BIOCHEMICAL AND ANTHROPOMETRIC CHARACTERISATION OF HYPERTENSION IN KUMASI

A THESIS SUBMITTED IN
FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE
OF

MASTER OF PHILOSOPHY

In the
Department of Molecular Medicine,
School of Medical Sciences
College of Health

by

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JANUARY, 2016

DECLARATION

With the exception of references and quotations from other sources which have all been credited, I hereby declare that this piece of work is the original research work of mine and that no part of it has been presented elsewhere. Also, I would like to say that any errors of judgment, facts, omissions and style remain my liability.

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ABSTRACT

The surge in prevalence of chronic non-communicable diseases like hypertension and chronic kidney disease has been linked with modifiable lifestyle practices and increased body fat. This study sought to evaluate the association between different modifiable lifestyle practices, adiposity indices, biochemical parameters and target cardiac and kidney organ damage among hypertensives in Kumasi. Using a hospital-based case–control study design, 241 Ghanaian indigenes from the Kumasi metropolis were recruited for this study. The case group was made up of, 180 hypertensives and 61 normotensives served as controls. In addition to socio-demographic data, all participants underwent standard haemodynamic, anthropometric, biochemical and cardiac organ damage assessment. In general, the case group presented with a significantly poorer atherogenic lipid profile compared to their counterparts in the control group. Increasing atherogenic dyslipidaemia was more prevalent with the presence of cardiac target organ damage. The prevalence of chronic kidney disease (CKD) ranged between 13.3% to 16.6% depending on the equation used in estimating the glomerular filtration rate (eGFR). Chronic kidney disease was significantly higher among self-reported smoker and alcoholic hypertensives. Among the commonly used athropometric measures, a population-specific threshold for waist circumference of >75cm for females and >80cm for male were the best adiposity indices for discriminating hypertension. However significant improvement in prediction was achieved with the use of conicity index (>1.08 female, >1.05 male). The sole reliance on body mass index in the determination of obesity and associatd health risks must be discontinued to incorporate more sensitive anthropometric markers.

DEDICATION

This work is dedicated to my sons Kwame Ofori Acheampong, Kofi Adu Owusu and their father Kweku Ofori Acheampong my beloved husband. They have been the motivational strength behind this work. Again I dedicate this work to Dr. W.K.B.A Owiredu my wonderful supervisor for all the sacrifices he has made to bring me this far in this project.

ACKNOWLEDGEMENT

To the one who strengthens me to do all things; to he who is able to complete whatsoever he has began in me; the Omnipotent God for bringing me this far, may his name be praised. My sincere gratitude goes to my supervisors, Dr W. K. B. A. Owiredu, Dr. I. K. Owusu and Dr. E.F. Laing for their immense support, advice; guidance and patience from the beginning of my project life to date. It took time though but I think I have finally "responded to treatment". God richly bless you. I wish to show my sincere gratitude to my colleague and friend Mr. James Osei-Yeboah for all the support and advice you offered me throughout this project, you are part of this success, brother. I say a big thank you to the entire staff and postgraduate students of the Molecular Medicine Department-KNUST, the staff of specialist consulting room one of Komfo Anokye Teaching Hospital and the entire staff os Precise Specialist Clinic - Asokwa for the diverse support, God richly bless you.

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ABREVIATIONS

AgRP	Agouti-Related Peptide
a-MSH	A-Melanocyte-Stimulating Hormone
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BP	Blood Pressure
CHD	Chronic Heart Disease
CI	Conicity Index
CKD	Chronic Kidney Disease
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DM-HPT	Diabetes Mellitus-Hypertension
DXA	Dual-Energy X-Ray Absorptiometry
ECV	Extra Cellular Volume
Egfr	Estimated GFR
ESRD	End-Stage Renal Disease
ETA	Endothelin Receptors- Type A
ETB	Endothelin Receptors- Type B
FFAs	Free Fatty Acids
GFR	Glomerular Filtration Rate
HDLc	High Density Lipoprotein Cholesterol
HPT	Hypertension
HTN	Hypertension
ICAM	Inter-Cellular Adhesion Molecule-1
IDF	International Diabetic Federation
IL-1	Interleukin-1
INTERSALT	International Study of Salt and Blood Pressure
LDL	Low Density Lipoprotein
Ln CRP	Logarithm Of C-Reactive Protein
MC3R	Melanocortin 3 Receptor
MDRD	Modification of Diet in Renal Disease

NO	Nitric Oxide
NPY	neuropeptide Y
PAI-1	plasminogen activator inhibitor-1
PCR	Plasma Creatinine
PH	Pulmonary hypertension
POMC	Proopiomelanocortin
RAS	Rennin-Angiotensin system
ROS	Reactive oxygen species
SAT	Subcutaneous Peripheral Adipose Tissue
SNS	Sympathetic Nervous System
TC	Total Cholesterol
TG	Triglycerides
TNFR	Tumour Necrosis Factor receptor
TNFα	Tumour Necrosis Factor-α
VAT	Visceral Adipose Tissue
VCAM	Vascular Cell Adhesion Molecule-1
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist to Hip ratio
WHtR	Waist to Height ratio

Chapter 1 INTRODUCTION

1.1 BACKGROUND INFORMATION

Cardiovascular disease accounts for approximately 30% of all deaths (Santulli, 2013). High blood pressure and its sequelae are strongly associated with overall cardiovascular risk and are a major health concern the world over (Agyemang *et al.*, 2005; Santulli, 2013). Even though detection is said to be limited in Africa the prevalence of hypertension is increasing rapidly (Cappuccio *et al.*, 2006). Major health budgetary drains in sub-Sahara countries are attributable to infectious diseases, with inadequate attention to the control and treatment of the upsurge of chronic non-communicable diseases like hypertension (Abanilla *et al.*, 2011; Agyemang *et al.*, 2013). Evidence from previous works on the major causes of morbidity and mortality points to a rapid epidemiological transition from only communicable to a double burden of infectious and chronic diseases among the Ghanaian population (Aikins, 2010; Agyemang *et al.*, 2013). Among the list of non-communicable diseases plaguing the general Ghanaian population, hypertension is said to be the most prevalent (Akosa and Armah, 2005; Bosu, 2010; Addo *et al.*, 2013). Poor control of blood pressure has been implicated in the development of complications leading to prime target organ damage like the heart and kidney among Ghanaian hypertension groups (Addo *et al.*, 2009; Agyemang *et al.*, 2013).

A reciprocal or bidirectional relationship has been postulated for hypertension and end stage chronic kidney disease (ESCKD) (Stenvinkel *et al.*, 2008). Hypertension is a key pathogenic factor linked to deterioration of kidney function, whilst the most common forms of secondary hypertension are attributable to chronic kidney disease (Haroun *et al.*, 2003; Tedla *et al.*, 2011; Morgado and Neves, 2012). According to Commodore-Mensah *et al.* (2014), hypertension is the principal cause of renal failure in Ghana , whilst Owiredu *et al.* (2012b) estimated a 20 folds higher risk of death through cardiovascular complications among chronic kidney disease (CKD) patients than any other cause in general population.

Attributable factors for this change in disease burden trends in the population are among others, increasing life expectancy and lifestyle modification brought about by urbanization leading to a surge in the prevalence of contributeng factox such as obesity, physical inactivity, stress, unhealthy diet, dyslipidaemia, et cetera and this is well established (Aikins, 2010; Entsua-Mensah *et al.*, 2012; Addo *et al.*, 2013; Santulli *et al.*, 2013a). There is proof that hypertension is related to increases in body fat is well established in literature (Blair *et al.*, 1984; Gillum *et al.*, 1998; Backé *et al.*, 2011; Anoop *et al.*, 2015; Chandra and Turer, 2015; Parab-Waingankar and Rao, 2015; Sundgren *et al.*, 2015; Wang *et al.*, 2015; Zhang and Wang, 2015). Earlier studies have reported high levels of dyslipidaemia among hypertensive populations in Kumasi (Eghan and Acheampong, 2003; Micah and Nkum, 2012).

The outcome of epidemiological studies on the impact of obesity in chronic kidney disease (CKD) remain conflicting, with numerous well designed studies even suggesting a survival advantage for obese end stage renal disease (ESRD) patients (Axelsson, 2008; Agarwal *et al.*, 2010; Iglesias and Díez, 2010).

Regarding the association between hypertension and obesity, excess body fat is usually identified by proxy anthropometric indicators which has proven to be effective (Redon, 2001; Reddy *et al.*, 2010; Beck *et al.*, 2011; Munaretti *et al.*, 2011; Rani and Neelambikai, 2013). However, debate exists among scholars on the performance of the different anthropometric parameters, their optimal threshold cut-off points, gender and ethnic variations (Molarius and Seidell, 1998; Beck *et al.*, 2011; Munaretti *et al.*, 2011).

1.2 JUSTIFICATION

Studies on cardiovascular risk in relation to anthropometric factors are limited in sub-Sahara Africa (Adedoyin, 2008). In recent times the World Health Organisation/International Association for the Study of Obesity/International Obesity Task Force (WHO/IASO/IOTF) have suggested the use of lower obesity measurements in Asian and other places to direct healthcare professionals to endorse healthy life and weight control (Anuurad *et al.*, 2003; Kanazawa *et al.*, 2005; Fan *et al.*, 2007; Owiredu *et al.*, 2008). The International Diabetes Federation (IDF) task force on epidemiology and prevention in an attempt to harmonizing the definition of metabolic syndrome also proposed the use of ethnic based

anthropometric threshold cut-offs (Alberti *et al.*, 2009). To resolve the differing predictive thresholds of the clusters of risk factors for cardiovascular diseases, the general consensus is that components cut-off should be ethnic–specific adjusted to suit their usage in different ethnic groups (Owiredu *et al.*, 2008; Alberti *et al.*, 2009; Simmons *et al.*, 2010). Owiredu *et al.* (2008) and Frank *et al.* (2013) have reported different population-specific adiposity cut-off points from the europid thresholds in use for increased health risk and diabetes respectively among sub-populations in Kumasi. There is therefore the need to evaluate the population-specific optimal thresholds and performance of routinely used anthropometric indices as well as less common candidate anthropometric measures in this setting. The biochemical characterization of hypertensives by renal function, lipid abnormalities vis-à-vis target cardiac organ damage evaluated by the use of X-ray, echocardiogram and electrocardiograph would throw light on the prognostic role of these parameters among hypertensives in Ghana, since there is paucity of data in the Ghanaian literature.

1.3 MAIN OBJECTIVE

This study sought to assess the association between different modifiable lifestyle practices, adiposity indices, atherogenic dyslipidaemic parameters, renal function parameters and hypertension as well as the predictive implications for levels of these parameters in target cardiac organ damage among an urban Ghanaian hypertensive population and as well determine the optimal threshold points and

the discriminative power of these parameters as discriminators of high blood pressure.

1.3.1 Specific Objectives

- To characterise hypertension through modifiable lifestyle practices, anthropometry and biochemical parameters
- To determine the predictive implications for levels of biochemical parameters in target cardiac organ damage among an urban Ghanaian hypertensive population
- To determine the population- specific optimal threshold points and the discriminative power of routinely used anthropometric indices as well as less common candidate anthropometric measures as discriminators of high blood pressure

Chapter 2 LITERATURE REVIEW

2.1 HYPERTENSION

2.1.1 Definition and Epidemiology

Hypertension is a vital public health burden in both developing and advanced countries (Tedla *et al.*, 2011; Addo *et al.*, 2013). It was recorded as a medical condition by Huang Ti around 2600BC; which has shaped the course of modern history (Mayet and Hughes, 2003; O'Shaughnessy and Karet, 2004; O'Shaughnessy and Karet, 2006) and the outcomes of hypertension such as myocardial infarction, stroke, and heart failure, it is projected that it will soon be the principal cause of death in the world (Mayet and Hughes, 2003; Oparil *et al.*, 2003; Wang *et al.*, 2012; Agyemang *et al.*, 2013). The main hemodynamic aberration in HPT is an increase in peripheral resistance due to changes in vascular structure (reduced lumen diameter and arterial wall thickening) and function (increased vasoconstriction and/or decreased vasodilatation) (Oparil *et al.*, 2003; Kotchen, 2010; Shimbo *et al.*, 2010). The WHO ranks coronary heart and cerebrovascular morbidities as the principal cause of death globally. (DrenjančevićPerić *et al.*, 2010). For the last centuries, hypertension has been named as one(1) of the top ten major causes of global disability adjusted life years (Drenjančević-Perić *et al.*, 2010) and affects roughly 25% of the adult population. It is projected that the hypertension prevalence would go as high as sixty per cent (60%) by 2025, when a total of about 1.56 billion people may be affected (Adrogué and Madias, 2007; Drenjančević-Perić *et al.*, 2010; Kotchen, 2010). Until now, hypertension was thought to be uncommon

in rural Africa (Cappuccio *et al.*, 2004); but, hypertension and its associated complications, which includes stroke, heart failure, and renal failure, have been increasingly diagnosed (AL-Hamdani, 2010; Wang *et al.*, 2012; Landsberg *et al.*, 2013) in blacks all over the world (Cappuccio *et al.*, 2004; Micah and Nkum, 2012; Wang *et al.*, 2012). The growing rates of deaths due to cardiovascular disease (CVD), especially stroke, have been unprecedented (Agyemang *et al.*, 2013) and the prevalence of hypertension is expected to increase even further if broad and effective preventive measures are not taken (Bosu, 2010; Addo *et al.*, 2013). This is especially true for Ghana where the second leading cause of outpatient morbidity in adults older than 45 years is hypertension (Agyemang *et al.*, 2005; Bosu, 2010; Abanilla *et al.*, 2011; Addo *et al.*, 2013). In Ghana, earlier studies revealed hypertension prevalence of 4.5% among those living in rural settlements and of 8% to 13% in the urban areas (Cappuccio *et al.*, 2004). An increase in diseases associated with hypertension does not only depict a high prevalence of hypertension, but it also indicates inadequacy in the rates of detection, treatment and control (Cappuccio *et al.*, 2006; Addo *et al.*, 2013). It was observed in an examination of post-mortem records at the Korle-Bu teaching hospital in Accra between 1994 and 1998 that, stroke was the cause of 11 % of deaths in adults aged 20 years or more, most of which were haemorrhagic (Addo *et al.*, 2013) and hypertension was a predominant factor in these strokes (Addo *et al.*, 2013).

The prevalence of hypertension in Accra was found to be 28.3% (crude) and 27.3% (age-standardized) in a study conducted in Ghana (Cappuccio *et al.*, 2004). At the age of less than 40 the prevalence of hypertension was higher among men than in women but becomes in both sexes after 40 years (Cappuccio *et al.*, 2004; Bosu, 2010). In another study, the prevalence of hypertension in older age was higher in women than in men (Bosu, 2010; Micah and Nkum, 2012). In the Ashanti region of Ghana, hypertensive-related vascular diseases (namely stroke, renal and heart failure) accounted for a significant proportion of morbidity and mortality (Cappuccio *et al.*, 2006; Agyemang *et al.*, 2013). In mixed populations, the prevalence of hypertension was higher in urban than in rural populations (Bosu, 2010). In four of six rural populations, prevalence of hypertension (BP ≥ 140/90mmHg) was 24% or higher (Bosu, 2010). In a study of adult patients from Komfo Anokye Teaching Hospital (KATH), Kumasi, 17.9% of acute medical admissions were ascribed to cardiovascular causes including hypertension, heart failure and stroke (Agyemang *et al.*, 2013).

2.1.2 Dyslipidaemia in Hypertension and CKD

Dyslipidaemia is a known to have a complementary relationship with chronic kidney disease (CKD), increased triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDLc) (Wang *et al.*, 2008; Bentley *et al.*, 2012). The relationship between lipids and kidney function in general, however, is not clear. Evidence suggests that hypertension is related to cardiovascular disease (CVD) in

terms of pathophysiological mechanisms (Halperin *et al.*, 2006; Shimbo *et al.*, 2010). Thus, dyslipidaemia, a strong predisposing factor of CVD, may lead to the pathogenesis of hypertension (Oparil *et al.*, 2003; Halperin *et al.*, 2006; Micah and Nkum, 2012).

2.1.2.1 Atherogenic Indices

Atherogenic index is the ratio of TC to HDL and is used as a predictor of atherosclerosis and cardiovascular risk with a higher ratio indicating an increased risk and vice-versa (Micah and Nkum, 2012). Studies revealed that the serum lipid levels in healthy Nigerians was found to be generally lower than in Caucasians (Amato *et al.*, 2011; Micah and Nkum, 2012) and similar findings were obtained in studies in Ghana where lipid disorders are common (Micah and Nkum, 2012). In the findings of Micah and Nkum (2012), mean Atherogenic index was 3.40 and there were no significant differences among sex, age or clinical groups. The reports of Owiredu *et al.* (2008) in Ghana, was conflicting to earlier findings by Eghan and Acheampong (2003) where the total serum cholesterol levels are higher in the presence of hypertension and diabetes type II. Increased concentrations of plasma non-HDL-C, TC and the TC/HDL-C ratio are independently associated with a consequent increased risk in the pathogenesis of hypertension and vice versa in higher concentrations of HDL-C (Halperin *et al.*, 2006). Atherogenic lipid abnormalities clearly cause impairment of endothelial function (Oparil *et al.*, 2003; Halperin *et al.*, 2006) and this may perhaps be through impaired production and activity nitric oxide, as well as changes in endothelin-1 and endothelin A and B

receptor expression, (Oparil *et al.*, 2003; Halperin *et al.*, 2006; Kotchen, 2010; Kotsis *et al.*, 2010; Shimbo *et al.*, 2010) and the endothelium is unable to respond to changes in intravascular conditions to expand and constrict as needed (Drenjančević-Perić *et al.*, 2010; Kotsis *et al.*, 2010; Shimbo *et al.*, 2013). This vasodysregulation can cause impairment in vasodilatation in response to appropriate stimuli and ultimately leading to increased resting blood pressure. Plasma lipid abnormalities and insulin resistance have been associated with sympathetic hyper function, (Halperin *et al.*, 2006; Kotchen, 2010; Landsberg *et al.*, 2013), which seems to play a role in the development of hypertension (Halperin *et al.*, 2006; Kotchen, 2010; Horita *et al.*, 2011; Landsberg *et al.*, 2013). It has been suggested that hypertension and dyslipidaemia are associated (Oparil *et al.*, 2003; Kotchen, 2010; Horita *et al.*, 2011; Micah and Nkum, 2012; Landsberg *et al.*, 2013) because they form part of the metabolic syndrome, and that possibly insulin resistance or hyperinsulinaemia, (Halperin *et al.*, 2006; Kotchen, 2010; Horita *et al.*,

2011; Landsberg *et al.*, 2013) may unite the various abnormalities of the syndromes (Halperin *et al.*, 2006). Dyslipidaemia is one of the causes of atherosclerosis (Oparil *et al.*, 2003; Drenjančević-Perić *et al.*, 2010; Kotchen, 2010; Shimbo *et al.*, 2010) and it is a major complication of HPT (Micah and Nkum, 2012). Acute coronary syndromes are responsible for most of the morbidity caused by coronary atherosclerosis. Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries (Shimbo *et al.*, 2010). Since high plasma levels

of cholesterol, especially LDL-cholesterol, are one of the dorminant risk factors of atherosclerosis, the process of atherogenesis is said to consist largely of the deposition of lipids within the artery wall. The insights of the scientific community in the pathophysiology of this important disease have evolved substantially over the past century (Oparil

et al., 2003).

2.1.2.2 Impairment of endothelial function

Nitric oxide is an effective vasodilator and prevents platelet adhesion and aggregation. It is also suppresses the movement and multiplication of vascular smooth-muscle cells. Nitric oxide is produced by normal endothelial cells in response to a number of stimuli such as changes in blood pressure, shear stress, and pulsatile stretch, and plays a vital role in the regulation of blood pressure, thrombosis, and atherosclerosis (Oparil *et al.*, 2003; Shimbo *et al.*, 2010). In healthy persons, the cardiovascular system is exposed to unremitting nitric oxide-dependent vasodilator tone, but nitric oxide-related vascular relaxation is reduced in hypertensives (figure 2.1).

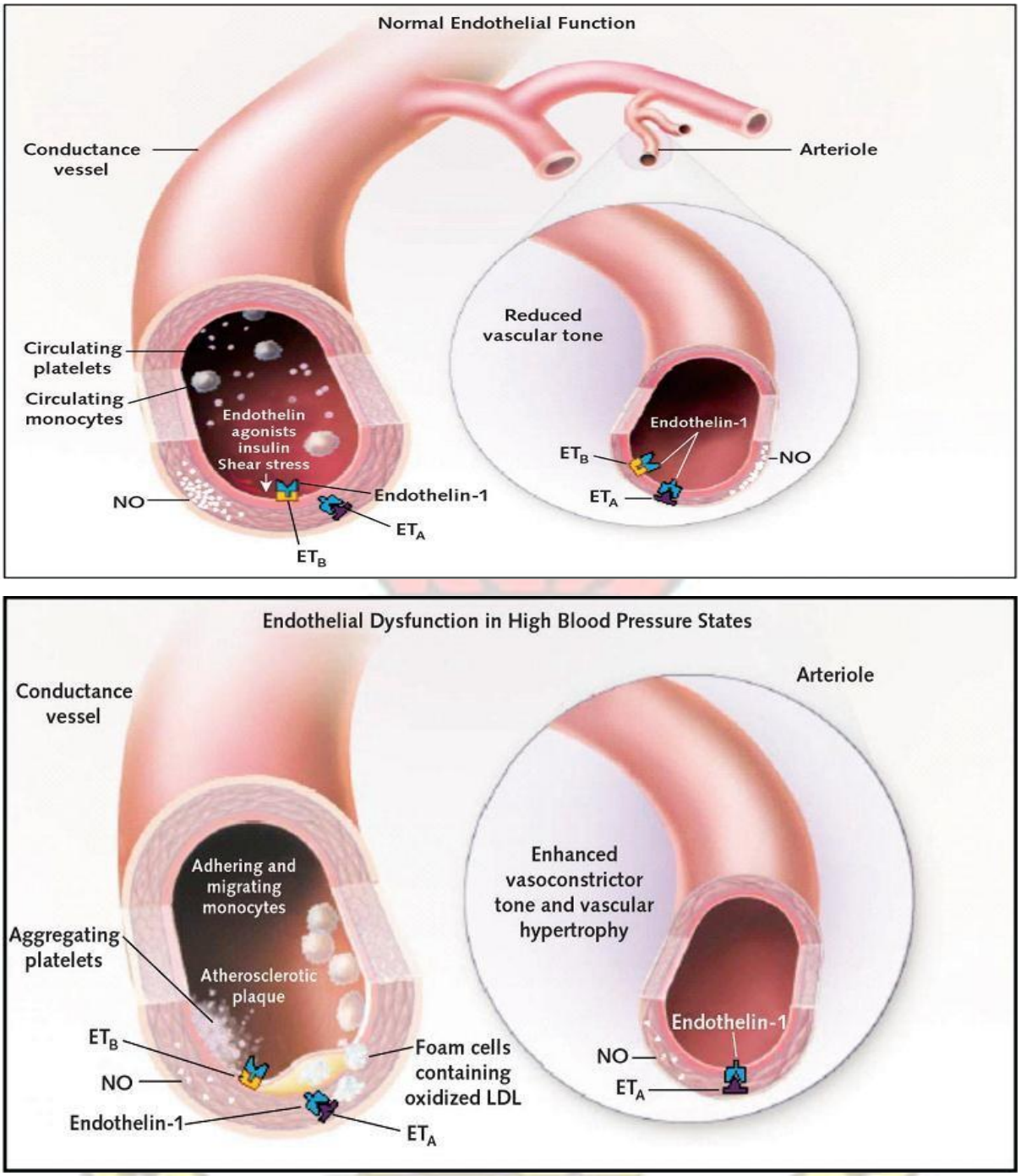

FIGURE 2-1 : ENDOTHELIAL DSYFUNCTION INDUCED HYPERTENSION

Large conductance vessels (left) and resistance arterioles (right), above.

In normal conductance arteries (up), platelets and monocytes circulate freely, and the peroxidation of low-density lipoprotein is averted by a large formation of nitric oxide (no). At the small arterioles level, reduced vascular tone is kept by continuous release of nitric oxide.

Endothelin-1 normally does not induce vasoconstriction or if it does, only minimally by activating endothelin receptors (eta) (type a) situated on smooth-muscle cells. Endothelin-1 contributes to the release of basal nitric oxide by stimulating endothelin receptors (etb) (type b) located on endothelial cells. In hypertensives, the microvasculature (below) has decreased nitric oxide activity and improved eta-mediated vasoconstrictor activity of endothelin-1 which results in increased vascular tone and medial hypertrophy, with a consequential increase in systemic vascular resistance. In the region of conductance arteries, a similar imbalance is seen in the activity of endothelial factors which leads to a proatherosclerotic milieu. This promotes the peroxidation of low-density lipoprotein (ldl), the adhesion and migration of monocytes, and the formation of foam cells. The above activities lead to the development of atherosclerotic plaques, and the rupture of which, in situations where there is enhanced platelet aggregation and impaired fibrinolysis, results in acute intravascular thrombosis. This explains the increased risk for cardiovascular events in hypertensives. These mechanisms may occur in populations with high normal blood pressure and may predispose them to increased cardiovascular risk (oparil *et al.*, 2003).

The observation that in vivo delivery of super oxide dismutase reduces blood pressure and restores nitric oxide bioactivity provides an empirical evidence that oxidant stress precipitates the activation of nitric oxide and the impairment of endothelial function in hypertensives (Oparil *et al.*, 2003; Shimbo *et al.*, 2010). Though a lot of efforts have been made to explain the mechanism of dietary salt intake in the development of hypertension, the underlying mechanisms of salt intake that cause the endothelial dysfunction in salt-sensitive hypertension have still not been elucidated (Drenjančević-Perić *et al.*, 2010). However, there is evidence that normal regulation of the renin-angiotensin system (RAS) plays a vital function in the mechanisms of vascular relaxation that are dysfunctional in hypertension. This could partly cause the high blood pressure maintained by an elevated total peripheral resistance (Oparil *et al.*, 2003; Drenjančević-Perić *et al.*,

2010). Angiotensin II has been suggested to promote the formation of superoxide at levels that affect blood pressure minimally (Oparil *et al.*, 2003). Increased oxidant stress and impaired endothelial function may thus be a predisposing factor to hypertension (Oparil *et al.*, 2003; Drenjančević-Perić *et al.*, 2010).

2.1.3 Inflammatory markers (C-reactive protein, TNF-α and IL-6) and Hypertension

TNFα is a pleiotropic 157-amino acid peptide cytokine (Horita *et al.*, 2011). It is committed in various physiological reactions, such as inflammation, proliferation, cell differentiation, and cell death including cell apoptosis (Horita *et al.*, 2011). TNFα binds to TNF receptor (TNFR), which has two subtypes, called TNFR1 and TNFR2 (Horita *et al.*, 2011). It has been proposed for a long that TNFα causes insulin resistance (Kotchen, 2010; Horita *et al.*, 2011; Landsberg *et al.*, 2013). The findings of Uysal et al. as reported by Horita *et al.* (2011) have it that mice lacking TNFα function do not develop obesity-induced insulin resistance. However, TNFα alone may be insufficient to induce insulin resistance (Horita *et al.*, 2011). Interestingly, there are controversial papers about the effect of TNFα on sodium reabsorption (Horita *et al.*, 2011). In particular, pro-inflammatory adipokines, such as leptin, tumour necrosis factor-alpha and inteleukin-6, have been associated with an increased risk of mortality (Iglesias and Díez, 2010). Serum C-reactive protein (CRP) concentration has been known as a marker of systemic

inflammation (Ruperto *et al.*, 2013b). A rising level of CRP can also have direct downstream proinflammatory effects, including activation of complement, tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and especially IL-6 (Ruperto *et al.*, 2013b). Human adipose tissue was recently shown to be a hormonally active system that secretes a host of inflammatory cytokines including IL-6, which stimulates hepatic production of CRP (Oparil *et al.*, 2003; Ruperto *et al.*, 2013b). In studies of the general population, a correlation between circulating C-reactive proteins (CRP) levels and body fat mass has been elucidated (Ruperto *et al.*, 2013b). Particularly, visceral adipose tissue dispersed within the intra-abdominal cavity and around the immediate environment of the omentum and mesentery has been demonstrated to be the adipose depot with the highest involvement in systemic inflammation (Ruperto *et al.*, 2013b).

2.1.4 Presumed Pathophysiology of Salt-Induced Hypertension

Salt sensitivity is a condition defined by significant variations in blood pressure in direct relation to the sodium content of the diet (Oparil *et al.*, 2003; O'Shaughnessy and Karet, 2004; O'Shaughnessy and Karet, 2006; Rodríguez-Iturbe *et al.*, 2012) and is present in 80% of hypertensive individuals older than 60 years (O'Shaughnessy and Karet, 2004; Rodríguez-Iturbe *et al.*, 2012). The interaction between the in-vivo imbalances (basically in the kidney) and the external environment results in primary hypertension and sodium has been identified long as the essential environmental factor. (Adrogué and Madias, 2007; Rodríguez-Iturbe *et al.*, 2012).

Many studies has shown how the bad effect of excess of sodium on arterial blood pressure (Adrogué and Madias, 2007). On the contrary, potassium has usually been seen as a minor contributing factor in the pathogenesis of hypertension, yet, enough evidence suggests that low potassium concentration has a crucial role in hypertension and its cardiovascular disorders (Adrogué and Madias, 2007). Current proof as well as classic studies point to the interplay of sodium and potassium as the main environmental factor in the development of primary hypertension and its cardiovascular sequelae (Adrogué and Madias, 2007). The association of sodium intake and hypertension was elucidated roughly 40 years ago by Guyton et al. (Oparil *et al.*, 2003; O'Shaughnessy and Karet, 2004; Drenjančević-Perić *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012). They postulated that sodium balance after subsequent dietary salt intake is controlled by the pressurenatriuresis mechanism. Sodium loading is accompanied with a temporary increase in blood pressure which returns to normal after pressure-natriuresis and regulation of extracellular volume (ECV) (Blaustein and Hamlyn, 2010; Drenjančević-Perić *et al.*, 2010; Kotsis *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012; Landsberg *et al.*, 2013). Some individuals have dysfunction in sodium elimination mechanisms, thus, sodium retention causes expansion of ECV, causing higher cardiac output with tissue perfusion that exceeds metabolic needs (Blaustein and Hamlyn, 2010; Drenjančević-Perić *et al.*, 2010; Kotchen, 2010; Kotsis *et al.*, 2010). Peripheral tissue vasculature responds by activating autoregulatory vasoconstriction, causing a further upsurge in peripheral resistance

(Drenjančević-Perić *et al.*, 2010). Studies performed on transplanted kidney patients and the above proofs, places the kidney in a central position in the regulation of blood pressure (Blaustein and Hamlyn, 2010; Drenjančević-Perić *et al.*, 2010). Current findings have revealed that the mechanisms involved in hypertension associated with high salt intake are multifaceted and that multiple interrelated factors participate in the pathophysiology of hypertension. High sodium concentrations may also, in addition to effects mediated by ECV expansion, have direct hypertensive actions, such as induction of cardiac myoblast and smooth muscle cell hypertrophy (O'Shaughnessy and Karet, 2004; O'Shaughnessy and Karet, 2006; Blaustein and Hamlyn, 2010; Drenjančević-Perić *et al.*, 2010; Kotchen, 2010; Landsberg *et al.*, 2013), activation of NF- B in proximal tubular cells (leading to renal inflammation) (Drenjančević-Perić *et al.*, 2010), changes in the RAS, induction of oxidative stress, and others. A dysregulation of sodium metabolism can also be related to changes in genes and receptors associated with mineralocorticoid synthesis and function (Drenjančević-Perić *et al.*, 2010; Kotchen, 2010). Primary hypertension and age-related increases in blood pressure are seen mostly in populations where the consumption of sodium is more than 100 mmol daily but almost absent in populations in which people consume less than 50 mmol of sodium chloride daily (Adrogué and Madias, 2007). The findings of the International Study of Salt and Blood Pressure (INTERSALT) showed that regardless of the fact that individual sodium intake in most countries

globally exceeds 100 mmol daily; most individuals have normal blood pressure. It seems, then, that intake of sodium that exceeds 50 to 100 mmol daily is essential but not adequate for the pathogenesis of primary hypertension (Adrogué and Madias, 2007; Drenjančević-Perić *et al.*, 2010). A randomized controlled trials reported that reducing intake of sodium by 50 mmol daily reduces systolic blood pressure by a mean of 4 mmHg and diastolic blood pressure by 2.5 mmHg in hypertensives and by an average of 2.0 mmHg in systolic blood pressure and an average of 1.0 mmHg in diastolic blood pressure among normotensive participants (Adrogué and Madias, 2007). Sodium sensitivity; which is an increase in blood pressure as a result of higher sodium chloride consumption than that in the baseline diet, appears to be a precursor of hypertension in normotensives (Adrogué and Madias, 2007; Landsberg *et al.*, 2013). Dietary potassium exerts a great dose-dependent inhibitory effect on sodium sensitivity. (Adrogué and Madias, 2007; Landsberg *et al.*, 2013).

2.1.5 Anthropometric indices

There is an overwhelming epidemiological proof that anthropometric indices are strongly correlated with cardiovascular mortality and morbidity (Brar, 2013). Azimi–Nezhad *et al.* (2009) disputed the fact that, although some investigators have proposed that waist circumference (WC) is a superior indicator because it requires only one measurement and correlates well with visceral adiposity, their

results indicate that waist-to-height ratio (WHtR) is better than WC which was consistent with other reports from studies in Japan and India (Azimi–Nezhad *et al.*, 2009). Waist-to-height ratio have been reported as a better screening measure cardiovascular risk factors when compared with body mass index (BMI), and WC (Azimi–Nezhad *et al.*, 2009; Khader *et al.*, 2010; Ashwell *et al.*, 2012; Lee *et al.*, 2015). However, in a review of 78 studies conducted during 1950-2008, as reported by Nadeem *et al.* (2013), WHtR and WC were seen to be better predictors of cardiovascular diseases. It was also found in the same study in Pakistani that, BMI is the best indicator of insulin resistance among male adults, while conicity index was the best indicator in female adults (Nadeem *et al.*, 2013). Another study in Pakistan also elucidated that WHtR was found to be a superior index for the prediction of the presence of central adiposity and hypertension (HTN); while BMI was a strong indicator of dyslipidemia. The study proposed that, the combination of WHtR and BMI can increase the explanatory power of each index alone (Syed *et al.*, 2009). Lee and Kim (2014) also suggested the use of the combination of the anthropometric indices which seems to slightly improve the predictive power for hypertension. Report from studies which were conducted among Indian adolescents; Brar (2013) also reported that WC is a better anthropometric indicator for detecting cardiovascular risk factor among adolescents boys than in girls whereas Ghosh and Bandyopadhyay (2013) was of the view that WC is the best adiposity measure in predicting hypertension in girls..

2.1.5.1 Anthropometric indices in relation to hypertension

Overweight and obesity have been found to be major determinants of hypertension and its prevalence is increasing globally (Azimi–Nezhad *et al.*, 2009). Anthropometric characteristics such as waist circumference (WC), waist: hip ratio (WHR), body mass index (BMI), and waist: height ratio (WHtR), have been associated with an increased risk of hypertension (HTN) regardless of age and ethnicity (Azimi–Nezhad *et al.*, 2009; Khader *et al.*, 2010; Nadeem *et al.*, 2013). BMI is generally accepted as a good estimate of general obesity, while other indices are indicators of central adiposity (Azimi–Nezhad *et al.*, 2009). Statistical evidence from studies involving more than 300,000 adults in several ethnic groups, shows the superiority of WHtR over WC and BMI for detecting cardiometabolic risk factors such as hypertension in both sexes (Ashwell *et al.*, 2012). WHR was not a significant predictor of hypertension and WC, the most widely used indicator of abdominal adiposity in children, was also better than WHR and CI in identifying children with high trunk fat measured with DXA according to Ghosh and Bandyopadhyay (2013). It is argued that WHR was largely influenced by skeletal structure and correlated poorly with central adiposity (Ghosh and Bandyopadhyay, 2013). Conicity index (Ci) may be a very useful parameter to differentiate between individuals with abdominal adiposity and those who are not necessarily obese. Conicity index (Ci) has a positive correlation with both serum

triglycerides and the logarithm of C-reactive protein (Ln CRP) and negatively correlated with plasma HDL-C (Ruperto *et al.*, 2013b).

2.1.5.2 Anthropometric indices cut-offs

Optimal cut-off values are dependent on sex, age, and the prevalence of the risk factor being screened where higher cut-off values were found among women and older age groups (Azimi–Nezhad *et al.*, 2009). Recent works have identified geographic specific cut-offs for these anthropometric indices (BMI, WC, HC, WHR and WHtR) (Azimi–Nezhad *et al.*, 2009; Nadeem *et al.*, 2013); for instance in South Asians, the relationship between risk of DM and BMI appears to differ from Caucasian populations (Azimi–Nezhad *et al.*, 2009). According to the WHO definition as reported by Azimi–Nezhad *et al.* (2009); Nadeem *et al.* (2013), a BMI of

25–29.99 and (≥30 kg/m2 for Europeans and >25kg/m2 for Asians (Syed *et al.*, 2009; Cheong *et al.*, 2013)) were taken as cut-off values defining overweight and obesity, respectively and based on the ATP III definitions, central obesity was defined as WC >102 cm for males and >88 for females (Azimi–Nezhad *et al.*, 2009). WHO cutoffs for waist circumference is >94cm for males and >80cm for females for a high risk of metabolic complications, whereas this risk is substantially higher with WC of >102cm in males and >88cm in females. Similarly, WHO cut-offs for WHR for substantially higher risk of metabolic complications are >0.9 in males and >0.85 in females. According to the International Diabetic Federation (IDF), the cut-offs for

WC in different geographic locations are >94cm and >80cm for males and females respectively in Europeans, >90cm and >80cm for males and females respectively in South Asians, Chinese and Japanese (Cameron *et al.*, 2010; Nadeem *et al.*, 2013). The global standard of BMI is ≥ 25 for measurement of overweight for both sexes as reported by Azimi–Nezhad *et al.* (2009); Nadeem *et al.* (2013) but their proposed cut-offs for BMI ranged between 25.4 and 27.8 for women, and 25 and 26 for men, WC fall into a wider range (85–95 cm for men and 89–94.5 cm for women) and for WHtR 0.5 for men and 0.6 for women in Iranian and Pakistani adults which are similar to those previously reported by others. The cut-off value was 1.32 and 1.39 for conicity index in Pakistani adults as revealed by Nadeem *et al.* (2013). The WC cut-offs are lower in Africans; Nigerians, it is 75.6/71.5cm and Cameroonians; 80.5/81.5cm in males and females respectively.

2.1.6 Prevalence of Chronic kidney disease (CKD) among Hypertensives

Hypertension is both a vital cause and an outcome of chronic kidney disease (Kobori *et al.*, 2007; Bakris and Ritz, 2009). Chronic kidney disease (CKD) is therefore commonly seen in secondary hypertension and proof imply it is an independent predisposing factor for cardiovascular disease and mortality (ALHamdani, 2010; Tedla *et al.*, 2011; Morgado and Neves, 2012). Chronic Kidney Disease (CKD) is on the rise worldwide and a public health problem (Poudel *et al.*, 2011). High prevalence of CKD has been reported in various studies from various geographical locations (Poudel *et al.*, 2011). It is believed that primary kidney

disease cause about 1.2% of all deaths worldwide (Eastwood *et al.*, 2010), and many more kidney related deaths are the outcome of hypertension and type II diabetes mellitus (Oparil *et al.*, 2003; Eastwood *et al.*, 2010; Venugopal and Iyer, 2010). Nearly 30% of chronic renal failures in India are due to diabetic nephropathy (Venugopal and Iyer, 2010) and in the first world countries, CKD prevalence is 13% (Pabst *et al.*, 2012). End-stage renal disease (ESRD) significantly has a higher risk of death, cardiovascular disease, and requires specialized healthcare. Pulmonary hypertension (PH) has been associated with ESRD in patients maintained on longterm haemodialysis and PH has been estimated to account for 17–56% among these patients (Pabst *et al.*, 2012), and it is an independent predictor of death in such patients (Pabst *et al.*, 2012). Due to the lack of invasive hemodynamic data in studies, it is difficult to discriminate between pre-and post-capillary PH in patients with or without symptoms (Pabst *et al.*, 2012). Patients with chronic kidney disease (CKD) are at a greater risk of progressing to ESRD and for premature cardiovascular death (CVD) (Norris *et al.*, 2006; Pabst *et al.*, 2012; Rossi *et al.*, 2013). The extent of hypertension-related ESRD among blacks is emphasized by a six-fold higher occurrence than in whites; among 20 to 44 years old, the incidence of hypertension-related ESRD in blacks is 15 times that of whites (Norris *et al.*, 2006). Indeed, black race, male gender, hypertension, and hypercreatinaemia have been identified as powerful predisposing factors for the development of hypertensionrelated ESRD (Norris *et al.*, 2006; Pabst *et al.*, 2012). Hypertension is

an important cause of heart and renal failure in Ghana (Bosu, 2010). In Ghana, data on the prevalence of CKD has been varied over the years. Bamgboye in 2006 put the prevalence at 1.6% per million people, Addo et al., (2009) put the prevalence among Ghanaian hypertensives at 4% (Owiredu *et al.*, 2012b). In a recent publication, Osafo et al., (2011) put the prevalence at 46.9% among hypertensives in Ghana (Owiredu *et al.*, 2012b).

2.1.6.1 Biochemical renal profile, electrolytes and CKD

Reduced kidney function is accompanied with various biochemical abnormalities which includes serum concentration of sodium, potassium, calcium and phosphorus (Poudel *et al.*, 2011). Serum urea, creatinine, urinary total protein (UTP), urinary protein creatinine ratio (PCR) and estimated glomerular filtration rate (eGFR) are parts of the renal biochemical profile. Serum level of urea and creatinine was found to increase gradually with the stages of CKD. Similarly, UTP and PCR were also found to gradually increase with progressing stages of CKD. Since the functional mass of kidney decreases in CKD, eGFR also decreased with the stages (Poudel *et al.*, 2011). Systolic blood pressure increases up to the fourth category of CKD and eGFR also decreases with the age (Poudel *et al.*, 2011). It is known that MDRD-4 underestimates GFR in some groups, and also that sex, age and BMI can affect the accuracy of predictive equations (Eastwood *et al.*, 2010).

In populations with obesity, insulin resistance, and dyslipidaemia ("the metabolic syndrome"), hyperuricaemia mostly occurs because insulin stimulates sodium and

urate reabsorption in the proximal tubule (Johnson *et al.*, 2003; AL-Hamdani, 2010; Habbu *et al.*, 2014). Uric acid is increased in populations with renal disease as the result of reduction in GFR and renal urate excretion (Johnson *et al.*, 2003; ALHamdani, 2010; Habbu *et al.*, 2014). Alcohol intake results in elevated uric acid levels due to increased urate generation (from increased adenine nucleotide turnover) and decreased excretion (due to lactate blocking tubular transport of urate) (Johnson *et al.*, 2003). Uric acid is also commonly associated with hypertension and 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 (Johnson *et al.*, 2003). Whereas uric acid is considered an antioxidant, it is also pro-oxidative under certain conditions, especially when other antioxidants are at a low level (Johnson *et al.*, 2003). Soluble uric acid also stimulates human mononuclear cells to produce interleukin-1 β, interleukin-6, and tumour necrosis factor (TNF)-α (Johnson *et al.*, 2003). Patients with gout frequently have renal dysfunction (25% to 40% of cases), with histologic injury in the majority (Johnson *et al.*, 2003); no doubt as hyperuricaemia is clearly associated with renal disease, hypertension and CVD in humans (Johnson *et al.*, 2003; Oparil *et al.*, 2003; Rossi *et al.*, 2013). It is unclear whether it is an independent risk factor with a role in CVD or only a marker associated with CVD risk factors, such as obesity, diuretic use, insulin resistance, hypertension, and renal disease (Oparil *et al.*, 2003; Baker *et al.*, 2005; Mellen *et al.*, 2006; Zhou *et al.*, 2006; Adrogué and Madias, 2007; Drenjančević-Perić *et al.*, 2010).

The Systolic Hypertension in the Elderly Program (SHEP) trial (Oparil *et al.*, 2003), found that participants who developed hyperuricaemia while receiving chlorthalidone therapy sustained CVD events at a rate similar to the control group. Relation of serum uric acid to cardiovascular end points in hypertension: The LIFE study has shown that baseline serum uric acid level was associated with increased risk for CVD in women, even after adjustment for concomitant risk factors (Framingham risk score). Treatment with the uricosuric angiotensin II receptor blocker (ARB) losartan statistically significantly weakened the bioavailability serum uric acid in the LIFE trial, and this difference seemed to account for 27% of the total treatment effect on the composite CVD end point. These provocative findings suggest a need for further studies of the role of uric acid in the pathogenesis of hypertension and CVD in humans and its potential as a therapeutic target. Uric acid has been shown in a rodent model to stimulate renal afferent arteriolopathy and tubulointerstitial disease, leading to hypertension (Oparil *et al.*, 2003).

2.1.7 Mechanism of obesity-induced hypertension

Different fat depots (abdominal visceral, abdominal subcutaneous, total sub cutaneous and total body fat) are not equivalent from a functional point of view (Iglesias and Díez, 2010). Visceral adipose tissue (VAT) mass has a higher degree of metabolic activity compared with subcutaneous peripheral adipose tissue (SAT) (Iglesias and Díez, 2010; Kotchen, 2010; Mazairac and Joles, 2010; Landsberg *et al.*,

2013). VAT correlates directly with intrahepatic triglyceride content, a better marker of the metabolic derangements associated with obesity (Iglesias and Díez, 2010; Kotchen, 2010; Mazairac and Joles, 2010). Other fat depots such as abdominal subcutaneous, intra-organ and peri-organ fat may have metabolic activity between that of peripheral subcutaneous fat and VAT. Different factors such as capacity of pre-adipocyte differentiation, adipocyte apoptosis, lipolysis, lipogenesis, adipocyte receptors, and cytokines and adipokines secretion are also different among several types of fat depots (Iglesias and Díez, 2010; Kotchen, 2010). Recent studies have reported that abdominal fat plays an important role in metabolic syndrome, because it is predictive of sensitivity to insulin and is closely related to the development of type II diabetes, heart disease and cardiovascular mortality independent of total body fat (Iglesias and Díez, 2010; Kotchen, 2010; Landsberg *et al.*, 2013). The dramatic increase in the prevalence of obesity is a global phenomenon associated with increased risk of the development of cardiovascular and renal disease (Addo *et al.*, 2009; Re, 2009; Kotchen, 2010; Mazairac and Joles, 2010; Micah and Nkum, 2012; Landsberg *et al.*, 2013).

Although obesity confers an increased risk of mortality in the general population, (Kotchen, 2010; Landsberg *et al.*, 2013) observational reports in dialysis patients have suggested the opposite (Mafra *et al.*, 2008; Re, 2009; Agarwal *et al.*, 2010). In obesity, many factors act together to promote vasoconstriction and sodium retention. All together, these factors will lead to sustained hypertension (Oparil *et*

al., 2003; Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010; Rodríguez-Iturbe *et al.*, 2012). Obese individuals exhibit higher levels of office as well as ambulatory blood pressure (BP) throughout life (Kotchen, 2010). Obese people display higher BP levels than non-obese individuals even in the normotensive range (Kotsis *et al.*, 2010). Obesity, hypertension and other cardiovascular risk factors combined significantly increases the likelihood of adverse cardiovascular consequences, and raises considerations for effective treatment policies (Kotsis *et al.*, 2010).

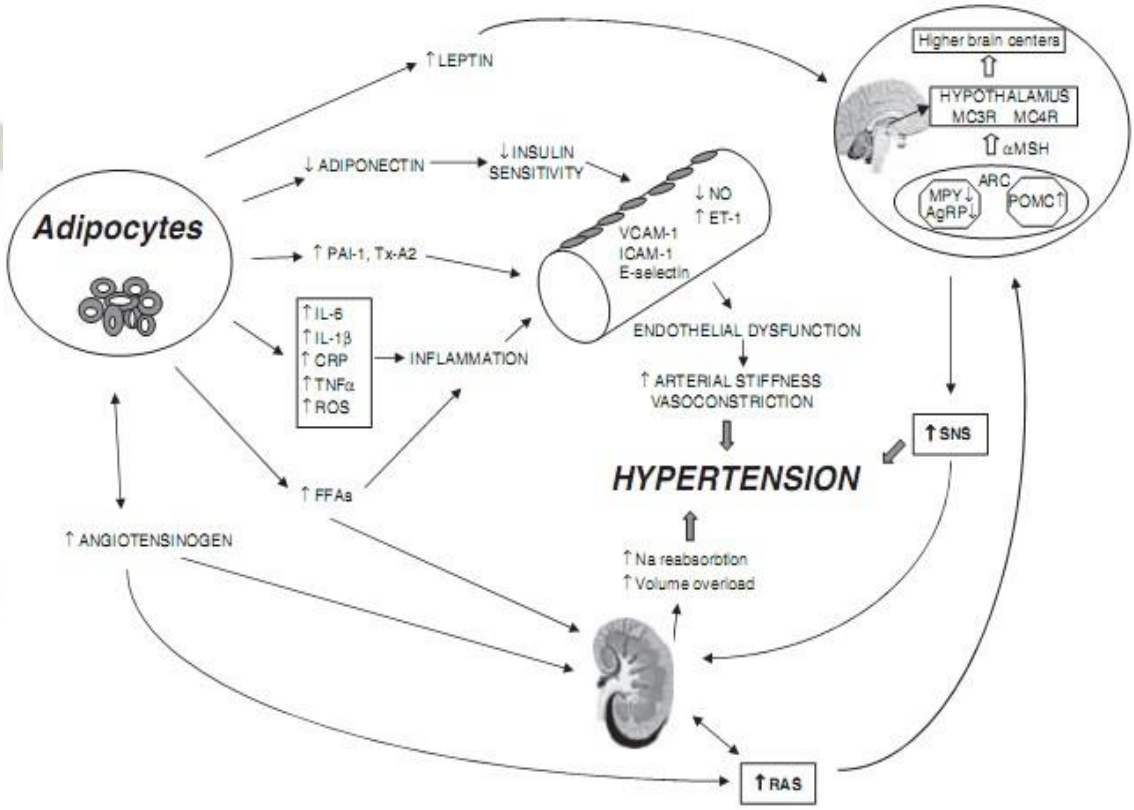

Figure 2-2: pathophysiology of obesity induced hypertension

Tnfa - tumour necrosis factor-a; crp- c - reactive protein; ros - reactive oxygen species; ffas - free-fatty acids; vcam-1 :- vascular cell adhesion molecule-1; sns - sympathetic nervous system; agrp - agouti-related peptide; npy - neuropeptide y; pomc - proopiomelanocortin; icam-1:- inter-cellular adhesion molecule-1; no - nitric

oxide; et-1 - endothelin-1; pai-1 - plasminogen activator inhibitor-1; tx-a2 - thromboxane a2; il-6 - interleukin-6; il-1b - iinterleukin-1b; ras - rennin-angiotensin system; arc: arcuate nucleus; a-msh - a-melanocyte-stimulating hormone; mc3r - melanocortin 3 receptor; mc4r - melanocortin 4 receptor (kotchen, 2010; kotsis *et al.*, 2010; landsberg *et al.*, 2013).

The mechanism through which obesity directly causes hypertension is still not understood. Studies have elucidated the function of adipose tissue derivatives (adipokines and cytokines), metabolic functions neurohumoral pathways, and modulation of pressor/depressor mechanisms in relation to the pathogenesis of hypertension. Hypertension caused by obesity may be the result of a combination or overlap of the above factors (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010; Landsberg *et al.*, 2013) (Figure 2-2).

These factors are renal mechanisms and sympathetic activation of the sympathetic nervous system (SNS).

2.1.7.1 Impairment of pressure natriuresis

The control mechanism of diuresis and natriuresis by arterial pressure according to the principle of infinite feedback gain appears to be shifted toward higher BP in overweight patients (Blaustein and Hamlyn, 2010; Kotchen, 2010; Kotsis *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012; Landsberg *et al.*, 2013). Defects in these mechanisms that cause increase in BP, upregulate water and sodium excretion through pressure natriuresis and diuresis. So long as excretion exceeds intake, the volume of extracellular fluid decreases causing a reduction in venous return and

cardiac output until the blood pressure normalizes (Oparil *et al.*, 2003; Re, 2009; Blaustein and Hamlyn, 2010; Kotchen, 2010; Kotsis *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012). Contrariwise, when blood pressure decreases, the kidney retains sodium and water until arterial pressure normalizes. During the initial phases of obesity, before loss of kidney (nephron) function because of injury to the glomerulus, primary salt retention occurs as a result of an increase in the reabsorption of renal tubules (O'Shaughnessy and Karet, 2004; Re, 2009; Kotsis *et al.*, 2010; RodríguezIturbe *et al.*, 2012; Landsberg *et al.*, 2013). This may be corrected by renal vasodilation, increased in the filtration rate of the glomerulus and increased in the filtered amount of water and electrolytes. As a result of a partial compensation, however, extracellular fluid volume is increased, resulting in a higher BP adjustment of the pressure natriuresis (Blaustein and Hamlyn, 2010; Kotchen, 2010; Kotsis *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012; Landsberg *et al.*, 2013). This resetting of the kidney-fluid apparatus to a higher BP level is coherent with the mechanism associated with the hypertension due to volume overload. Another significant cause of shift of pressure natriuresis towards hypertensive levels in obesity is the possibility of changes in intrarenal forces caused by changes in the histology of the medulla of the kidney that may put pressure on the loops of Henle and vasa recta (Kotchen, 2010; Kotsis *et al.*, 2010; Rodríguez-Iturbe *et al.*, 2012; Landsberg *et al.*, 2013). Recent data have revealed the association of a huge number of factors precipitating changes in kidney morphology, which, seems to be a

leading cause of gradual loss of nephron, having a great influence on the modification in pressure natriuresis (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010). Perivascular adipose tissue may have a direct effect on vascular function and insulin sensitivity (Mazairac and Joles, 2010). However, other than such general effects, renal sinus adiposity may influence renal function and blood pressure directly by local physical constraints (Mazairac and Joles, 2010).

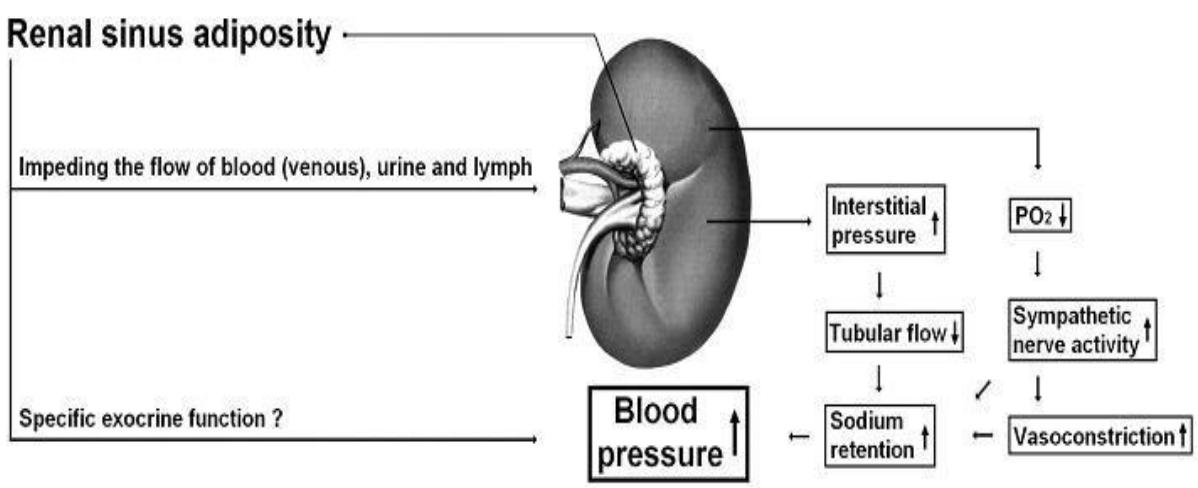

FIGURE 2-3 : RENAL SINUS ADIPOSITY

The accumulation of adipose tissue around the kidneys seems to cause physical compression of the organs emphasizing the vital function of visceral obesity in the pathogenesis of kidney disease (see figure above) (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010). The deposition of extracellular matrix all through the renal medulla is significantly expanded and the tissue proximal to the ducts of Bellini at the vascular end tends to slip from its usual position. An increase in materials rich in lipids and proteoglycans and increased numbers of interstitial cells compresses the renal parenchyma toward the pole of the kidney with a

consequent formation of enlarged, round-shaped kidneys in obese populations (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010). Activation of the reninangiotensin system (RAS) and increased sodium reabsorption is caused by renal compression which affects both vascular (notably the vasa recta) and tubular (the loops of Henle). Kidney injury in obesity appears to be dependent directly on the weight of the individual, as restricting dietary fat can improve the renal histology (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010). The primary histologic features are comparatively few lesions of focal-segmental glomerulosclerosis, intense glomerulomegaly due to glomerular hyalinosis and fibrosis, as well as lipid accumulation in the glomerulus and adhesion to Bowman's capsule (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010). Some studies suggest that lipid accumulation is as a result of modifications in fat metabolism. As to whether an increase in the production of lipogenic enzymes and reduction in the amounts of lipolytic factors could suggest direct lipotoxicity remains an area of active research (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010). Glomerulomegaly was observed in 100% of renal biopsies in a histopathologic study of glomerulopathy in obese populations. Notwithstanding the reported high incidence of glomerulomegaly, these glomerular changes cannot be compared with the nephropathy observed in diabetics, mainly because of the less severe changes in the mesangial space (Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010). In the absence of hypertension and diabetes

mellitus, glomerulopathy due to obesity *per se* may not promote renal impairment (Re, 2009). These findings suggest that obesity-related kidney damage can be likened to a special form of focal-segmental glomerulosclerosis which slowly progresses to end-stage kidney disease (Ejerblad *et al.*, 2006; Re, 2009; Kotsis *et al.*, 2010).

2.1.7.2 Role of RAS in obesity-related hypertension

It has been shown in several studies that plasma angiotensinogen II, plasma renin activity, and aldosterone values were having predominantly high levels in association with obesity (Oparil *et al.*, 2003; Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010; Landsberg *et al.*, 2013). The RAS represents a regulatory mechanism under normal conditions which prevents extreme variations in arterial pressure induced by changes in sodium intake. Cessation in the formation of Ang II during high-salt intake consequently decrease the rate of blood pressure elevation, which results in a leftward shift in the renal function curve closer to the initial blood pressure level (Re, 2009; Blaustein and Hamlyn, 2010; Drenjančević-Perić *et al.*, 2010; Kotchen, 2010; Kotsis *et al.*, 2010; Landsberg *et al.*, 2013). Numerous mechanisms are responsible for the RAS activation notwithstanding the significant volume expansion and sodium retention in obesity. Changes in intrarenal physical forces, generated from the accumulation of fat into and around the renal medulla seems to induce the secretion of renin by the kidney (Re, 2009; Drenjančević-Perić *et al.*, 2010; Kotsis *et al.*, 2010; Mazairac

and Joles, 2010; Landsberg *et al.*, 2013). The circulating RAS and tissue RAS constantly interact. Angiotensinogen (Ang I and II) are produced locally and simultaneously taken up by the cells, in which there is an overexpression of Ang II receptors. Angiotensinogen production is both a cause and effect of the hypertrophy of adipocytes and leads to an increase in blood pressure through the actions of Ang II, which activates systemic vasoconstriction, direct water and sodium retention and increased aldosterone production (Kobori *et al.*, 2007).

2.1.7.3 Sympathetic activation in obesity

Role of the sympathetic nervous system in the pathogenesis of cardiovascular diseases (figure below) (Oparil *et al.*, 2003)

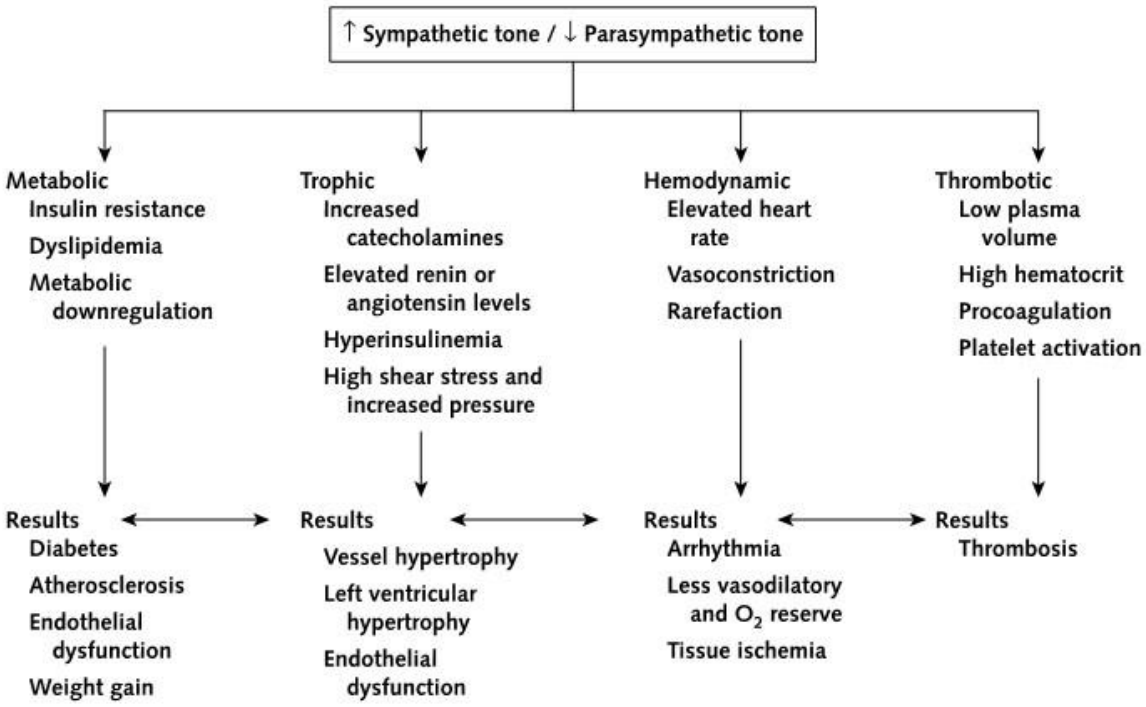

Figure 2-4 : Diagramatic presentation of the sympathetic and parasympathetic tone

The sympathetic nervous system (SNS) activation, measured directly or indirectly, has been considered to have a critical function in the pathogenesis of hypertension in obese individuals (Oparil *et al.*, 2003; Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010). Microneurograhic technique; a direct method of measuring elevated SNS activity, provides proof of high muscle SNS activity in obese individuals (Kotsis *et al.*, 2010; Landsberg *et al.*, 2013). Diets having high content of fat and carbohydrate has been considered to acutely stimulate peripheral a_1-and b-adrenergic receptors, leading to increased sympathetic activity and hypertension (Oparil *et al.*, 2003; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010; Landsberg *et al.*, 2013). Pharmacological blockade of adrenergic activity have been reported where (a combination of a-and b-adrenergic blockade or central sympathetic modulation by clonidine) significantly reduced the rise of

BP in obese individualss compared with lean patients with essential hypertension (Oparil *et al.*, 2003; Re, 2009; Kotsis *et al.*, 2010). Nonetheless, the increase in sympathetic activity did not seem to justify for the elevated heart rate in obesity; instead, the increased heart rate seems to be the consequence of decreased parasympathetic activity (Re, 2009; Kotsis *et al.*, 2010). Contrariwise, little reduction in weight is able to suppress the activity of the SNS. It has been recommended, however, that an increased efferent sympathetic activity in the peroneal nerves may not characterize all obese individuals, but only those

concurrently affected by obstructive sleep apnoea, a subject, which is still debatable (Kotchen, 2010; Kotsis *et al.*, 2010; Landsberg *et al.*, 2013). An exception has been observed in Pima Indians in relation to the high SNS activity and increased adiposity where though reported to have the highest prevalence of obesity and hyperinsulinaemia in the world, but have a relatively low presence of hypertension and atherosclerotic disease (Re, 2009; Kotsis *et al.*, 2010). The low muscle SNS activity reported in Pima Indians explains the possible variances between ethnic groups and confirms the physiological significance of the SNS upregulation as a significant mechanism of obesity-related hypertension (Re, 2009; Kotsis *et al.*, 2010). The mechanisms that have been suggested to be accountable for an elevated sympathetic activity in obesity includes dysfunction of the baroreceptor sensitivity, angiotensin (Ang) II, insulin high levels of circulating free-fatty acids (FFAs), and leptin (Oparil *et al.*, 2003; Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Mazairac and Joles, 2010; Landsberg *et al.*, 2013). Dysfunction in baroreflex sensitivity leads to the withdrawal of parasympathetic cardiac modulation, which even in the absence of an increase in arterial pressure occurs in obesity (Oparil *et al.*, 2003; Re, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Landsberg *et al.*, 2013). The actual mechanisms through which endogenous FFAs enhance vascular a-adrenergic sensitivity and consequentially increase a-adrenergic tone, have not been thoroughly studied (Re, 2009; Kotsis *et al.*, 2010). Binding of Lysophospholipids and free fatty acids (FFAs) to Na/K-ATPase affects the

interaction of the enzyme with neighbouring membrane proteins and activates the production of multiple signalling modules. Consequently, the epidermal growth factor receptor is induced and formation of reactive oxygen species (ROS) is increased (Oparil *et al.*, 2003; Kotsis *et al.*, 2010). This inhibits Na+, K+-ATPase and the sodium pump increasing vascular smooth muscle tone and resistance (Re, 2009; Kotsis *et al.*, 2010).

2.1.8 Risk factors Cardiovascular Diseases

There is a lot of epidemiological and clinical proof that light to moderate drinking is linked to total and ischaemic stroke, a reduced risk of coronary heart disease (CHD), and death in middle-aged and the elderly (Agarwal, 2002). The plausible mechanisms for the putative cardio-protective effects include low concentrations of low-density lipoprotein cholesterol, reduction in platelet aggregation, high concentrations of high-density lipoprotein cholesterol, prevention of clot formation, and lowering of plasma Apo lipoprotein α levels. Alcohol therefore lowers the risk of coronary vascular morbidities both by preventing the formation of atheroma and lowering the rate of blood coagulation (Agarwal, 2002).

The report of what is christened the 'Bordeaux effect', the suggestions that wine consumption explains the "French Paradox", the low incidence of coronary morbidity and mortality in France regardless of a remarkable dietary intake of saturated fats and alcohol (Renaud and de Lorgeril, 1992; Böhm *et al.*, 2004; Lippi *et al.*, 2010), has contributed to the heralding of intense research efforts aimed at

uncovering specific mechanisms involved in the cardio-protective and renal disease reversal benefits of alcohol. Among the kaleidoscope of suggested mechanisms explaining beneficial effects associated with light-to-moderate alcohol consumption in hypertension and chronic kidney disease patients are inhibition of lipid peroxidation (lipoproteins, membranes), mediated increases in high-density lipoprotein cholesterol levels, induced reduction of platelet aggregation and plasma fibrinogen, enhancement of fibrinolysis, chelation of copper, free-radical scavenging, alteration of eicosanoid synthesis et cetera (Gaziano *et al.*, 1993; Böhm *et al.*, 2004; Renaud *et al.*, 2004; Reynolds *et al.*, 2008; Collins *et al.*, 2009; Lippi *et al.*, 2010; Shimizu *et al.*, 2011).

Tthe apparent benefits of moderate drinking on kidney and coronary heart disease mortality are offset at higher drinking levels, suggesting J- or U-shaped relationship exists between alcohol consumption and coronary heart diseases by increasing risk of death from other types of heart diseases (cardiomyopathy, arrhythmia etc.), neurological disorders, cancer, liver cirrhosis, and traffic accidents (Agarwal, 2002; Klatsky, 2004; Reynolds *et al.*, 2008).

Recent report from the HUNT study suggested that smoking is not a major determinant of adverse blood pressure and other component cardiovascular disease risk factors (Åsvold *et al.*, 2014) and the report from the population-based Malmö-Diet-and-Cancer-Cohort which found that the associated risk of cardiovascular disease and cardiovascular disease mortality conferred by genetic

variation on chromosome 9p21 may be attenuated by smoking (Hamrefors *et al.*, 2014), however there is consensus on the association of smoking with adverse cardiovascular and renal outcome (Willett *et al.*, 1987; Orth *et al.*, 2000; Ishizaka *et al.*, 2008; Tolstrup *et al.*, 2013; Doyle *et al.*, 2014; Go *et al.*, 2014; Nance *et al.*, 2014). Plausible mechanisms of smoking attributed renal injury includes: increased blood pressure and heart rate; altered diurnal blood pressure rhythm; increased sympathetic nerve activity; nicotine induced mesangial cell proliferation and increased production of fibronectin; arteriosclerosis of renal and intrarenal arteries and arterioles; growth factors activation (angiotensin II, endothelin-1, and TGF-1); oxidative stress; impaired lipoprotein and glycosaminoglycan metabolism; tubulotoxicity; direct endothelial cells toxicity; increased clotting of platelets; modulation of immune mechanisms; vasopressin-mediated antidiuresis and insulin resistance (Haroun *et al.*, 2003; Orth and Hallan, 2008).

Chapter 3 MATERIALS AND METHODS

3.1 STUDY POPULATIONS

A hospital-based case–control study was conducted between November 2012 and September 2013. Two hundred and forty one (241) participants were involved in this study. One hundred and eighty (180) non-diabetic hypertensive patients attending clinic at the Komfo Anokye Teaching Hospital (KATH) and the Precise Specialist clinic all in Kumasi Ghana and sixty one (61) age matched normotensives controls from the Kumasi metropolis. The study participants were recruited purposively from a population of adult individuals between the ages of 22-87 years. Criteria for cases group were patients diagnosed with hypertension that were not suffering from diabetes and were of consent age. The control group were normotensive age matched healthy individuals with no past history of diabetes, cardiac, renal, hepatic dysfunction or dyslipidaemia, living in the Kumasi metropolis and consented to participation of this study.

3.2 ETHICAL APPROVAL

The participation of the respondents who are all indigenes of Ghana was voluntary and informed consent was obtained from each of them after thorough explanation of what the study entailed. This study was approved by the School of Medical Sciences and KATH Committee on Human Research Publications and Ethics (CHRPE/08/11).

3.3 SOCIO-DEMOGRAPHIC DATA CAPTURE (QUESTIONNAIRE)

Self-reported structured questionnaire were administered to determine duration of hypertension and treatment status, smoking status, alcohol intake, educational level, physical activity levels, occupation, the usage of non-prescribed orthodox and herbal medications, family history of hypertension, current and past symptoms of cerebrovascular disease, peripheral vascular and coronary heart diseases.

3.4 BLOOD PRESSURE (BP) MEASUREMENT

Blood pressure (BP) and pulse rate measurements were done using the Omron M5-I digital fully automatic blood pressures monitor (OMRON Healthcare Europe BV Wegalaan 57 NL-2132 JD Hoofddorp). After participants had sat quietly for at least ten minutes, three measurements were taken at one minute interval on the right arm in a seated position, with arm supported at heart level and feet flat on the floor using an appropriate sized cuff. Hypertension was diagnosed when the mean of the second and third blood pressure (BP) measurements was equal or above 140/90 mmHg or when participants reported use of antihypertensive medication which was verified from their hospital files (Owusu, 2007; Lemogoun *et al.*, 2003).

3.5 ANTHROPOMETRIC VARIABLES

Anthropometric measurements included height to the nearest millimeter without shoes and weight to the nearest 0.1 kg in light clothing. Participants were weighed on a

bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) and their height measured with a Seca stadiometer with the participant standing erect with back straight, heels together, and toes slightly apart at a 60 degree angle. Waist circumference (to the nearest centimeter) was measured with a Gulick II spring-loaded measuring tape (Gay Mills, WI) midway between the inferior angle of the ribs and the suprailiac crest. The hip circumference was measured as the maximal circumference over the hip circumference (HC) at the level of the widest diameter around the gluteal protuberance in centimetres. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). The waist to hip ratio (WHR) was calculated by dividing the waist circumference (cm) by the hip circumference (cm). Waist-to-Height Ratio was calculated by dividing the waist circumference (cm) by the height circumference (cm). Other calculated adiposity indices were as follows 1. Conicity Index (CI) (Ruperto *et al.* 2013)

$$CI = \frac{\text{Waist Circumference (m)}}{\left[0.109 \times \sqrt{\frac{\text{Weight (Kg)}}{\text{Height (m)}}}\right]}$$

2. Abdominal Volume Index (AVI) (Vuga, 2009)

$$AVI = \frac{\left[2(\text{Waist C (cm)})^2 + 0.7(\text{Waist C (cm)} - \text{Hip C (cm)})^2\right]}{1000}$$

3. BAI-Body Adiposity Index (Lategan *et al.*, 2014)

$$BAI = \frac{\text{Hip Circumference(cm)}}{[\text{Height (m)}]^{1.5}} - 18$$

3.6 CLINICAL ASSESSMENT

All the 241 participants underwent clinical assessment to determine target organ damage. Detailed history, physical examination, chest X-ray, 12-lead resting electrocardiogram (ECG) and transthoracic echocardiogram (ECHO) were done. All diagnosis and interpretation were performed by consultant Radiologist and Cardiologists.

3.7 DIAGNOSIS OF HEART FAILURE

Heart failure was diagnosed, using the modified Framingham criteria for diagnosis of heart failure (McKee *et al.*, 1971). Major criteria included: paroxysmal nocturnal dyspnoea, raised jugular venous pressure, cardiomegaly, basal crepitation, S3 gallop and acute pulmonary oedema. Minor criteria included: tachycardia, orthopnea, exertional dyspnea, nocturnal cough, hepatomegaly and diuretic use. Heart failure was diagnosed if the participant had two major and one minor or one major and two minor criteria. Other complications of hypertension included: Cardiomegaly (without heart failure), stroke or transient ischaemic attack and chronic kidney disease.

3.8 BIOCHEMICAL ASSAYS

Venous blood samples were collected after an overnight fast (8-12 hours) between 7 am and 10 am. About 5 ml of venous blood was drawn from the antecubital vein of which four (4) ml was dispensed into vacutainer® plain tubes and one (1) ml into fluoride oxalate tubes. After centrifugation at 500 g for 15 minutes, the serum and plasma were stored at - 80°C until assayed. Parameters that were determined include: fasting blood glucose (FBG) to exclude participants with diabetes, total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C). Serum low density lipoprotein cholesterol (LDL-C) was calculated using the Frederickson-Friedwald's formula according to which LDL-C = TC- TG/2-HDL-C, Urea, Creatinine, Uric Acid, Potassium, Sodium and Chloride. The methods adopted for the determination of the Urea, Creatinine, Uric Acid were predetermined by the reagent manufacturer – (Dialab GmbH, IZ- NÖ Süd, Hondastrasse, A-2351 Wiener Neudorf, Austria). With the exception of serum electrolytes all other biochemical analytical investigations were carried out at the Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) located at Kwame Nkrumah University of Science and Technology using the Mindray BA88A (Mindray).

Serum electrolytes assay was carried out at the department of clinical biochemistry in the Komfo Anokye teaching hospital using Ion Selective Electrode (ISE) method (AVL 9180 Electrolyte Analyzer, Roche Diagnostics, Switzerland) .

3.9 TOTAL CHOLESTEROL

3.9.1 Principle

The concentration of cholesterol was determined after enzymatic hydrolysis and oxidation. The colorimetric indicator is quinoneimine which is generated from 4aminoantipyrine and phenol by hydrogen peroxide under the catalytic action of peroxidise (Trinder's reaction).

3.10 HDL CHOLESTEROL

3.10.1 Principle

Low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons contained in serum are precipitated by the addition of Phosphotungstic Acid and Magnesium Chloride. High density lipoproteins (HDL) which remain in the supernatant (obtained after centrifugation) were then measured with Cholesterol reagent as described above.

3.11 TRIGLYCERIDES

3.11.1 Principle

The concentration of triglycerides was determined after enzymatic splitting with lipoprotein lipase. Indicator is quinoneimine which is generated from 4-aminoantipyrine and 4-chlorophenol by hydrogen peroxide under the catalytic action of peroxidase.

3.12 GLUCOSE

3.12.1 Principle

In the presence of glucose oxidase, glucose is oxidized to gluconic acid and hydrogen peroxide. Hydrogen peroxide reacts, in the presence of peroxidase, with phenol and 4aminoantipyrine to form a quinoneimine dye (Trinder's reaction). The intensity of the pink colour formed is proportional to the glucose concentration.

3.13 CREATININE

3.13.1 Principle

The enzymatic assay for creatinine involves a series of coupled enzymatic reactions including creatininase enzymatic conversion of creatinine into the product creatine which itself is converted to sarcosine by creatinase, followed by oxidation of sarcosine by sarcosine oxidase (SOD) producing hydrogen peroxide. In the presence of peroxidase (POD) the hydrogen peroxide is quantified at 550nm by the formation of a coloured dye.

3.14 DIAGNOSIS OF CHRONIC KIDNEY DISEASE

Estimate glomerular filtration rate (GFR) was calculated from serum creatinine as follows:

1. Four Variable Modification of Diet in Renal Disease

$$4V-MDRD: eGFR = 186\ X\ Scr^{-1.154} X\ Age^{-0.203} X\ (1.212)\ X\ (0.742\ \text{if female}$$

2. Chronic Kidney Disease Epidemiology collaboration- CKD-EPI

Gender	Serum Creatinine µmol/L(mg/dL)	Estimated Glomerular Equation
Female	≤62(≤0.7)	$eGFR = 166\,X\left(\frac{\text{Serum Creatinine}}{0.7^{-0.329}}\right)X\,(0.993)^{Age}$
Female	>62(>0.7)	$eGFR = 166\,X\left(\frac{\text{Serum Creatinine}}{0.7^{-1.209}}\right)X\,(0.993)^{Age}$
Male	≤80(≤0.9)	$eGFR = 163\,X\left(\frac{\text{Serum Creatinine}}{0.9^{-0.411}}\right)X\,(0.993)^{Age}$
Male	>80(>0.9)	$eGFR = 163\,X\left(\frac{\text{Serum Creatinine}}{0.9^{-1.209}}\right)X\,(0.993)^{Age}$

The eGFR results from the various renal function equations were used to stratify the study population into five categories corresponding with the five stages of CKD in the K/DOQI CKD classification (KDOQI, 2006). End stage chronic kidney disease was classified as eGFR < 60 mL/min/1.73 m^2 (stage 3, 4 and 5, see Table 5) (Levey *et al.*, 2005).

3.15 URIC ACID

3.15.1 Principle

This principle uses 4-Aminoantipyrine (4-AAP), Peroxidase (POD) and 2,4,6-Tribromo-3Hydroxybenzoic Acid (TBHBA).

3.16 ELECTROLYTES

3.16.1 Principle

The AVL 9180 Analyzer methodology is based on the ion-selective electrode (ISE) measurement principle to precisely determine the measurement values. There are six different electrodes: sodium, potassium, chloride, ionized calcium, lithium and a

reference electrode. Each electrode has an ion-selective membrane that undergoes a specific reaction with the corresponding ions contained in the sample being analysed. The membrane is an ion exchanger, reacting to the electrical charge of the ion causing a change in the membrane potential, or measuring voltage, which is built up in the film between the sample and the membrane.

A galvanic measuring chain within the electrode determines the difference between the two potential values on either side of the membrane. The galvanic chain is closed through the sample on one side by the reference electrode, reference electrolyte and the "open terminal". The membrane, inner electrolyte and inner electrode close the other side. A difference in ion concentrations between the inner electrolyte and the sample causes and electro-chemical potential to form across the membrane of the active electrode. The potential is conducted by a highly conductive, inner electrode to an amplifier. The reference electrode is connected to ground as well as to the amplifier. The ion concentration in the sample is then determined by using a calibration curve determined by measured points of standard solutions with precisely known concentrations.

3.17 MICROALBUMINURIA

3.17.1 Principle

The albumin present in the urine specifically binds with a soluble antibody-gold conjugate present on a zone on the test strip. Excess conjugate is retained in a separation zone containing immobilized human albumin. This allows only the conjugate-albumin

immunocomplex from the sample to reach the detection zone. After one minute, the intensity of the colour produced (white to red) is directly proportional to the albumin content in the urine.

The urine specimen should be collected in a clean, dry container Due to the physiological variation of albumin; three separate morning (midstream) urine samples were collected and analyzed within the week. Strips were used immediately after removing vial from the refrigerator. The test strip was dipped into the urine for 5 seconds making sure that the urine level is between the two black lines. The strip was withdrawn carefully avoiding touching the sides of the collection cup. The strip was placed on a nonabsorbent surface or across the top of the collection cup to allow excess urine to drain. After approximately 1 minute, the colour of the test pad was matched with the colour scale on the test strip vial. A wet detection area indicates that the reaction has come to an end.

3.18 Statistical Analysis

Normality of all continuous variables was tested. All non-parametric variables were normalized by log transformation before analysis and results converted by antilog where appropriate. Continuous variables are expressed as their mean ± Standard deviation (SD), whereas categorical variables were expressed as Figure and proportion. Comparisons of the general characteristics of the hypertensive group against the normotensive group were performed using unpaired t tests, chi (χ 2) tests, or Fisher exact tests where

appropriate. A posthoc linear contrast was used for trend analysis of continuous variables. Dyslipidaemic atherogenic scores were calculated as the additive score of the number of lipid abnormality recorded by an individual. The Youden Index was computed to identify population-specific cut-off points of selected parameters for the optimal differentiation between cases and controls. The Youden Index is derived from (sensitivity + specificity) - 1 and range from 0 to 1. Using the receiver operator characteristic curves (ROC), area under the curve (AUC), the discriminative power of the population-specific cut-off points for identifying hypertension cases was estimated (Frank *et al.*, 2013). A level of $p<0.05$ was considered as statistically significant for all analysis. IBM Statistical Package for the Social Sciences (SPSS) version 20.00, GraphPad Prism version 6.00 and MedCalc version 12.3.2 for windows were used for statistical analysis where appropriate (SPSS Inc, Chicago, USA; www.spss.com; GraphPad software, San

Diego California USA, www.graphpad.com; MedCalc software bvba, MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium, www.medcalc.org).

Chapter 4 RESULTS

4.1 SOCIO-DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

Out of the 241 study participants involved in this study, 180 classified as cases were hypertensive patients, the remaining 61 who had no hypertension were classified as controls. The mean age of the participants was 49.57±1.16, the age of the cases were comparable to that of the controls. The female population (62.70%) was higher than that for male. Majority (53.94%) of the study participants indulged in alcohol intake. The percentage of participants taking in alcohol was significantly higher among the case group (60.00%) compared to the controls (36.06%). Similarly, among the 13.28% of the total study population who admitted to smoking, majority (90.63%) were found to belong to the case group.

Majority 134(74.44%) of the people, who reported with hypertension belonged to the informal sector of employment; the converse was found among the control group. Even though a higher percentage of the case group were found to be engaged in some form of regular exercise compared to the controls, the percentage difference was not statistically significant. None of the controls presented with any of the complications associated with hypertension including chronic kidney disease (CKD), cardiomegaly, pedal oedema et

cetera. (Table 4 -1).

Table 4-1. Socio-demographic characteristic of the Population under Study stratified by hypertension status

Parameter	Total n=241	Control n=61	Case n=180	p-value
Age	49.57±18.01	49.63±4.53	50.88±11.94	0.8231
Gender				
Female	151(62.70%)	45(73.80%)	106(58.90%)	0.0460
Male	90(37.30%)	16(26.20%)	74(41.10%)	
Alcohol Usage				
No	111(46.06%)	39(63.94%)	72(40.00%)	<0.0001
Sometimes	29(12.03%)	12(19.67%)	17(9.44%)	
Always	101(41.91%)	10(16.39%)	91(50.56%)	
Smoking Status				
No	209(86.72%)	58(95.08%)	151(83.89%)	0.0421
Sometimes	8(3.32%)	2(3.28%)	6(3.33%)	
Always	24(9.96%)	1(1.64%)	23(12.78%)	
Employment Status				
Formal	91(37.76%)	45(73.77%)	46(25.56%)	<0.0001
Informal	150(62.24%)	16(26.23%)	134(74.44%)	
Family History of HPT	175(72.60%)	40(65.60%)	135(75.00%)	0.1840
Herbal Usage	136(56.40%)	33(54.10%)	103(57.22%)	0.7650
Non Prescribed Drugs	140(58.10%)	36(59.00%)	104(57.78%)	0.8820

Exercise	152(63.10%)	36(59.00%)	116(64.40%)	0.4480
Heart failure	153(63.50%)	0(0.00%)	153(85.00%)	<0.0001
Other complications	176(73.00%)	0(0.00%)	176(97.80%)	<0.0001

Data is presented as figure with percentage in parenthesis, mean±SD. p is significant at 0.005

Disparities in measured anthropometric markers among the case and control group were observed for both commonly used and candidate indices assessed for this study. With the exception of BMI and WHR, the case group presented significantly higher averages of all adiposity indices assessed compared to the control group (Table 4-2). In general, the case group presented with a significantly poorer atherogenic lipid profile compared to their counterparts in the control group, the exception though was observed with HDL where the converse was the case (Table 4-2).

Table 4-2: Haemodynamic, anthropometric, serum biochemical kidney profile and estimated glomerular filtration rate of the study population stratified by hypertension status

Parameter	Total	Control	Case	P-value
Haemodynamics Indices				
SBP(mmHg)	145.25±24.85	117.38±7.51	154.69±21.33	<0.0001
DBP(mmHg)	94.17±15.52	73.28±5.98	101.25±10.57	<0.0001
PULSE	73.25±21.5	51.41±7.08	80.66±19.63	<0.0001
MAP	111.20±17.13	87.98±4.95	119.06±11.81	<0.0001
Adiposity Indices				
Weight(Kg)	78.46±15.54	71.90±12.8	80.68±15.78	0.0001
Height(cm)	160.96±12.28	155.24±14.1	162.90±10.98	<0.0001
BMI(Kg/m^2)	29.52±4.7	29.36±5.08	29.58±4.58	0.7518
WC(cm)	89.29±20.72	69.10±12.23	96.13±18.43	<0.0001
HC(m)	94.06±25.23	71.82±12.17	101.59±24.04	<0.0001
WHR	0.96±0.06	0.96±0.05	0.97±0.06	0.7204
WHtR	0.56±0.13	0.45±0.08	0.59±0.12	<0.0001
AVI	16.86±8.02	9.86±3.51	19.24±7.73	<0.0001
Conicity	1.18±0.25	0.93±0.11	1.26±0.23	<0.0001
BAI	28.34±12.91	19.49±7.02	31.34±13.09	<0.0001

Glycaemic Index				
Glucose(mmol/L)	4.78±0.90	4.57±0.69	4.85±0.95	0.0349
Atherogenic Indices				
TC(mmol/L)	6.13±1.54	4.58±1.6	6.77±1.54	<0.0001
TG(mmol/L)	1.88±0.61	1.67±0.62	1.95±0.64	0.0010
LDL(mmol/L)	3.30±1.22	2.40±1.07	3.68±1.18	<0.0001
HDL(mmol/L)	2.09±1.01	1.71±0.72	2.24±1.02	<0.0001

Data is presented as mean ± standard deviation , SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, MAP-mean arterial pressure WC- Waist Circumference, HC-Hip Circumference, BMI-Body Mass Index, WHR- Waist-to-Hip Ratio, WHtR- Waist-to-Height Ratio, AVI-Abdominal Volume Index, BAI-Body Adiposity Index, TG-Triglyceride, HDL-High density lipoprotein, TC-Total Cholesterol, LDL-Low density lipoprotein

Among the two hundred and forty one (241) adult Ghanaians were recruited for the study, the socio-demographic characteristics of the participants were as shown in table 1. The 180(74.7%) hypertensives representing the case group, involved 40(6.6%) of newly diagnosed hypertensives who were not on any hypertensive drugs and were classified as drug-naive. Female participation was higher in each of the three categories of the study population. Significantly self-reported alcohol intake and smoking were both found to be more prevalent among the hypertensives, peaking in each case in the drug naive group. No significant differences were recorded in the rest of the socio-demographic parameters assessed between the three different groups of participants evaluated in this study (see Table 4-3).

Table 4-3 : Socio-demographic characteristics of the population under study stratified by hypertension and treatment status

Parameter	Control	HPT-Naive	HPT-Therapy	p-value
Respondents	61(25.3)	40(16.6)	140(58.1)	*nd*
Female	45(73.8)	22(55.0)	84(60.0)	0.0980
Male	16(26.2)	18(45.0)	56(40.0)	
Formal Sector	45(74.2)	10(24.4)	44(31.7)	< 0.0001
Informal Sector	16(25.8)	30(75.6)	96(68.3)	
Alcoholics	22(36.1)	32(80.0)	76(54.3)	<0.0001
Smokers	3(4.9)	9(22.5)	20(14.3)	0.0340

Exercise	36(59.0)	27(67.5)	89(63.6)	0.6760
Positive Family History	40(65.6)	31(77.5)	104(74.3)	0.3330
Herbal Medicine Intake	33(54.1)	24(60.0)	79(56.4)	0.8430
Non Prescribed drug intake	36(59.0)	22(55.0)	82(58.6)	0.9090

Data is presented as figure with corresponding percentage in parenthesis. HPT-Naïve- newly diagnosed hypertensive not on antihypertensive drugs, HPT-Therapy- Hypertensives on antihypertensives. p is significant at 0.005.

Among all the parameters evaluated as shown in table 4- 4, no statistically significant variation was recorded between the newly diagnosed hypertensives and their counterparts on treatment. Higher anthropometric indices were recorded among both hypertension groups compared with the normotensives, however in the case of body mass index (BMI) and waist-to-hip ratio (WHR) the difference was not statistically significant. The hypertensives presented with significantly higher mean serum biochemical indices of clearance and electrolytes levels than their normotensive counterpart. The average concentration of microalbumin excreted in the urine as well as, the glomerular filtration rate estimated by 4v-MDRD equation were comparable among the treatment naïve hypertensives and the normotensives (see Table 4-4).

Table 4-4: Haemodynamic, Anthropometric, serum biochemical kidney profile and estimated glomerular filtration rate of the study population stratified by hypertension status

Parameter	Control n-61	HPT- Naïve n-40	HPT-Therapy n-140	P-value
SBP(mmHg)	117.38±7.50	152.00±20.68	155.46±21.53	<0.0001
DBP(mmHg)	73.28±6.01	100.50±8.47	101.46±11.12	<0.0001
Pulse	51.41±7.11	76.85±13.91	81.74±20.94	<0.0001
MAP	87.98±4.92	117.67±11.45	119.46±11.95	<0.0001
WC(cm)	69.10±12.26	97.65±17.71	95.69±18.69	<0.0001
HC(cm)	71.82±12.18	102.20±20.24	101.42±25.08	<0.0001
BMI($Kg/m^{2)}$	29.36±5.08	29.80±4.49[a]	29.52±4.61[a]	0.9018
WHR	0.96±0.08	0.97±0.06[a]	0.97±0.00[a]	0.9356
WHtR	0.45±0.08	0.60±0.70	0.59±1.54	<0.0001
AVI	9.86±3.51	19.74±7.34	19.09±7.81	<0.0001

Conicity Index	0.93±0.86	1.28±0.25	1.25±0.24	<0.0001
BAI	19.49±7.03	31.14±10.12	31.40±13.84	<0.0001
Potassium	3.20±8.04	3.76±6.64	3.82±12.19	0.0001
Sodium	134.89±10.54	139.43±20.24	146.86±28.28	<0.0001
Chloride	94.89±10.54	106.13±7.08	112.73±12.19	<0.0001
Urea	3.71±0.70	5.66±1.96	5.77±1.66	<0.0001
Creatinine	69.08±11.56	86.81±27.13	91.71±28.16	<0.0001
Uric Acid	125.68±7.97	157.19±6.77	176.66±12.42	<0.0001
Microalbuminuria	4.52±8.90	5.60±7.65[a]	7.38±13.25	0.0336
4v-MDRD	127.63±8.04	101.78±7.15[a]	87.05±12.54	0.0002
CKD-EPI	131.23±8.04	90.33±6.70	81.49±12.42	<0.0001

Data is presented as mean ± standard deviation. HPT-Naïve- newly diagnosed hypertensive not on antihypertensive drugs, HPT-Therapy- Hypertensives on anti-hypertensives, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, MAP- mean arterial pressure WC- Waist Circumference, HC-Hip Circumference, BMI-Body Mass Index, WHR- Waist-to-Hip Ratio, WHtR- Waist-to-Height Ratio, AVI-Abdominal Volume Index, BAI-Body Adiposity Index, 4v-MDRD – four variable Modification of Diet in Renal Disease, CKD-EPI – Chronic Kidney Disease Epidemiology collaboration. Bonfferroni post hoc [a] no statistical significant difference compared with control.

Among the participants with hypertension, increasing pulse rate was significantly associated increasing levels of all adiposity markers measured with the exception of waist to hip ratio (WHR) after adjusting for age and gender. Pulse rate was also found to be associated with increased levels of Total Cholesterol (TC), Triglyceride (TG), and inversely associated with high density lipoprotein cholesterol (HDL). In general, positive additive change in the adiposity indices (WC, HC, WHtR, CI, AVI, BAI) were associated with corresponding increases in TC, and TG levels, but reductive changes in HDL among the hypertension subpopulation (Table 4 - 5).

Table 4-5: Partial correlation coefficients of Anthropometric variables, Haemodynamic, Atherogenic Indices of control group (upper right sided), Indices of Case group (Lower left sided). Adjusted for age, gender and medication

Parameter	SBP	DBP	Pulse	MAP	WC	HC	BMI	WHR	WHtR	Conicity	AVI	BAI	TC	TG	LDL	HDL
SBP		.14	.14	.60**	.05	.04	.09	.05	.04	.00	.04	.02	.01	.08	-.24	.08
DBP	.38**		.04	.88**	.10	.11	.14	.01	.09	.05	.10	.09	.04	-.03	.09	.02
Pulse	.02	.01		.10	.17	.19	.19	.01	.16	.09	.17	.14	.08	.24	.12	.06
MAP	.84**	.83**	.02		.10	.11	.16	.03	.10	.04	.10	.09	.04	.02	-.04	.06
WC	.04	-.06	.59**	-.01		.95**	.53**	.32*	.87**	.89**	.99**	.65**	-.14	.10	.09	.14
HC	.02	-.03	.66**	-.01	.94**		.52**	.03	.84**	.83**	.95**	.72**	-.13	.13	.13	.15
BMI	-.05	.04	.17*	-.01	.36**	.32**		.13	.83**	.12	.53**	.87**	-.16	.01	.18	.05
WHR	.04	-.01	.08	.02	.07	-.16*	-.01		.25	.34**	.32*	-.08	-.05	-.04	-.12	.03
WHtR	.08	-.08	.55**	.00	.93**	.87**	.41**	.07		.61**	.86**	.92**	-.20	.05	.12	.12
Conicity	.10	-.08	.51**	.02	.87**	.81**	-.10	.08	.80**		.88**	.33**	-.09	.15	.02	.16
AVI	.04	-.06	.65**	-.01	.99**	.96**	.32**	.07	.92**	.87**		.64**	-.15	.08	.09	.12
BAI	.06	-.05	.60**	.01	.86**	.90**	.38**	-.13	.95**	.73**	.87**		-.20	.04	.15	.09
TC	-.01	-.14	.15*	-.09	.32**	.35**	.03	-.10	.33**	.33**	.33**	.35**		.30*	.29*	.13
TG	.06	.08	.15*	.09	.28**	.24**	-.05	-.11	.26**	.28**	.28**	.21**	.24**		.04	.34**
LDL	-.02	-.04	-.06	-.03	.08	.06	.00	-.10	.11	.13	.07	.10	.38**	.33**		.10
HDL	-.05	.08	-.16*	.02	-.18*	-.17*	-.02	-.05	-.15*	-.17*	-.18*	-.13	.11	.35**	.36**	

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, MAP- Mean Arterial Pressure, BMI-Body Mass Index, WC- Waist Circumference, HCHip Circumference, WHR- Waist-to-Hip Ratio, TG-Triglyceride, HDL-High density lipoprotein, TC-Total Cholesterol, LDL-Low density lipoprotein, FBS - Fasting blood sugar. p is significant at *0.05 ; **0.01

Among the general study population after adjusting for age and gender, positive additive changes in waist-to-height ratio (WHtR) as well as both the abdominal body frame factors (Waist circumference – WC ; Hip circumference - HC), the abdominal body region volumetric models for central obesity (Conicity index – CI; Abdominal volume index - AVI) and body fat deposition (Body adiposity index-BAI) were associated with corresponding incremental changes in the haemodynamic measures (Hypertension), the serum biochemical kidney profile measures and renal insufficiency (decreasing eGFR). Among the hypertensive subpopulation positive association was observed between the anthropometric measures and the serum biochemical kidney profile (K^+, Na^+, Cl^-, Urea, Creatinine, and UA) as well as renal insufficiency. With the exception of pulse, no significant correlation was observed between the anthropometric measures and the haemodynamic measures among the hypertensive subpopulation.

Among both the general study population and the hypertension subgroup, increasing levels of serum potassium, urea, creatinine and uric acid were associated with increasing renal insufficiency. Significant association between the haemodynamic measures and the serum biochemical kidney profile was more profound in the general study population than the hypertension subgroup (see Table 4 - 6).

Table 4-6: Partial correlation coefficients of Haemodynamic parameters, Anthropometric variables, and biochemical kidney markers of study population (upper right sided), Indices of hypertension group (Lower left sided). Adjusted for age and gender.

Index	SBP	DBP	Pulse	MAP	WC	HC	BMI	WHR	WHtR	CI	AVI	BAI	K^+	Na^+	CL^-	Urea	Creat	UA	MA	MDRD	EPI
SBP		.51**	.20**	.85**	.20**	.16*	-0.03	0.04	.19**	.24**	.18**	.30**	0.07	.23**	.39**	.21**	.15*	0.10	-0.09	-0.03	-0.06
DBP	.39**		.25**	.89**	.19**	.19**	0.05	0.00	0.12	.17**	.16*	.28**	0.01	.35**	.52**	0.11	.13*	0.01	0.01	0.00	-0.02
Pulse	0.02	0.01		.26**	.64**	.69**	.17**	0.07	.58**	.57**	.68**	.66**	.22**	.20**	.40**	.22**	0.05	.29**	0.01	-0.01	-0.01
MAP	.83**	.83**	0.02		.22**	.20**	0.01	0.02	.18**	.24**	.19**	.31**	0.04	.33**	.53**	.18**	.16*	0.06	-0.04	-0.01	-0.05
WC	0.04	-0.07	.60**	-0.02		.95**	.37**	0.1	.93**	.89**	.99**	.86**	.19**	.14*	.40**	.29**	.21**	.44**	0.08	-.18**	-.20**
HC	0.02	-0.04	.66**	-0.01	.94**		.33**	-0.12	.88**	.84**	.96**	.90**	.23**	.13*	.35**	.26**	.21**	.47**	0.06	-.21**	-.21**
BMI	-0.06	0.01	.18*	-0.03	.37**	.32**		0.03	.47**	-0.03	.33**	.43**	0.02	0.00	0.09	0.01	0.06	-0.03	0.12	-0.11	-0.10
WHR	0.04	-0.02	0.08	0.01	0.07	-.16*	0.00		0.10	0.10	0.09	-0.10	-0.04	0.00	0.03	0.07	-0.08	-0.09	0.01	.17**	0.09
WHtR	0.07	-0.09	.55**	-0.01	.93**	.86**	.42**	0.07		.80**	.92**	.95**	.16*	0.12	.33**	.29**	.20**	.43**	0.1	-.21**	-.22**
CI	0.10	-0.08	.51**	0.01	.87**	.81**	-0.09	0.08	.80**		.89**	.75**	.16*	.15*	.37**	.29**	.19**	.49**	0.05	-.16*	-.18**
AVI	0.04	-0.07	.65**	-0.02	.99**	.96**	.33**	0.07	.92**	.87**		.88**	.21**	0.11	.36**	.29**	.20**	.46**	0.07	-.18**	-.20**
BAI	0.05	-0.07	.60**	-0.01	.86**	.89**	.39**	-0.13	.95**	.73**	.87**		.24**	.25**	.40**	.35**	.27**	.52**	0.11	-.30**	-.32**
K^+	0.02	-0.10	.21**	-0.05	.20**	.24**	0.09	-0.05	.19*	.15*	.22**	.21**		.21**	0.11	.20**	.16*	.19**	-0.03	-.14*	-0.11
Na^+	0.06	.16*	0.04	0.14	-0.06	-0.04	-0.04	-0.02	-0.04	0.04*	0.06	-0.02	.20**		.35**	.16*	0.10	-0.03	-0.02	0.08	0.02
CL^-	0.12	0.10	0.09	0.13	0.14	0.11	0.04	0.06	0.10	0.12	.16*	0.06	0.03	0.03		.31**	.18**	.21**	0.08	-0.04	-0.08
Urea	0.09	-0.12	0.08	-0.02	.20**	.17*	0.00	0.09	.22**	.19*	.21**	.20**	.18*	0.04	0.02		.38**	.29**	-0.05	-.23**	-.27**
Creat	0.09	0.04	-0.03	0.08	.17*	.17*	0.07	-0.11	.17*	0.14*	.16*	.17*	0.15	0.05	0.06	.36**		.30**	.,0.02	-.80**	-.79**
UA	0.02	-0.14	.24**	-0.07	.45**	.46**	-0.06	-0.13	.43**	.49**	.45**	.42**	.18*	-0.12	0.11	.24**	.27**		0.02	-.29**	-.27**
MA	-0.13	-0.06	-0.04	-0.11	0.02	0.00	0.10	0.04	0.05	0.00	0.02	0.03	-0.04	-0.08	0.09	-0.09	0.03	0.03		-0.05	-0.05
MDRD	-0.02	0.04	0.01	0.01	-.20**	-.22**	-0.13	0.21	-.22**	-.16*	-.19*	-.24**	-.15*	0.10	0.00	-.23**	-.81**	-.29**	-0.06		.90**
EPI	-0.03	0.05	0.04	0.01	-.20**	-.21**	-0.13	0.11	-.22**	-.17*	-.19*	-.22**	-0.12	0.05	-0.01	-.26**	-.80**	-.26**	-0.06	.90**	

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, MAP- Mean Arterial Pressure WC- Waist Circumference, HC-Hip Circumference, BMI-Body Mass Index, WHR- Waist-to-Hip Ratio, WHtR- Waist-to-Height Ratio, CI-Conicity Index, AVI-Abdominal Volume Index, K^+-Potassium, Na^+Sodium, CL^-- Chloride, Creat- Creatinine, UA-Uric Acid, MA-Microalbumin , MDRD – four variable Modification of Diet in Renal Disease, EPI – Chronic Kidney Disease Epidemiology collaboration.

Dyslipidaemia was significantly higher among the hypertensive group compared to their control counterparts. Majority of the normotensive group presented with no atherogenic scores. The hypertensive patients were however found to cluster along increasing atherogenic scores. (Table 4 - 7).

Table 4-7: Prevalence of Obesity, Hypertension, Dyslipidaemia indices of study population stratified by hypertension status

Parameter	Total	Control	Case	p-value
Haemodynamic Indices				
Pulse rate	150(62.2%)	2(3.3%)	148(82.2%)	<0.0001
Adiposity Indices				
Abdominal Obesity	169(70.1%)	13(21.3%)	156(86.7%)	<0.0001
Obesity	122(50.6%)	31(50.8%)	91(50.6%)	0.5450
Central Obesity	1137(56.8%)	26(42.6%)	111(61.7%)	0.0070
Dyslipidaemia parameters				
Raised TC	148(61.4%)	14(23%)	134(74.4%)	<0.0001
Raised TG	76(31.5%)	5(8.2%)	71(39.4%)	<0.0001
Reduced HDL	96(39.8%)	7(11.5%)	89(49.4%)	<0.0001
Raised LDL	127(52.7%)	2(3.30%)	125(52.7%)	<0.0001
Atherogenic Scores				
None	49(20.3%)	39(63.9%)	10(5.6%)	<0.0001
One	53(22.0%)	17(27.9%)	36(20.0%)	
Two	54(22.4%)	4(6.6%)	50(27.8%)	
Three	54(22.4%)	1(1.6%)	53(29.4%)	
Four	31(12.4%)	0(0.0%)	31(17.2%)	

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, TG-Triglyceride, HDL-High density lipoprotein, TC-Total Cholesterol, LDL-Low density lipoprotein

Among the component atherogenic indices assessed between the study participants who take alcohol and those who do not take alcohol, significantly higher numbers of patients who take alcohol presented with hypertriglycelaemia (32%), reduced high density lipoprotein- HDL (45%), and raised low density lipoprotein- LDL (59%) compared to (22%, 27%, and 45% respectively) among those who do not take alcohol (Fig. 4-1A). Majority of the participants who smoke presented with raised Total cholesterol – TC (87%) and Triglyceride – TG (56%) (Fig 4-1C).

Patients who did not partake in exercise in general presented with high levels of components of dyslipidaemia (Fig. 4-1B). No significant difference in terms of components of dyslipidaemia was found among users and non-users of non-prescribed medication, even though in most cases patients using non-prescribed medication presented with higher percentage of abnormalities (Fig. 4-1D).

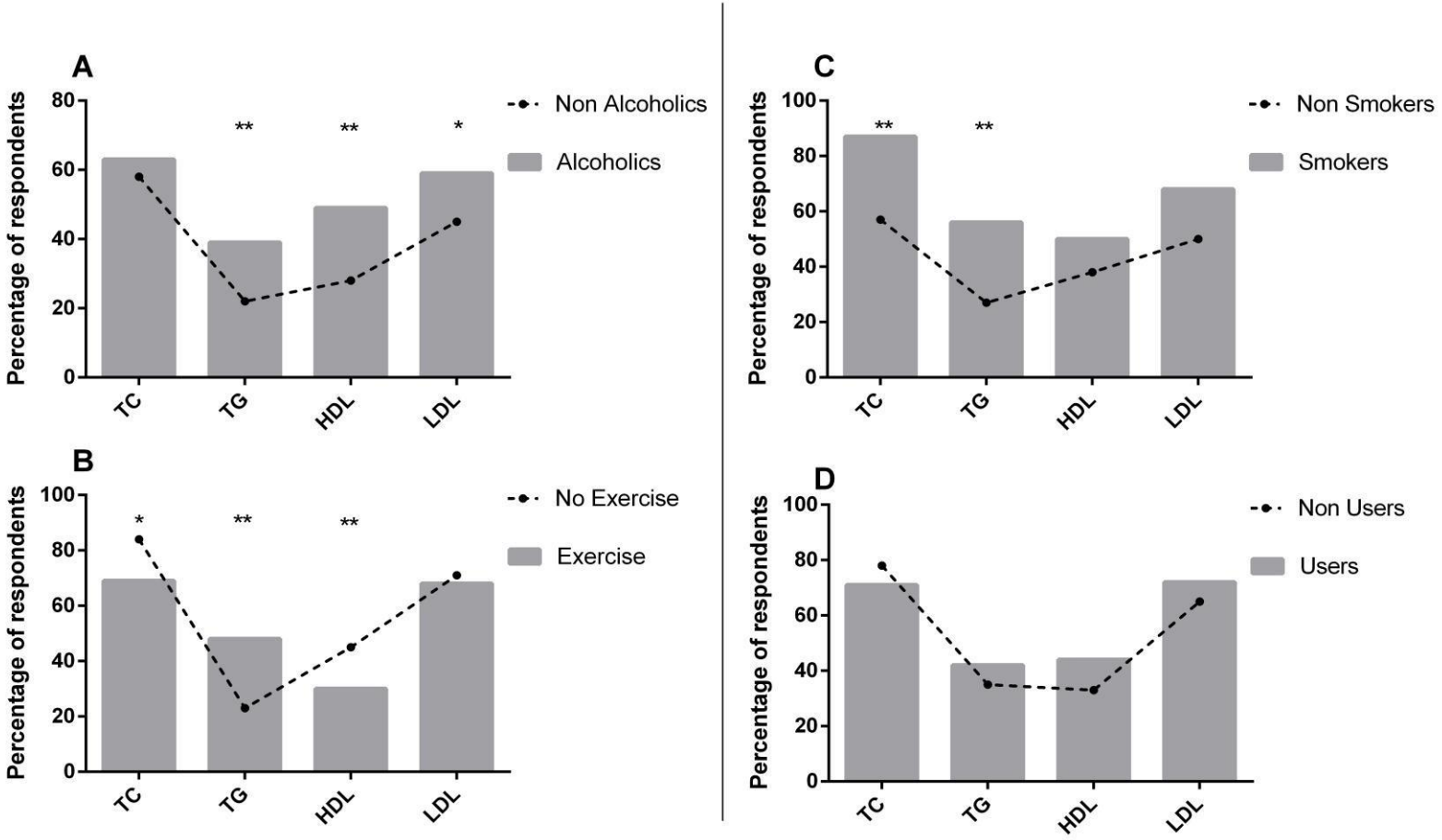

Figure 4-1 : Component dyslipaedemia stratified by socio-demographic characteristic among hypertension

population : TC-Total Cholesterol, TG- Triglyceride, HDL-High density lipoprotein, , LDL-Low density lipoprotein, Non Users & Users of non-prescribed medication. p is significant at 0.05*, 0.01, 0.001*****

In general patients who consume alcohol showed increased cluster across increasing atherogenic scores and the opposite was observed in those who did not take alcohol (Fig. 4-2A). All the patients who smoked recorded at least one atherogenic abnormality with increasing percentage cluster across increasing atherogenic scores (Fig. 4-2B).

In general patients who exercised actively showed lower atherogenic scores compared to those who did not partook in exercise (Fig. 4-2C). The hypertensive population presenting with nonspecific sinuses exhibited an increased trend of clustering across increasing atherogenic scores, with the opposite observed with those without an abnormal electrocardiograph (ECG) (Fig. 4-2D). Patients presenting with Cardiomegaly and those with heart enlargement significantly showed a pattern of increased clustering with increasing atherogenic scores (Figure 4 - 2E & 2F).

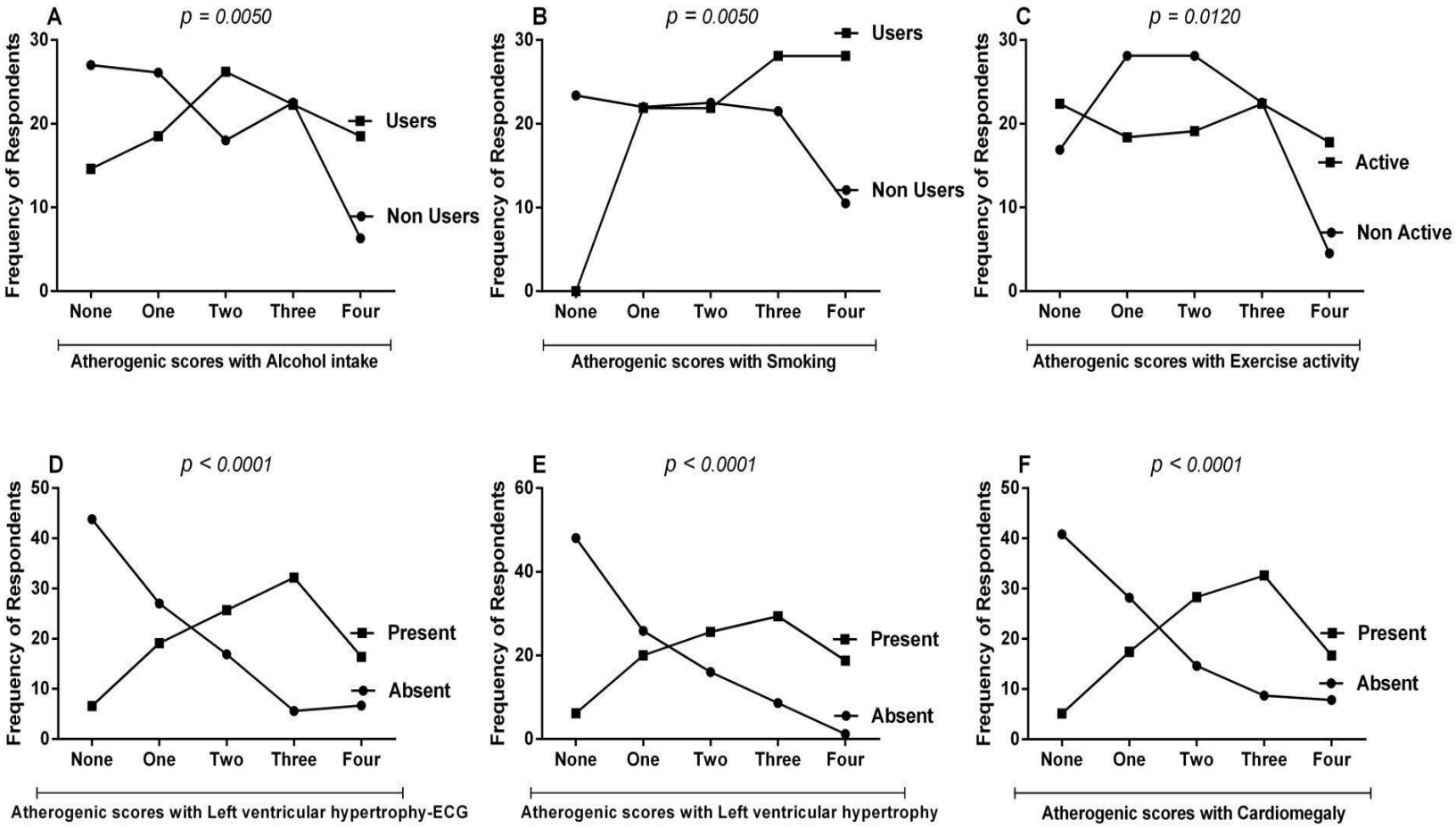

Figure 4-2: Atherogenic scores stratified by socio-demographic characteristics and clinical disease characteristics

After assessing selected variables for progressive linear increment or decline from the first through to the fourth quartile of the haemodynamic parameters using linear contrast analysis, a significant additive incremental linear relationship was observed for age, waist circumference and all component atherogenic lipid indices measured with increasing quartile levels for both systolic and diastolic blood pressure. In the case of quartile cluster distribution for pulse rate, significant additive linear relationship was observed for age, all anthropometric indices and all component atherogenic lipid parameters measured except for waist to hip ratio and triglyceride levels respectively (Table 4 - 8).

Table 4-8: Linear contrast analysis of quartile cluster distributions of Haemodynamic indices stratified by Age, Adiposity and Atherogenic parameters

Parameter		Q-1	Q-2	Q-3	Q-4	*p- linear trends*
Systolic Blood Pressure	Age	28.82±1.80	41.19±3.13	56.60±1.38	59.92±1.26	<0.001
	WC	72.20±2.02	85.19±3.80	97.13±2.18	94.94±2.09	<0.001
	BMI	29.10±0.67	30.16±0.83	29.51±0.52	29.62±0.53	0.73
	WHR	0.97±0.01	0.97±0.01	0.96±0.01	0.97±0.01	0.89
	TG	1.84±0.57	1.90±0.58	2.21±0.58	2.20±0.58	<0.001
	HDL	2.06±0.61	2.33±0.63	2.63±0.612	2.65±0.61	<0.001
	TC	4.67±1.55	5.58±1.59	7.16±1.56	6.58±1.56	<0.001
	LDL	2.06±0.61	2.33±0.63	2.63±0.612	2.65±0.61	<0.001
Diastolic Blood Pressure	Age	24.45±0.63	45.96±2.30	58.40±1.17	57.40±1.93	<0.001
	WC	68.03±1.99	93.10±2.94	93.29±1.97	93.45±2.06	<0.001
	BMI	28.74±0.85	29.55±0.62	29.36±0.46	30.44±0.64	0.12
	WHR	0.97±0.01	0.97±0.01	0.96±0.01	0.97±0.01	0.97
	TG	1.87±0.57	1.91±60.57	2.22±0.58	2.25±0.58	0.001
	HDL	1.90±0.57	2.04±0.57	2.54±0.58	2.74±0.59	<0.001
	TC	4.59±1.56	6.28±1.58	6.74±1.56	6.24±1.57	<0.001
	LDL	1.96±0.59	2.62±0.58	3.07±0.58	3.14±0.58	<0.001
Pulse Rate	Age	28.48±1.88	52.45±2.42	57.09±1.34	56.69±1.51	<.001
	WC	70.56±2.02	84.88±1.79	92.82±1.82	105.25±2.71	<0.001
	BMI	28.82±0.72	29.18±0.58	29.12±0.57	30.84±0.54	0.03
	WHR	0.96±0.01	0.96±0.01	0.97±0.07	0.97±0.01	0.33
	TG	1.85±0.57	2.21±0.58	2.16±0.58	2.10±0.58	0.05
	HDL	2.04±0.61	2.49±0.62	2.84±0.62	2.44±0.61	0.001
	TC	4.58±1.56	6.46±1.58	6.57±1.56	6.97±1.57	<0.001
	LDL	2.14±0.62	3.08±0.62	3.25±0.61	3.21±0.61	<0.001

Data is presented as mean ± standard deviation, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, BMI-Body Mass Index, WC- Waist Circumference, WHR- Waist-to-Hip Ratio, TG-

Triglyceride, HDL-High density lipoprotein, TC-Total Cholesterol, LDL-Low density lipoprotein.Q-1 - First quartile,
Q-2 - Second quartile, Q-3 - Third quartile, Q-4 - Fourth quartile

In general, percentage cluster distributions by dyslipaemia were observed to significantly increase progressively from the first to the fourth quartile of all haemodynamic parameters evaluated in this study. Categorization by systolic blood pressure observed in participants presenting with at least one lipid abnormality were 39.3%, 77.8%, 95.0% and 93.6% at the first, second, third and fourth quartile respectively. The percentage population clusters recorded for diastolic blood pressure were (39.5%, 72.3%, 94.5%, 93.6%) and pulse rate were (37.0%, 87.5%, 92.5%, 95.3%) for the first, second, third and fourth quartile respectively.

As seen in Fig. 3, participants presenting with significantly higher multiple atherogenic scores were found to cluster at the upper quartiles of systolic blood pressure, diastolic blood pressure and pulse rate. Whilst majority of participants with no or single lipid atherogenicity clustered at the first and second quartiles of the haemodynamic parameters measured (SBP, DBP, and pulse rate) (Figure 4-3).

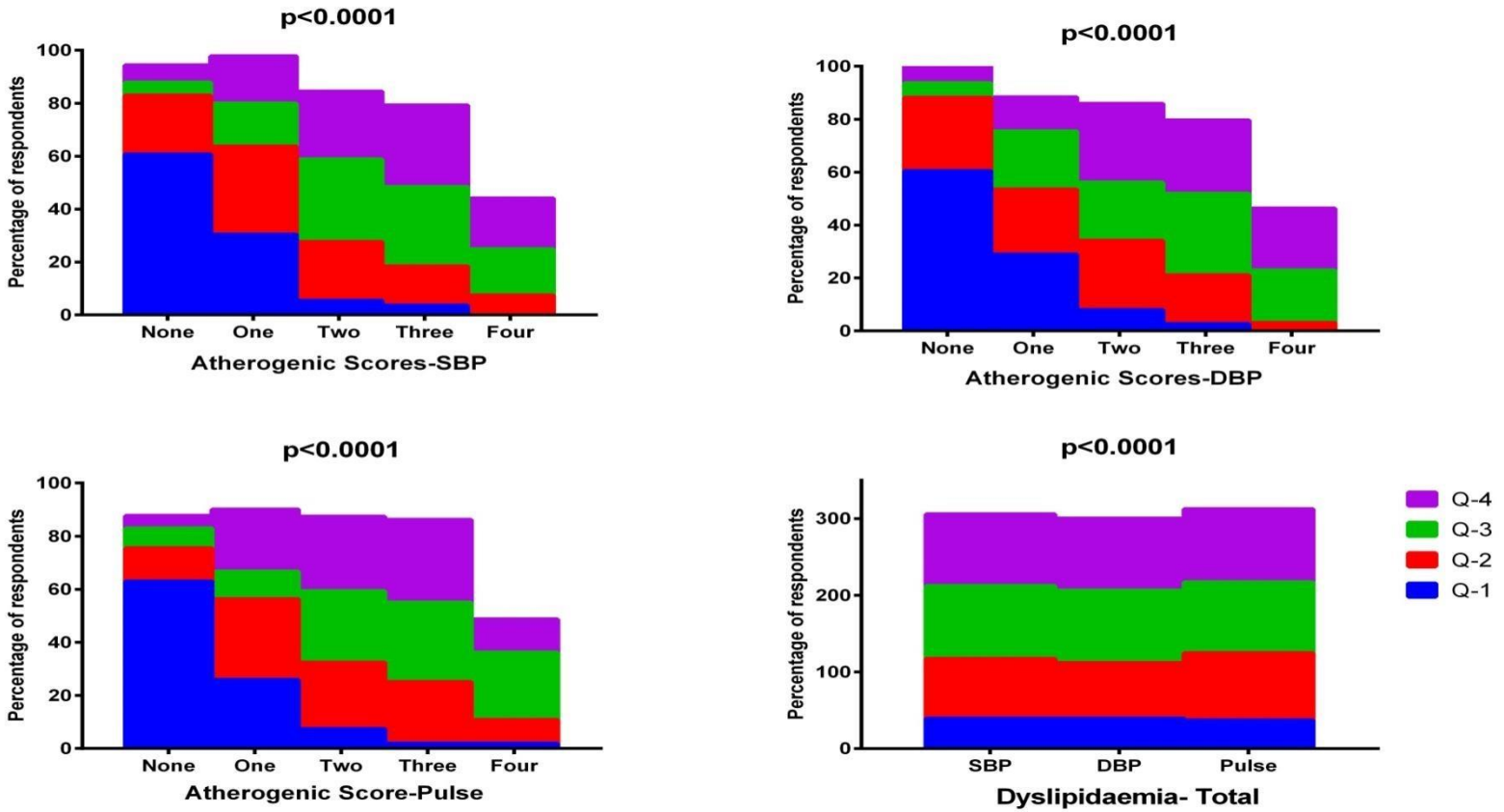

Figure 4-3: Atherogenic dyslipidaemia quartile cluster distributions with Haemodynamic parameters. SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure Q-1 - First quartile, Q-2 - Second quartile, Q-3 - Third quartile, Q-4 - Fourth quartile

Among the total population of 241 participants, 13.3% presented with chronic kidney disease (CKD) when assessed by the four-variable Modification of Diet in Renal Disease (4v-MDRD) equation. The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) recorded 14.5%. All patients presenting with CKD belong to the hypertension group. All CKD patients observed were in the third stage (see Table 4-9).

Table 4-9: Estimates of the prevalence of CKD in the study population using the renal function equations

Parameter	4v-MDRD	CKD-EPI

eGFR	Total	Control	Case	Total	Control	Case
Stage 1 (≥ 90)	120(49.80)	57(93.40)	63(35.00)	117(48.50)	59(96.70)	58(32.20)
Stage 2 (60 to 89)	89(36.90)	4(6.60)	85(47.20)	89(36.90)	2(3.30)	87(48.30)
Stage 3 (30 to 59)	32(13.30)	0(0.00)	32(17.80)	35(14.50)	0(0.00)	35(14.50)
Stage 4 (15 to 29)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Stage 5 (<15)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
CKD (Stage3+4+5)	32(13.30)	0(0.00)	32(17.80)	35(14.50)	0(0.00)	35(19.40)

Data is presented as absolute values with corresponding percentage in parenthesis. 4vMDRD – four variable Modification of Diet in Renal Disease, CKD-EPI – Chronic Kidney Disease Epidemiology collaboration, eGFR – estimated Glomerular Filtration Rate, CKD – Chronic Kidney Disease

Among the hypertensive patients who were newly diagnosed and thus treatment naïve and those who were on therapy irrespective of the equation used in assessing glomerular filtration rate, the group on therapy recorded a greater percentage of end stage Chronic Kidney Disease (CKD) than their naïve counterparts, however with the exception of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see fig.4-4A), this difference was not statistically significant. Significant gender differences in the incidence of CKD was observed. Using the CKD EPI equation 22.6% of hypertensive females presented with CKD compared to 14.9% of male hypertensives (see fig.4-4C). Twenty-one and seven percent (21.7%) of females compared to 12.2% of male presented with CKD as per the four variable Modification of Diet in Renal Disease (4v-MDRD) equation (see fig.4-4D).

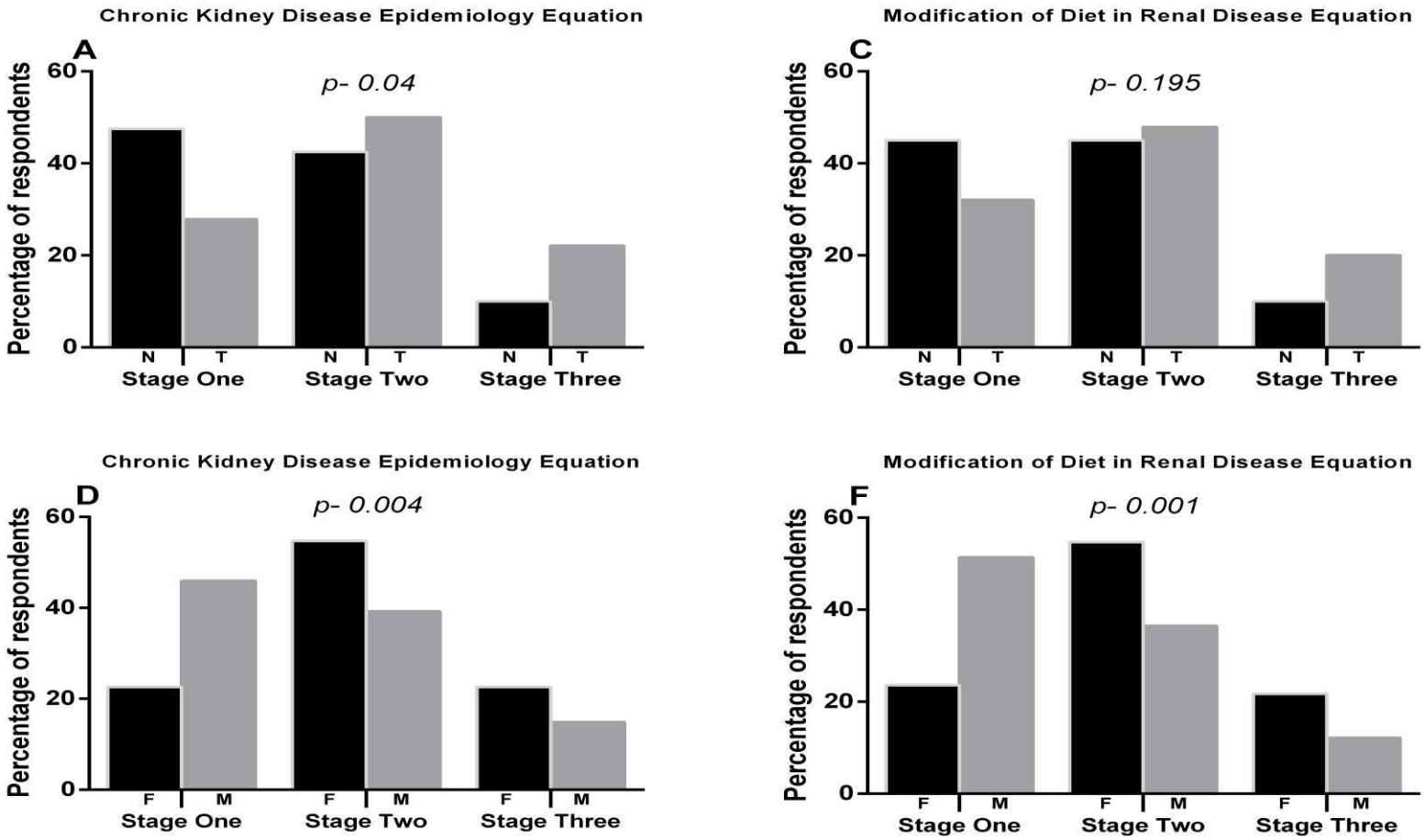

Figure 4-4: Estimates of the prevalence of CKD in the study population using the renal function equations stratified by therapy and gender. N-Drug Naïve, T-therapy, F-Female, M-Male.

Irrespective of the equation used in estimating the glomerular filtration rate (GFR), self-reported non-alcoholics presented with significantly higher percentage of chronic kidney disease (CKD) than the alcoholics (23.6%, vrs 16.7% and 20.8% vrs 15.7) for Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and four-variable Modification of Diet in Renal Disease (4v-MDRD) equations respectively.

From figure 4-5C, significantly higher percentage of smokers (37.9%) were observed with CKD, compared to their counterparts who did not smoke (15.9%), a similar outcome was observed with the use of the 4v-MDRD where (37.9%) of smokers presented with CKD compared to (13.9%) of non-smokers (see Figure 4-5).

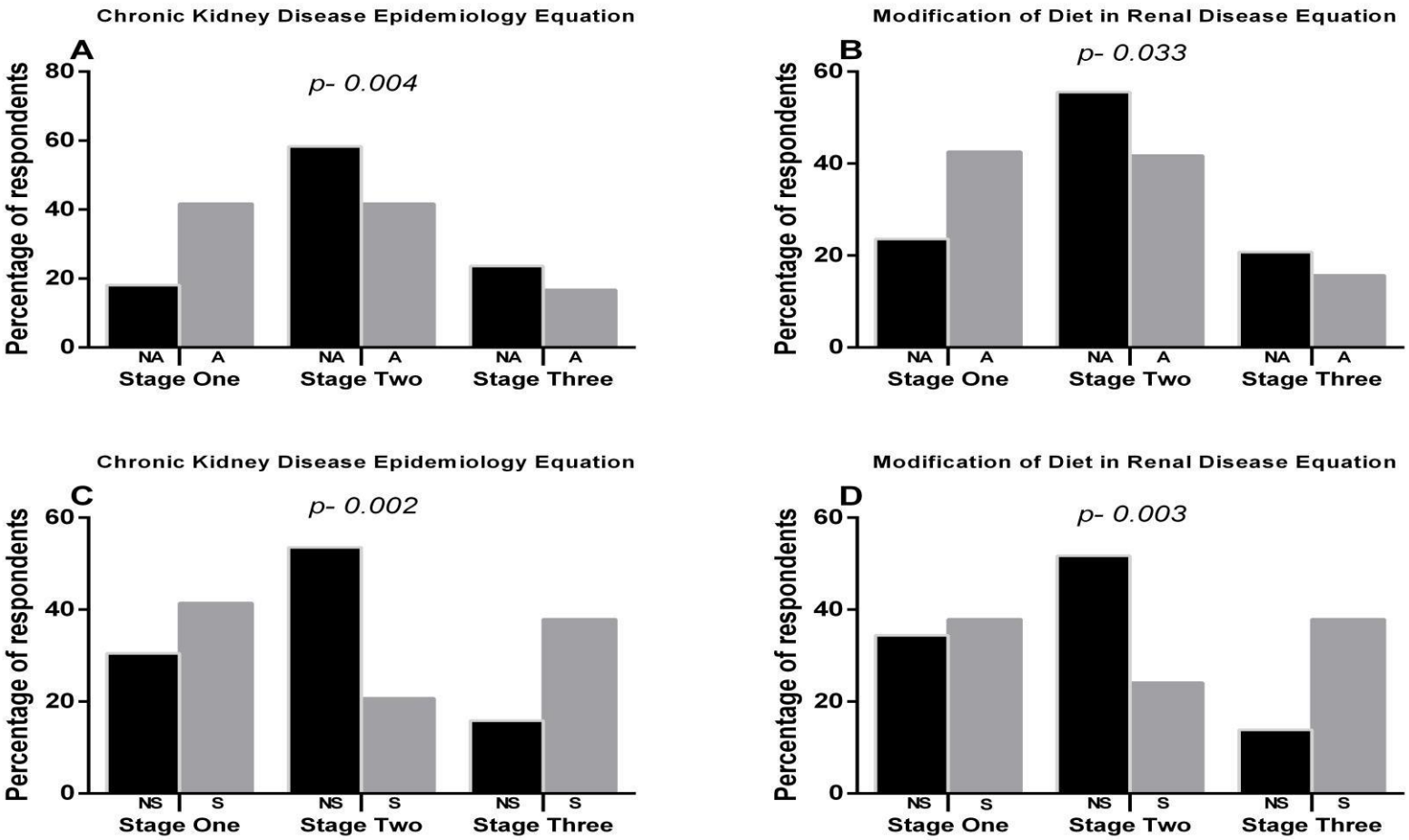

Figure 4-5 : Estimates of the prevalence of CKD in the study population using the renal function equations stratified by alcohol consumption and smoking status. NA- Non-Alcoholic, A-Alcoholic, S-Smoker,NS- NonSmoker

Almost all participants presenting with chronic kidney disease (CKD) clustered at the upper quartiles (3rd and 4th) of systolic blood pressure. Percentage cluster distribution by CKD was observed to be significantly tilted toward the upper quartiles of diastolic blood pressure. Though not statistically significant, majority of CKD participants clustered in the third and fourth quartiles of pulse, irrespective of the renal function equation used. Majority of participants presenting with microalbuminuria clustered in the upper quartiles of the haemodynamic parameters evaluated (see Figure 4-6).

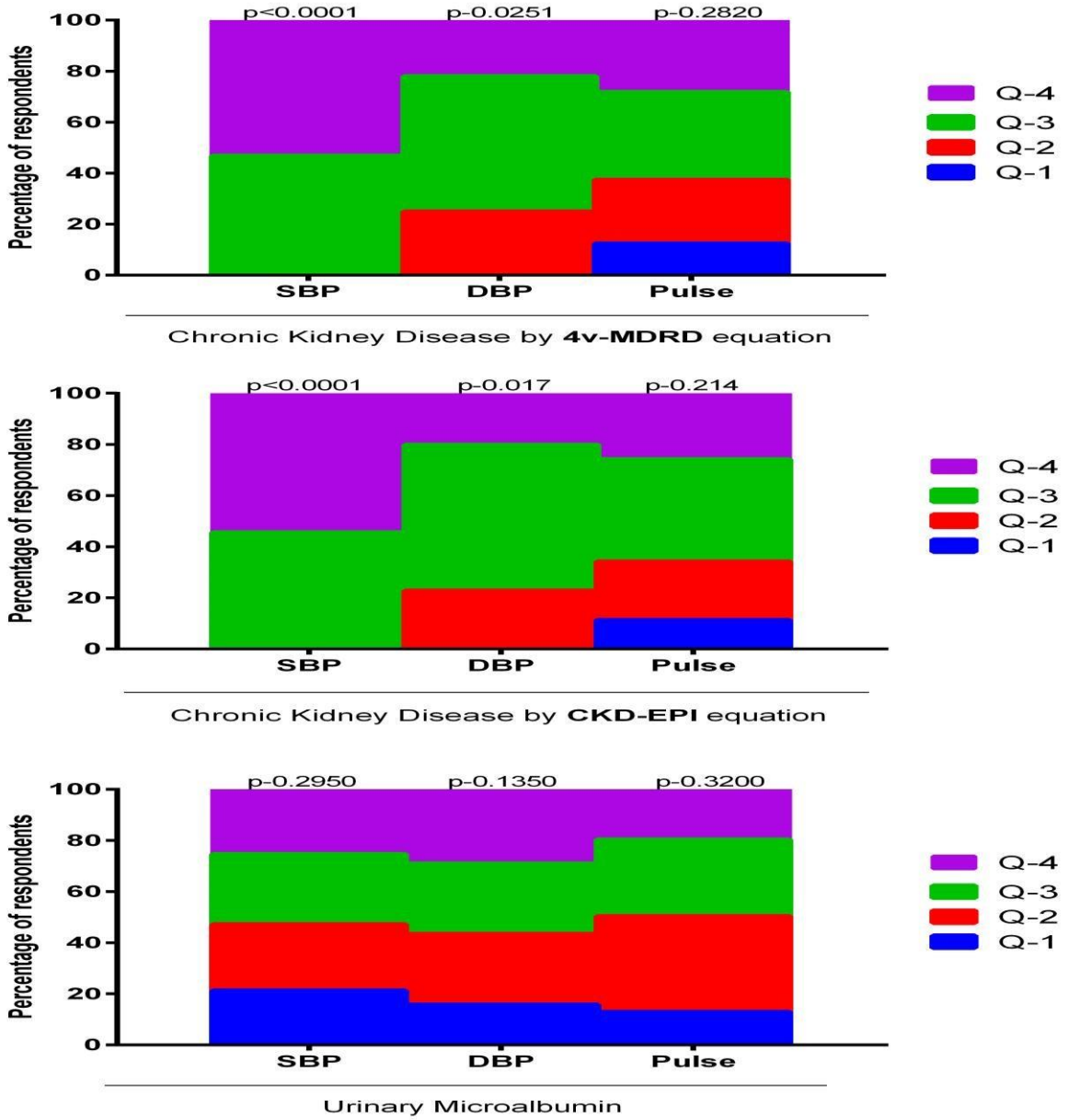

Figure 4-6 : Renal insufficiency quartile cluster distributions with haemodynamic parameters. SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure Q-1 - First quartile, Q-2 - Second quartile, Q-3 - Third quartile, Q-4 - Fourth quartile. P-value for Linear by linear association is significant at 0.05 for two tail

The prevalence of microalbuminuria among the alcoholic participants was 32.4% compared to 27.8% among the non alcoholics. Study participants who smoked recorded a higher percentage of microalbuminuria compared to non-smokers and also a higher number of smokers were found to cluster at increasing levels of microalbuminuria compared to non-smokers. Patients using herbal medicine had higher microalbuminuria (32.7%) than those who were not using herbal medications (27.6%). Even though higher microalbuminuria was observed among the physically active group, severity of microalbuminuria was more profound in their non-active counterparts (see Figure 4-7).

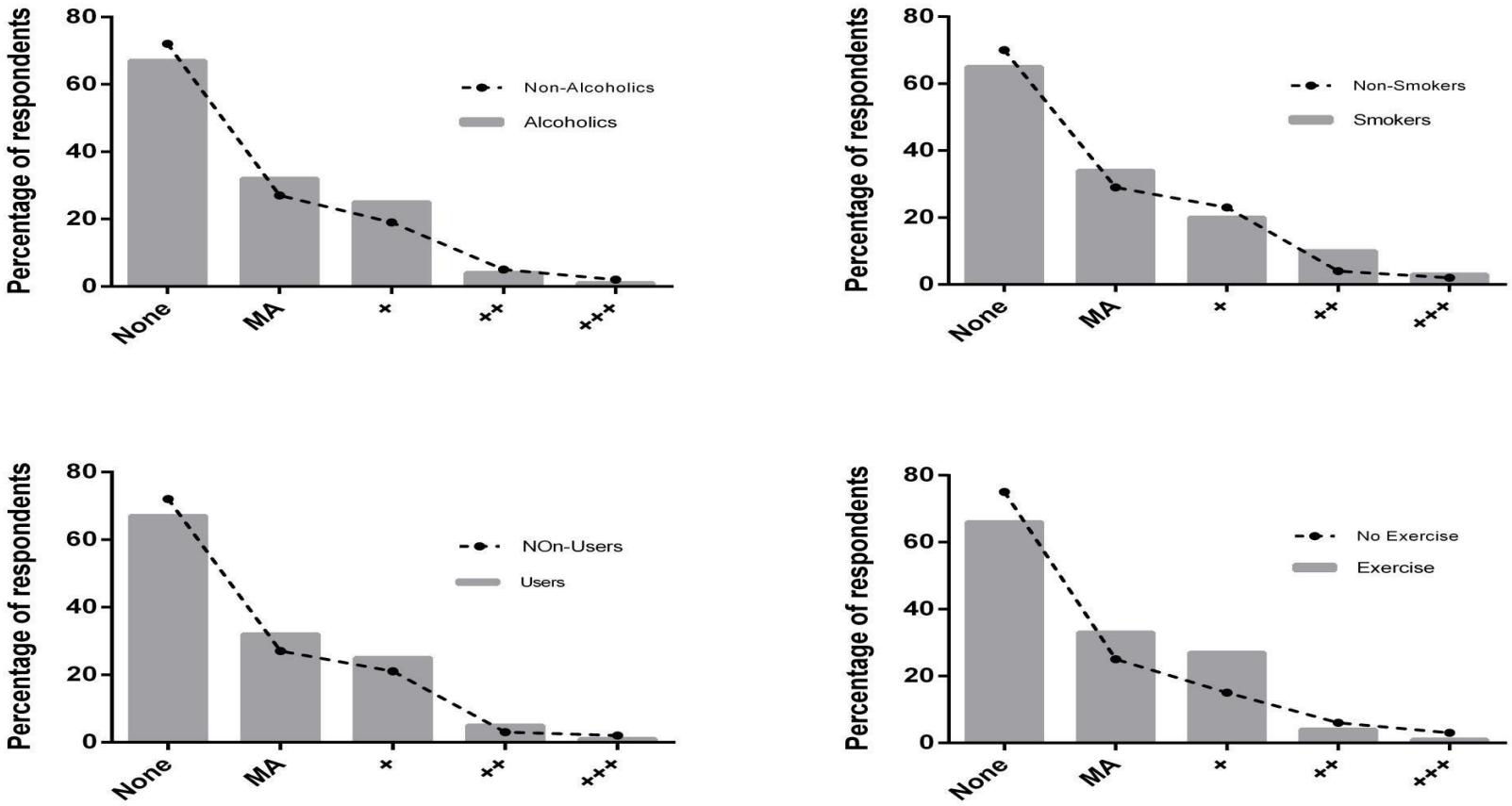

Figure 4-7: Prevalence of microalbuminuria among hypertension participants stratified by sociodemographic characteristics. MA- Microalbuminuria. A. Alcohol intake, B. Smoking status, C. Herbal Medicine intake and D. Physical Activity level. +=positive uninary microalbunin (30mg/dl), ++=positive uninary microalbunin (100mg/dl) and +++ =positive uninary microalbunin (300mg/dl)

In general significant additive linear relationship was observed for all serum renal biochemical parameters assayed with progressive quartile increment of haemodynamic indices. The exception was observed with the average levels of uric acid among the diastolic quartile cluster distribution, where no significant linearity was observed. Irrespective of the renal function equation used in the estimation of the glomerular filtration rate among the study population, participants presenting with cardiac abnormalities (left ventricular hypertrophy-electrocardiograph, left ventricular hypertrophy-echocardiograph, cardiomegaly-X-ray) recorded significant prevalence of chronic kidney disease than their counterparts who were without the specific abnormal heart condition (see Table 4-10).

Table 4-10: Staged renal insufficiency stratified by the presence of clinical manifestation of cardiac disorder (nonspecific sinuses, left ventricular hypertrophy, heart enlargement)

Parameter	Equation	Condition	Stage – 1	Stage - 2	Stage - 3	Stage - 4	p-value
Left Ventricular Hypertrophy Electrocardiograph	**4v-MDRD**	*Absent*	66(74.12)	17(19.10)	6(6.74)	0(0.00)	p<0.0001
		Present	54(35.53)	72(47.37)	26(17.11)	0(0.00)	
	CKD-EPI	*Absent*	66(74.16)	17(19.10)	6(6.74)	0(0.00)	p<0.0001
		Present	51(33.55)	72(47.37)	29(19.08)	0(0.00)	
Left Ventricular Hypertrophy Echocardiograph	**4v-MDRD**	*Absent*	62(76.54)	16(19.75)	3(3.70)	0(0.00)	p<0.0001
		Present	58(36.25)	73(45.63)	29(18.13)	0(0.00)	
	CKD-EPI	*Absent*	64(79.00)	14(17.30)	3(3.70)	0(0.00)	p<0.0001
		Present	53(33.10)	75(46.90)	32(20.00)	0(0.00)	

Cardiomegaly (X-Ray)	**4v-MDRD**	*Absent*	74(71.80)	21(20.40)	8(7.80)	0(0.00)	P <0.0001
		Present	46(33.30)	68(49.30)	24(17.40)	0(0.00)	
	CKD-EPI	*Absent*	64(79.00)	14(17.30)	3(3.70)	0(0.00)	p<0.0001
		Present	53(33.10)	75(46.90)	32(20.00)	0(0.00)	

Data is presented as figure with percentage in parenthesis. 4v-MDRD - fourvariable Modification of Diet in Renal Disease , CKD-EPI -Chronic Kidney Disease Epidemiology Collaboration equation.

Using the relative operative characteristics analysis, a population and gender specific diagnostic criterion for the prediction of hypertension and the discriminating power was determined for commonly used anthropometric measures. With the exception of BMI, for both sexes and waist-to-hip ratio (WHR_M) for male participants, all the commonly used anthropometric measures evaluated for this study demonstrated significant ability of differentiating between hypertensives and normotensives at various optimal thresholds among the study population. At a cut-off point of >75cm and >80cm the waist circumference was the anthropometric measure of choice among the commonly used measures of obesity based on their discriminatory power (Area under the curve - AUC), medical usefulness (Youden J index), sensitivity and specificity (Table 4-11).

Table 4-11: Receiver operative characteristics threshold Cut-off values of commonly used anthropometric variables and their ability to predict hypertension

Parameter	Cutoff	Sensitivity	Specificity	(AUC)	P -value	Youden J
WC_F	>75	90.57(83.3 - 95.4)	77.78(62.9 - 88.8)	0.911	<0.0001	0.6834
WC_M	>80	81.08(70.3 - 89.3)	81.25(54.4 - 96.0)	0.885	<0.0001	0.6233
BMI_F	>28.3	66.98(57.2 - 75.8)	48.89(33.7 - 64.2)	0.546	0.3781	0.1587
BMI_M	≥31.02	64.86(52.9 - 75.6)	62.50(35.4 - 84.8)	0.561	0.4951	0.2736
WHR_F	>0.97	45.28(35.6 - 55.2)	77.78(62.9 - 88.8)	0.616	0.0205	0.2306
WHR_M	>0.91	85.14(75.0 - 92.3)	0.00(0.0 - 20.6)	0.523	0.7648	0.1486

$WHtR_F$	>0.49	83.02(74.5 - 89.6)	75.56(60.5 - 87.1)	0.870	<0.0001	0.5857
$WHtR_M$	>0.53	70.27(58.5 - 80.3)	75(47.6 - 92.7)	0.833	<0.0001	0.5541

WC- Waist Circumference, BMI-Body Mass Index, WHR- Waist-to-Hip Ratio, WHtR-Waist-to-Height Ratio, F-Female and M-Male. AUC - Area under the Receiver operative characteristics curve.

Using the relative operative characteristics analysis, a population and gender specific diagnostic criterion for the prediction of hypertension and the discriminating power was determined for candidate anthropometric measures. All candidate anthropometric measures evaluated for this study demonstrated significant ability of differentiation in both sexes between hypertensives and normotensives at various optimal thresholds. The leading candidate anthropometric index was conicity index at a gender specific optimal threshold of >1.08 for females and >1.05 for males (Table 4-12).

Table 4-12: Receiver operative characteristics threshold values of selected less commonly used candidate anthropometric variables and their ability to predict hypertension

Parameter	Cutoff	Sensitivity	Specificity	(AUC)	P -value	Youden J
CI$_F$	>1.08	80.19(71.3 - 87.3)	95.56(84.9 - 99.5)	0.944	<0.0001	0.7574
CI$_M$	>1.05	87.84(78.2 - 94.3)	87.5(61.7 - 98.4)	0.937	<0.0001	0.7534
AVI $_F$	>11.25	91.51(84.5 - 96.0)	77.78(62.9 - 88.8)	0.910	<0.0001	0.6929
AVI $_M$	>12.83	81.08(70.3 - 89.3)	81.25(54.4 - 96.0)	0.885	<0.0001	0.6233
BAI$_F$	>22.85	83.96(75.6 - 90.4)	71.11(55.7 - 83.6)	0.827	<0.0001	0.5507
BAI$_M$	>16.96	91.89(83.2 - 97.0)	50(24.7 - 75.3)	0.764	0.0001	0.4189

C. I-Conicity Index, AVI-Abdominal Volume Index, BAI-Body Adiposity Index, $_F$Female and $_M$-Male. AUC - Area under the Receiver operative characteristics curve.

On the comparative performance of anthropometric indices as predictors of hypertension, Conicity index irrespective of gender outperformed all other anthropometric measures evaluated in this study by presenting a significantly higher discriminatory power (Area under the curve - AUC) compared to every other index of body adiposity in this study. Among the male population the performance of WC, AVI and WHtR were comparable. However WC and AVI were found to significantly better predict hypertension among female population than WHtR. The performances of BMI and WHtR among the study population irrespective of gender was near to a worthless test (AUC- 0.5) (Table 4-13).

Table 4-13: Comparism of ROC AUC for discriminating performance of anthropometric variables for hypertension. Upper right sided Male, Lower Lift sided Female

Parameter	AUC_{Female}	WC	WHR	WhtR	BMI	CI	AVI	BAI
AUC_{Male}		0.885	0.523	0.833	0.561	0.937	0.885	0.764
WC	0.911		0.36±0.08***	0.05±0.03	0.32±0.11**	0.05±0.02*	0.00±0.00	0.12±0.06*
WHR	0.616	0.30±0.05***		0.31±0.09***	0.04±0.13	0.41±0.08***	0.36±0.08***	0.24±0.12*
WhtR	0.870	0.04±0.02**	0.25±0.06***		0.27±0.13*	0.10±0.04**	0.05±0.03	0.07±0.03*
BMI	0.546	0.37±0.05***	0.07±0.07	0.32±0.04***		0.38±0.10***	0.32±0.11**	0.20±0.14
CI	0.944	0.03±0.01*	0.33±0.05***	0.07±0.02**	0.39±0.05***		0.05±0.02*	0.17±0.06**
AVI	0.910	0.001±0.001	0.29±0.05***	0.04±0.02**	0.36±0.05***	0.04±0.01*		0.12±0.06*
BAI	0.827	0.08±0.03**	0.21±0.07**	0.04±0.05*	0.28±0.04***	0.12±0.03***	0.08±0.03**	

Data is presented as AUC and difference in AUC ± Standard error of the difference in AUC. WC- Waist Circumference, BMI-Body Mass Index, WHR- Waist-to-Hip Ratio, WHtR- Waist-to-Height Ratio, C. I-Conicity Index, AVI-Abdominal Volume Index, BAI-Body Adiposity Index

Chapter 5 DISCUSSION, CONCLUSION & RECOMMENDATION

5.1 DISCUSSION

5.1.1 Hypertension and socio-demography

Hypertension is regarded as a major public health problem (Owiredu *et al.*, 2012a) and the leading aetiology of cardiovascular diseases (Owusu *et al.*, 2013; Santulli, 2013), cardiomegaly (Akosa and Armah, 2005) and heart failure (Owusu and Boakye, 2013) among the Ghanaian population. Majority of the hypertensive (74.44%) patients were employed in the informal sector (Table 41) and this validates the assertion by Bosu (2010) in a comprehensive review of hypertension that the phenomenon affects every thrust of society rather than the prevailing myth that hypertension is a major problem in only the affluent population. Though increasing age was found to be associated with hypertension the critical age threshold of 39 years was observed as the diagnostic age of hypertension in this study population. This finding, affirms reports of various studies that have reported that the onset of hypertension and its complications occur in a relatively young population among Ghanaians (Akosa and Armah, 2005; Bosu, 2010; Afoakwah *et al.*, 2012; Duah *et al.*, 2013).

5.1.2 Hypertension and Modifiable Lifestyle practices

Alcohol consumption was significantly more profound among the hypertensives than the normotensives (Table 4-1). Among the hypertensive

population, unfavourable lipid outcome as well as a greater cluster of participants with multiple atherogenic abnormalities were observed with selfreported alcohol intake (Fig. 4-1A & Fig. 4-2A) . Various studies in different sub populations in Ghana have found positive association of alcohol consumption with hypertension (Bosu, 2010; Afoakwah *et al.*, 2012; Addo *et al.*, 2013)

5.1.3 Body anthropometry and hypertension

Various studies have reported varied association between body adiposity and hypertension (Redon, 2001; Boustany *et al.*, 2004; Davy and Hall, 2004; Rahmouni *et al.*, 2005; Cappuccio *et al.*, 2008). In Ghana positive association has been reported among various populations between body adiposity and hypertension (Duda *et al.*, 2007; Owiredu *et al.*, 2008; Bosu, 2010; Addo *et al.*, 2013). In the present study, among the commonly used anthropometric parameters, visceral adiposity measured by the proxy marker of waist circumference (Nagaretani *et al.*, 2001) was found to be significantly higher among the cases than the control. Even though the body mass index of the cases was higher than the controls, the difference was not statistically significant (Table 4-2). Interestingly the number of participants presenting with total body obesity was found to be comparable among the two groups, however significantly greater numbers of hypertensive patients presented with abdominal/central obesity compared to their control counterparts, (table 4-5). These findings are consistent with the results of an earlier study by Owiredu

et al. (2008), where they found a close association between hypertension (SBP, DBP) and central obesity (waist circumference) but not with other commonly used adiposity indices (BMI, WHR, WHtR) among a Pentecostal population in the Kumasi metropolis. According to Kotchen et al., (2008) (Kotchen *et al.*, 2008) although the measurement of waist circumference includes both subcutaneous and visceral adipose tissue, visceral adipose tissue independent of total body fat has been found to be the most consistent correlate of hypertension (Siani *et al.*, 2002; Cassani *et al.*, 2009) and this seems to be the case in this present study. Although the causal relationship between adiposity and hypertension is yet to be clearly delineated, in the view of Reddy *et al.* (2010) the mechanism of obesity-associated hypertension appears to be associated with inadequate vasodilatation in the face of the increased blood volume and cardiac output, which are the natural consequences of an increased body mass (Cassani *et al.*, 2009). Obesity may lead to hypertension via pathways that stimulate sympathetic nerve activity (SNA), the renin-angiotensin-aldosterone system, insulin resistance, altered vascular function and physical compression of the kidneys, all of which can cause sodium retention (Kotchen *et al.*, 2008; Mathieu *et al.*, 2009; Kotchen, 2010; Kotsis *et al.*, 2010; Reddy *et al.*, 2010). These mechanisms underlying the blood pressure – adiposity relationship in hypertensive individuals is suggested by some authors to be modulated by a combination of environmental and genetic factors (Kotchen *et al.*, 2008; Poirier,

2008; Santulli *et al.*, 2013b). After adjusting for age, gender and hypertension treatment status, no association was found between the adiposity and haemodynamic indices among the normotensives, however among the hypertensives increasing waist, hip circumference, waist-to-hight ratio as well as body mass index were associated with increasing pulse in this study. There was also an increasing linear trend of average waist circumference with a progressive quartile clustering of the study population with all haemodynamic indices (SBP, DBP and Pulse) assessed in this study (table 4-8). This finding is more consistent with the concept of accentuated association of hypertension with regional body fat distribution rather than the extent of total body fat accumulation (Mazairac and Joles, 2010; Matsuzawa *et al.*, 2011). Fat tissues have been identified as an important endocrine organ engaged in the secretion of many bioactive molecules such as angiotensinogen, angiotensin II, and adipokines (Mazairac and Joles, 2010). Overweight and obesity are associated with adipose tissue dysfunction, characterized by enlarged hypertrophied adipocytes, increased infiltration by macrophages and marked changes in secretion of adipokines and free fatty acids resulting in chronic vascular inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system and sympathetic overdrive, eventually leading to hypertension (Dorresteijn *et al.*, 2012). However in the pathogenicity of adiposity, android (mainly visceral) and renal sinus fat depots have been viewed to be more pathologic than gynoid (mainly subcutaneous) depots (Daniels *et al.*, 1999;

Sironi *et al.*, 2004; Chughtai *et al.*, 2010). Visceral adiposity (mesenteric and omentum fat) induces excess free fatty acids into the liver through accelerated lipogenesis and lipolysis which eventually cause the enhancement of hypertension through atherosclerosis (Matsuzawa *et al.*, 1994; Matsuzawa *et al.*, 1995). Among the hypertensive population, this study has established an association between central obesity as indicated by waist circumference (WC) with raised TC, TG and reduced HDL through a positive correlation with TC and TG but an inverse correlation with HDL (Table 4-5).

5.1.4 Dyslipidaemia and hypertension

Consistently high prevalence of dyslipidaemia has been reported in previous studies which evaluated lipid levels among both the hypertensive and normotensive populations in the Kumasi metropolis (Eghan and Acheampong, 2003; Micah and Nkum, 2012). The finding of the current study confirms the prevalence of high atherogenic dyslipidaemia among the population as reported by the earlier reports. With the exception of the HDL level, unfavorable lipid profile was significantly higher among the hypertensives compared to their normotensive counterparts. Thus a discrepancy arises in this report compared with the former (Eghan and Acheampong, 2003) where higher HDL levels were recorded in the normotensives group, but concordance was established with similar findings of higher HDL level in hypertensives (Micah and Nkum, 2012). Disordered reduced HDL recorded a lower percentage among the normotensive group in contrast to the earlier

observation in the latter study. This suggests that the attributed factors which were mainly socio-demographic transformation through life-style modification to affluence and sedentary attitudes coupled with psychosocial distress brought about by increasing urbanization of the population in Kumasi is still persistent or has probably worsened (Eghan and Acheampong, 2003; Owiredu *et al.*, 2008; Micah and Nkum, 2012). Among the possibilities put forward by Abdulle (2008) in accounting for the occurrence of a better lipid profile among hypertensives were excess mortality among hypertensives with unfavorable lipid profiles which may infer lower levels among survivors and the effects of lipid lowering medications. However the latter suggestion was found not to be plausible from this study since significantly higher levels of HDL and lower percentage of reduced HDL abnormality was exhibited in treatment naïve, newly diagnosed hypertensive patients compared to normotensives controls. In the present study independent of age, gender, medications, TG and TC were positively associated with pulse whilst HDL was inversely associated with pulse among the hypertensives. Multiple dyslipidaemia atherogenic scores were more profound among the cases (74.4%) with only 8.2% of the normotensives recording multiple atherogenic scores. Though no significant relationship was observed in the total population between the lipid parameters and the primary haemodynamic measures (SBP, DBP), component atherogenic lipid indices measured was found to increase with quartile levels for both systolic and diastolic blood pressure. Increasing percentage cluster distribution

by atherogenic dyslipidaemia was observed to significantly increase in magnitude with progressive quartile grading of haemodynamic readings (SBP, DBP and Pulse rate). Also the upper quartile of SBP, DBP and Pulse rate recorded significantly higher multiple atherogenic abnormalities (Fig. 4-3). This finding is consistent with that of Halperin *et al.* (2006) who reported an association of the higher quintile of TC, non-HDL-C, and TC/HDL-C ratio with increased risks of developing hypertension, compared with participants in the lowest quintile.

Though the biological mechanism through which atherogenic lipids influence hypertension is still a subject of intense scientific research, the critical role played by lipids in the induction of endothelial dysfunction as well as alterations in endothelin-1 and endothelin A and B receptor expression are the most important event in the pathogenesis of hypertension(Halperin *et al.*, 2006; Anjum *et al.*, 2013). Experimental studies suggest a direct role for HDL-C in promoting cholesterol efflux (reverse cholesterol transport) from foam cells in the atherosclerotic plaque depots in blood vessels to the liver for excretion. HDL-C also exhibits potent anti-inflammatory and antioxidant effects that inhibit the atherogenic process and thus lower HDL-C which has much influence on hypertension development (Osuji *et al.*, 2012). The physiological balance between the potent vasodilator endothelium derived nitric oxide (NO) and various endothelium derived vasoconstrictors and the sympathetic nervous system is associated with vascular homeostasis (Vallance and Chan,

2001; Raij, 2006). Endothelium derived nitric oxide among its' anti-atherogenic functions has been reported to maintain blood vessel tone through the suppression of platelet aggregation, leucocyte migration, and cellular adhesion to the endothelium, vascular smooth muscle cell proliferation and migration, activation and expression of certain adhesion molecules, and influence production of superoxide anion (Vallance and Chan, 2001; Wierzbicki, 2002; Kawashima and Yokoyama, 2004). Pro-atherogenic lipids, such as oxidized low-density lipoprotein (oxLDL) inhibit signal transduction from receptor activation to endothelial nitric oxide synthase (eNOS) activation and therefore reduce the bioavailability of NO (Vallance and Chan, 2001; Wierzbicki, 2002; Kawashima and Yokoyama, 2004). Links between dyslipidaemia and hypertension has been established through mechanisms such as angiotensin I overexpression, insulin resistance and sympathetic hyperfunction (Halperin *et al.*, 2006).

Higher dyslipidaemic atherogenic scores were found to significantly cluster with poor prognostic presentation of clinical cardiac target organ damage among the hypertensives (nonspecific sinuses or left ventricular hypertrophy, cardiomegaly). According to Gulati *et al.* (2012), who termed the coexistence of dyslipidaemia and hypertension 'LIPITENSION' the co-existence of the two risk factors has more than an additive adverse impact on the vascular endothelium and CVD development. Left ventricular hypertrophy is an ominous harbinger of coronary disease, (Kannel, 2002) and Sundström *et al.*

(2001), in a 20 years prospective longitudinal cohort study found lipids as an important predictor of the onset of left ventricular hypertrophy (LVH). Among a Ghanaian population, hypertension has been found to account for 78.4% cases of cardiomegaly in a pathological review by Akosa and Armah (2005). To the best of our knowledge no known study has evaluated dyslipidaemic atherogenic abnormalities among Ghanaian hypertensive patients with target cardiac organ damage, thus the characterization of the hypertensive participants in the present study by lipid abnormalities vis-à-vis target cardiac organ damage evaluated by the use of X-ray, echocardiogram and electrocardiograph does not only throw light on the role of dyslipidaemia in worsening prognosis among hypertensives in Ghana, but also is a novelty in its setting.

5.2 RENAL IMPAIRMENT AND HYPERTENSION

Earlier reports by Addo *et al.* (2009) and Osafo *et al.* (2011) put the calculated incidence of renal insufficiency (eGFR <60mL/min/1.73 m^2; stages 3, 4 & 5) among different hypertensive populations in Accra Ghana at 4.1% and 27.8% respectively. The estimates of hypertensive kidney target organ damage burden for the present study (17.80% - 19.40%) compared to the earlier records in the previous studies but were higher than the former and lower than the latter. The difference in CKD burden for the hypertensive cohort was perhaps due to differences in study population characteristics, thus the work of Addo

et al. (2009) involved a population survey whilst that of Osafo *et al.* (2011) and the present study were hospital based studies. Again the fact that the study of Osafo *et al.* (2011) included 14.7% of participants with preexisting diabetes mellitus, whereas the present study involved only non-diabetic hypertensives may account for the higher CKD incidence recorded in the previous report. Adu (2013) in an editorial in the Ghana Medical Journal estimated the prevalence of hypertension in the African population at 10% and posited that hypertension accounts for 38.8% of the aetiology of CKD and is possibly the leading cause of target kidney organ damage among this population.

The incidence of CKD was higher among hypertensives on treatment than the treatment naïve. The increased duration of chronic diseases like hypertension has usually been linked with deterioration of sequelae and survival. Also the institution of drug therapy in the management of hypertension is usually associated with advancing disease state and this may account for the higher target kidney organ damage observed among the hypertensives on treatment. Gender differences in health vary according to differential vulnerabilities in males and females, which may be as a result of biological or socio-demographic differences (Saeed *et al.*, 2011; Shin *et al.*, 2012). In the case of chronic kidney disease among hypertensives , vulnerability seems to be more tilted toward the female gender than the male (Haroun *et al.*, 2003; Wang *et al.*, 2008). This finding is in agreement with observations made in this study (see figure 1).

Wang *et al.* (2008) have suggested that the stronger association between obesity and chronic kidney disease in women than in men could account for this phenomenon. In Ghana, obesity is reported to be significantly higher among females than in males (Amoah, 2003; Biritwum *et al.*, 2005). Among hypertensives obesity was found to be significantly higher (p-0.0337) among females (57.5%) compared to the males (40.5%).

5.2.1 Modifiable life-style trait and kidney outcome in hypertension

The raging debate of alcohol consumption as a modifiable life-style trait influencing both hypertension and kidney outcomes in the scientific literature has become even more intense in recent times because of the great importance it confers due to the seemingly large numbers of the population any prognostic outcome may affect. In the recent study, self-reported alcohol consumption was recorded among more than half of the study population 130(53.9%) with a significantly higher presence among the hypertensives than the normotensives (see Table 4-1). Deleterious association of alcohol consumption with hypertension are available in the Ghanaian literature (Bosu, 2010; Afoakwah *et al.*, 2012; Addo *et al.*, 2013). Plausible mechanisms elucidated for such adverse effects include stimulation of corticosteroid, catecholamine, vasopressin production and drug interaction causing resistance to drug therapy and direct pressor effect due to alcohol induced arteriolar vasoconstriction (Potter *et al.*, 1984; Beilin and Puddey, 1992; Klatsky, 2004).

Our finding in the current study is consistent with that of Renaud *et al.* (2004) and Reynolds *et al.* (2008) both of whom reported an inverse association between alcohol consumption and chronic kidney disease among hypertensives (see figure 4-5). However due to our inability to determine the threshold dose level of alcohol intake among the study population, drawing inferences for causality of alcohol dose response was not possible (Dufour, 1999; Klatsky, 2004). It is therefore appropriate to concur with Reynolds *et al.* (2008) who called for caution in the interpretation of similar results, since epidemiologically a suggested J- or U-shaped relationship exists between alcohol consumption and coronary heart diseases. Thus the apparent benefits of moderate drinking on kidney and coronary heart disease mortality are offset at higher drinking levels by increasing risk of death from other types of heart diseases (cardiomyopathy, arrhythmia etc.), neurological disorders, cancer, liver cirrhosis, and traffic accidents (Agarwal, 2002; Klatsky, 2004).

There is consensus on the association of smoking with adverse cardiovascular and renal outcome (Willett *et al.*, 1987; Orth *et al.*, 2000; Ishizaka *et al.*, 2008; Tolstrup *et al.*, 2013; Doyle *et al.*, 2014; Go *et al.*, 2014; Nance *et al.*, 2014). In the present study self-reported smoking was 13.3% among the total study population and significantly higher among the hypertensives compared to normotensives (16.1% vrs 4.9%). In agreement with the findings of adverse renal events associated with cigarette smoking among various study

populations (Stengel *et al.*, 2003; Yamagata *et al.*, 2007; Ishizaka *et al.*, 2008; Maeda *et al.*, 2011; Ryom *et al.*, 2014), current smoking status was associated with chronic kidney disease among hypertensives (see figure 4-5). Plausible mechanisms of smoking attributed renal injury include: increased blood pressure and heart rate; altered diurnal blood pressure rhythm; increased sympathetic nerve activity; nicotine induced mesangial cell proliferation and increased production of fibronectin; arteriosclerosis of renal and intrarenal arteries and arterioles; growth factor activation (angiotensin II, endothelin-1, and TGF-1); oxidative stress; impaired lipoprotein and glycosaminoglycan metabolism; tubulotoxicity; direct endothelial cells toxicity; increased aggregation of platelet; modulation of immune mechanisms; vasopressinmediated antidiuresis and insulin resistance (Haroun *et al.*, 2003; Orth and Hallan, 2008).

5.2.2 Obesity and kidney outcomes in hypertension

Excess weight gain is a major risk factor for essential hypertension and endstage renal disease (ESRD) (Hall *et al.*, 2004; Mathieu *et al.*, 2009). In the present study higher anthropometric indices were recorded among the hypertensive groups compared to the normotensives and after adjusting for age and gender, positive additive changes in anthropometric indices were associated with corresponding incremental changes in the haemodynamic measurements

(hypertension), the serum kidney profile estimates and renal insufficiency

(decreasing eGFR). According to the Guyton hypothesis, sustained hypertension can occur only when there is a derangement of pressurenatriuresis (Re, 2009; AL-Hamdani, 2010; Tedla *et al.*, 2011). Obesity related resetting of the kidney-fluid apparatus to a hypertensive level is consistent with the model of hypertension by volume overload (Kotsis *et al.*, 2010). Documented pathogenic mechanisms include enhanced sympathetic nervous system activity, increased activity of the systemic renin-angiotensin system, low atrial natriuretic peptide levels and physical compression of the kidneys by fat deposits within and around the kidneys, coupled with increased abdominal pressure due to accumulation of excess visceral fat, all of which can cause sodium retention (Sharma *et al.*, 2001; Hall *et al.*, 2004; Hall *et al.*, 2010; Mazairac and Joles, 2010). This enhanced sodium avidity shifts the pressure natriuresis curve to the right, thereby necessitating higher arterial pressure to excrete the day's salt intake and maintain sodium balance and volume homeostasis (Re, 2009; Landsberg *et al.*, 2013).

There is an accumulating body of clinical and experimental data implicating obesity as an important causative factor in renal disease (Hall, 2003; Ejerblad *et al.*, 2006; Navaneethan *et al.*, 2012). Several alterations in renal structure and function have been associated with obesity (Rahmouni *et al.*, 2005). The compensatory mechanisms to maintain sodium balance in obesity in the longterm leads to increased systemic arterial pressure, creating a

haemodynamic burden on the kidneys that causes glomerular injury (Hall *et al.*, 2004).

Deposition of extracellular matrix throughout the renal medulla and the ducts of Bellini compresses the renal parenchyma toward the pole of the kidney resulting in the formation of round-shaped, enlarged kidneys in obese persons (Kotsis *et al.*, 2010).

5.2.3 Hypertension and Chronic kidney disease

There is intense debate as to whether hypertension causes kidney disease or vice versa (Haroun *et al.*, 2003). High blood pressure is a key pathogenic factor that contributes to the deterioration of kidney function (Bakris and Ritz, 2009). Conversely, chronic kidney disease (CKD) is the most common form of secondary hypertension (Tedla *et al.*, 2011), thus making the kidney both a cause and a victim of hypertension (Morgado and Neves, 2012). In the current study chronic kidney disease was observed only among the participants presenting with hypertension, irrespective of the predictive equation used in estimating the glomerular filtration rate. The association between hypertension and CKD was also evident as percentage cluster distribution of participants presenting with chronic kidney disease predominantly segregated with the upper quartiles (3rd and 4th quartiles) of the haemodynamic indices (SBP, DBP, pulse, see figure 4-6). The strength of association was found to be more pronounced with systolic blood pressure, rather than diastolic blood pressure posing a greater risk for cardiovascular events and kidney disease progression.

5.2.4 Serum Electrolytes and kidney outcome in hypertension

Serum elevation of kidney excretory products like electrolytes and metabolites of purine and amino acid catabolism (uric acid and urea) in hypertensives have traditionally been attributed to decreased glomerular filtration rate (GFR) as a result of the effect of hypertension on renal function. A reduction in renal blood flow as a consequence of increasing renal vascular resistance leads to decreased distal tubular flow rate which leads to increased reabsorption and decreased excretion (Johnson *et al.*, 2003; AL-Hamdani, 2010; Habbu *et al.*, 2014). Significantly higher levels of serum electrolytes as well as urea and uric acid were observed among the hypertensive subgroup compared to their normotensive counterparts (see Table 4-4). The assertion that observed relationship between serum kidney excretory products with hypertension and renal disease are pathogenically inert, and only secondary to residual confounding factors are giving way to a more pathophysiological active independent attribution of cause and progression of hypertension and renal disease (Baker *et al.*, 2005; Mellen *et al.*, 2006; Zhou *et al.*, 2006; Adrogué and Madias, 2007; Drenjančević-Perić *et al.*, 2010).

Linear additive relationship was observed for all serum electrolytes as well as urea and uric acid with progressive quartile increment of haemodynamic indices measured in this study. After adjusting for age and gender in the present study, surfeit urea and uric acid were significantly associated with renal insufficiency (see Table 4-6). Often considered a beneficial antioxidant,

recent epidemiologic and experimental studies have demonstrated that hyperuricaemia is a major and an independent risk factor for the development of renal disease, hypertension and adverse cardiovascular outcome (Johnson *et al.*, 2003; Baker *et al.*, 2005; Johnson *et al.*, 2005; Mellen *et al.*, 2006; Perlstein *et al.*, 2006). Possible adverse effects of uric acid on the vasculature have been linked to increased chemokine and cytokine expression (Kanellis and Kang, 2005), induction of renal vasoconstriction mediated by endothelial dysfunction and activation of the renin-angiotensin system (Johnson *et al.*, 2005), stimulation of oxidative stress in vascular smooth muscle cell (VSMC) proliferation, mediated by the mitogen-activated protein (MAP) kinase pathway (Corry *et al.*, 2008) and increased vascular C-reactive protein (CRP) expression (Kanellis and Kang, 2005).

5.2.5 Anthropometric indices and predictive performance

Excess weight gain is a major risk factor for essential hypertension and for endstage renal disease (ESRD) (Hall *et al.*, 2004; Mathieu *et al.*, 2009). In the present study higher anthropometric indices were recorded among the hypertensive groups compared to the normotensives and after adjusting for age and gender, positive additive changes in anthropometric indices were associated with corresponding incremental changes in the haemodynamic measures (Hypertension). According to the Guyton hypothesis, sustained hypertension can occur only when there is a derangement of pressure-natriuresis (Re, 2009; AL-Hamdani, 2010; Tedla *et al.*, 2011). Obesity related

resetting of the kidneyfluid apparatus to a hypertensive level is consistent with the model of hypertension by volume overload (Kotsis *et al.*, 2010). Documented pathogenic mechanisms includes enhanced sympathetic nervous system activity, increased activity of the systemic renin-angiotensin system, low atrial natriuretic peptide levels and physical compression of the kidneys by fat deposits within and around the kidneys, coupled with increased abdominal pressure due to accumulation of excess visceral fat, all of which can cause sodium retention

(Sharma *et al.*, 2001; Hall *et al.*, 2004; Hall *et al.*, 2010; Mazairac and Joles, 2010). This enhanced sodium avidity shifts the pressure natriuresis curve to the right, thereby necessitating higher arterial pressure to excrete the day's salt intake and maintain sodium balance and volume homeostasis (Re, 2009; Landsberg *et al.*, 2013).

5.3 AMTHROPOMETRIC INDICES AND CRITERION THRESHOLD FOR HYPERTENSION

Anthropometric indices provide an effective, simple, inexpensive, and noninvasive means for a first-level screening for hypertension (Silva *et al.*, 2013). Among different populations, varied predictive performances of different anthropometric indices for health and disease with varied threshold cutoff values have been reported (Valdez *et al.*, 1993; Kim *et al.*, 2000; Taylor *et al.*, 2000; Shidfar *et al.*, 2012; Freedman *et al.*, 2013; Lichtash *et al.*, 2013; Nadeem *et al.*, 2013; Silva *et al.*, 2013; Vinknes *et al.*, 2013; Lategan *et al.*, 2014).

In recent times the World Health Organisation/International Association for the Study of Obesity/International Obesity Task Force (WHO/IASO/IOTF) have suggested consideration of using lower obesity measurements in Asian and other places to guide health care professionals to promote healthy life and weight control (Anuurad *et al.*, 2003; Kanazawa *et al.*, 2005; Fan *et al.*, 2007; Owiredu *et al.*, 2008). The International Diabetes Federation (IDF) task force on epidemiology and prevention in an attempt to harmonizing the definition of metabolic syndrome also proposed the use of ethnic based anthropometric threshold cutoffs (Alberti *et al.*, 2009). With the exception of BMI, for both sexes and waist-to-hip ratio (WHR_M) for male participants, all the commonly used anthropometric measures evaluated for this study demonstrated significant ability of differentiating between hypertensives and normotensives at various optimal thresholds among the study population (Table 4-11).

In agreement with Désilets *et al.* (2006) who suggested that standard anthropometric indices of obesity may not be as effective in populations of African descent compared with whites, unless appropriate cut-off values are defined, a waist circumference of greater than 80cm and 75cm for men and women respectively was found to be significant predictors of hypertension.

Compared to currently recommended cutoff point of a waist circumference of ≥94cm for men and ≥80cm for women for sub-Sahara African population proposed by the IDF (Europid) and ≥102cm for men and ≥93cm for women proposed by the National cholesterol education programme adult treatment

panel III (NCEP ATP III) (Thomas *et al.*, 2005; Zimmet *et al.*, 2005; Alberti *et al.*, 2009). This study buttresses the earlier finding that lower cutoff of obesity indices are needed for association with increased health risks among the Ghanaian population (Owiredu *et al.*, 2008).

5.4 COMPARATIVE PERFORMANCE OF ANTHROPOMETRIC INDICES AS PREDICTORS OF HYPERTENSION

We evaluated comparatively gender stratified performance of seven anthropometric indices as predictors of hypertension among a Ghanaian population. Conicity index, waist circumference, abdominal volume index, waist to height ratio and body adiposity index significantly identified hypertension among both female and male study participants but with various different predictive power of hypertension (Table 4-13).

Conicity index outperformed all other anthropometric variables as the anthropometric marker of choice for the prediction of hypertension. Among the male study participants, the use of conicity index improved the prediction of hypertension by 5.7% against its closest anthropometric competitors (WC and AVI) and 79.2% against the worst (WHR). For the female study population, conicity index predicts hypertension 3.6% and 72.9% better than waist circumference and body mass index, the closest and poorest competitors respectively. According to Valdez *et al.* (1993), the advantages of conicity index includes a built-in adjustment of waist circumference for height and weight,

allowing direct comparisons of abdominal adiposity between individuals or even between populations.

The findings of this study confirmed the limited role of waist to hip ratio (WHR) and body mass index (BMI) in predicting hypertension in general and especially in African populations (Mafra *et al.*, 2008; Vuga, 2009; Thierry *et al.*, 2014). The limitation associated with waist to hip ratio is that it co-varies with hip circumference which makes it have a high preponderancy of underestimating the risk of abdominal obesity in those with high hip circumference and thus not a good estimate of abdominal region expansion (Vuga, 2009). Body mass index (BMI) measures total body mass which includes both fat and lean mass (Mafra *et al.*, 2008), body adiposity index (BAI) reflect percentage body adiposity (Bergman *et al.*, 2011), whereas the rest of the anthropometric parameter considered in this study are used as proxy measures for abdominal fat distribution (Guerrero-Romero and Rodríguez-Morán, 2003; Thierry *et al.*, 2014). Different fat depots (abdominal visceral, abdominal subcutaneous, total subcutaneous and total body fat) are not equivalent from a functional point of view, with visceral adipose tissue (VAT) composed of adipocytes of smaller size and less storage capacity, more vascular with increased sympathetic innervation and a large number of β3-adrenergic receptors, which facilitates a higher metabolic activity compared with subcutaneous peripheral adipose tissue (SAT) (Iglesias and Díez, 2010). As visceral obesity cannot be identified by the body mass index (Després, 2014),

its functional significance in predicting its risk on the sequelae hypertension is poor (Lee *et al.*, 2008).

5.5 CONCLUSION

In this urban population, higher altered lipid scores and abdominal obesity aggravated by lifestyle choices including alcohol consumption, smoking and physical inactivity constitute significant risk for cardiovascular complications among hypertensives. Chronic kidney disease was associated with hypertension and cardiac abnormalities, whilst smoking increased kidney target organ damage among hypertensives.

Body mass index and waist-to-hip ratio were poor predictors of hypertension in the general study population. Among the commonly used anthropometric measures, waist circumference at a lower threshold (>75cm female, >80cm male) than cureently recommended cutoffs was the index of choice for the prediction of hypertension, however significant improvement in prediction was achieved with the use of conicity index (>1.08 female, >1.05 male).

5.6 RECOMMENDATIONS

- Moderation of alcohol intake and smoking among hypertensives should be encouraged

- Regular physical activity should be encouraged as component of management of of hypertension where it is not done
- The sole reliance on body mass index in the determination of obesity and associatd health risks must be discontinued to incorporate more sensitive anthropometric markers.
- Further studies with larger sample size is recommended to validate the use of lower ethnic specific criterion threshold of anthropometric indices among the Ghanaian popuatlion as predictors of associated health risks.

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