duration of illness since longer duration of illness is associated with hyperuricemia. (Bilal & tahir, 2014)

3.4.2.2 Exclusion Criteria

1. Patients with malignancies

2. Patients on chemotherapy
3. Critically ill patients
4. Pregnant women

3.4.3 Sample size

The sample size required in order to have 95% confidence interval of the population proportion of 58% (Mwongera, 1981) was estimated using the following formula (Cochran, 1963).

$$n = \left(\frac{Z_{1-\alpha/2}}{\delta}\right)^2 P(1-P)$$
$$= \left(\frac{1.96}{0.05}\right)^2 0.58 \times 0.42$$
$$= 375$$

Where P is the population proportion of patients with hyperuricemia among hypertensive ones, δ is the margin of error equal to the 5% used in this case and $Z_{1-\alpha/2}$ is the $(1-\alpha/2)\times 100\%$ quantile of the standard normal distribution.

Correcting for the finite population size of around 170 per month for 6 months leads to $(n/(1+n/N) = 375/(1+375/1020) = 275)$, where N is the population size in six months. This is the minimum sample size that can be collected. This means that any number greater than this can be sampled provided that it does not amount to unnecessary harm of the patients or unnecessarily inflated cost of research.

3.5 Study procedure

Potential participants presenting for care at medical outpatient clinics were screened by the nurse by reviewing their medical charts and reported the eligible ones to the principal investigator. The principal investigator reviewed the sampled charts and approached the identified patients. Those who met the inclusion criteria had their consent obtained. If they were not fasted, then they were rescheduled for another day.

The patients' self-reported bio data and a comprehensive medical history of current and past illnesses, including but not limited to: duration of hypertension, history of diabetes, stroke, alcohol use and cigarette smoking as well as medication use including hypertension medication, drugs for diabetes, and lipid lowering agents being used. Those who reported duration of hypertension illness less than 2 years were eligible.

Physical examination of all the study participants was performed. Patient's weight was taken and recorded to the nearest half kilograms (kg) using a standard weighing scale with the patients dressed in light clothing and without shoes. Height was taken against a vertical scale with the patient standing upright and without shoes and recorded to the nearest centimeter (cm). Body Mass Index (BMI) was then calculated as weight in kg /height in (m^2) and the degree of obesity was classified based on National institute of Health (NIH) cut offs (National Institutes of Health (NIH) National Heart, Lung, and Blood Institute, 1998).

Blood pressure measurement was done after a patient had rested for at least 5 minutes. Two readings were taken and the average was recorded in the questionnaire. Patients who reported history of diabetes, was verified from the records. The patients who were not known hypertensive but with BP readings of systolic above 140mmHg and diastolic of more than 90mmHg had their charts reviewed and if they had high Blood pressure during their last visit they were considered hypertensive.

After the questionnaire was filled and the patient reported to have fasted, Blood samples were drawn procedure explained in Appendix VI. 2mls for uric acid (Appendix VII), 2mls put in an EDTA bottle for total cholesterol, LDL, HDL and triglycerides (Appendix VIII) and 2mls blood sample was taken for determination of serum creatinine (Appendix VIII).

The estimated glomerular filtrate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease-Epidemiology Consortium) equation, expressed as a single equation:

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] X 1.159 [if black]

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.(Levey & Stevens, 2010; Levey et al., 2009)

This formula was preferred based on the recent local study which showed that CKD-EPI was superior to other equations for the estimation of eGFR among HIV infected patient in MTRH (Wyatt et al., 2013). This was however true for patients with eGFR of more than 90ml/min/1.73 m^2. Though there is no evidence to suggest this applies to all patients, this is the only formula that has been validated locally.

All laboratory investigations were carried out at the MTRH laboratory according to good laboratory and clinical guidelines/practices (AppendixV-IX). The procedures were carried out by the principal investigator, research assistant and a trained laboratory technician.

The principal investigator interviewed the patients and recorded a detailed medical history, physical findings and drew blood for the various laboratory tests.

The research assistant facilitated triage of the patients and took blood samples to the laboratory for analysis and followed up laboratory results.

Trained laboratory technician carried out the laboratory tests as per the required standards and regulations.

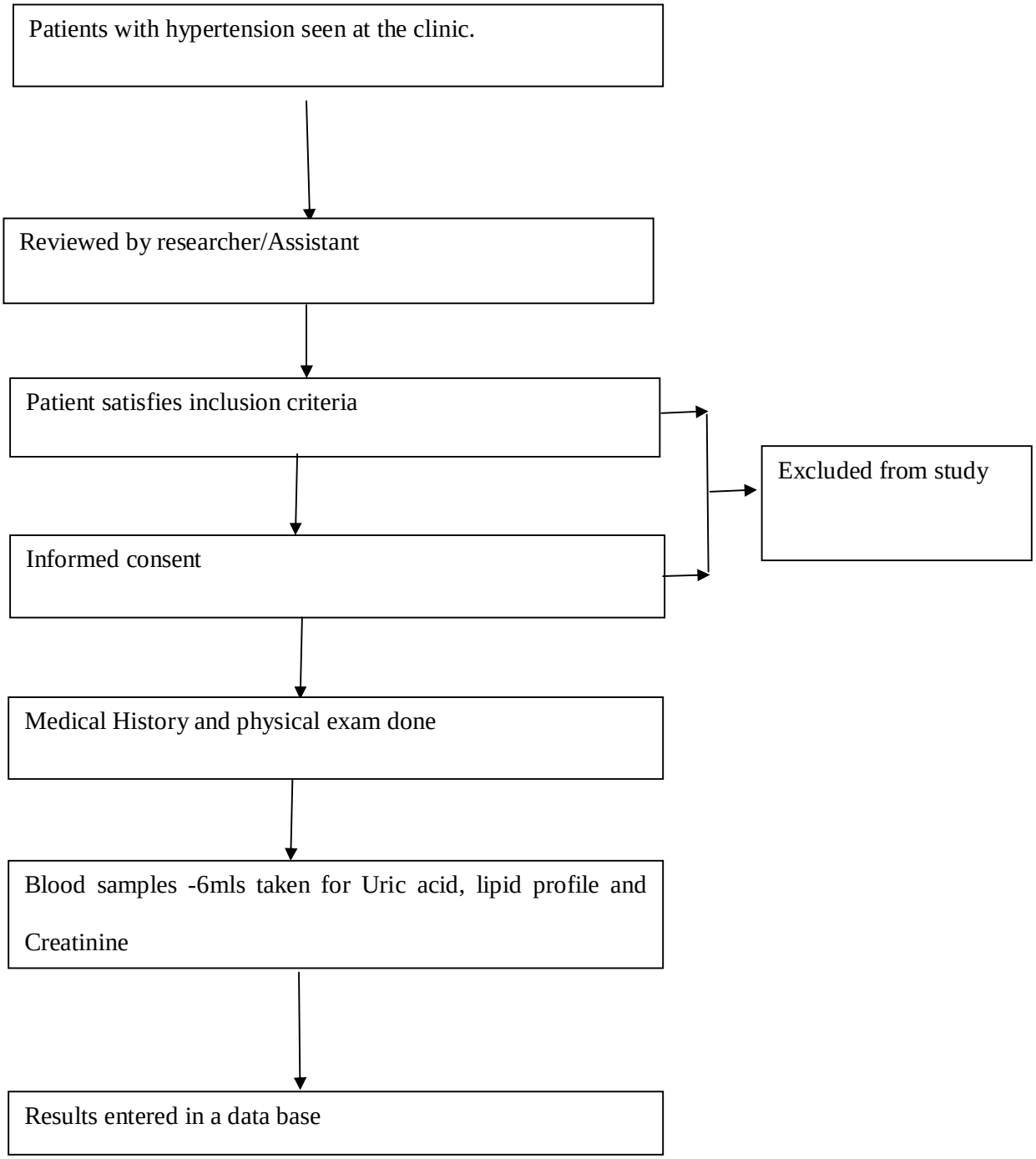

Figure 2: Algorithm of the study procedure

3.6 Data Collection Tools and management

3.6.1 Data collection

Data was collected between January and September 2015, using interviewer administered structured questionnaire (Appendix I). The data collection tool was validated by monitoring the data trends during data collection. Medical records were also reviewed and relevant clinical and laboratory data were obtained and entered into the data collection form. The variables collected included demographic characteristics such as age, gender, history of smoking, alcohol use, diet and occupation. Medical and family history of hypertension, diabetes and kidney disease were also obtained. Other variables collected included; laboratory parameters (FBS, creatinine and lipid profile). The dependent/outcome variables are the levels of uric acid for the hypertensive patients. The data was later double-entered into a computer Microsoft Excel database and pass-worded.

3.6.2 Enrollment of participants

At the clinic, subjects aged more than 18 years were screened for detection of hypertension, defined as values >140 mmHg SBP and/or >90mmHg DBP, or taking antihypertensive medication. The subjects were interviewed with help of appropriate schedule to elicit information regarding their socio demographic characteristics, behavioral parameters and disease related parameters. Blood sample (4mls) was taken for analysis of serum uric acid, lipid profile, creatinine and fasting blood sugar.

3.6.3 Data Management

Data was entered into excel database. It was de –identified and encrypted. Pass word was known to the principle investigator. Database was also backed up for recovery when necessary.

After data entry the questionnaires were kept in a cabinet and locked.

3.6.4 Data Analysis and Presentation

Data analysis was done using STATA version 13 special edition. Categorical variables were summarized as frequencies and corresponding percentages. Continuous variables that assumed Gaussian distribution were summarized as mean and the corresponding standard deviation (SD).Continuous variable that violated the Gaussian assumptions were summarized as median and the corresponding inter quartile range (IQR). Inferential statistics were used to draw conclusions about the population. Significance tests such as the two-sample t-test for comparison of two normally distributed continuous variables, two-sample Wilcoxon rank sum test (aka Mann Whitney U test) for non-Gaussian distributed continuous variables, and Pearson's Chi Square test for categorical variables were used. Gaussian assumptions were assessed empirically using Shapiro Wilk test.

3.7 Ethical Considerations

This study was carried out with the approval of the Institutional Research and Ethics Committee (IREC) of MTRH and Moi University School of Medicine and permission from MRTH management. A signed written informed consent was obtained for each participant who was included in this study (Appendix II). Confidentiality was maintained throughout the study by pass-wording database and limiting its access only to principal investigator and research assistants. Interviews were carried out in a consultation room to ensure privacy and convenience. All participants including those who declined consent

received the same level of care awarded to all other patients irrespective of their participation. There were very minimal anticipated risks to the participants attributable to this study except the physical pain and discomfort associated with sample collection. Questionnaires will be shredded after three years or publication of the study findings. There was no conflict of interest in this study and no incentives were used to recruit patients. Patients were informed of their results and the same availed to their primary clinicians. This thesis shall be availed at the MUSOM library. It will also be published in a reputable journal and presented in professional conferences and seminars.

3.8 Dissemination of results

The results of the study will be disseminated through a written thesis and an oral defense in a forum that shall be convened by the school of medicine. The results will also be shared with MTRH and published in peer-reviewed journal.

Chapter Four: Results

4.1 Screening and enrollment into the study

Between January and September 2015 a total of 505 patients with hypertension were screened at the medical outpatient clinics in MTRH, of which 275 patients were enrolled. The details are shown in figure 3.

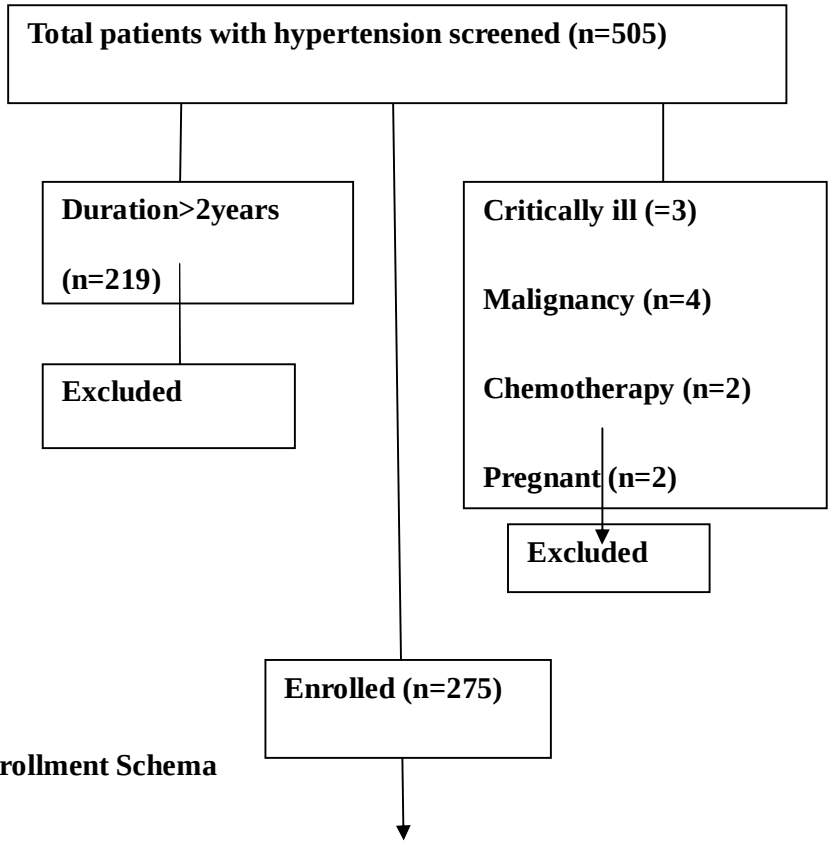

Figure 3: Enrollment Schema

4.2 Socio-demographic characteristics of the patients

The patients' age ranged from 18 to 90 years with a mean age of 54.2 years (SD 14.3 years) and the majority being in the age group 41-70 years (68.7%) (Figure 4).

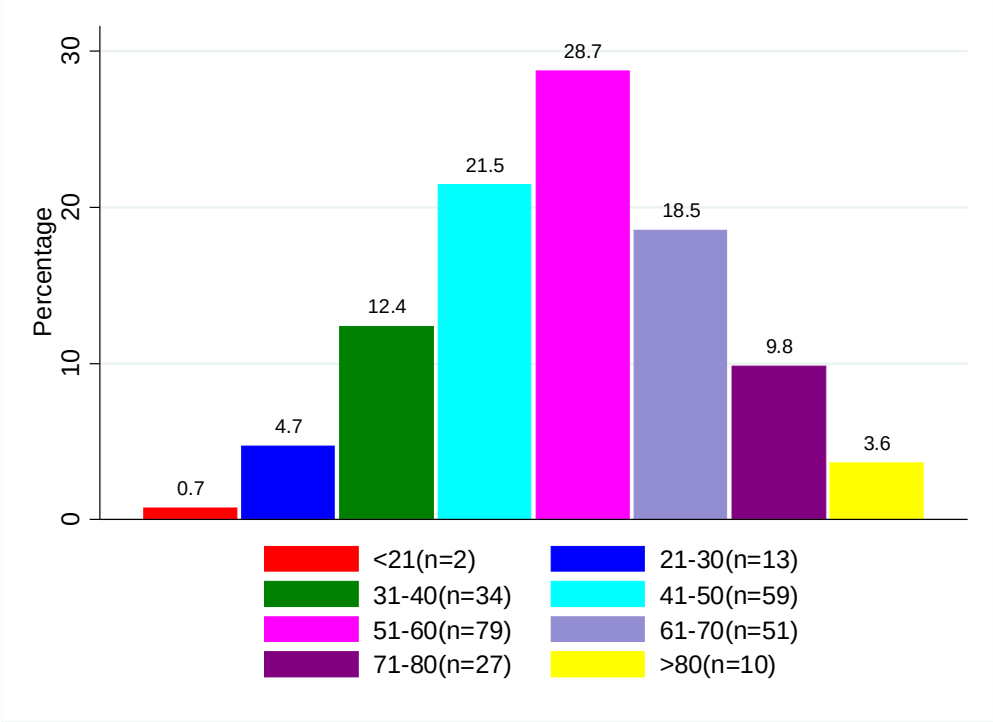

Figure 4: Age categories of the patients

Two thirds of the patients were female with male to female ratio of 1:2, females being 182 (66%) of the patients. More than two thirds, 215 (78.2%) were not employed. Thirty five, 12.7%, had a history of smoking, 59 (21.5%) had a history of alcohol use. (Table 1)

Table 1: Socio-demographic characteristics of the patients

Variable	**n(%) or Mean**
Age	54.2 ± 14.3
Female	182 (66.2%)
Employed	60 (21.8%)
Smoking	35 (12.7%)
Alcohol use	59 (21.5%)

4.3 Clinical characteristics of the patients

4.3.1 Medical history of the patients

The median duration of illness after diagnosis was 6months (IQR: 2, 18).

Out of the 275 patients, 29 (10.6%) had a history of stroke and another 42 (15.3%) had a history of diabetes. Treatment history showed that 40 (14.6%) patients were on furosemide, 114 (41.5%) were on hydrochlorothiazide, 29 (10.6%) were on amlodipine, and 125 (45.5%) were on Nifedipine. Eighty four, 30.6%, were using enalapril while 10 (3.6%) were on beta blockers (carvedilol-5 or propranolol-2 or atenolol-3).Twenty three 23 (8.4%) were on atorvastatin for treatment of dyslipidemia. (Table 2)

Table 2: Medical history of the patients

Variable	**Numbers(n=275)**	**Percentages**
Family history of hypertension	129	46.9%
History of stroke	29	10.6%
History of DM	42	15.3%
History of Kidney disease	15	5.5%
Treatment		
Furosemide	40	14.6%
Hydrochlorothiazide	114	41.5%
Amlodipine	29	10.6%
Nifedipine	125	45.5%
Enalapril	84	30.6%
Beta blockers	10	3.6%
Angiotensin Receptor blocker	50	18.2%
Aspirin	15	5.5%
Diabetes Mellitus treatment	38	13.8%
Statins(atorvastatin)	23	8.4%

4.3.2 Clinical and laboratory characteristics of the patients

Majority of the patients 258 (93.8%) had normal physical examination findings. Median BMI of 28.9 (IQR: 26.1, 33.4) kgs/m^2. The median systolic blood pressure (SBP), and diastolic blood pressure (DBP) were 154.0 (IQR: 139.0, 166.0) mm Hg, and 94.0 IQR: (85.0, 102.0) mm Hg respectively.

More than 70% had SBP> 140 mm Hg, and more than half had DBP>90 mm Hg. This gives the proportion of patients with uncontrolled blood pressure as 214 (77.8%). Other clinical characteristics are summarized in Table 3.

Median serum uric acid was 338.5 (IQR: 270.0, 415.0) mmol/l ranging between 135.1 and 707.0 mmol/L respectively, with the prevalence of hyperuricemia in this cohort was 44.0% (95% CL: 28.0%, 50.0%).

Lipid profiles showed that the median total cholesterol, HDL, LDL, and triglycerides were 4.9 (IQR: 4.0, 5.7) mmol/l; 1.0 (IQR: 0.8, 1.3) mmol/l; 2.9 (IQR: 2.1, 3.7) mmol/l, and 1.3 (IQR: 1.1, 1.8) mmol/l respectively. There were 248(90.2%) participants with dyslipidemia; elevated total cholesterol, 114 (41.5%); decreased HDL, 207 (75.3%), elevated LDL, 125 (45.5%), and elevated triglycerides, 87 (31.6%).Median creatinine was 66.0 (IQR: 53.0, 82.2) mmol/l, and median eGFR was 110.5 (IQR: 88.7, 122.7) ml/min per 1.73m^2 (Range3.3-164.3 ml/min per 1.73$m^{2)}$. Participants were assessed for chronic kidney disease; 24 (8.7%) were in stage 3 or 4. Other clinical and laboratory characteristics are summarized in Table 4

Table 3: Clinical characteristics of the patients

Variable	**Mean(SD) or median (IQR)**	**Number n=275**	**Percentage (%)**
Height (cm)	161.0(158.0, 168.0)		
Weight (Kgs)	76.0 (69.0, 86.0)		
BMI (Kg/m^2)	28.9(26.1,33.4)		
Underweight (<18.5)		0	0%
Normal(18.5-25)		49	17.8%
Overweight(25-30)		108	39.3%
0bese(>30)		**118**	**42.9%**
Systolic blood pressure	154(139.0,166.0)		
>140mmHg		**199**	**72.4%**
<140mmHg		76	27.6%
Diastolic blood pressure	94.0(85.0,102.0)		
>90mmHg		**159**	**57.8%**
<90mmHg		116	45.2%
SBP>140 DBP>90		**214 (77.8%)**	
Pulse		85.0 ± 13.2	

Table 4: Laboratory characteristics of the patients

Variable	**Median(IQR)**	**Number(n)=275**	**percentage**
Uric acid(mmol/L)	338.5(270.0, 415.0)		
Hyperuricemia		**121**	**44%**
Males>420umol/l		**35**	**37.6%**
Females>320umol/l		**86**	**47.3%**
Total cholesterol	4.9 (4.0, 5.7)		
<5.17mmol/l		161	58.5%
>5.17mmol/l		114	41..5%
HDL mmol/l	1.0 (0.8, 1.3)		
High(M>1.03,F>1.29)		85	30.9%
Low(M<1.03,F>1.29)		190	69.1%
LDL	2.9 (2.1, 3.7)		
<2.6mmol/l		150	54.5%
>2.6mmol/l		125	45.5%
Triglycerides	1.3 (1.1, 1.8)		
<1.7mmol/l		188	68.4%
>1.7mmo/l		87	31.6%
Any Dyslipidemia			
Yes		**248**	**90.2%**
No		37	9.8%
Creatinine	66.0 (53.0, 82.2)		
eGFR(ml/min/1.73m^2)	110.5 (88.7, 122.7)	251	91.3%
Above 60		9	3.3%
30-60		5	1.8%
15-30		**10**	**3.6%**
<15			

4.5 Associations between hyperuricemia and patients' characteristics

4.5.1 Associations between hyperuricemia and socio-demographics characteristics of the patients

There was no significant association between hyperuricemia and demographic characteristics (Table 5). Age was not associated with the presence of hyperuricemia, p=0.739. Grouping subjects by age groups showed that a higher proportion of participant aged at least 40 years suffered hyperuricemia but this was no significant. Gender was not associated with the presence of hyperuricemia, p=0.128.

Table 5: Association between hyperuricemia and socio-demographic characteristics.

Variable	**No hyperuricemia n=154**	**Hyperuricemia n=121**	**p-value**
Mean age (years)	55.0 (46.0, 61.0)	55.0 (45.0, 66.0)	0.739
Gender Male Female	 58(37.7%) 96(62.3%)	 35(28.9%) 86(71.1%)	0.128
History of smoking Yes No	 22(14.3%) 132(85.7%)	 13(10.7%) 108(89.8%)	0.382
Alcohol use Yes No	 32(20.8%) 122(79.2%)	 27(22.3%) 94(77.7%)	0.758

4.5.2 Association between hyperuricemia and medical history of the patients

Use of lipid drugs was associated with the presence of hyperuricemia, p=0.010. Other characteristics did not show any significant associations (Table 6)

Table 6: Association between hyperuricemia and medical history of the patients

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Reported history of stroke			
Yes	14(9.1%)	15(12.4%)	0.376
No	140(90.9%)	106(87.6%)	
Reported history of diabetes			
Yes	20(13.0%)	22(18.2%)	0.235
No	134(87.0%)	99(81.8%)	
Reported family history of hypertension			
Yes	74(48.1%)	55(45.5%)	0.668
No	80(51.9%)	45(54.5%)	
Reported family history of kidney disease			
Yes	6(3.9%)	9(7.4%)	0.199
No	148(96.1%)	112(92.6%)	
Hypertension control agents			
Hydrochlorothiazide	58(37.7%)	56(46.3%)	0.150
Furosemide	19(12.3%)	21(17.4%)	0.241
Amlodipine	14(9.2%)	15(12.4%)	0.376
Nifedipine	74(48.1%)	51(42.2%)	0.329
ACEI	47(30.5%)	37(30.6%)	0.992
ARB	29(18.8%)	21(17.4%)	0.753
Beta blockers	6(3.9%)	4(3.4%)	0.531[f]
Diabetes control agents			
Yes	21(13.6%)	17(14.1%)	0.921
No	133(86.3%)	104(85.9%)	
Lipid lowering agents			
Yes	7(4.6%)	16(13.2%)	**0.010**
No	147(95.4%)	105(86.8%)	

"f"- Fisher's exact p value was reported because the expected cell value of the created 2x2 table was less than 5, a violation of Chi Square assumption

4.5.3 Association between hyperuricemia and clinical characteristics of the patients

Systolic, and diastolic blood pressures were not associated with the presence of hyperuricemia, p=0.540, and 0.943, respectively. Grouped blood pressures did not show any evidence of association between hyperuricemia and higher blood pressure levels.

Body mass index (BMI) was associated with the presence of hyperuricemia, p=0.033. Stratified by gender, this association was no longer there, p=0.244 among female and 0.064 among male. Participants who had hyperuricemia were more likely to be obese compared to those without hyperuricemia, median BMI, 30.2 (IQR: 26.5, 33.9) Kg/m^2 vs. 28.4 (IQR: 25.6, 32.6) kg/m^2.

Grouped BMI showed that higher BMI levels were associated with hyperuricemia, p=0.036(Table 7)

Table 7: Association between hyperuricemia and clinical characteristics of the patients

Variable	**Normal uric acid (n=154)**	**Hyperuricemia (n=121)**	**P-value**
Median duration of illness	6.0 (2.0, 12.0)	6.0 (2.0,18.0)	0.402
Mean BMI(kg/m2)	28.4 (25.6, 32.6)	30.2 (26.5, 33.9)	**0.033**
Mean SBP(mm/Hg)	156.0(141,164.0)	150.0(133, 169)	0.540
Mean DBP(mm/Hg)	93.5(87.0,102.0)	96.0(82.0,104.0)	0.943
Mean pulse rate(beats/min)	84.1±13.7	84.3±12.6	0.164
BMI Underweight (<18.5) Normal(18.5-25) Overweight(25-30) 0bese(>30)	 0(0%) 34 (22.1%) 63 (40.9%) 57 (37.0%)	 0(0%) 15 (12.4%) 45 (37.2%) 61 (50.4%)	**0.036**
SBP >140mmHg <140mmHg	 116 (75.3%) 38(24.7%)	 83 (68.6%) 17(31.4%)	0.312[f]
DBP >90mmHg <90mmHg	 92 (59.7%) 62(40.3%)	 67 (55.4%) 54(44.6%)	0.184

"f"- Fisher's exact p value was reported because the expected cell value of the created 2x2 table was less than 5, a violation of Chi Square assumption

4.6 Association between hyperuricemia and laboratory findings

Elevated cholesterol was not associated with hyperuricemia, 55 (45.5%) vs. 59 (38.3%), p=0.233. Participants with low HDL were more likely to have hyperuricemia, median HDL, 0.9 (IQR: 0.7, 1.2) vs. 1.1 (IQR: 0.9, 1.4) mmol/l, p=<0.0001. Elevated triglycerides was also associated with the presence of hyperuricemia, 49 (40.5%) vs. 38 (24.7%), p=0.005.

Dyslipidemia was associated with the presence of hyperuricemia, 118 (97.5%) vs. 130 (84.4%), p<0.0001.

Low eGFR levels were associated with the presence of hyperuricemia, median eGFR: 103.4 (IQR: 74.5, 134.8) vs. 121.7 (108.0, 148.5), p<0.0001. Chronic kidney disease stage 3 or worse was associated with the presence of hyperuricemia, 20 (16.5%) vs. 1 (0.7%), p<0.0001. (Table 8)

Table 8: Association between hyperuricemia and laboratory findings

Variable	Normal uric acid (n=154)	Hyperuricemia (n=121)	p-value
Mean total cholesterol	4.9 (4.1, 5.6)	4.9 (3.8, 5.8)	0.919
Mean HDL	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)	**<0.0001**
Median LDL	2.9 (2.3, 3.5)	2.9 (2.0, 3.8)	0.964
Median triglycerides	1.3 (1.1, 1.7)	1.4 (1.2, 2.1)	0.061
Median eGFR	116.6 (102.3, 127.4)	101.6 (73.9, 118.5)	**<0.0001**
LDL >2.50mmo/l <2.50mmo/l	 68(44.1%) 86(55.84%)	 57 (47.1%) 64(52.9%)	0.626
Total cholesterol >5.17mmol/l <5.17mmol/l	 59 (38.3%) 95(61.7%)	 55 (45.5%) 66(54.5%)	0.233
Triglycerides >1.8mmol/l <1.8mmo/l	 38 (24.7%) 116(75.3%)	 49 (40.5%) 72(59.5%)	**0.005**
HDL* Low high	 91 (59.1%) 63(40.9%)	 99 (81.8%) 22(18.2%)	**0.001**
Dyslipidemia	122 (79.2%)	116 (95.9%)	**<0.0001**
eGFR above 60 30-60 15-30 <15	 150(97.4%) 3(2%) 0(0%) 1(0.7%)	 101(83.5%) 6(5%) 5(4.1%) 9(7.4%)	**<0.0001**[f]
Stage 3 or worse CKD	4(2.6%)	20(16.5%)	**<0.0001**

"f"- Fisher's exact p value was reported because the expected cell value of the created 2x2 table was less than 5, a violation of Chi Square assumption

Dyslipidemia-Defined as elevated total cholesterol, low-density lipoprotein (LDL), triglycerides or low levels of high-density lipoprotein (HDL).

Table 9: Factors associated with presence of hyperuricemia

Variable	**Odds Ratio (95% CL)**
Age (per 10 years increase)	**0.71 (0.56, 0.90)**
Female	**2. 18 (1.15, 4.15)**
BMI (per 5 units increase)	**1.50 (1.13, 1.99)**
eGFR (per 30 units increase)	**0.32 (0.22, 0.48)**
Dyslipidemia	**4.40 (1.12, 17.19)**
Lipid drugs (ATOV)	**4.63 (1.42, 15.13)**
Drugs for diabetes mellitus	**0.23 (0.06, 0.95)**
Nifedipine	**0.44 (0.24, 0.82)**
ARB	**0.39 (0.17, 0.92)**
HCTZ	1.57 (0.88, 2.81)
Aspirin	3.01 (0.68, 13.32)
History of diabetes mellitus	2.75 (0.73, 10.35)

The results show that old age was associated with decrease in the risk of hyperuricemia. That is, comparing two participants, the one older than the other by five years has 29% reduced risk of hyperuricemia, OR: 0.71 (95% CL: 0.56, 0.90), after adjusting for the covariates shown in Table 9.

Female participants were associated with more than twice the risk of hyperuricemia, OR: 2.18 (95% CL: 1.15, 4.15). A participant with 5 units of BMI higher than another has 50% increased risk of hyperuricemia, OR: 1.50 (95% CL: 1.13, 1.99).higher values of eGFR are protective. The model results show that a participants with 30 units of eGFR

higher than another had 68% reduced risk of hyperuricemia, OR: 0.32 (95% CL: 0.22, 0.48).

Participants who had dyslipidemia had more than four times the risk of hyperuricemia compared to those who did not have, OR: 4.40 (95% CL: 1.12, 17.19). The use of lipid drugs was associated with almost five times increased risk of hyperuricemia, OR: 4.63 (95% CL: 1.42, 15.13).

Similarly, the use of diabetes mellitus drugs adjusting for the presence of diabetes mellitus was associated with 87% reduced risk of hyperuricemia, OR: 0.23 (95% CL: 0.06, 0.95). The use of Nifedipine was associated with 56% reduced risk of hyperuricemia, OR: 0.44 (95% CL: 0.24, 0.82) while the use of ARB was associated with 61% reduced risk of hyperuricemia, OR: 0.39 (95% CL: 0.11, 0.92).

Chapter Five: Discussion

5.1 Prevalence of hyperuricemia among hypertensive patients

In the last decade interest in uric acid has resurfaced after a long period of inertia, largely reflecting results from experimental studies that show detrimental effects of uric acid on blood pressure and kidney function.

The prevalence of hyperuricemia varies in different populations and areas. In our study we found a prevalence of 37.6% among male hypertensive patients and 47.3% among female hypertensive patients. According to a study done in Nigeria they found a prevalence of 59% among the male hypertensive patients and 62% among the female patients(Emokpae & Abdu, 2013) . This could be explained by the lower cutoff uric acid level was> 5.5mg/dl for both sexes and in our study the cut off was>5.7mg/dl for female patients and >7mg/dl for the male patients. Therefore these figures are considered high. In Cameroon a study done to find out the relationship between Uric Acid and Hypertension in Adults in Fako Division, found a 49.5% of hypertensive patients both male and female had hyperuricemia(Nguedia Assob et al., 2014). This finding is comparable to our study since the overall prevalence was 44%. In Mali they got a higher prevalence of 66.7% among 51 hypertensive patients on follow up for 40 months(Oumar1 et al., 2015). This could be explained by the longer duration of illness in this study compared to ours which was 24 months.

In Kenya a study by Mwongera *et al* found an incidence of 27.5% among untreated hypertensive patients and 58.3% among the treated hypertensive patients(Mwongera, 1981). The treated hypertensives could relate to our study but the duration of illness was longer than that of our study, in our study all of our patients were on treatment focusing mainly on those who had been on medication for less than 2 years, which could explain the slightly higher prevalence in this study.

A study done in Taiwan by Lin *et al* on hypertensive patients on treatment found a prevalence of 35% among male patients and 45% among female patients(Lin et al.) and a study done among US adults hypertensive patients got a prevalence of 41.7%(Gonzalez, & DeVries ,2001). These findings are comparable to our results 37.3% and 47.3% respectively.

An increased serum urate concentration is a frequent finding in patients with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension(Cannon, 1966).In our study the overall prevalence of hyperuricemia was high at 44%. The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption(Messerli, 1980)Hypertension also results in microvascular disease, and this can lead to local tissue ischemia(Puig & Ruilope,1999). In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis. Ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation(Friedl, 1991)

5.2 Patients' characteristics and associations with hyperuricemia

5.2.1 Socio-demographic characteristics

There was a female predominance (66%) in our study. This could be a reflection of health seeking behavior among the sexes rather than higher incidences among female. This is supported by a study recently done in Nairobi slums that revealed that female

patients are more likely to seek health care than their male counterparts(Muriithi et al, 2013).

The study by Jules *et al* in Cameroon found that females were 169 (56.9%) and 128 (43.1%) males, which also shows a slight predominance of females(Nguedia et al, 2014). The patients' age ranged from 18 to 90 years with a mean age of 54.2 years (SD 14.3 years) and the most frequent age group were aged 41-70 years being189 (68.7%),which is almost similar to the Cameroon study where the mean age of study participants was 41.95 ± 14.83 years (range: 20-76 years)(Nguedia et al, 2014) and the Nigerian study, males ranged from 27 years to 75years with a mean of 51.2 ± 12.1 years, while the ages of the females ranged from 18 years to 84 years with a mean of 51.8± 16.4 years(Emokpae & Abdu, 2013).Mwongera study done in 1981 in KNH was in a younger age group with most of the patients being between 30 – 50yrs(Mwongera, 1981).In Mali their patients were almost similar to our study, aged 46 - 60 and those over 60 years represented the majority with respectively 39,2%,37,3%(Oumar1 et al., 2015).According to WHO in 2008, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension; the number of people with hypertension rose from 600 million in 1980 to 1 billion in 2008 .The prevalence of hypertension is highest in the African Region at 46% of adults aged 25 and above, while the lowest prevalence at 35% is found in the Americas(WHO, 2013) This fact is in agreement with our findings since most of the hypertensive patients in the study were above 25years.

In this study age was not associated with the presence of hyperuricemia, p=0.739. Grouping subjects by age groups showed that a higher proportion of participant aged at least 40 years had hyperuricemia but there was no significant association. This was not consistent with studies done on age and uric acid, so we further analyzed the data by adjusting for the covariates and we were able to show that old age was associated with lower risk of hyperuricemia. That is, comparing two participants, the one older than the

other by five years has 29% reduced risk of hyperuricemia, OR: 0.71 (95% CL: 0.56, 0.9.This is in line with a study done in Cameroon by Jules *et al* and by Lu z *et al* in china where they found a significant negative correlation between uric acid and age(Lu et al., 2009; Nguedia et al, 2014).However, Teng et al reported a contrary result wherein uric acid was associated with the risk of hypertension in the elderly(Teng et al.) The differences with our study might be explained by differences in population characteristics.

Thirty five, 12.7%, had a history of smoking and 59 (21.5%) had a history of alcohol use. This is in contrast with Jules *et al*. Cameroon study that found that majority of the patients (53%) reported history of smoking and 46% alcohol use(Nguedia et al , 2014). The above study established a significant association between history of smoking ($r=0.377$; $P<0.0001$), and alcohol consumption ($r=0.391$; $P<0.0001$) with hyperuricemia. In our study there was no significant association ($p=0.382$).The differences between these two studies could be under reporting by patients in our study and behavioral variations of patients in Cameroon. The decrease of uric acid in smokers can be explained by the inactivation of xanthine oxidase by cyanide, which is eliminated as thiocyanate (Mouhamed et al.)

5.2.2 Clinical and laboratory characteristics of the patients

In our study, the median duration of illness after the diagnosis was 6 months (IQR: 2, 18), the KNH study did not analyze the mean duration of illness. In Mali the study by Oumar *et al* on hypertensive patients on treatment had a mean duration of 10.73 months(Oumar1 et al., 2015). The difference could be because the upper limit of our study was 24 months and in this study it was 40 months hence the longer duration of the mean.A study by Muhammed *et al* on frequency of hyperuricemia among 356 hypertensive patients in pakistan , they divided the patients into two groups according to duration of illness, among the 155(43.18%) patients with 1-20 years duration of hypertension, hyperuricemia was seen in 50(32.3%) patients, out of 204(56.82%) patients with 21-41 year duration , hyperuricemia was seen in 100(49%) hence showing that hyperuricemia increases with duration of illness(Bilal & tahir,2014)

Significant number of patients42.5 %(female 47.8% and male 33.3%) had a BMI above 30kg/$m^{2.}$ The Mali study, similarly found 41.2% of the study subjects being overweight(Oumar1 et al., 2015). The Cameroon study just calculated the mean and did not stratify them like in our study and got a mean BMI 26.41 ± 4.80 kg/m2 (17-44 kg/ m2) 169 (56.9%) were females(Nguedia et al., 2014). This could be as a result of dietary changes and sedentary lifestyle among the population. There was significant association between hyperuricemia and BMI (p=0.033).However in the Mali study(Oumar1 et al., 2015) they did not find an association thou there study was limited because of a small sample size of 51 patients. In china a cross-section study(Fan et al.) was performed in 5235 hypertensive patients aged 40 - 75 years old at Xinyang a rural town showed that with an increase of body mass index (BMI), the prevalence of obesity and serum uric acid level increased significantly in both sexes [BMI < 25, > or = 30. It is important to

note that in the US participants aged 20 years and older from the National Health and Nutrition Examination Survey from 1999–2012 were used to evaluate the separate and combined effects of hyperuricemia and overweight/obesity on the risk of prevalent hypertension among different race, gender and age groups. Participants (31 473) were used to estimate separate and combined effects on the prevalence of hypertension. The magnitude of odds ratio (OR) from the combination of hyperuricemia and overweight/obesity (OR=4.53, 95% CI 4.05–5.07) was significantly higher than both hyperuricemia (OR=2.62, 95% CI 2.07–3.32) and overweight/obesity (OR=2.08, 95% CI 1.89–2.30). Combined effect of hyperuricemia and overweight/obesity on the risk of hypertension is much stronger than any separate one(Han et al.,2014).

Blood pressure was noted to be poorly controlled in our patients with more than 70% with SBP> 140 mm Hg and more than half had DBP>90 mm Hg. This gives a proportion of 77.8 % (214) of subjects with blood pressure of >140/90 mm/hg. This was almost similar to the African study in Mali(Oumar1 et al., 2015) where the mean blood pressure of their subjects was SBP of 163.14 and a DBP of 98.02 . Poor adherence and health seeking behavior could be responsible for poor blood pressure control as a significant number (77.8%) of the patients had a high blood pressure (Bp ≥140/90) on the day of enrollment.

However, the study in Cameroon(Nguedia et al., 2014)Had a lower proportion of 32.7% with a blood pressure of > 140/90mm/hg. In this study they recruited both hypertensive patients and normotensives that were controls, therefore explaining the lower blood pressures in this study.

Our study did not establish an association between blood pressure and hyperuricemia similarly to the Mali study, also in the UK (Dawson et al,2013.)Established that serum

uric acid at baseline did not predict the longitudinal changes in both SBP and DBP, suggesting that there was no evidence that increasing serum uric acid level has a detrimental effect on BP control in adults with treated hypertension, suggesting that uric acid level does not influence response to pharmacotherapy for hypertension. However in the Cameroon(Nguedia et al, 2014)they found a significant independent association between uric acid with both systolic and diastolic blood pressure; an increase in both systolic and diastolic blood pressure was also marked by a corresponding increase in serum uric acid concentration, Nigerian study(Emokpae & Abdu, 2013)there was significantly positive correlation between SUA and systolic blood pressure ($r=0.192$; $p<0.001$) and between SUA and diastolic blood pressure ($r=0.216$; $p<0.001$).These two studies compared patients with hypertension and controls whose blood pressure was less than 120/80 mm/hg ,in our study and the Mali study all participants were known hypertensives, hence there was no significant association. In the Framingham Heart Study they investigated the relationship of serum UA to hypertension incidence and blood pressure (BP) progression in 3329 participants they found that serum UA was positively associated with changes in systolic ($P=0.02$) and diastolic pressure 4 years later ($P=0.04$) and concluded that serum UA level was an independent predictor of hypertension incidence and longitudinal BP progression at short-term follow-up in their community-based sample(Sundstrom et al.).

History of stroke (H=12.4%, N=9.1%) and diabetes (H=18.2%, N=13%), was found to be higher among patients with hyperuricemia but was not statistically significant. A systematic review and meta-analysis of 16 prospective cohort studies found that the elevated serum uric acid level in adults is associated with a modest but statistically significant increased risk of stroke incidence and mortality(Kim et al., 2009). Elevated serum uric acid independently predicts stroke and excess mortality in patients with non–

insulin-dependent diabetes mellitus (Lehto, 1998) whereas in the general elderly population, it is independently associated with increased incidence of fatal stroke(Mazza et al., 2001).In patients with diabetes, elevated serum uric acid is thought to play a role, along with obesity, blood pressure, and insulin resistance, in the metabolic syndrome that may be responsible for endothelial dysfunction.

In a study by Weir *et al*, on 3731 patients and measured serum urate in 2498 participants ,Elevated urate level predicted a lower chance of good 90-day outcome (odds ratio, 0.78 per additional 0.1 mmol/L; 95% confidence interval, 0.67 to 0.91) independently of stroke severity and other prognostic factors. Vascular event risk increased with urate level (relative hazard, 1.27 per additional 0.1 mmol/L; 95% CI, 1.18 to 1.36). Higher urate levels have a greater effect on vascular event rates in the presence of diabetes (additional relative hazard, 1.22 per additional 0.1 mmol/L; 95% CI, 1.06 to 1.41). They concluded that independently of other prognostic factors, higher serum urate levels predicted poor outcome. (Weir et al, 2003)

Diuretic (Furosemide and hydrochlorothiazide) use was associated with hyperuricemia but there was no significance, calcium channel blocker (CCB)was associated with 55% reduced risk of hyperuricemia, OR: 0.45 (95% CL: 0.24, 0.84) while the use of angiotensin receptor blocker (ARB) was associated with 61% reduced risk of hyperuricemia, OR: 0.39 (95% CL: 0.17, 0.90).The KNH study by Mwongera F.K *et al* also showed that patients on thiazide had higher levels of uric acid but was also not significant. Diuretics have a propensity to increase serum uric acid levels even in small doses and it increases is dose- dependent fashion(Ariel J. Reyes, 1993),(A. J. Reyes, 2005)

The hypouricemic effect of losartan may be due to losartan targeting the urate anion exchange and diminish urate reabsorption in the proximal convoluted tubule; as a result,

the urate excretion fraction is increased by 13%-30% and increases renal uric acid excretion(Puddu et al., 2001)the parent molecule losartan, not its active E-3174 metabolite, is the active agent blocking uric acid reabsorption. The uricosuric action of losartan is not shared by other antihypertensive agents. ACE inhibitors and CCBs increase uric acid excretion but the effect is modest.(A. e. al, 2004)

Dyslipidemia, a known risk factor for hypertension, was also prevalent among these patients (90.2%). This was shown by high prevalence of low HDL (75.3%) and high LDL (45.5%) and high triglycerides of 31.6%. The fact that only 8.4% of the patients were on statins could be attributed to low utilization of the screening services for dyslipidemia among the patients. Dyslipidemia, low HDL and triglycerides was associated with the presence of hyperuricemia. The Nigerian study (Emokpae & Abdu, 2013) found that although total cholesterol, triglyceride and other lipoproteins were within normal limits of the reference ranges, statistically significant differences were observed when compared in those with elevated SUA and those without it. In Cameroon(Nguedia et al., 2014)Observed a significant correlation between uric acid and triglycerides. A study was done to investigate the independent relation between serum uric acid and lipid profiles using The Third National Health and Nutrition Examination Survey (NHANES III), which represents a well-designed population-based study with a large sample size of US adults, they concluded that serum LDL cholesterol, triglycerides, total cholesterol, apolipoprotein-B levels, ratio of triglycerides to HDL cholesterol, and ratio of apolipoprotein-B to AI are strongly associated with serum uric acid levels, whereas serum HDL cholesterol levels are significantly inversely associated(Peng et al.).Triglycerides have been linked to insulin resistance which promotes hypertension through renal tubular sodium reabsorption, augmentation of the sympathetic nervous system reactivity and activation of the renin–angiotensin system (Mazzali et al., 2001).

Given that uric acid can also induce the Renin-angiotensin system it is possible that they both have an additive effect on the blood pressure response. Serum uric acid has been shown to be associated with lipid level even in normal subjects (Russo et al, 1996). It is also known to be associated with lipids and other components of the metabolic syndrome (Daniel I Feig & Johnson, 2003; Nakanishi et al., 2003). Studies of possible association between lipid and high blood pressure have yielded different conclusions. This may be due to differences in the patient's characteristics such as age, sex, risk factor levels and geographical location.

The median eGFR was 110.5 (IQR: 88.7, 122.7) ml/min per 1.73m^2. Low eGFR levels were associated with the presence of hyperuricemia, median eGFR: 103.4 (IQR: 74.5, 134.8) vs. 121.7 (108.0, 148.5), $p<0.0001$. Chronic kidney disease stage 3 or worse was associated with the presence of hyperuricemia, 20 (16.5%) vs. 1 (0.7%), $p<0.0001$.Similarly the Nigerian study(Emokpae & Abdu, 2013) also found a statistically significant difference when urea and creatinine of the patients with hyperuricemia were compared with the patients whose uric acid was within the reference limit $p<0.001$ and $p<0.005$ respectively. In Cameroon study(Nguedia Assob et al et al., 2014)and the KNH study(Mwongera, 1981) there was higher 9levels of creatinine and urea in patients with hyperuricemia but not statistically significant. In a study done on treated hypertensives in the UK(Dawson et al.)They found a linear decrease in eGFR with increasing quartiles of serum uric acid in both men and women. Patients in the highest quartile of uric acid showed a 10.7 (95% CI, 13.6–7.9) mL/min per 1.73 m^2 and 12.2 (95% CI, 15.2–9.2) mL/min per 1.73 m^2 decrease in eGFR in men and women, respectively, compared with the lowest quartile. In Taiwan(Lin et al.)in a study done on 2145 hypertensive subjects from 19 hospitals in four areas and they found that serum uric acid values correlated significantly with four quintiles of serum creatinine($p<0.0001$) independent of diuretic use.

Serum uric acid is eliminated principally by the kidneys, and while there is a compensatory increased removal by the gut in the setting of renal insufficiency, this is not completely effective, and serum uric acid increases as the GFR falls, with approximately half of the subjects becoming hyperuricemia by the time dialysis is initiated(Suliman et al., 2006). This makes it very difficult to assess the role of uric acid in the progression of renal disease in subjects with CKD based on epidemiological studies. In addition, the experimental studies suggest that uric acid may cause kidney disease primarily by causing systemic and glomerular hypertension, but in renal disease this mechanism may become less relevant as systemic hypertension commonly develops as a consequence of sodium and water retention. As such, it is not surprising that, in subjects with established CKD, serum uric acid has often(Sturm et al., 2008) not been found to predict progression. Nevertheless, some studies have found an elevated uric acid level to predict progression in subjects with established CKD, especially in diabetes and IgA nephropathy(Shi et al.)

5.3 Summary of the key findings

In summary, there was a high prevalence (44%) of hyperuricemia among this population, there is a significant role of uric acid in development of hypertension and its complications hence can be used as a marker of disease progression and existence of metabolic syndrome among these patients. Known risk factors for hyperuricemia such as BMI, dyslipidemia, female sex, creatinine and low eGFR were prevalent in this population. The study established a significant association between hyperuricemia and these risk factors. Therefore, uric acid should be considered as one of the major risk factors for development of complications among hypertensive patients.

5.4 Limitation of study

1. Blood pressure was only measured during one visit it is possible that some individuals were misclassified owing to the white coat effect.

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Chapter Six: Conclusions and Recommendations

6.1 Conclusions

1. There was high prevalence (44%) of persistent hyperuricemia in hypertensive patients at Moi Teaching and Referral Hospital.
2. There was a high prevalence of traditional risk factors for a hyperuricemia and hypertension such as; dyslipidemia, High BMI and low eGFR among the hypertensive patients.
3. There was a significant positive association between high serum creatinine, low eGFR, dyslipidemia and hyperuricemia, patients on losartan were noted to have low uric acid levels.

6.2 Recommendations

1. Use of losartan and calcium channel blockers lowers uric acid level and should be considered in patients with hyperuricemia.
2. Subsequent longitudinal studies to be done to determine utility of uric acid monitoring in blood pressure control.
3. A study on cardiovascular disease outcomes (acute coronary events, strokes, cardiovascular mortality) should be done on both arms of patients to clearly define the role of hyperuricemia in these patients.

REFERENCES

Addo. (2007). Hypertension in sub-saharan Africa: a systematic review. *Hypertension, 50*(6), 1012-1018. doi: 10.1161/hypertension aha.107.093336

Alderman (2004). Uric acid: role in cardiovascular disease and effects of losartan. *Current Medical Research and Opinion, 20*(3), 369-379. doi: 10.1185/030079904125002982

Alderman and Brenner (1988). Glomeruli and blood pressure Less of one, more the other? *American journal of hypertension, 1*(4 Pt 1), 335-347.

Alderman (1989). Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ, 298*(6673), 564-567.

Alderman. (1999). Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension, 34*(1), 144-150.

Alwan, A. (2011). *Global status report on noncommunicable diseases 2010*: Italy,World Health Organization.

Athyros, V. G., Mikhailidis, D. P., Liberopoulos, E. N., Kakafika, A. I., Karagiannis, A., Papageorgiou, A. A., . . . Elisaf, M. (2007). Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: A subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. *Nephrology Dialysis Transplantation, 22*(1), 118-127. doi: 10.1093/ndt/gfl538

Bilal, m. h., & tahir (2014), M. Frequency of Hyperuricemia in Hypertensive patients presenting at DG Khan Hospital, DG Khan.Pakistan

Bosu, W. K. (2010). Epidemic of hypertension in Ghana: a systematic review. *BMC Public Health, 10*(1), 418.

Brand. (1985). Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. *American Journal of Epidemiology, 121*(1), 11-18.

Cannon. (1966). Hyperuricemia in primary and renal hypertension. *New England Journal of Medicine, 275*(9),C 457-464.

Carretero. (2000). Essential hypertension part I: definition and etiology. *Circulation, 101*(3), 329-335.

Chaves, F. J., Corella, D., Blesa, S., Mansego, M. L., Marin, P., Portoles, O., . . . Redon, J. (2007). Xanthine oxidoreductase polymorphisms: influence in blood pressure and oxidative stress levels. *Pharmacogenet Genomics, 17*(8), 589-596. doi: 10.1097/01.fpc.0000239970.23723.38

Committee, G. (2003). 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension, 21*(6), 1011-1053.

Culleton. (1999). Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Annals of internal medicine, 131*(1), 7-13.

Dawson, J., Jeemon, P., Hetherington, L., Judd, C., Hastie, C., Schulz, C., . . . Walters, M. Serum uric acid level, longitudinal blood pressure, renal function, and long-term mortality in treated hypertensive patients. *Hypertension. 2013 Jul;62(1):105-11. doi: 10.1161/HYPERTENSION American Heart Association.113.00859. Epub 2013 May 20.*

Dodt, C., Wellhoner, J. P., Schutt, M., & Sayk, F. (2009). [Glucocorticoids and hypertension]. *Internist (Berl), 50*(1), 36-41. doi: 10.1007/s00108-008-2197-6

Doring, A., Gieger, C., Mehta, D., Gohlke, H., Prokisch, H., Coassin, S., . . . Meisinger, C. (2008). SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nature Genetics, 40*(4), 430-436. doi: 10.1038/ng.107

Emokpae, A. M., & Abdu, A. (2013). Serum uric acid levels among Nigerians with essential hypertension. *Nigerian Journal of Physiological Sciences, 28*(1), 41-44.

Eslami. (2004). P-329: Inhibition of oxidative stress and improvement of nitric oxide production by ACE inhibitors and AT1 receptor blockers in uric acid stimulated vascular smooth muscle cells. *American Journal of Hypertension, 17*(S1), 155A-156A.

Eswar Krishnan, C Kent Kwoh, H Ralph Schumacher, Kuller.L, (2007). Hyperuricemia and Incidence of Hypertension Among Men Without Metabolic Syndrome. Hypertension.

Fan, X. H., Sun, K., Wang, Y. B., Dang, A. M., Zhou, X. L., Zhang, H. M., . . . Hui, R. T. (2009), [Prevalence and associated risk factors of hyperuricemia in rural hypertensive patients]. *Zhonghua Yi Xue Za Zhi;89(38):2667-70*.

Feig, D. I. (2012). Hyperuricemia and Hypertension. *Advances in Chronic Kidney Disease, 19*(6), 377-385.

Feig, D. I. (2012). The role of uric acid in the pathogenesis of hypertension in the young. *The Journal of Clinical Hypertension, 14*(6), 346-352.

Feig, D. I., & Johnson, R. J. (2003). Hyperuricemia in childhood primary hypertension. *Hypertension, 42*(3), 247-252.

Feig, D. I., Kang, D.-H., & Johnson, R. J. (2008). Uric acid and cardiovascular risk. *New England Journal of Medicine, 359*(17), 1811-1821.

Feig, D. I., Nakagawa, T., Karumanchi, S. A., Oliver, W. J., Kang, D.-H., Finch, J., & Johnson, R. J. (2004). Hypothesis: uric acid, nephron number, and the pathogenesis of essential hypertension. *Kidney international, 66*(1), 281-287.

Feig, D. I., Soletsky, B., & Johnson, R. J. (2008). Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *Jama, 300*(8), 924-932. doi: 10.1001/jama.300.8.924

Forman. (2007). Plasma uric acid level and risk for incident hypertension among men. *American Society of Nephrology, 18*(1), 287-292. doi: 10.1681/asn.2006080865

Franse, L. V., Pahor, M., Di Bari, M., Shorr, R. I., Wan, J. Y., Somes, G. W., & Applegate, W. B. (2000). Serum uric acid, diuretic treatment and risk of cardiovascular events in the

Systolic Hypertension in the Elderly Program (SHEP). *Journal of Hypertension, 18*(8), 1149-1154.

Friedl. (1991). Role of oxygen radicals in tourniquet-related ischemia-reperfusion injury of human patients. *Klin Wochenschr. 1991 Dec 15;69(21-23):1109-12.*

Gagliardi. (2009). Uric acid: A marker of increased cardiovascular risk. *Atherosclerosis. 2009 Jan;202(1):11-7. doi: 10.1016/j.atherosclerosis.2008.05.022. Epub 2008 May 21.*

Galvan, A. Q., Natali, A., Baldi, S., Frascerra, S., Sanna, G., Ciociaro, D., & Ferrannini, E. (1995). Effect of insulin on uric acid excretion in humans. *American Journal of Physiology-Endocrinology And Metabolism, 268*(1), E1-E5.

Gruskin, A. B. (1985). The adolescent with essential hypertension. *American Journal of Kidney Disease, 6*(2), 86-90.

Gustafsson, D., & Unwin, R. (2013). The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. *BMC Nephrol, 14*, 164. doi: 10.1186/1471-2369-14-164

Haig, A. (1889). On uric acid and arterial tension. *British medical journal, 1*(1467), 288.

Han, G. M., Gonzalez, S., & DeVries,(2014) D. Combined effect of hyperuricemia and overweight/obesity on the prevalence of hypertension among US adults: result from the National Health and Nutrition Examination Survey. *Journal of Human Hypertension, 28*(10), 579-586.

Hediger, M. A. (2004). [Physiology and biochemistry of uric acid]. *Ther Umsch, 61*(9), 541-545. doi: 10.1024/0040-5930.61.9.541

Hwang. (1987). Fructose-induced insulin resistance and hypertension in rats. *Hypertension, 10*(5), 512-516.

Iu, R. (1990). [Parameters of uric acid metabolism in healthy children and in patients with arterial hypertension]. *Pediatriia*(8), 19-22.

James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., . . . Ortiz, E. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama, 311*(5), 507-520. doi: 10.1001/jama.2013.284427

Johnson, D. I. F. a. R. J. (2007). The Role of Uric Acid in Pediatric Hypertension. *Journal Renal Nutrition , 17(1): 79–83.*

Joshi, M. D., Ayah, R., Njau, E. K., Wanjiru, R., Kayima, J. K., Njeru, E. K., & Mutai, K. K. (2014). Prevalence of hypertension and associated cardiovascular risk factors in an urban slum in Nairobi, Kenya: A population-based survey. *BMC public health, 14*(1), 1177.

Kanbay, M., Huddam, B., Azak, A., Solak, Y., Kadioglu, G. K., Kirbas, I., . . . Johnson, R. J. A, (2011) randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clinical Journal of the American Society of Nephrology, 6*(8), 1887-1894.

Kang, D.-H. (2012). Hyperuricemia: A non-traditional risk factor for development and progression of chronic kidney disease? *Kidney Research and Clinical Practice, 31*(3), 129-131.

Kedar. (2002). A perspective on diet and gout. *Advances in Chronic Kidney Disease, 19*(6), 392-397.

Kim, S. Y., Guevara, J. P., Kim, K. M., Choi, H. K., Heitjan, D. F., & Albert, D. A. (2009). Hyperuricemia and Risk of Stroke: A Systematic Review and Meta-analysis. *Arthritis and rheumatism, 61*(7), 885-892. doi: 10.1002/art.24612

Lackland, D. T., & Egan, B. M. (2007). Dietary salt restriction and blood pressure in clinical trials. *Current hypertension reports, 9*(4), 314-319.

Lee, J. E., Kim, Y. G., Choi, Y. H., Huh, W., Kim, D. J., & Oh, H. Y. (2006). Serum uric acid is associated with microalbuminuria in prehypertension. *Hypertension, 47*(5), 962-967. doi: 10.1161/01.HYP.0000210550.97398.c2

Lehto. (1998). Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke, 29*(3), 635-639.

Leyva, F., Anker, S., Swan, J., Godsland, I., Wingrove, C., Chua, T.-P., . . . Coats, A. (1997). Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *European heart journal, 18*(5), 858-865.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., . . . Andrews, K. G. (2013). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2224-2260.

Lin, C.-S., Lee, W.-L., Hung, Y.-J., Lee, D.-Y., Chen, K.-F., Chi, W.-C., & Chang, S.-C.(2012), Prevalence of hyperuricemia and its association with antihypertensive treatment in hypertensive patients in Taiwan. *International journal of cardiology, 156*(1), 41-46.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T. B., Flegal, K., . . . Hong, Y. (2009). Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 119*(3), e21-181. doi: 10.1161/circulationaha.108.191261

Lu, Z., Dong, B., Wu, H., Chen, T., Zhang, Y., Wu, J., & Xiao, H. (2009). Serum uric acid level in primary hypertension among Chinese nonagenarians/centenarians. *Journal of Human Hypertension, 23*(2), 113-121.

Maesaka, J. K., & Fishbane, S. (1998). Regulation of renal urate excretion: a critical review. *American Journal of Kidney Diseases, 32*(6), 917-933.

Mahomed, F. (1879). On chronic Bright's disease, and its essential symptoms. *The Lancet, 113*(2899), 399-401.

Many. (1996). Hyperuricemia and xanthine oxidase in preeclampsia, revisited. *American journal of obstetrics and gynecology, 174*(1), 288-291.

Mathenge. (2010). Urbanization, ethnicity and cardiovascular risk in a population in transition in Nakuru, Kenya: a population-based survey. *BMC Public Health, 10,* 569. doi: 10.1186/1471-2458-10-569

Mazza, A., Pessina, A. C., Pavei, A., Scarpa, R., Tikhonoff, V., & Casiglia, E. (2001). Predictors of Stroke Mortality in Elderly People from the General Population: The CArdiovascular STudy in the ELderly. *European journal of epidemiology, 17*(12), 1097-1104. doi: 10.2307/3582740

Mazzali, M., Hughes, J., Kim, Y. G., Jefferson, J. A., Kang, D. H., Gordon, K. L., . . . Johnson, R. J. (2001). Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension, 38*(5), 1101-1106.

Mazzali, M., Kanellis, J., Han, L., Feng, L., Xia, Y. Y., Chen, Q., . . . Johnson, R. J. (2002). Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol, 282*(6), F991-997. doi: 10.1152/ajprenal.00283.2001

Mellen, P. B., Bleyer, A. J., Erlinger, T. P., Evans, G. W., Nieto, F. J., Wagenknecht, L. E., . . . Herrington, D. M.(2006).Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. *Hypertension.;48(6):1037-42. Epub 2006 Oct 23*.

Messerli. (1980). Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Annals of internal medicine, 93*(6), 817-821.

Milionis, H. J., Kalantzi, K. J., Goudevenos, J. A., Seferiadis, K., Mikhailidis, D. P., & Elisaf, M. S. (2005). Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. *Journal of Internal Medicine, 258*(5), 435-441. doi: 10.1111/j.1365-2796.2005.01565.x

Mittal, B. V., & Singh, A. K. (2010). Hypertension in the developing world: challenges and opportunities. *American Journal of Kidney Diseases, 55*(3), 590-598.

Mouhamed, D. H., Ezzaher, A., Neffati, F., Douki, W., Gaha, L., & Najjar, M. F. (2011). Effect of cigarette smoking on plasma uric acid concentrations. *Environmental health and preventive medicine, 16*(5), 307-312.

Muriithi, M. K.(2013) The determinants of health-seeking behavior in a Nairobi Slum, Kenya. *European Scientific Journal, 9*(8).

Mwongera. (1981). hyperuricemia in patients with essential hypertension.kenyatta National Hospital.Kenya.(Thesis). Nairobi University Kenya.

Nakanishi, N., Okamoto, M., Yoshida, H., Matsuo, Y., Suzuki, K., & Tatara, K. (2003). Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *European journal of epidemiology, 18*(6), 523-530.

Nguedia Assob et al, J. C., Ngowe, M. N., Nsagha, D. S., Njunda, A. L., & Waidim, Y. (2014). The Relationship between Uric Acid and Hypertension in Adults in Fako Division, SW Region Cameroon. *Journal of Nutrition and Food Sciences, 4*(257), 2.

O'Brien, E., Asmar, R., Beilin, L., Imai, Y., Mallion, J.-M., Mancia, G., . . . Palatini, P. (2003). European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *Journal of Hypertension, 21*(5), 821-848.

Okpechi, I., Oluleye, T. S., Bekibele, C. O., Adedapo, K. S., Adebiyi, A. A., Ogah, O. S., & Salako, B. L. (2007). Unexpectedly high prevalence of target-organ damage in newly diagnosed Nigerians with hypertension: cardiovascular topic. *Cardiovascular Journal of South Africa, 18*(2), 77-83.

Oumar1, H. O. H., , M. I., , M. A. K., , D. A., , D. I. B., , . . . Bocary3, D. M. (2015). Prevalance of hyperuricemia in arterial hypertension. *science journal of clinical medicine. 8*(3), 103-107.

Ouppatham, S., Bancha, S., & Choovichian, P. (2008). The relationship of hyperuricemia and blood pressure in the Thai army population. *J Postgrad Med, 54*(4), 259-262.

Peng, T.-C., Wang, C.-C., Kao, T.-W., Chan, J. Y.-H., Yang, Y.-H., Chang, Y.-W., & Chen, W.-L.(2015) Relationship between Hyperuricemia and Lipid Profiles in US Adults. *BioMed research international.*

Prepared, b. (2005). JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart, 91*(Suppl 5), v1-v52. doi: 10.1136/hrt.2005.079988

Puddu, P. E., Lanti, M., Menotti, A., Mancini, M., Zanchetti, A., Cirillo, M., . . . Panarelli, W. (2001). Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population Study. *Acta cardiologica, 56*(4), 243-251.

Puig, J. G., & Ruilope, L. M(1999). *Uric acid as a cardiovascular risk factor in arterial hypertension*: Journal of Hypertension;17(7):869-72.

Qiao, S., Ye, Q., Dou, Y., Li, M., Kou, Y., Qian, D., . . . Wang, G. (2013). Analysis for hypertension and related risk factors of physical examination population. *International journal of clinical and experimental medicine, 6*(9), 785.

Rahman, T. T. A. (2014). Prevalence of Hyperuricemia among Hospitalized Elderly Patients and Its Association with Metabolic Syndrome. *Advances in Aging Research, 3*(04), 329.

Ramsay, L. E. (1979). Hyperuricaemia in hypertension: role of alcohol. *BMJ, 1*(6164), 653-654.

Reyes, A. J. (1993). Renal Excretory Profiles of Loop Diuretics: Consequences for Therapeutic Application. *Journal of Cardiovascular Pharmacology, 22*, S11-S23.

Reyes, A. J. (2005). The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. *European Journal of Heart Failure, 7*(4), 461-467. doi: 10.1016/j.ejheart.2004.03.020

Russo, C., Olivieri, O., Girelli, D., Guarini, P., & Corrocher, R. (1996). Relationships between serum uric acid and lipids in healthy subjects. *Preventive medicine, 25*(5), 611-616.

Salako BL, Ogah OS, Adebiyi AA,Okpechi(2007). Unexpectedly high prevalence of target-organ damage in newly diagnosed Nigerians with hypertension. *Cardiovascular Journal of Africa*. 2007;18(2):77–83.

Sanchez-Fructuoso, A., Torralbo, A., Arroyo, M., Luque, M., Ruilope, L., Santos, J., . . . Barrientos, A. (1996). Occult lead intoxication as a cause of hypertension and renal failure. *Nephrology Dialysis Transplantation, 11*(9), 1775-1780.

Segura. (2007). Obesity, essential hypertension and renin-angiotensin system. *Public Health Nutrition, 10*(10a), 1151-1155. doi: 10.1017/s136898000700064x

Selby. (1990). Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *American Journal of Epidemiology, 131*(6), 1017-1027.

Shi, Y., Chen, W., Jalal, D., Li, Z., Mao, H., Yang, Q., . . . Yu, X. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. *Kidney and Blood Pressure Research, 35*(3), 153-160.

Soletsky, B., & Feig, D. I. (2012). Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension, 60*(5), 1148-1156. doi: 10.1161/hypertensionaha.112.196980

Stabouli. (2011). The role of obesity, salt and exercise on blood pressure in children and adolescents. *Expert Review of Cardiovascular Therapy, 9*(6), 753-761. doi: 10.1586/erc.11.63

Sturm, G., Kollerits, B., Neyer, U., Ritz, E., Kronenberg, F., & Group, M. S. (2008). Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Experimental gerontology, 43*(4), 347-352.

Suliman, M. E., Johnson, R. J., GarcÃ-a-LÃ³pez, E., Qureshi, A. R., Molinaei, H., Carrero, J. J. s., . . . Lindholm, B. (2006). J-shaped mortality relationship for uric acid in CKD. *American Journal of Kidney Diseases, 48*(5), 761-771.

Sundstrom, J., Sullivan, L., D'Agostino, R. B., Levy, D., Kannel, W. B., & Vasan, R. S(2009). Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. *Hypertension. 2005 Jan;45(1):28-33. Epub.*

Syamala. (2007). Association between serum uric acid and prehypertension among US adults. *Journal of Hypertension, 25*(8), 1583-1589. doi: 10.1097/HJH.0b013e32813aeb6c

Taniguchi, Y., Hayashi, T., Tsumura, K., Endo, G., Fujii, S., & Okada, K. (2001). Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. *Journal of Hypertension, 19*(7), 1209-1215.

Teng, F., Zhu, R., Zou, C., Xue, Y., Yang, M., Song, H., & Liang, J. Interaction between serum uric acid and triglycerides in relation to blood pressure. *Journal of Human Hypertension, 25*(11), 686-691.

Tuohimaa, P. (2009). Vitamin D and aging.*Journal of Steroid Biochemistry and Molecular Biology, 114*(1-2), 78-84.

van Rooyen, J. M., Kruger, H. S., Huisman, H. W., Wissing, M. P., Margetts, B. M., Venter, C. S., & Vorster, H. H. (2000). An epidemiological study of hypertension and its determinants in a population in transition: the THUSA study. *J Hum Hypertens, 14*(12), 779-787.

Verdecchia, P., Schillaci, G., Reboldi, G., Santeusanio, F., Porcellati, C., & Brunetti, P. (2000). Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. *Hypertension, 36*(6), 1072-1078.

Viazzi, F., Parodi, D., Leoncini, G., Parodi, A., Falqui, V., Ratto, E., . . . Deferrari, G. (2005). Serum uric acid and target organ damage in primary hypertension. *Hypertension, 45*(5), 991-996.

Viazzi, F., Parodi, D., Leoncini, G., Parodi, A., Falqui, V., Ratto, E., . . . Pontremoli, R.(2005) Serum uric acid and target organ damage in primary hypertension. *Hypertension.;45(5):991-6. Epub 2005 Mar 21.*

Vitart, V., Rudan, I., Hayward, C., Gray, N. K., Floyd, J., Palmer, C. N., . . . Wright, A. F. (2008). SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nature Genetics, 40*(4), 437-442. doi: 10.1038/ng.106

Watanabe, S., Kang, D. H., Feng, L., Nakagawa, T., Kanellis, J., Lan, H., . . . Johnson, R. J. (2002). Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension, 40*(3), 355-360.

Weir et al (2003). Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. *Stroke, 34*(8), 1951-1956. doi: 10.1161/01.str.0000081983.34771.d2

Whitworth, J. A. (2003). World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *Journal of Hypertension, 21*(11), 1983-1992. doi: 10.1097/01.hjh.0000084751.37215.d2

WHO. (2002). *The world health report 2002: reducing risks, promoting healthy life*: World Health Organization.Geneva.

WHO. (2009). The world health report 2008: primary health care now more than ever. Geneva; 2008: WHO Press.

WHO. (2013). A global brief on hypertension: silent killer, global public health crisis. Geneva: WHO; 2013: WHO/DCO/WHD/2013.2).[Links].

Wofford, M. R., & Hall, J. E. (2004). Pathophysiology and treatment of obesity hypertension. *Current pharmaceutical design, 10*(29), 3621-3637.

Appendix I: Data Collection Form

Demographic/ Biodata

IP.NO…….. Serial number……..

Age……..…years Gender…….

Ethnicity……. Residence……

Occupation……..…

Medical History

Duration of illness (months)…….Yes/No

H/O Hypertension:…….Yes/No

H/O Stroke:……....Yes/No

H/O Ischemic Heart Disease:……Yes/No

H/O Diabetes.....Yes/No

Family & social history

H/O Smoking:…….....Yes/No

H/O hypertension in the family…..……..Yes/No

H/O kidney disease in the family…….....Yes/No

High red meat Diet intake (a) Daily (b) One-two times/week (c) More than two times/week (d)Monthly (e) Others, specify ……

Alcohol use (a) Yes (b) No

Treatment history:

Hypertension drugs (tick appropriate)

A. Diuretics .....type

…….....…….

B. CCB:.....type:

…….....…….

C. ACE I.....types:

…….....….

D.ARB…..….....

E. B blocker

…….....

F. other

(specify)….....……

Use of lipid lowering agents (tick appropriate)

Are you on any lipid lowering agents?

(A). Yes. (B) No

If Yes, specify the

drugs.....

Are you on any other medicine?

(A) Yes (B) No……

If Yes to question above, name these drugs

.....

If female, LMP:

.....

EXAMINATION

General:

Pallor	☐	Jaundice	☐	Edema	☐
Dehydration	☐	Lymphadenopathy	☐		

Height……..…cm **Weight:**……kg

BMI ……kg/m^2

Vital signs:

BP: ……/……mmHg Pulse: ……../min

Temp: ……^{o}C $SPO_{2:}$ ……..%

Do you have any of these symptoms

Leg swelling Yes ☐ No ☐

Chest pain Yes ☐ No ☐

Heart failure Yes ☐ No ☐

Heart attack Yes ☐ No ☐

Others……

Any family history of heart disease

Yes ☐ No ☐

If so, who? Nuclear family ☐ Extended family ☐

Chest examination:

Normal ☐ Abnormal ☐

Heart examination:

Normal ☐ Abnormal ☐

Abdominal examination:

Normal ☐ Abnormal ☐

Nervous system examination:

Normal ☐ Abnormal ☐

Other findings

……

……

……

LABORATORY RESULTS

Laboratory test	**Results**	**Date**
Uric acid		
Creatinine		
Lipid profile		
Fasting blood sugar		

Appendix II: Consent Form (A. English Version)

My name is Sylvia Mibey. I am a qualified doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Masters degree in Internal Medicine at Moi University. I would like to recruit you into my research which is to study if newly diagnosed hypertensive patients could have high serum uric acid levels.

ABOUT HYPERTENSION AND HYPERURICEMIA

Hypertension is associated with high serum uric acid levels which can increase the chances of one to getting renal disease, heart disease and stroke. We shall screen you for other diseases, which can increase uric acid and if you have any of those conditions you shall be excluded from the study although you will be appropriately offered treatment for your respective condition.

For us to know whether you have hyperuricemia, we will request you to undergo some tests preceding which you shall have to answer a few questions on your pertinent medical history. We will take a blood sample (4mls) to check whether you have high uric acid level, lipid profile ,creatinine and also your blood sugar. You will be expected to make any payment for these tests

We will keep all your test results in confidence and keep you informed of the results. Treatment does not depend on your participation in this study. We will offer appropriate treatment for any condition that we find from assessing you and from your test results. This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital.

If you need further clarifications please contact IREC using the address below.

The Chairman IREC,

Moi Teaching and Referral Hospital,

PO Box 3,

Eldoret.

Tel: 33471/2/3

My cell phone number is: 0723647419

Adults above 18 years of age

I have been adequately informed that I am being recruited in a study to find out if I have hyperuricemia. The investigator has also informed me that my participation in this study is voluntary and will not exclude me from my routine care even if I were to opt out. He has also informed me that I'll not be required to pay for the tests done for the purposes of this study.

Sign: ……

Name: ……

Date: ……

Appendix III: Consent Form (B.Kiswahili)

Jina langu ni Daktari Sylvia Mibey. Mimi ni daktari aliyefuzu na kusajiliwa na bodi ya madaktari wa Kenya (Kenya Medical Practitioners and Dentists Board). Mimi nimsomiwashahada ya juu (Masters) ya udaktari (Internal medicine) katika chuo kikuu cha Moi University. Nimekuona leo kwa sababu ninafanya uchunguzi kujua kama watu wazima walio na ugonjwa wa shinikizo la damu huenda wakawa na hyperuricemia.

KUHUSUSHINIKIZO LA DAMU NA HYPERURICEMIA

Shinikizo la damu kuhusishwa na kuongezeka kwa uric acid kwa damu,ambayo inaweza kusababisha ugonjwa wa figo, ugonjwa wa moyo na kiharusi. Ili kufanya uchunguzi huu,tutahakikisha kuwa hunamagonjwa mengine ambayo yanajulikana kusababisha uricacid kuongezeka kwa damu. Ukipatikana kuwa unayo mojawapo wa magonjwa yoyote hayo,hutahitajika kushiriki katika uchunguzi huu lakini utahudumiwa na kutibiwa ugonjwa huo vilivyo.Tutakuuliza maswali kuhusu magonjwa yoyote mengine unayoweza kuwanayo au unayotibiwa,historia ya jamii yako,madawa yoyote unayotumia na kasha tutakupima

Ilitujue kama unayo ugonjwa huu wa hyperuricemia, tutakuomba tufanye uchunguzi kadhaa.kwa hivyo tutakupima ili tuona kama damu ina kimbia .Tutapima damu ilitujue kiwango ya uricacid ,hali ya figo sukari na mafuta kwa mwili .Tutayaweka matokeo yako kwanjia ya kuheshimu haki yako. Tutakujulisha kuhusu matokeo yako na maana kwa afya yako. Tuta kupa matibabu iwapo utachagua ama usichague kushiriki katika uchunguzi huu Tutakupa matibabu yafaayo.Uwe huru kuuliza maswali yoyote Uchunguzi huu umehidhinishwa na kamati ya kusimamia machunguzi ya wasomi na haki ya wanaochunguzwa (Institutional Research and Ethics Committee-IREC) katika

chuo kikuu cha Moi University na hospitali kuu ya Moi Teaching and Referral.Iwapo unahitaji maelezo zaidi tafadhali wasilianana IREC kwa kutumia anwani ifuatayo.

Mwenyekiti IREC,

Moi Teaching and Referral Hospital,S. L. P. 3,

Eldoret.

Simu: 33471/2/3

Nambari yangu yasimu yarununi: 0723647419

IDHINIYAKO:

Walio na miaka 18 nazaidi

Nimeelezwa ipasavyo ya kwamba ninashiriki katika uchunguzi wa usomi utakayo chunguza iwapo nina kiwango ya juu ya uric acid, ugonjwa ambao mimi kwa ajili ya kuwa na ugonjwawashinikizo la damuninawezakuwanayo.

Mchunguzipiaamenielezakuwasitakosamatibabuyanguyakawaidaiwaponishirikikatikauchunguzi au nisiposhiriki.

Pianimeelezwakuwasitahitajikakulipiachochotekinachohusiananauchunguzihuu.

Sahihi: ……

Jina: ……

Tarehe:

……

Appendix IV: Procedure For Measuring Blood Pressure

Blood pressure will be taken using an Omron M2 compact upper arm blood pressure monitor (**Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015**).

The patient should be in a quiet place, in a relaxed sitting position with no tight fitting clothing on the upper arm, or any thick clothing such as a sweater.

The patient sits upright with the back straight and places the arm on the table so that the cuff is on the same level as the heart. The cuff is wrapped on the right arm such that the bottom of the cuff is at least 1cm above the elbow. It is then fastened snugly. The start button on the machine is then pressed and automatically the cuff begins to inflate and the machine takes a reading. The blood pressure results as well as a heart rate reading are then displayed on the screen.

Should an error occur, the cuff is deflated and the process is repeated. High blood pressure readings are confirmed manually using a mercury sphygmomanometer.

The blood pressure machines are calibrated every week.

Appendix V: Procedure For Testing Blood Glucose

Instrument used: HemoCue Glucose 201+

Principles:

The HemoCue Glucose 201+ is a system for the determination of the total amount of glucose in whole blood. Capillary, venous or arterial blood may be used. It utilises a modified glucose dehydrogenase method. A chromogen compound is added to the reagents with saponin used for haemolysing the erythrocytes. The absorbance is measured at two wavelengths (660 and 840nm) to compensate for turbidity.

Testing Procedure: Procedure is explained to the subject and consent obtained. . A drop of blood from the blood collected from the vein for other tests, is placed at the tip of the microcuvette allowing it to fill in a continuous process making sure that there are no air bubbles. Wipe off excess blood on the outside of the microcuvette tip without drawing blood out of the cuvette. If there are air bubbles, the test is repeated with a new sample of blood.Place the filled microcuvette in the cuvette holder within 40 seconds of filling the cuvette. Push the cuvette holder to its measuring position. Test results are automatically displayed in 40-240 seconds.

Quality Control

The HemoCue Glucose 201+ analyser has an internal electronic „SELFTEST". Every time the analyser is turned on, it will automatically verify the performance of the optronic unit of the analyser. This test is performed every second hour if the analyser is left turned on.

Measuring range:

0-30 mmol/L (0-540mg/dL). Results above 30mmol/L (540mg/dL) will be displayed as HHH.

IVD Medical Device Directive:

The HemoCue Glucose 201+ complies with the IVD Medical Device Directive 98/79/EC and carries the CE mark. 61

Appendix VI: Procedure for Drawing Blood

The procedure is explained to the patient and verbal consent sought.

Universal precautions will be observed.

A tourniquet is applied at a distal site about 5cm proximal to the selected site of venipuncture. The patient makes a fist without pumping the hand. The phlebotomist puts on a pair of clean gloves. The selected site is cleaned thoroughly with methylated spirit or povidone Iodine starting with the center and working outward. It is then allowed to dry.

The patient's arm is grasped firmly using the thumb to keep the skin taut and to anchor the vein. A sterile Vacutainer® system (**Becton, Dickinson and Company, 1 Becton Drive, Franklin Lakes, NJ USA 07417**) is opened and the blood collection needle inserted gently into the lumen of the vein at an angle of 15- 30^{o}, then the other end is attached to a Vacutainer® blood collection bottle. Blood flows freely into the bottle due to negative pressure. 2ml of blood for serum creatinine, 2mls for uric acid determination will be collected in a plain bottle and another 2ml will be collected in a S.S.T-bottle to be used for determination of the lipid profile.

After adequate blood has been collected, the tourniquet is released then the Vacutainer® needle is removed gently and an alcohol impregnated swab is applied at the site under pressure. Pressure is applied for a whole minute then the site is reassessed for continued bleeding. The area is dressed with a dry gauze and tape.

Appendix VII: Procedure For Determining Serum Uric Acid

Blood in plain Vacutainer® bottles are taken immediately to the lab. Serum may be stored for up to one day at 2 to 25^{o}C, up to seven days at 4 to 8^{o}C and up to six months at -20 to -80^{o}C.

The bottle is set onto a centrifuge and spun at 3000 rpm for 3 minutes to separate the serum from the cells. The supernatant (serum) is carefully suctioned using a micropipette and transferred to a sample cup. The sample cups are systematically set on a rack that goes onto a Cobas Integra® 400 plus analyzer

The cassette COBAS INTEGRA uric acid VER.2

It contains an in vitro diagnostic reagent system intended for determination of uric acid concentration in serum, plasma and urine.

The Roche assay described here is a slight modification of the colorimetric method.

The modification were developed by siedel. In this reaction,the peroxide reacts in the presence of peroxidase(POD),TOOS and 4-aminophenazone to form a quinoneimine dye.

The intensity of the red colour formed proportional to the uric acid concentration and is determined photometrically by measuring the increase in absorbance at 532nm.

Test principle Enzymatic calorimetric test.

Uricase cleaves uric acid to form allantoin and hydrogen peroxide.sdc

Uric acid + 2 H_2O + O_2 ⟶ Allantoin + CO_2 + H_2O_2

$2H_2O_2$ + H^+ + $TOOS^a$ + 4- aminophenazone ⟶ quinine- diimine dye + 4 H_2O

The color intensity of the quinine- diimine formed is directly proportional to the uric acid concentration and is determined by measuring the increase in absorbance at 552 nm.

a) N- acetyl – N- (2-hydroxyl – 3 sulfopropyl)-3- methylalanine)

Quality control

For all this quality control are run daily

Appendix VIII: Procedure For Lipid Profile

HDL CHOLESTEROL liquicolor is a homogenous enzymatic assay for the quantitative determination of HDL cholesterol. Blood is drawn after an overnight fast.

Method

The assay combines two specific steps: 1st step chylomicrons, VLDL and LDL cholesterol are specifically eliminated and destroyed by enzymatic reactions. In the second step remaining cholesterol from HDL fraction is determined by well-established specific enzymatic reactions in the specific surfactants for HDL.

CHOLESTEROL liquicolor CHOD-PAP-Method Enzymatic Colometric Test for cholesterol with Lipid Clearing Factor (LCF)

Method

The cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from hydrogen peroxide and 4-aminophenazone in the presence of phenol and peroxidase.

TRIGLYCERIDES liquicolor GPO-PAP Method Enzymatic Colometric Test for Triglyceridess with Lipid clearing Factor (LCF)

Method

The triglycerides are determined after enzymatic hydrolysis with lipases.Indicator is quinoneiminine formed fromhydrogen peroxide, 4-amino-antipyrine and 4-chlorophenol under the catalytic influence of peroxidase.

Quality control

For all this quality control are run daily

Appendix IX: Procedure For Determining Serum Creatinine

Blood in plain Vacutainer® bottles are taken immediately to the lab. Serum may be stored for up to one day at 2 to 25^{o}C, up to seven days at 4 to 8^{o}C and up to six months at -20 to -80^{o}C.

The bottle is set onto a centrifuge and spun at 3000 rpm for 3 minutes to separate the serum from the cells. The supernatant (serum) is carefully suctioned using a micropipette and transferred to a sample cup.

The sample cups are systematically set on a rack that goes onto a Cobas Integra® 400 plus analyzer (**Roche Diagnostics, 9115 Hague Road, PO Box 50457, Indianapolis, IN 46250-0457**). This is an autoanalyzer that uses the Jaffe reaction to quantify creatinine; creatinine reacts with picric acid in the presence of an alkaline pH to produce a yellow-red complex that has a maximum absorbance at 512nm. The rate of dye formation is proportional to the level of creatinine in the sample. The analyzer reads out this absorbance and based on its software it calculates the serum creatinine. It prints out the result on paper.

The result is reported in µmol/L alongside reference serum creatinine levels.

Quality control checks are run daily.

Appendix IX. Timelines

	I4	May I4		July-I4	Sept-I4	Oct-I4		I4		Aug- 15	Dec-15
Developing proposal(Introduction, Literature review & Methodology)											
Presenting proposal to supervisors											
Developing data collection tools											
Proposal Submission to IREC											
Piloting data collection tools											
Finalization of data collection tools											
Data collection											
Data entry, coding and cleaning											
Interim analysis											
Final Analysis											
Thesis write up(results, discussion)											
Notice of intent to submit											
Mock defense											
Submission of Thesis for Examination											
Thesis defense											
Graduation											

Appendix X. Budget

Items	**Quantity**	**Unit Price (Kshs)**	**Total (Kshs)**
Stationery & Equipment			
Printing Papers	5 reams	500.00	2,500.00
Black Cartridges	2	2,000.00	4,000.00
Writing Pens	1 packet	500.00	500.00
Flash Discs	1	2,000.00	2,000.00
Box Files	2	200.00	400.00
Document Wallets	2	50.00	100.00
Research Proposal Development			
Printing drafts & final proposal	10 copies	500.00	5,000.00
Photocopies of final proposal	6 copies	100.00	600.00
Binding of copies of Proposal	5 copies	100.00	500.00
Serum Uric acid tests	272	300	81,600.00
Creatinine tests	272	250	68,000.00
Lipid profile tests	272	800	217,600.00
Random blood sugar tests	272	50	13,600.00
Biostastician	1	10,000.00	10,000.00
Printing of drafts and final thesis	10 copies	800.00	8,000.00
Photocopy of final thesis	6 copies	200.00	1,200.00
Binding of thesis	6 copies	300.00	1,800.00
Total			**417,400**
Contingencies (10% of Total)			**41,740.00**
Grand Total			**459,140.00**

Appendix XI: Formal Approval Letter

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2014/183
Approval Number: 0001289

2nd October, 2014

Dr. Sylvia Chemutai Mibey,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
02 OCT 2014
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Mibey,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Hyperuricemia among Newly Diagnosed Hypertensive Patients attending Moi Teaching and Referral Hospital, Eldoret, Kenya."

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1289*** on 2nd October, 2014. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 1st October, 2015. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix XII: Approval To Conduct Research

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke
P. O. Box 3
ELDORET

Ref: ELD/MTRH/R.6/VOL.II/2008

2nd October, 2014

Dr. Sylvia Chemutai Mibey,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Hyperuricemia among Newly Diagnosed Hypertensive Patients attending Moi Teaching and Referral Hospital, Eldoret, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. JOHN KIBOSIA
DIRECTOR
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD, HRISM

Appendix XIII: Approval of Amendment

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference

IREC/2014/183
Approval Number: 0001289

3rd July, 2015

Dr. Sylvia Chemutai Mibey,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
03 JUL 2015
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr. Mibey,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Hyperuricemia among Hypertensive Patients Attending Moi Teaching and Referral Hospital, Eldoret, Kenya".

We note that you are seeking to make an amendment as follows:-

1. To change the title to include all hypertensives.

The amendment has been approved on 3rd July, 2015 according to SOP's of IREC. You are therefore permitted to continue with your research.

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: Director - MTRH Dean - SPH Dean - SOM
Principal - CHS Dean - SOD Dean - SON