

**METABOLIC SYNDROME IN ACUTE STROKE SURVIVORS AT KORLE-BU  
TEACHING HOSPITAL**

**BY**

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**DECLARATION**

I, ABABIO EDWARD, author of this dissertation do hereby declare that, with the exception of references to other people’s work which has been duly cited, this work has entirely resulted from my personal original research under supervision of Dr. D. A. Antwi and Rev. Dr. C. Antwi-Boasiako and has not been presented for another degree elsewhere.

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## DEDICATION

This work is dedicated to the Almighty God and my Resident Pastor of Missionaries of Christ Church Rev. Emmanuel Frimpong for his immense support. To my brothers and sisters in the Lord.



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To God be the glory great things he has done. My utmost gratitude goes to God for giving me life, strength, good health and the knowledge to start and complete this work. My very special gratitude go to my able supervisors Dr. Daniel. A. Antwi (Head, Department of Physiology, School of Biomedical and Allied Health Sciences), Rev. Dr. Charles Antwi Boasiako (Department of Physiology, School of Biomedical and Allied Health Sciences). I will also appreciate the immense contribution made by Rev. Emmanuel Frimpong (Department of Physiology, School of Biomedical and Allied Health Sciences).

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## ABSTRACT

**Background:** The presence of metabolic syndrome (MetS) has been associated with an increased risk of stroke. The indicators of MetS that predispose individuals to stroke still persist after stroke. There is insufficient information on MetS in acute ischaemic and haemorrhagic stroke survivors at Korle-Bu Teaching Hospital.

**Aim:** This study assessed metabolic syndrome in acute stroke survivors at Korle-Bu Teaching Hospital.

**Method:** This was a cross-sectional study involving patients at the Medical ward, Stroke unit and Polyclinic of the Korle-Bu Teaching Hospital (KBTH) between October 2014 and April 2015. A total of 150 (73 males and 77 females) stroke survivors comprising 102 (68%) ischaemic stroke survivors and 48 (32%) haemorrhagic stroke survivors were sampled for the study. The National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criterion was used for defining MetS.

**Results:** The incidence of MetS among the study population was 60% using the NCEP ATP III criteria. Out of the 60% with MetS, the prevalence was significantly higher in ischaemic stroke patients compared to haemorrhagic stroke patients (43.3% vs 16.7%;  $p=0.0185$ ). The prevalence of MetS was significantly higher in Ischaemic patients than Haemorrhagic stroke survivors (68% vs 32%;  $p=0.0005$ ). The prevalence of MetS was higher in female stroke survivors compared to male stroke survivors but was not statistically significant (34.7% vs 25.3%;  $p=0.3398$ ). The frequency of MetS was significantly higher in the age group of 50-60 years compared to others ( $p<0.05$ ). High blood glucose, high blood pressure and high waist circumference (obesity) were the most prevalent MetS components (64%, 61% and 58%) respectively. There were significant

associations between high fasting blood glucose, high blood pressure and waist circumference with stroke ( $p=0.003$ ,  $p=0.03$ , and  $p=0.02$ ) respectively.

**Conclusion:** Metabolic syndrome is high in acute stroke patients at Korle-Bu Teaching Hospital. There is high prevalence of metabolic syndrome in ischaemic stroke than haemorrhagic stroke. Female stroke patients have higher frequency of metabolic syndrome than males. Regular monitoring and treatment of components of metabolic syndrome should be considered a standard medical and rehabilitation care for stroke survivors.

**LIST OF ABBREVIATIONS**

A	:	Ambulating Stroke Survivor
ADL	:	Activities of Daily Living
ADP	:	Adenosine diphosphate
AHA	:	American Heart Association
AMP	:	Adenosine Monophosphate
ATP	:	Adenosine Triphosphate
AVM	:	Arteriovenous Malformation
BMI	:	Body Mass Index
BP	:	Blood Pressure
CHD	:	Coronary Heart Disease
CHEP	:	Canadian hypertension Education Programme
CNS	:	Central Nervous System
cm	:	Centimeter
CT	:	Computerized Topography
CVA	:	Cerebrovascular Accident
CVD	:	Cardiovascular Disease
DBP	:	Diastolic Blood Pressure
DHDL	:	Decrease High Density Lipoprotein
FBG	:	Fasting Blood Glucose
FDPS	:	Finnish Diabetes Prevention Study
GLU	:	Plasma Glucose

HBP	:	High Blood Pressure
HDL-C	:	High Density Lipoprotein Cholesterol
HFBG	:	High Fasting Blood Glucose
HK	:	Hexokinase
H <sub>2</sub> O <sub>2</sub>	:	Hydrogen Peroxide
ICH	:	Intracerebral Haemorrhage
IL-6	:	Interleukin-6
L	:	Left Side Affected
LDL	:	Low density Lipoprotein
MetS	:	Metabolic Syndrome
mmHg	:	Millimeter Of Mercury
mmol/l	:	Millimole Per Litre
MRI	:	Magnetic Resonance Imaging
NA	:	Non-Ambulating Stroke Survivor
NAD <sup>+</sup>	:	Nicotinamide adenine dinucleotide (oxidized)
NADH	:	Nicotinamide adenine dinucleotide (reduced)
NCEP	:	National Cholesterol Education Programme
NHNES	:	National Health and Nutrition Examination Survey
NIH	:	National Institute Of Health
NINDS	:	National Institute of Neurological Disorders And Stroke

NMDA	:	N-Methyl-D-Aspartate
OT	:	Occupational Therapy
PAI-I	:	Plasminogen Activator Inhibitor-I
PGP	:	Post-Rehabilitation Guideline Panel
PPAR $\gamma$	:	Peroxisome proliferator activated receptor $\gamma$
PT	:	Physical Therapy
R	:	Right Side Affected
RAAS	:	Renin-Angiotensin Aldosterone System
RTGL	:	Raised Triglycerides
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
SLP	:	Speech Language Pathology
SPSS	:	Statistical Package For Social Sciences
TC	:	Total Cholesterol
TG	:	Triglyceride
TGL	:	Triglyceride
TIA	:	Transient Ischaemic Attack
TNF	:	Tumour Necrosis Factor
T2D	:	Type 2 Diabetes
USDPP	:	United States Diabetes Prevention Programme
VLDL	:	Very Low Density Lipoprotein
WC	:	Waist Circumference

WHO : World Health Organization

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## CHAPTER ONE

### 1.0 INTRODUCTION

#### 1.1 Background to the study

Stroke is a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intra-cerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) (Sacco *et al.*, 2013). Stroke is categorised as either cerebral haemorrhage or cerebral infarction (Ischaemic Stroke) (Sacco *et al.*, 2013). Ischaemic stroke accounts for 80-85% of all strokes, whereas haemorrhagic stroke accounts for 15-20% (Beal, 2010). A stroke affecting one of the three prominent central nervous system pathways: the spinothalamic tract, corticospinal tract and dorsal column (medial lemniscus) will result in hemiplegia, muscle weakness of the face, numbness, reduction in sensory or vibratory sensation, initial flaccidity (hypotonicity) replaced by spasticity (hypertonicity), hyperreflexia, and obligatory synergies (O'Sullivan and Schmitz, 2007). Other areas of the brain such as the brainstem, cerebral cortex and cerebellum may be involved which produce many symptoms such as balance problems and nystagmus, aphasia and altered walking gait respectively (O'Sullivan and Schmitz, 2007).

Stroke remains the first cause of adult neurological disability in developing and developed countries (Opara and Jaracz, 2010; Marzolini *et al.*, 2009). It is the world's second leading cause of mortality, resulting 6,000,000 deaths annually (Woodruff *et al.*, 2011). It is estimated that the lifetime risk for stroke is between 8% and 10% (Seshadri *et al.*, 2006). Community-based studies in African countries have shown that cerebrovascular diseases represent up to 10% of the causes of death and that the prevalence of important risk factors for stroke (hypertension, diabetes and

smoking) is increasing (Walker *et al.*, 2000; Van der Sande *et al.*, 2001; Kahn *et al.*, 1999). Evidence in sub-Saharan Africa suggests that case fatality rates for stroke may be higher than those in high-income countries (Walker *et al.*, 2000) and contribute significantly to the burden of disease (Mensah *et al.*, 2008; Agyemang and Owusu-Dabo, 2008; Connor *et al.*, 2007; Walker *et al.*, 2000). The increasing rates of cardiovascular disease (CVD) mortality, particularly stroke in Ghana, have been unprecedented (Addo *et al.*, 2008; Cappuccio *et al.*, 2004; Agyemang, 2006). In Accra, CVD rose from being the seventh and tenth cause of death in 1953 and 1966 respectively to number one cause of death in 1991 and 2001 (Agyei-Mensah and Aikins, 2010).

Several risk factors associate to predispose individuals to stroke (Ashtari *et al.*, 2012). These risk factors are classified as modifiable and non-modifiable (Ashtari *et al.*, 2012). The modifiable risk factors include hypertension (Alter *et al.*, 1994; Lai *et al.*, 1994), diabetes mellitus (Hier *et al.*, 1991), smoking, physical inactivity (Xu *et al.*, 2007) and atrial fibrillation (Alter *et al.*, 1994). The non-modifiable risk factors comprise age, gender, race and heredity (Ashtari *et al.*, 2012; Sacco *et al.*, 1995). In addition to these traditional risk factors, there are other discovered risk factors such as elevated homocysteine (Boysen *et al.*, 2003), hypercoagulable states (Takano *et al.*, 1992), patent foramen ovale (Bogousslavsky *et al.*, 1996) and metabolic syndrome (MetS) (Liou *et al.*, 2008).

Metabolic syndrome is a constellation of cardiometabolic risk factors including dyslipidaemia, hypertension, hyperglycaemia, central obesity and endothelial dysfunction (Gundogan *et al.*, 2009; Calbo *et al.*, 2007; Boronat *et al.*, 2005). Metabolic syndrome has emerged as a novel risk factor in cardiovascular disease due to its potential for predicting stroke in population-based studies (Mi *et al.*, 2012). Metabolic syndrome has insulin resistance as the core mechanism and

abdominal obesity as the prominent clinical manifestation (Mi *et al.*, 2012). There is also evidence to suggest a genetic basis for the MetS (Hegele, 2003). The presence of MetS has been associated with an increased risk of stroke (Juan *et al.*, 2007). The association between MetS and stroke has been confirmed in other populations integrated by elderly subjects and the frequency of MetS has been reported to be significantly higher in patients with a history of atherothrombotic or non-embolic ischaemic stroke (Milionis *et al.*, 2005; Nimoniya *et al.*, 2004; Suk *et al.*, 2003). This association supports the clinical use of the MetS in the identification of subjects who are at an increased risk of experiencing a stroke.

Long-term follow-up population-based studies have demonstrated that healthy individuals with the MetS are at a markedly increased risk for major cardiovascular events, including stroke and cardiovascular mortality (McNeill *et al.*, 2005; Dekker *et al.*, 2005; Isomaa *et al.*, 2001). Moreover, the risk for incident ischaemic stroke seems to augment with the increasing number of components of the MetS, all of which have been individually associated with an increased risk for future cerebral ischaemic events (Chen *et al.*, 2006; Kurl *et al.*, 2006). Studies have shown that MetS significantly increases the risk of stroke events, as well as all-cause mortality (Karapanayiotides *et al.*, 2004; Megherbi *et al.*, 2003; Kiers *et al.*, 1992). The Hisayama study in Japan has reported that existence of MetS increased the incidence of stroke by 1.9 and 1.5-fold in males and females respectively (Ninomiya *et al.*, 2007). In the National Health and Nutrition Examination Survey among 10357 subjects, the prevalence of MetS was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of vascular disease 22.8% (Nimoniya *et al.*, 2004). The MetS was independently associated with stroke history in all ethnic groups and in both sexes (Arenillas *et al.*, 2007).

In Ghana, the prevalence of hypertension, diabetes, insulin resistance, hyperlipidaemia and obesity which are individual components of MetS are on the increase (Amoah *et al.*, 2003; Amoah *et al.*, 2002; Nyarko *et al.*, 1997; Pobee, 1992). Also, there has been a documented increase in CVD morbidity and case fatality in Ghana (Biritwum *et al.*, 2000). Moreover, most of the risk factors of stroke constitute MetS. Again these risk factors in MetS may persist after stroke increasing risk of recurrent stroke. Therefore, studying MetS in stroke survivors in Ghana will add to knowledge regarding MetS in stroke survivors in Ghana. Thus, studying MetS among the stroke types will help assess the risk of recurrent stroke and provide a paradigm shift in risk factor modification after stroke in order to prevent recurrent stroke and to improve the quality of life of stroke patients. Therefore, the purpose of this study is to assess metabolic syndrome in acute stroke patients.

## **1.2 Problem Statement**

The components of metabolic syndrome that may predispose individuals to stroke still persist after stroke. Findings of previous studies support metabolic syndrome as a risk factor for a recurrent stroke or future cerebral ischaemic event (Boden-Albala *et al.*, 2008; Iso *et al.*, 2007; Kurl *et al.*, 2006; Koren-Morag *et al.*, 2005). Approximately, 30% of individuals with stroke are at risk of sustaining a second stroke (Kelly *et al.*, 2007). Stroke is characterized by high rates of recurrence and mortality (Hillen *et al.*, 2003; Mohan *et al.*, 2011). Given that MetS is associated with an increased risk of recurrent stroke warrants its study in stroke population at Korle-Bu Teaching Hospital. This is because metabolic abnormalities and risk factors that integrate MetS have been associated with worsening of stroke outcomes.

Most of the studies on MetS and cerebrovascular disease have been restricted to the field of primary stroke prevention (Arenillas *et al.*, 2007). However, little is known about the impact of MetS on acute stroke prognosis. Moreover, there is paucity of data regarding the impact of metabolic syndrome on stroke survivors and the association between MetS and risk of recurrent stroke in stroke survivors at Korle-Bu Teaching Hospital.

### **1.3 Justification of the study**

Significant elevation in individual components of MetS such as elevated triglyceride, decreased high density lipoprotein (DHDL) cholesterol, elevated blood pressure, elevated fasting plasma glucose and central obesity is well established as one of the sequelae of stroke (Lee *et al.*, 2012). This is becoming significantly evident that reversing these abnormalities through appropriate treatments may play a role in the secondary prevention of stroke (Black-Schaffer *et al.*, 1999). The notion that MetS is associated with an increased risk for future stroke reaffirms the need to study MetS in stroke survivors and to develop treatment strategies directed to control this syndrome and each of its components.

Evidence suggests that decreasing the individual components of MetS in stroke survivors may be comparable in many ways to preventing a second stroke, improving recovery time and quality of life of stroke survivors (Gordon *et al.*, 2004). Furthermore, multiple risk factors associated with stroke including hypertension, coronary heart disease, diabetes, elevated triglycerides, and obesity which are also risk factors for MetS worsen recovery and compound the loss in movement and overall functioning in stroke survivors (Black-Schaffer *et al.*, 1999).

Assessing these individual components and collectively as MetS may increase the appreciation of the relationship between individual MetS components and also, have a favourable effect on the prevention of recurrent stroke. This is because, the findings of this study will reveal whether or not stroke survivors at Korle-Bu Teaching Hospital are at high risk of recurrent stroke. Hence, there is the need to assess MetS among stroke survivors at Korle-Bu Teaching Hospital. Furthermore, the recognition and management of MetS have been recently included in stroke prevention international guidelines (Goldstein *et al.*, 2006).

#### **1.4 Hypothesis**

The study was based on the Null's hypothesis that, no difference in metabolic syndrome exists between the acute stroke types.

#### **1.5 Aim of the study**

The aim of this study is to assess metabolic syndrome in acute stroke survivors at Korle-Bu Teaching Hospital.

#### **1.6 Specific objectives**

The specific objectives of this study were to:

- 1 Compare the prevalence of metabolic syndrome between ischaemic and haemorrhagic strokes.
- 2 Compare metabolic syndrome between male and female stroke survivors.
- 3 Compare prevalence or frequencies of components of metabolic syndrome between ischaemic and haemorrhagic strokes.
- 4 Determine the association between metabolic syndrome and stroke.

## CHAPTER TWO

### 2.0 LITERATURE REVIEW

#### 2.1 Definition of Stroke

Stroke is defined as a rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin (Stokes, 2004). Stroke is used synonymously with cerebrovascular accident (CVA) and is a variety of disorders characterized by sudden onset of neurological deficits brought about by vascular injury to the brain (Baer and Durward, 2004). Vascular events lasting less than 24 hours are defined as transient ischemic attack (TIA) (Scalding and Gibbs, 1994).

#### 2.2 Epidemiology of Stroke

Stroke is a global health problem and is the third commonest cause of death after heart disease and cancer (Banerjee and Das, 2006). It is the leading cause of long term physical and mental disability and has enormous emotional and socioeconomic influence on patients, their families and health services worldwide (WHO, 2003). The number of patients with stroke will increase in the future because of demographic changes which include improved survival (ageing) and living conditions, advanced economies and improved technology (Struijs *et al.*, 2005). This is because, the incidence of stroke increases dramatically with age, doubling after 65 years of age with 28% occurring in individuals younger than 65 years of age (Thom *et al.*, 2006). Men are 1.25 times more likely to suffer stroke than women (NINDS, 1995), yet 60% of deaths occur in women (Thompson and Johnson *et al.*, 1993). Comparative study for first ever stroke attack in the US has shown that African-Americans have twice the risk of stroke than the whites (American Heart

Association, 2005). Stroke, apart from causing 5.5 million deaths each year, is also responsible for the loss of 49 million disability-adjusted life years worldwide (WHO, 2004a).

People affected by stroke living in the low socioeconomic countries might experience more severe strokes and lower survival after stroke, due to late hospital presentation and incomplete treatment of hypertension (Cox *et al.*, 2006; Weir *et al.*, 2005). The WHO (2000), predicted that by 2020, stroke and other cardiovascular diseases will cause 34% of deaths in developing countries and it is expected to be the leading cause of loss of healthy life-years. Current stroke rates in developing countries are higher than developed countries (Pais, 2006). Stroke is emerging as a leading cause of preventable death and disability in adults in developing nations (Lemogoum *et al.*, 2005), although Pongvarin, (1998), Feigin *et al.* (2003) and Connor, (2004) reported that the information relating to stroke is limited in many of the developing countries. Murray and Lopez (1996) and Cox *et al.* (2006) found that stroke in the developing world is assuming increasing importance with two-thirds of all stroke deaths happening in these countries. Also, Walker *et al.*, (2003) and Lemogoum *et al.*, (2005) reported that in some of these countries, especially in Sub-Saharan Africa, stroke mortality and case fatality exceed those in the developed world. Feigin *et al.* (2003) and Lemogoum *et al.*, (2005) further reported that stroke also occurs at much earlier ages in Sub-Saharan Africa, resulting in a greater number of years of prospective life lost. Walker *et al.*, (2005) suggested that case fatality due to stroke is based almost entirely on in-hospital mortality figures, as those who die in their homes are less frequently or not reported at all. In 2005, there was estimated 16 million first causes of stroke and 5.8 million stroke deaths (Strong *et al.*, 2007) leading to 10% of deaths worldwide (WHO, 2004). The incidence of stroke in the western world is generally cited to be 150-250 per 100000. Over the past two decades, the world has become increasingly aware that stroke is not restricted

to the developed world, but the problem affects all people, regardless of whether they live in developed or developing countries (Lopez *et al.*, 2006; Pais, 2006).

In Ghana, 69% of stroke patients died in less than 24 hours after onset of stroke between 1994 and 1998 (Wiredu and Nyame, 2001). A report by Nyame *et al.* (1994) indicated that stroke was the leading neurological condition at the Korle Bu Teaching Hospital (KBTH) in Accra and it had an alarming case fatality rate of 41.9% to 50.3% for the period between 1990 and 1993. A study carried out by Eghan *et al.* (2001) at the Komfo Anokye Teaching Hospital (KATH), Ghana reported a stroke mortality rate of 26%.

### **2.3 Classification of Stroke and Pathophysiology**

The classification of stroke is primarily based on the underlying pathology (Bamford *et al.*, 2001). Stroke is non-progressive in nature and generally divided into two broader types based on their aetiologies: ischaemic 80-85% and haemorrhagic 15-20% (O'Young and Steins, 2002). Stroke could also be caused by congenital abnormalities of blood vessels known as arteriovenous malformations (AVMs) and can result in spontaneous intracranial haemorrhage (Fawcus, 2000). Transient ischaemic attack (TIA) is a temporary neurological deficit lasting for less than 24 hours but with eventual resolution (Bramer and Spires, 2002). The difference between stroke and TIA is that stroke occurs with neurological deficit and lasts for more than 24 hours (Bramer and Spires, 2002) whereas TIA may last for a lesser period and is a forewarning that a stroke may occur. The cause of a few more strokes (10%) is either unknown or more unusual (O'Young *et al.*, 2002).

### 2.3.1 Ischaemic Stroke

Ischaemic stroke occurs as a result of decreased or cessation of blood supply to part of the brain leading to dysfunction and necrosis of the brain tissue in that area (Shuaib and Hachinski, 1991). Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 seconds and after a few hours, it will suffer irreversible injury leading to death of the tissue (infarction) (Shuaib and Hachinski, 1991). The reduction to flow of blood or blockage may be due to thrombosis, embolism or systemic hypoperfusion (Brammer, 2002).

After seconds to minutes of cerebral ischaemia, the ischaemic cascade is initiated (Woodruff *et al.*, 2011). This is a series of biochemical reactions in the brain and other aerobic tissues, which usually proceed for two to three hours, but can last for days, even after normal blood flow returns (Woodruff *et al.*, 2011). The cascade occurs as follows: (1) without adequate blood supply and lack of oxygen, brain cells lose their ability to produce energy, particularly adenosine triphosphate (ATP), (2) cells in the affected area switch to anaerobic metabolism, which leads to a lesser production of ATP but releases lactic acid as by-product. Lactic acid is an irritant and has the potential to destroy cells by disruption of the normal acid-base balance in the brain, (3) ATP-dependent ion transport pumps fail, causing the cell membrane to become depolarized, leading to a large influx of ions, including calcium ( $\text{Ca}^{2+}$ ) and an efflux of potassium, (4) Intracellular calcium levels become too high and trigger the release of the excitatory amino acid neurotransmitter glutamate (5) Glutamate stimulates AMP receptors and  $\text{Ca}^{2+}$  permeable NMDA receptors, which leads to even more calcium influx into cells, (6) Excess calcium entry overexcites cells and activates proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischaemic cascade in a process called excitotoxicity, (7) As the cell membrane is broken down by phospholipases, it

becomes more permeable, and more ions and harmful chemicals enter the cell, (8) Mitochondria break down, releasing toxins and apoptotic factors into the cell, (9) Cells experience apoptosis, (10) If necrosis occurs it releases glutamate and toxic chemicals into the environment around it. Toxins poison nearby neurons, and glutamate can overexcite them and (12) The loss of vascular structural integrity results in a breakdown of the protective blood brain barrier and contributes to cerebral oedema, which can cause secondary progression of the brain injury (Woodruff *et al.*, 2011; Liu *et al.*, 2010).

### **2.3.2 Haemorrhagic Stroke**

Haemorrhagic stroke occurs from either intracerebral haemorrhage or subarachnoid hemorrhage (Katzan and Skidmore, 2002). Stroke resulting from intracerebral haemorrhage is the result of the rupture of a vessel within the brain parenchyma (Katzan and Skidmore, 2002). Subarachnoid hemorrhage however, occurs when there is bleeding into the subarachnoid space following rupture of a berry aneurysm near the circle of Willis (Chambers, 2003). The onset of a haemorrhagic stroke is usually dramatic with an otherwise healthy patient in a fit abruptly developing severe headache and major neurological deficits within minutes with a rapid rise in intracranial pressure (Lopez *et al.*, 2006). The resulting haematoma compresses the brain structures beneath thereby causing further neurological deficits (Roth, 2002). Thus, the haematoma can distort and injure tissue (Testai and Aiyagari, 2008). In addition, the pressure may lead to a loss of blood supply to affected tissue with resulting infarction and the blood released by brain haemorrhage appears to have direct toxic effects on brain tissue and vasculature (Testai and Aiyagari, 2008).

## 2.4 Risk Factors

Several risk factors associate to predispose individuals to stroke (Ashtari *et al.*, 2012). The risk factors can be grouped into modifiable and non-modifiable risk factors (Ashtari *et al.*, 2012). The modifiable risk factors are those risk factors that are modifiable with behavioural and lifestyle changes (Ashtari *et al.*, 2012). These factors include: obesity, sedentary lifestyle, cigarette smoking and alcohol abuse (Ashtari *et al.*, 2012). Smoking doubles the risk of stroke and increases both haemorrhagic and ischaemic stroke risk and a wide variety of other health problems (Lemogoum *et al.*, 2005; Stanton *et al.*, 2005). The number of smokers worldwide was estimated to be 1.3 billion in 2003, of which 82% are in developing countries (Thun and Da Costa, 2003). Mackay and Ericksen (2002) reported that during the 20th century, 100 million individuals died worldwide as a result of tobacco-related diseases. Smoking is particularly strong and important when combined with other risks including hypertension and diabetes (Lemgoum *et al.*, 2005). While tobacco use is decreasing in developed countries due to strong tobacco control programs, the opposite trend is observed in many developing countries (Mackay and Mensah, 2004). Current overall prevalence of tobacco smoking is 36% among men and 11% among women in Sub-Saharan Africa (Mackay and Eriksen, 2002). The Global Youth Tobacco Survey indicates that greater than 10% of 13- to 15-year-olds use tobacco in many Sub-Saharan Africa countries and this prevalence can be as high as 33% in South Africa (Asma *et al.*, 2002). Obesity is considered an epidemic health problem as populations adopt sedentary lifestyles and increase their caloric intake (Monteiro *et al.*, 2000; Seidell, 2000). It is further reported as a major risk factor for many chronic diseases including hypertension, type 2 diabetes mellitus, coronary heart disease and stroke (Thompson *et al.*, 1999). Obesity is usually defined as a Body Mass Index

(BMI) of  $30\text{kg/m}^2$  or higher while overweight is defined as a BMI between 25 and  $29.9\text{kg/m}^2$  (Seidell and Flegel, 1997).

Other modifiable risk factors which can be controlled in addition to behavioural and lifestyle changes by medical care include: hypertension, diabetes, myocardial infarction, valvular defects, prior history of stroke and Transient Ischaemic Attack (TIA). Hypertension is the strongest risk factor compared to other modifiable risk factors especially in middle and late adult life in both males and females (Collins and McMahon, 1994). Following hypertension, diabetes and smoking are also rated as major risk factors of stroke. Diabetes has been associated with high risk for stroke and other cardiovascular diseases (Cubriilo-Turek, 2004; Smith and Maynard 2004; Gray *et al.*, 2001). Overall, individuals with diabetes have a 2 to 3 fold increased risk of stroke and other cardiovascular diseases compared with individuals without diabetes (Hobbs, 2006; Goldberg, 2000).

Non-modifiable risk factors include: age, gender, race, family history and genetics (Cubriilo-Turek, 2004). These constitute risk factors which cannot be modified with behavioural and lifestyle changes (Ashtari *et al.*, 2012). Age is the single most important and most powerful risk factor for stroke (Cubriilo-Turek, 2004). Cubriilo-Turek (2004) reported that, the risk of stroke increases with age such that each decade after 55 years doubles stroke rate in both men and women. Pais, (2006) also reported age (over 55years in men and 65 years in women) as one of the most important risk factors.

In addition to these traditional risk factors of stroke, there are other risk factors that can cause stroke. These include: elevated homocysteine (Boysen *et al.*, 2003), hypercoagulable states (Takano *et al.*, 1992), patent foramen ovale (Bogousslavsky *et al.*, 1996) and metabolic

syndrome (MetS) (Liou *et al.*, 2008). Metabolic syndrome has emerged as a novel risk factor in cardiovascular disease due to its potential for predicting stroke in population-based studies (Mi *et al.*, 2012).

## 2.5 Clinical Features of Stroke

Clinical features of stroke typically start suddenly seconds to minutes and in most cases do not progress further with features depending on the area of the brain affected (Post Stroke Rehabilitation Guideline, 1995). The more extensive the area of the brain affected the more bodily functions that are likely to be lost (Colebatch and Gandevia, 1989). Most of the features are seen on only one side of the body (unilateral) and is usually contralateral to the side of the brain affected (Aslan and Ozgirgin, 2004). Gilroy *et al.* (1995) described the features resulting from specific areas of brain affectation as follows:

- Frontal lobe (right): deviation of the head and eyes to the right, left facial palsy and left hemiparesis or hemiplegia. Frontal lobe (left): aphasia and deviation of head and eyes to the left, right facial palsy and right hemiparesis or hemiplegia. Frontal lobe (medial): sensory loss on contralateral lower limb with hemiplegia or hemiparesis. Frontal lobe (bilateral): coma, quadriplegia, bowel and bladder incontinence and memory loss.
- Thalamus: vomiting, stupor, coma, gaze palsy and hemi-sensory loss.
- Parietal lobe: hemi-sensory loss, hemi-sensory neglect, dyslexia, agraphia and dysphasia.
- Angular gyrus: word blindness, agraphia, right-left confusion and finger agnosia.
- Temporal lobe: reduced discrimination of sounds, pitch and tone and visual perceptual difficulties.

- Occipital lobe: hemianopia or contralateral blindness with bilateral involvement, ipsilateral third nerve palsy with diplopia cerebellar ataxia and contralateral hemiparesis

## **2.6 Impact of Stroke**

Stroke patients present with a number of physical and psychological impairments consistent with physiologic and environmental limitations (Murray *et al.*, 2012). Majority of the people experience serious impairments in the early stages of stroke. These impairments include paralysis, sensory disturbances, language and speech difficulties, cognitive problems and emotional disturbances (Bergen and Silberberg, 2002; Bruno, 2004). The impairment affects the patient's social interactions, vocational life, as well as their activities of daily living. Approximately 10% of stroke survivors have no disability and are able to function independently, another 10% are institutionalized because of severe disability and are unable to achieve functional independence in a home setting regardless of intensive rehabilitation input, the remaining 80% have mild to moderately severe disability and could benefit from intensive rehabilitation (Aslan *et al.*, 2004; Zorowitz *et al.*, 2002; Reddy and Reddy, 1997). Recovery is a continuous process with stages sometimes overlapping and complete recovery does not occur in all patients (National Institute of Health, 2003). Regardless of the exact cause recovery depends on the size and location of the damaged area in the brain, the bigger the area and the more complex activities the area controls, the worse resultant condition (Kistler and Stanford, 1999; Reddy and Reddy, 1997).

## **2.7 Metabolic Syndrome and Stroke**

### **2.7.1 Definition of Metabolic Syndrome**

Metabolic syndrome is a cluster of cardiometabolic risk factors including dyslipidaemia, hypertension, hyperglycaemia, central obesity and endothelial dysfunction (Gundogan *et al.*, 2009; Calbo *et al.*, 2007; Boronat *et al.*, 2005). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III provides the current diagnostic standard that describes metabolic syndrome as a constellation of clinical characteristics associated with an increase in risk of developing type-2 diabetes and atherosclerotic cardiovascular disease (NCEP, 2001). Haffner *et al.* (2006) defined MetS as collection of metabolic abnormalities associated with insulin resistance that predisposes affected individuals to accelerated atherosclerosis and consequently increased risk of cardiovascular events (Haffner *et al.*, 2006).

### **2.7.2 Pathophysiology of Metabolic Syndrome**

The biochemical perturbations observed in the metabolic syndrome include changes in glucose tolerance and lipoprotein levels as well as alterations in inflammatory mediators and pro-coagulant factors (Arbeeny *et al.*, 2001). Multiple organ systems are affected, including adipose, muscle, hepatic, nervous and adrenal tissues, but from a clinical standpoint, the most important site of impact is the vasculature (Toalson *et al.*, 2004). Cumulative effects of classical risk factors such as glucose intolerance, dyslipidemia and hypertension contribute to increased risk of cardiovascular disease seen in individuals with metabolic syndrome (Alberti and Zimmet, 1998). Hyperinsulinaemia, a surrogate for insulin resistance and a marker for metabolic syndrome, is associated with a 2- to 3-fold increase in cardiovascular disease independent of classical risk factors (Reaven, 2002; Howard *et al.*, 1996). Other components of this syndrome that may contribute to a proatherogenic state include increased levels of plasminogen-activator inhibitor-I

(PAI-I), angiotensin II, interleukin-6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) (Dandona *et al.*, 2003; Das *et al.*, 2002).

Impaired insulin responsiveness (insulin resistance) is presumed to be central to the metabolic syndrome and may provide the underlying process from which other abnormalities evolve (Ford *et al.*, 2002). Regarding resistance to insulin, unchecked lipolysis leads to increased delivery of free fatty acids to the liver for triglyceride synthesis and packaging into very low-density lipoprotein (VLDL) particles (Ford *et al.*, 2002). Higher VLDL levels contribute to lower HDL levels because of the reciprocal exchanges between these lipoproteins mediated by cholesterol ester transfer protein (Ford *et al.*, 2002). It has been shown that blood pressure is related to insulin resistance independent of differences in age, gender and degree of obesity (Ferrannini *et al.*, 1997; Zavaroni *et al.*, 1992). Given that, insulin can stimulate endothelium-dependent vasodilation and also blunted in insulin-resistant individuals, provides a plausible mechanism to explain the elevation of blood pressure in metabolic syndrome (Steinberg *et al.*, 1996). Evidence that insulin resistance underlies the metabolic syndrome is also provided by the fact that pharmacologic treatment with insulin sensitizers (such as thiazolidinediones) can have beneficial effects not only on glucose and lipids, but also on blood pressure and on the inflammatory and proatherogenic derangements previously noted (Arner, 2003; Lyon *et al.*, 2003).

Visceral obesity has been suggested as the primary determinant of insulin resistance and represents the fundamental pathophysiological change leading to metabolic syndrome (Kahn and Flier, 2000; Wajchenberg, 2000). Adipocyte-derived humoral factors that are released in proportion to visceral fat stores mediate effects on insulin sensitivity including: free fatty acids (FFAs), TNF $\alpha$ , IL-6 and resistin (Dandona *et al.*, 2003; Kahn and Flier, 2000). There is a strong

support for FFA as inducer of insulin resistance in muscles and liver (Kahn and Flier, 2000). The role of leptin in insulin resistance is unclear (Kahn and Flier, 2000). Whereas some studies suggest that leptin may impair insulin action, leptin therapy dramatically improves insulin sensitivity in patients with lipodystrophy (Lyon *et al.*, 2003; Petersen *et al.*, 2002). Insulin resistance can also occur in lean individuals, which may be due to inherited insulin receptor and post-receptor defects (Hunter and Garvey, 1998). Despite this, the central role of visceral obesity in most cases of insulin resistance and the metabolic syndrome appears to be widely accepted.

The role of glucocorticoids in the pathogenesis of the metabolic syndrome is that excess cortisol can produce insulin resistance and the typical metabolic syndrome cluster is apparent from the clinical manifestation of Cushing's syndrome (Toalson *et al.*, 2004). However, it has been proposed that "subclinical Cushing's syndrome" may be a relatively common cause of visceral obesity and the insulin resistance syndrome (Bjorntorp and Rosmond, 1999). These may be due to functioning adrenal adenomas (Tauchmanova *et al.*, 2002), but physical stress or psychological stress have also been suggested as common causes of relative and potentially relevant hypercortisolaemia (Bjorntorp and Rosmond, 1999). This mechanism is especially attractive as an explanation for the higher prevalence of the metabolic syndrome and type 2 diabetes mellitus among patients with severe mental illness in the light of evidence for hypothalamic-pituitary-adrenal (HPA) axis overactivity and central adiposity (Toalson *et al.*, 2004).

### 2.7.3 Diagnostic Criteria for Metabolic Syndrome

One of the criteria used in diagnosing MetS is the NCEP-ATP III. The NCEP-ATP III uses three (3) of the five (5) components or indicators for diagnosing the presence of metabolic syndrome. The NCEP-ATP III criteria for MetS include the following components/indicators and their cut points:

1. Abdominal obesity/waist circumference:  $\geq 102$  (40 inches) in men;  $\geq 88$  (35 inches) in women,
2. Elevated triglycerides:  $\geq 1.7$ mmol/l (150 mg/dL) or on drug therapy for elevated triglycerides,
3. Low HDL cholesterol:  $< 0.9$ mmol/l (40 mg/dL in men) or  $< 1.01$ mmol/l (50 mg/dL in women) or on drug therapy for low HDL,
4. Borderline hypertension:  $\geq 130/85$ mmHg or on drug therapy for elevated blood pressure and
5. Fasting hyperglycemia:  $\geq 6.1$ mmol/l (100 mg/dL) or on drug therapy for elevated glucose (NCEP, 2001).

The International Diabetes Federation (IDF) has reported recent definition of the metabolic syndrome (Alberti *et al.*, 2005). The NCEP-ATP III and IDF are shown in table 1 below:

**Table 2.7.3: Current Criteria for the Diagnosis of the Metabolic Syndrome**

	NCEP-ATP III	IDF
Hypertension	Current antihypertensive therapy OR SBP $\geq$ 130 OR DBP $\geq$ 85	Current antihypertensive therapy OR BP $\geq$ 130/85
Dyslipidemia - Elevated Triglycerides	Plasma triglycerides $\geq$ 150 mg/dL	Plasma triglycerides $\geq$ 150 mg/dL <i>or</i> specific treatment for high triglycerides
Dyslipidemia - Depressed HDL	HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women	HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women <i>or</i> specific treatment for low HDL
Obesity	Waist circumference $\geq$ 40 inches in men or $\geq$ 35 inches in women	Waist circumference $>$ 37 inches in men or $>$ 31.5 inches in women
Glucose	Fasting blood glucose $\geq$ 100 mg/dL	Fasting glucose $\geq$ 100 mg/dL OR previously diagnosed type 2 diabetes
Requirements for diagnosis	Any 3 of the above criteria.	Waist circumference criteria PLUS any 2 of other criteria.

NCEP-ATP III = National Cholesterol Education Project Adult Treatment Panel; IDF = International Diabetes Federation; BP = blood pressure; HDL = high-density lipoprotein; BMI = body mass index; IGT = impaired glucose tolerance (Kendall and Harmel, 2002).

## **2.7.4 Components of Metabolic Syndrome and Stroke Risk**

According to ATP III, the presence of at least three of the following indicates metabolic syndrome: high fasting blood glucose, elevated blood pressure, raised triglycerides, decreased high density lipoprotein cholesterol and high waist circumference (central obesity) (NCEP, 2001).

### **2.7.4.1 Abdominal Obesity**

Abdominal obesity is the form of obesity most strongly associated with the metabolic syndrome (NCEP, 2001). It presents clinically as increased waist circumference (>102cm in men and 88cm in women) (NCEP, 2001). Metabolic syndrome has insulin resistance as the core mechanism and abdominal obesity as the prominent clinical manifestation (Mi *et al.*, 2012). Health problems including diabetes, coronary artery disease, ischaemic stroke, respiratory failure and cancer are strongly associated with excess weight gain (Brown *et al.*, 2009). A substantial body of evidence has documented that increased adiposity is associated with an increased risk of stroke (Strazzullo *et al.*, 2010). A meta-analysis found that between the BMI ranges of 25 to 50, each increase of 5 on the BMI scale was associated with a 40% increased risk of stroke mortality; however, there was no relationship in the lower BMI ranges (Suk *et al.*, 2003). Recently, the American Heart Association and American Stroke Association recommended that the treatment of obesity is critical for both primary (Goldstein *et al.*, 2011) and secondary (Olson *et al.*, 2013) stroke preventions.

Inconsistent results about the association between obesity and stroke risk have been reported. A recent analysis showed that BMI and abdominal obesity do not increase cardiovascular disease risk when data about systolic blood pressure, history of diabetes and lipid dysfunction were

analysed (Wormser *et al.*, 2011). On the other hand, while one study reported that BMI was associated with an increased risk of stroke in both sexes and abdominal obesity only in men (Hu *et al.*, 2007); another study reported that women aged 35 to 54 years are more likely to be obese and morbidly obese than in the previous decade and that their abdominal obesity however, was an independent risk factor for stroke (Towfighi *et al.*, 2010).

#### **2.7.4.2 Hyperglycemia (Diabetes Mellitus)**

Type II diabetes (T2D) is one of the fastest growing diseases in terms of new diagnoses around the world (Billings and Florez, 2010). It is characterized by insulin resistance and insulin deficiency. Diagnosis of T2D consists of either fasting plasma glucose above 100mg/dl or  $\geq 6.1$ mmol/l (NCEP, 2001). The Centre for Disease Control (CDC) has claimed that 7% of the American population has the disease (Billings and Florez, 2010). In Ghana, the prevalence of hypertension, diabetes, insulin resistance, hyperlipidaemia and obesity which are individual components of MetS are on the increase (Amoah *et al.*, 2003). The growing levels of obesity are directly associated with the increasing prevalence of T2D (Tekola-Ayele *et al.*, 2013). The T2D has been linked as a leading risk factor for ischaemic stroke (Tanaka *et al.*, 2013). Aging contributes to a heightened state of inflammatory response and microglia activation (Suridjan *et al.*, 2014). Inflammatory cytokines, such as interleukin-6(IL-6), have been shown to increase concomitantly with increasing levels of blood glucose (Johansen, 2007). It has become well known that inflammatory cytokines play a major role in neural injury (Johansen, 2007). The increasing release of inflammatory cytokines associated with ischaemic stroke in T2D patients has been shown to exacerbate the damage caused by the stroke (Srinivasan and Sharma, 2011) and lead to worsened outcome (Belloho *et al.*, 2011). While T2D is not the sole cause of stroke, it does negatively affect the outcome of ischaemic injury (Srinivasan and Sharma, 2011).

Therefore, management of hyperglycaemia is one of the recommended guidelines during acute stroke care (Srinivasan and Sharma, 2011). The T2D and increased stroke risk have also been linked with hypertension (Polonsky *et al.*, 2010). The T2D can potentially exacerbate hypertension, due to added stress placed on the arterial walls, thereby also increasing the risk of thromboembolic stroke (Cade, 2008 and Polonsky *et al.*, 2010). Unfortunately, most patients at risk for stroke present with a metabolic syndrome consisting of T2D, hypertension and obesity (Hanchaiphibookul *et al.*, 2013). The metabolic syndrome has been linked to poor cardiovascular outcomes in adults as well (Kim *et al.*, 2012). According to a recent study, a person with hypertension is 2.4 times more likely to have cerebrovascular disease (Chung *et al.*, 2013).

After ischaemic stroke, hyperglycaemia is an acute indicator of endocrine stress and neuroinflammation (Radermecker and Scheen, 2010). Sustained hyperglycemia leads to the formation of advanced glycosylated end products, which trigger the release of reactive oxygen species (Biessels *et al.*, 2013). Advanced glycosylated end products also lead to increased vascular permeability and decreased vascular dilation, thus worsening ischemic stroke outcome. Controlling hyperglycemia has been shown to have a 42% relative risk reduction for ischemic stroke (Li *et al.*, 2012). The most successful treatment regimens include a combination of healthy diet, regular exercise, and anti-hyperglycaemic therapy (Bleich *et al.*, 2011). Rapid and sufficient correction of hyperglycaemia has been shown to reduce infarct development and expansion in ischemic stroke (Bruno *et al.*, 2010). Furthermore, diabetes increase rates of intracerebral haemorrhage following tissue plasminogen activator administration, emphasizing the need for blood glucose control upon patient arrival (Fan *et al.*, 2013). The most widely established risk factors associated with stroke recurrence are diabetes mellitus (Sacco *et al.*, 1994) and atrial

fibrillation (Elneihoum *et al.*, 1998). Mi *et al.* (2012) demonstrated that metabolic syndrome was associated with an increased risk of stroke recurrence. After further controlling for its components, metabolic syndrome lost its association with stroke recurrence. However, high fasting plasma glucose remained as an independent predictor for stroke recurrence.

### **2.7.4.3 Hypertension**

Hypertension can be classified as either primary or secondary hypertension (Goldstein *et al.*, 2011). Secondary hypertension can be caused by medical conditions or as the result of various medications (Goldstein *et al.*, 2011). Diagnosis for hypertension consist of blood pressure greater than or equal to 130/85mmHg (NCEP, 2001). Unlike secondary hypertension, the cause of primary hypertension is idiopathic (Carretero and Oparil, 2000). Primary hypertension is responsible for 95% of all hypertension cases and negatively affects multiple organ systems (Carretero and Oparil, 2000). Hypertension is a very common condition which frequently remains undiagnosed until relatively late in its course, leading to a variety of other life-threatening conditions like kidney damage and heart failure (Carretero and Oparil, 2000). It is a very prominent feature of the metabolic syndrome, present in up to 85% of patients (Goldstein *et al.*, 2011). Insulin resistance and the resulting hyperinsulinemia induce blood pressure elevation by the activation of sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) with consequential sodium retention and volume expansion, endothelial dysfunction and alteration in renal function (Goldstein *et al.*, 2011). Age is one of the most predominant risk factors for hypertension according to a recent National Health and Nutrition Examination Study report. Akpalu *et al.* (2011) in a study on metabolic syndrome among patients with cardiovascular diseases in Ghana demonstrated that the relatively high prevalence of MetS could

be due to the high prevalence of MetS components especially hypertension and central obesity as well as the low levels of physical activity.

#### **2.7.4.4 High density lipoprotein**

Decreased high density lipoprotein is considered as a component of metabolic syndrome. According to the NCEP ATP III, high density lipoprotein <0.9mmol/l in men and <1.01 mmol/l in female is indicated as MetS (NCEP, 2001). Prospective cohort studies generally support an inverse association between HDL-C levels and the risk of ischaemic stroke (Tirschwell *et al.*, 2004; Amarenco *et al.*, 2008; Wannamethee *et al.*, 2000). The prediction of stroke in the general population in Europe (EUROSTROKE) study found an increase in HDL-C was associated with an increased risk of cerebral infarction in women (Bots *et al.*, 2002). The Asia Pacific Cohort Studies (Woodward *et al.*, 2007) and the Women's Health Study (Kurth *et al.*, 2007) did not find any association between HDL-C and ischaemic stroke risk and the lack of association in these studies may be due to using an overall definition of ischaemic stroke (Woodward *et al.*, 2007).

Few studies assessed the association between HDL-C and the risk of haemorrhagic stroke, (Tirschwell *et al.*, 2004; Bots *et al.*, 2002) and no significant association has been reported. Age (Lewington *et al.*, 2007), gender (Kurth *et al.*, 2007), blood pressure (Lewington *et al.*, 2007; Bowman *et al.*, 2003), BMI (Hu *et al.*, 2007) and diabetes (Tirschwell *et al.*, 2004) are major determinants for the risk of ischaemic stroke. People with dyslipidemia may often have high BMI, high blood pressure, and diabetes, and all these factors are associated with the physiological effects of serum lipids on the stroke risk (Lewington *et al.*, 2007; Tirschwell *et al.*, 2004; Hu *et al.*, 2007).

#### 2.7.4.5 Raised Triglyceride

Elevated Triglyceride is considered as one of the components of metabolic syndrome. Elevated Triglyceride  $\geq 1.7$ mmol/l is considered as an indicator of metabolic syndrome (NCEP, 2001). Triglycerides are associated with atherosclerosis; however, triglycerides in themselves are not causal in the pathogenesis of atherosclerosis, however they are a marker of high levels of atherogenic lipoprotein remnants (very low density lipoproteins and intermediate density lipoproteins) (Benn *et al.*, 2007). Elevated non-fasting triglycerides but not cholesterol levels were associated with an increased risk of ischaemic stroke (Tanne *et al.*, 2001). Benn *et al.*, (2007) in the Danish study, looked at almost 14,000 men and women, all white, in Copenhagen, who had had baseline triglyceride and cholesterol levels taken between 1976 and 1978 and who were then followed for up to 33 years. During that time, 837 women and 837 men had an ischaemic stroke. For both men and women, higher non-fasting triglyceride levels were linked with an increased risk of stroke, even after adjusting for age, gender, smoking, alcohol use, lipid-lowering therapy, hormone therapy (in women) and other factors. Women with triglyceride levels of 443 mg/dl had nearly quadruple the risk of suffering a stroke, compared to women whose levels were less than 89 mg/dl. Those with levels between 89 and 177 mg/dl had a 20 percent increased risk.

Tanne *et al.*, (2001) demonstrated the links among blood lipids and, in particular, high blood triglycerides and the risk of ischemic stroke. Individuals with high triglycerides usually also have high blood pressure, insulin resistance and obesity – a cluster of abnormalities that is called the metabolic syndrome. The American Heart Association characterizes "normal" triglyceride levels as lower than 150 mg/dl. Based on the findings of this latest study, desirable levels of triglycerides are found to be less than 180 to 200 mg/dl (Benn *et al.*, 2007). Benn and colleagues

suggested that patients should attempt to reach this goal through lifestyle changes [weight loss, reduction of intake of saturated fatty acids, cholesterol, and alcohol, more exercise, and cessation of smoking.

### **2.7.5 Metabolic Syndrome and Stroke Prevalence**

There is increased prevalence of metabolic syndrome in patients with stroke (Arenillas *et al.*, 2007). The presence of MetS has been associated with an increased risk of prevalent stroke in the existing literature. In the National Health and Nutrition Examination Survey (NHNES), out of 10, 357 participants, the prevalence of MetS was significantly higher in persons with self-reported history of stroke (43.5%) than in participants with no history of vascular disease (22.8%) (Ninomiya *et al.*, 2004). The MetS was independently associated with stroke history in all ethnic groups and in both sexes. The association between MetS and stroke has been confirmed in other populations integrated by elderly subjects, and the frequency of MetS has been reported to be significantly higher in patients with a history of atherothrombotic or non-embolic ischemic stroke (Milionis *et al.*, 2005; Ninomiya *et al.*, 2004; Suk *et al.*, 2003). This association supports the clinical use of the MetS in the identification of subjects who are at an increased risk of experiencing a stroke.

Studies have demonstrated that healthy individuals with MetS are at a markedly increased risk for major cardiovascular events, including stroke and cardiovascular mortality (Dekker *et al.*, 2005; McNeill *et al.*, 2005; Isomaa *et al.*, 2001). Adjusted risk ratios for incident ischaemic stroke associated with MetS in prospective studies range between 2.1 and 2.47, and a hazard ratio as high as 5.15 has been reported (Chen *et al.*, 2006; Koren-Morag *et al.*, 2005; Kurl *et al.*, 2006; Najarian *et al.*, 2006). This predictive capacity appears not to be influenced by the MetS

definition used and shows no significant variation across the studied sex, age, or ethnic groups (Najarian *et al.*, 2006; Koren-Morag *et al.*, 2005). Moreover, the risk for incident ischaemic stroke seems to augment with increasing number of components of MetS, all of which have been individually associated with an increased risk for future cerebral ischemic events (Chen *et al.*, 2006; Kurl *et al.*, 2006).

The increase in risk for incident cerebral ischaemic events observed in patients with MetS may be greatly in part due from the potential capacity of MetS to enhance the development and progress of atherosclerotic lesions affecting brain-supplying large arteries (Olijhoek *et al.*, 2004). Insulin resistance may represent a crucial factor underlying the association of MetS with atherosclerosis, because it is known to cause multiple pro-atherothrombotic effects both on the fibrinolytic system and on the vascular endothelium (Balletshofer *et al.*, 2003). The prevalence of increased carotid intima-media thickness and of asymptomatic carotid atherosclerotic plaques has been consistently shown to be higher in individuals with the MetS (Bonora *et al.*, 2003; Golden *et al.*, 2002). Subjects with MetS are also at increased risk for progressive carotid atherosclerosis, although the question regarding whether the metabolic risk factors that compound the MetS synergize to produce carotid atherosclerosis beyond what is expected from their individual effects remains unclear (Bonora *et al.*, 2003). Insulin resistance may have a deleterious role in all the stages of carotid atherosclerosis, from endothelial dysfunction to plaque growth; therefore, interventions targeting insulin resistance may reduce carotid atherosclerosis development in patients with MetS and type 2 diabetes (Ishizaka *et al.*, 2003; Langenfeld *et al.*, 2003).

The importance of the relationship between MetS and intracranial atherosclerosis has been first stressed by two studies (Ovbiagele *et al.*, 2006; Bang *et al.*, 2005). The MetS was present in approximately half of the patients with symptomatic intracranial atherosclerosis and may be burdened with an excess risk for recurrent ischemic events (Ovbiagele *et al.*, 2006). The fact that intracranial arteries show proneness to be affected by the MetS may reflect the existence of relevant topographic variations in the vessel sensitivity to the metabolic abnormalities associated with MetS such as oxidative stress (D'Armiento *et al.*, 2001). Finally, the association between type-2 diabetes mellitus and a higher number of intracranial atherostenoses, observed in European-Mediterranean patients with intracranial atherosclerosis, suggests that insulin resistance might play a prominent role in the development of this disease (Arenillas *et al.*, 2004).

The notion that the MetS is associated with an increased risk for future stroke reaffirms the need to develop preventive strategies directed to control the syndrome and each of its component conditions (Arenillas *et al.*, 2007). The recognition and management of MetS have been recently included in stroke prevention international guidelines (Goldstein *et al.*, 2006). However, there is still controversy regarding whether the individual components of MetS are equivalent or even better predictors of incidence of cardiovascular disease than the MetS itself and whether the MetS is really more useful than validated risk factor scales in the stratification of stroke risk (Reaven, 2006; Wannamethee *et al.*, 2005).

## **2.8 Management of Stroke**

The aim of stroke management is to minimize the volume of brain that is irreversibly damaged, preventing complications, reducing the patients' disabilities and handicap through rehabilitation and reducing the risk of recurrent episodes (Boon *et al.*, 2006). A stroke is a medical emergency and its treatment depends on the severity and causes.

### **2.8.1 Medical Management of Stroke**

Ischaemic stroke is managed with clot-busting drugs and this starts within three hours (Ingram and Sedlak, 2002). Immediate treatment not only improves the chances of survival, but may also reduce the amount of complications resulting from the stroke (Adams *et al.*, 2003). Aspirin is the best-proven immediate treatment after an ischaemic stroke to reduce the likelihood of having another stroke and a dose of it is usually given (Rostai, 2009). Other blood-thinning drugs, such as warfarin (Coumadin) and heparin also may be given (Shi *et al.*, 2007). Some stroke patients can benefit from an injection of tissue plasminogen activator (TPA) because it is potent clot-busting drug that help in the early recovery of stroke victims. Surgical procedures may be also performed such as carotid endarterectomy and angioplasty (Simard *et al.*, 2011).

Surgery may be used to treat a haemorrhagic stroke or prevent another one (Fox *et al.*, 2004). The most common procedures used include aneurysm clipping and arteriovenous malformation (AVM) removal may carry some risks. There may be recommendation of one of these procedures if there is a high risk of spontaneous aneurysm or AVM rupture (American Heart Association, 2007).

### 2.8.2 Treatment of Metabolic Syndrome

There are two objectives in managing the syndrome namely: reducing the underlying causes and treating the associated risk factors (Grundy *et al.*, 2004). The first line of treatment of MetS is lifestyle therapy because it can improve all aspects of the syndrome. According to the NCEP ATP III the presence of MetS is an indication for intensive lifestyle modification (NCEP, 2001). Lifestyle therapy or modification is the most effective therapeutic intervention for patients with metabolic syndrome (Luchsinger, 2006). In a meta-analysis, lifestyle interventions reduced diabetes by approximately one-half and pharmacologic interventions by approximately one-third (Gillies *et al.*, 2007). Major lifestyle studies included the Finnish Diabetes Prevention Study (FDPS) (Tuomilehto *et al.*, 2001) and the U.S. Diabetes Prevention Program (DPP) (Knowler *et al.*, 2002), with both studies reporting reductions in development of diabetes by 58%.

It has been found that, weight loss, increased physical activity and an anti-atherogenic diet can improve all of the metabolic abnormalities without pharmaceutical intervention (Grundy *et al.*, 2005). Weight loss has a huge impact in improving the risk factors of the metabolic syndrome. Several studies have shown that losing just 7% to 10% of initial body weight is sufficient to improving waist circumference, elevated triglycerides and low HDL-cholesterol, trunk fat and plasma glucose (Fernandez, 2007). Anderssen *et al.* (2007) reported that, the combination of diet and exercise interventions was significantly more effective than either diet or exercise alone in the treatment of the metabolic syndrome after a one year study. Two out of three cases were reversed with the combination versus only about 1 in 3 in each of the other groups (Anderssen *et al.*, 2007). Exercise has many positive effects in people with metabolic syndrome such as

improving insulin action, glucose metabolism, aerobic metabolism, mitochondrial density and respiratory chain proteins (Wells *et al.*, 2008).

Currently, there are no drugs specifically for treating metabolic Syndrome (Grundy *et al.*, 2005). Nevertheless, drug therapy is often needed to control risk factors when lifestyle change alone is not enough (Grundy *et al.*, 2005). Thus, as MetS progresses, drug therapy directed at individual risk factors may be needed (Cortez-Diaz *et al.*, 2007). Pharmaceutically, specific therapies targeting insulin resistance (insulin sensitizers) may offer additional benefit in stroke prevention beyond the risk reduction achieved by treating the individual components of the MetS (Arenillas *et al.*, 2007). Thiazolidinediones (glitazones) improve insulin sensitivity and lower blood glucose in type-2 diabetes and in non-diabetic patients with a recent transient ischaemic attack or stroke and impaired insulin sensitivity (Kernan *et al.*, 2003; Laffitte *et al.*, 2003; Maeda *et al.*, 2001). The best known mechanism of action of glitazones is their capacity to act as agonists of the receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), resulting in activation of lipid metabolism, glucose uptake and anti-inflammatory actions (Deeb *et al.*, 1998). The reduction in blood glucose is often accompanied by reductions in circulating insulin, inflammatory markers and triglycerides. In addition, glitazones have beneficial effects on the cardiovascular system independently of its effect on glycemic control such as antiatherogenic and antihypertensive effects (Qayyum and Schulman, 2006; Langenfeld *et al.*, 2005; Pfutzner *et al.*, 2005). Therefore, the overall pattern of changes induced by glitazones suggests a general improvement in various risk factors that might reduce cardiovascular morbidity and mortality (Langenfeld *et al.*, 2005; Pfutzner *et al.*, 2005).

Pioglitazone has been shown to reduce the combined secondary end point of all-cause mortality, myocardial infarction and stroke compared with placebo on top of glucose-lowering, antiplatelet, antihypertensive, and lipid-altering therapies in 5238 patients with type-2 diabetes who had a high risk of macrovascular events (Qayyum and Schulman, 2006). The effect was consistent across all the individual components of the composite end point. The pioglitazone-treated group had a better metabolic profile in terms of glucose, high-density lipoprotein cholesterol, and triglyceride concentrations and a better blood-pressure profile at the end of the study. However, thiazolidinediones are hampered by adverse effects related to increased weight gain, fluid overload and congestive heart failure, thus, the role of glitazones in prevention of cardiovascular diseases is not fully defined (Dormandy *et al.*, 2005; Yki-Jarvinen, 2005).

Experimental findings suggest that glitazones could have cytoprotective effects in acute cerebral ischemia (Romera *et al.*, 2007). Glitazones have been described to decrease infarct size in experimental models after middle cerebral artery occlusion through different mechanisms that include decreased activation of microglia and macrophages, reduced excitotoxic-mediated brain ischemic damage, decreased expression of inflammatory mediators such as interleukin-1 $\beta$ , cyclooxygenase-2, and inducible nitric oxide synthase (iNOS) as well as increase in the antioxidant enzyme Cu, Zn-SOD (Romera *et al.*, 2007; Kahn *et al.*, 2006; Pereira *et al.*, 2006). Other non-thiazolidine PPAR $\gamma$  agonists such as the endogenous cyclopentenone prostaglandin 15-delta12, 14-prostaglandin J2 (15d-PGJ2) share these neuroprotective effects of glitazones in experimental models of ischaemic stroke or intracerebral haemorrhage (Pereira *et al.*, 2006; Zhao *et al.*, 2006). Importantly, high plasma levels of 15d-PGJ2 have been associated with good neurological outcome and smaller infarct volume in patients with an acute atherothrombotic

stroke and recent preliminary data suggest that current treatment with glitazones may improve functional recovery after stroke (Blanco *et al.*, 2005).

In addition to treating insulin resistance as a central mechanism of MetS, therapies targeting individual components of MetS are essential. A randomized controlled trial showed that exercise training in people with MetS increases insulin sensitivity, decreases blood pressure, reduces triglycerides, increases HDL, reduces inflammation and improves endothelial function (Carroll and Dufield, 2004; Hamdy *et al.*, 2003) as opposed to physical inactivity. Thus, a modest amount of moderate-intensity exercise performed for 30 minutes daily with no change in diet can significantly improve MetS (Johnson *et al.*, 2007). Beyond diet and exercise, several oral anti-diabetic agents have been shown to reduce the development of diabetes in patients with Impaired Glucose Tolerance (IGT) such as metformin, acarbose and troglitazone (Abuissa *et al.*, 2005). Reducing LDL cholesterol to the new lower limit of below 70 mg/dL, owing to the highly increased risk of CVD should be a priority in managing MetS (Zieve, 2004). Also, improving the more typical lipid abnormalities seen in patients with metabolic syndrome - higher triglyceride and apolipoprotein B levels, lower HDL cholesterol and apolipoprotein levels is paramount to treating MetS (Zieve, 2004). Hypertension should be managed aggressively, with a target of 130/80 mm Hg or below (Abuissa *et al.*, 2005). Aspirin therapy is recommended if cardiovascular risk is high (Liberopoulos *et al.*, 2005).

### 2.8.3 Rehabilitation after Stroke

Stroke rehabilitation is the process by which those with disabling strokes undergo treatment to help them return to normal life as much as possible by regaining and relearning the skills of everyday living (Opara, 2009). It also aims to help the survivor understand and adapt to difficulties, prevent secondary complications and educate family members to play a supporting role (Belciug, 2009). A rehabilitation team is usually multidisciplinary as it involves staff with different skills working together to help the patient (Opara, 2009). These include physicians trained in rehabilitation medicine, clinical pharmacists, nursing staff, physiotherapists, occupational therapists, speech and language therapists, and orthotists (West *et al.*, 2005). Some teams may also include psychologists and social workers, since at least one third of the people manifest post stroke depression. Validated instruments such as the Barthel scale may be used to assess the likelihood of a stroke patient being able to manage at home with or without support subsequent to discharge from hospital (Opara, 2006)

Good nursing care is fundamental in maintaining skin care, feeding, hydration, positioning, and monitoring vital signs such as temperature, pulse, and blood pressure. Stroke rehabilitation begins almost immediately (West *et al.*, 2005). For most people with stroke, physical therapy (PT), occupational therapy (OT) and speech-language pathology (SLP) are the cornerstones of the rehabilitation process. The PT and OT have overlapping areas of expertise, however PT focuses on joint range of motion and strength by performing exercises and re-learning functional tasks such as bed mobility, transferring, walking and other gross motor functions (Kelly *et al.*, 2010).

Rehabilitation involves working on the ability to produce strong movements or the ability to perform tasks using normal patterns (Latash and Anson, 1996). Emphasis is often concentrated on functional tasks and patient's goals. One example physiotherapists employ to promote motor learning involves constraint-induced movement therapy. Through continuous practice the patient relearns to use and adapt the hemiplegic limb during functional activities to create lasting permanent changes (O'Sullivan, 2007). Occupational therapy is involved in training to help relearn everyday activities known as the Activities of daily living (ADLs) such as eating, drinking, dressing, bathing, cooking, reading and writing, and toileting. Speech and language therapy is appropriate for patients with the speech production disorders: dysarthria (Mackenzie, 2011) and apraxia of speech (West *et al.*, 2005) aphasia (Kelly *et al.*, 2010) cognitive-communication impairments and/or dysphagia (problems with swallowing) (Kelly *et al.*, 2010).

## **CHAPTER THREE**

### **3.0 METHODOLOGY**

#### **3.1 Study Site**

The study was conducted at the Korle-Bu Teaching Hospital in the Greater Accra Region. The hospital is the largest referral hospital in Ghana. Recruitment of participants and blood sampling were carried out at the Medical Ward, Stroke Unit and Polyclinic Ward. The stroke unit is a recently incorporated special unit of the hospital for providing intensive care for acute stroke patients until discharge. The samples were analysed at the Central Laboratory department of the Korle-Bu Teaching Hospital.

#### **3.2 Study Design**

The study was a cross-sectional study.

#### **3.3 Study Population**

All stroke survivors admitted at the Medical Ward, Stroke Unit and Polyclinic Ward of Korle Bu Teaching Hospital who met the inclusion criteria and consented to participate in the study. Subjects were recruited based on the following inclusion and exclusion criteria:

### 3.3.1 Inclusion criteria

Participants were recruited if the following criteria were met:

Stroke diagnosed by a physician with computerized topography (CT scan) or magnetic resonance imaging (MRI).

Patients with at least one stroke episode.

Stroke with hemiplegia or hemiparesis.

Stroke duration of less than 2 weeks.

### 3.3.2 Exclusion criteria

Participants were excluded from the study based on the following:

Stroke as a result of primary or metastatic neoplasm, post-seizure paralysis and head trauma.

Stroke patients who were unconscious.

Stroke duration of more than 2 weeks.

### 3.4 Sample Size Determination

The sample size for this study was calculated from the formula:

$$n = \frac{Z^2 (0.5)(0.5)}{E^2} \quad (\text{Cochran, 1963})$$

Where n is the sample size sample size; Z is the coefficient of significance (1.96) for significance level ( $\alpha$ ) of 5% (0.05) and E being the allowable error margin of 8%. Thus, substituting these parameters in the formula above, the sample size, n was 150.

### **3.5 Sampling Technique**

A consecutive sampling method was used to get eligible participants into the ischaemic and haemorrhagic stroke groups by clinical diagnosis from computerized topography scan (CT scan).

### **3.6 Procedures for Data Collection**

Participants were informed about the study through verbal invitations at the Medical Ward, Stroke Unit and Polyclinic Ward of Korle-Bu Teaching Hospital. A written informed consent was obtained from the participants. Eligible participants who consented to participate in the study were made to complete a clinical survey form. This provided information on their biodata, previous medical history and duration of the stroke.

#### **3.6.1 Blood Sample Collection**

About 5 ml of venous blood sample was collected from the antecubital veins of the study participants after an overnight fast (12 – 16) hours. The time for blood sampling was fixed at 7:00 am. Two (2) mls of the blood sample was dispensed into fluoride oxalate tube and the other 3 mls into vacutainer plain tubes. Blood samples in vacutainer tubes were centrifuged at 500g for 15 minutes and the serum aliquoted into labeled eppendoff tubes. Samples were stored at -20°C until laboratory analyses were performed.

### 3.6.2 Data Collection

#### 3.6.2.1 Anthropometric Measurements

Height to the nearest centimetre without shoes was measured against a wall-mounted ruler and weight to the nearest 0.1 kg in light clothing on a bathroom scale (Zhongshan Camry Electronics Co. Ltd. Guangdong, China). The body mass index (BMI) was calculated by dividing weight (kg) over the height squared ( $m^2$ ). Waist circumference (to the nearest centimetre) was measured with a Gulick II spring-loaded measuring tape (Gay Mill, WI) midway between the inferior angle of the ribs and the suprailiac crest. Abdominal obesity (waist circumference  $>102$  cm for men or  $>88$  cm for women) was considered a component of MetS (NCEP, 2001).

#### 3.6.2.2 Fasting blood glucose

Plasma glucose (GLU) was measured with the glucose hexokinase method (Pointe 180 QT analyzer, Bayer Diagnostics, Tarrytown, NY, USA). Hexokinase (HK) phosphorylates glucose with ATP to produce glucose-6-phosphate, which is oxidized by glucose-6-phosphate dehydrogenase to 6-phosphogluconate with the simultaneous reduction of  $NAD^+$  to NADH. The resulting increase in absorbance at 340nm was directly related to the concentration of glucose in the sample. A raised fasting glucose ( $\geq 6.1$  mmol L<sup>-1</sup>) was considered a component of MetS (NCEP, 2002).



### 3.6.2.3 Total Cholesterol

The VITROS CHOL Slide method was performed using the VITROS CHOL Slides and the VITROS Chemistry Products Calibrator Kit 2 on VITROS 250/350/950 and 5, 1 FS Chemistry Systems and the VITROS 5600 Integrated System. The VITROS CHOL Slide is a multilayered, analytical element coated on a polyester support. The method was based on an enzymatic method similar to that proposed by (Allain *et al.*, 1974). A drop of patient sample was deposited on the slide and was evenly distributed by the spreading layer to the underlying layers. The Triton X-100 (TX100) surfactant in the spreading layer aids in dissociating the cholesterol and cholesterol esters from lipoprotein complexes present in the sample. Hydrolysis of the cholesterol esters to cholesterol was catalyzed by cholesterol ester hydrolase. Free cholesterol was then oxidized in the presence of cholesterol oxidase to form cholestenone and hydrogen peroxide. Finally, hydrogen peroxide oxidizes a leuco dye in the presence of peroxidase to generate a colored dye. The density of dye formed was proportional to the cholesterol concentration present in the sample and was measured by reflectance spectrophotometry.

### 3.6.2.4 HDL Cholesterol

The VITROS dHDL Slide method was performed using the VITROS dHDL Slides and the VITROS Chemistry Products Calibrator Kit 25 on VITROS 250/350/950 and 5,1 FS Chemistry Systems and the VITROS 5600 Integrated System. The VITROS dHDL Slide is a multilayered analytical element coated on a polyester support. The method was based on a non-HDL precipitation method similar to one used by (Burstein *et al.*, 1970) followed by an enzymatic detection similar to that proposed by (Allain *et al.*, 1974). A drop of patient sample was deposited on the slide and was evenly distributed by the spreading layer to the underlying layers. HDL was separated by the precipitation of non-High Density Lipoproteins (non-HDL)

using phosphotungstic acid (PTA) and magnesium chloride ( $MgCl_2$ ) in the spreading layer. The Emulgen B-66 surfactant in the spreading layer aids in the selective dissociation of the cholesterol and cholesterol esters from the HDL lipoprotein complexes present in the sample. Hydrolysis of the HDL-derived cholesterol ester to cholesterol was catalyzed by a selective cholesterol ester hydrolase. Free cholesterol was then oxidized in the presence of cholesterol oxidase to form cholestenone and hydrogen peroxide. Finally, hydrogen peroxide oxidizes a leuco dye in the presence of peroxidase to generate a colored dye. The density of dye formed was proportional to the HDL cholesterol concentration present in the sample and was measured by reflectance spectrophotometry.

### **3.6.2.5 Triglycerides**

The VITROS TRIG Slide method was performed using the VITROS TRIG Slides and the VITROS Chemistry Products Calibrator Kit 2 on VITROS 250/350/950 and 5, 1 FS Chemistry Systems and the VITROS 5600 Integrated System. The VITROS TRIG Slide is a multilayered, analytical element coated on a polyester support. The analysis was based on an enzymatic method as described by (Spayd *et al.*, 1978). A drop of patient sample was deposited on the slide and was evenly distributed by the spreading layer to the underlying layers. The Triton X-100 surfactant in the spreading layer aids in dissociating the triglycerides from lipoprotein complexes present in the sample. The triglyceride molecules were then hydrolyzed by lipase to yield glycerol and fatty acids. Glycerol diffuses to the reagent layer, where it was phosphorylated by glycerol kinase in the presence of adenosine triphosphate (ATP). In the presence of L- $\alpha$ -glycerol phosphate oxidase, L- $\alpha$ -glycerophosphate was then oxidized to dihydroxyacetone phosphate and hydrogen peroxide. The final reaction involved the oxidation of a leuco dye by hydrogen peroxide, catalyzed by peroxidase, to produce a dye. The density of the dye formed was

proportional to the triglyceride concentration present in the sample and was measured by reflectance spectrophotometry.

### **3.6.2.6 Blood Pressure Measurements**

Blood pressure was measured with a random zero sphygmomanometer, according to the Canadian Hypertension Education Programme (CHEP) protocol, after a 5-min rest (Padwal *et al.*, 2009). The cuff was placed so that the lower edge is 3 cm above the elbow crease and the bladder was centered over the brachial artery. Participants rested comfortably for 5 min in the seated position with back support. The arm was bare and supported with the blood pressure cuff at heart level, because a lower position would result in an erroneously higher systolic blood pressure and diastolic blood pressure. Blood pressure  $\geq 130/85$ mmHg or on treatment for hypertension was considered a component of MetS (WHO, 1999).

### **3.6.3 Definition of Metabolic Syndrome**

Metabolic syndrome was defined using the NCEP ATP III criteria of 3 or more of the following (NCEP, 2001).

High fasting plasma glucose (HFBG)  $\geq 6.1$ mmol/L or documented use of anti-diabetic medication.

High blood pressure (HBP)  $\geq 130/85$ mmHg or documented use of anti-hypertensive medication.

Decreased high density lipoprotein (DHDL) cholesterol (men  $\leq 0.9$ mmol/L, women  $\leq 1.01$ mmol/L).

Raised Triglycerides (RTGL)  $\geq 1.7$ mmol/L.

Abdominal/ central obesity (high waist circumference):  $\geq 102\text{cm}$  in men,  $\geq 88\text{cm}$  in women.

### **3.7 Statistical Analyses**

The data were entered into and analysed with the Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics were used to summarise data. Age, duration of stroke, anthropometric variables and levels of MetS components were presented in means plus or minus standard deviations (SD) (means  $\pm$  SD). Frequencies were presented in percentages. Tables and graphs were used to present data. The independent *t*-tests for means and proportions were used to find differences between means and proportions respectively. Chi-Square was used to find the association between stroke and MetS as well as between stroke and the components of MetS.

## CHAPTER FOUR

### 4.0 RESULTS

#### 4.1 Characteristics of Study Participants

A total of 150 acute stroke patients were studied. The mean age of the participants was  $57\pm 13$  years. Analysis showed that 46.7% of the participants were males and 53.3% females. About 68% of the participants had ischaemic stroke whereas 32% had haemorrhagic stroke. The results showed that 63.3% of the participants had stroke affecting the right side of the body with 36.7% having stroke affecting the left side. The mean duration of stroke was  $2.3\pm 1.3$  weeks. About 36.7% of the participants were ambulant whereas 63.3% were non-ambulant. The details of characteristics of study participants between ischaemic and haemorrhagic strokes are presented in Table 4.1.

**Table 4.1 Characteristics of the study population**

<b>General Characteristics</b>	<b>Ischaemic Stroke</b>	<b>Haemorrhagic Stroke</b>
<b>Gender</b>		
Male n (%)	43(28.7)	27(18)
Female n (%)	52(34.7)	28(18.6)
<b>Age (years)</b>		
	58±13	56±13
<b>Duration of Stroke (weeks)</b>		
	1.84±0.88	2.74±1.68
<b>Stroke Types n (%)</b>		
	95(63.3)	55(36.7)
<b>Side of Body Affected n (%)</b>		
Right	52(34.6)	43(28.7)
Left	30(20.0)	25(16.7)
<b>Ambulation</b>		
Non-Ambulant n (%)	35(23.3)	60(40)
Ambulant n (%)	15(10)	40(26.7)

SD: standard deviation; R: right side affected; L: left side affected; A: Ambulating stroke survivors; NA = non-ambulating stroke survivors.

## 4.2 Comparing Anthropometric and Physiological Parameters between Ischaemic and Haemorrhagic Stroke

Table 4.2 presents the anthropometric and physiological parameters of the study participants. The mean differences in height, weight, BMI, SBP, DBP and waist circumference were not significant between ischaemic and haemorrhagic stroke ( $p>0.05$ ).

**Table 4.2 Comparing Anthropometric and Physiological Parameters between Ischaemic and Haemorrhagic Stroke**

<b>Anthropometric variables</b>	<b>Ischaemic Stroke (mean±SD)</b>	<b>Haemorrhagic Stroke (mean±SD)</b>	<b>p-value</b>
<b>Height (m)</b>	1.6±0.1	1.7±0.1	0.793
<b>Weight (kg)</b>	79.1±7.8	77.5±6.3	0.209
<b>BMI (kg/m<sup>2</sup>)</b>	30.1±3.8	27.6±3.1	0.065
<b>SBP (mmHg)</b>	145±22.1	153.5±19.7	0.552
<b>DBP (mmHg)</b>	91.4±17.4	90.2±16.9	0.702
<b>Waist circumference(cm)</b>	106.9±7.8	103.8±7.8	0.637

SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

### 4.3 Comparing Prevalence of MetS score between ischaemic and haemorrhagic strokes.

Table 4.3 shows the comparison of proportions of participants having indicators of MetS between ischaemic and haemorrhagic strokes. There were no significant differences in the proportions of MetS score 0 (no indicator), 1 (only one indicator) and 2 (only two indicators) ( $p>0.05$ ); However, the proportion of participants having at least three MetS components (3 indicators or more) between ischaemic and haemorrhagic stroke was significant ( $p=0.0185$ ). Also, difference in total proportions of participants having indicators of MetS between ischaemic and haemorrhagic stroke was significant ( $p=0.0005$ ).

**Table 4.3 Comparing Prevalence of MetS Score between ischaemic and haemorrhagic strokes.**

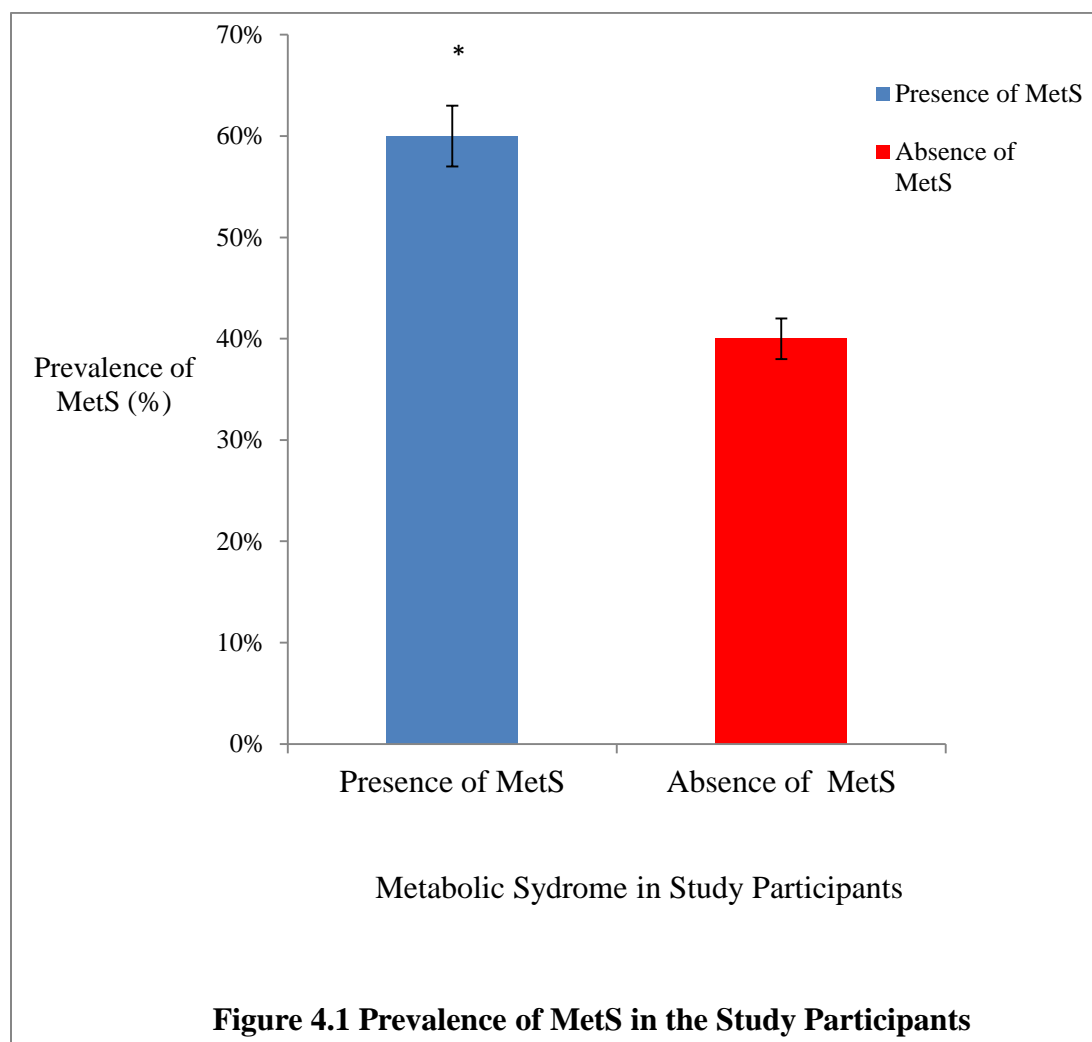
<b>Number of MetS Indicators</b>	<b>Ischaemic Stroke n(%)</b>	<b>Haemorrhagic Stroke n(%)</b>	<b>p-value</b>
<b>0</b>	2(1.3%)	1(0.7%)	0.9625
<b>1</b>	10(6.7%)	12(8%)	0.9077
<b>2</b>	25(16.7%)	10(6.6%)	0.4596
<b>≥3</b>	65(43.3%)	25(16.7%)	0.0185*
<b>TOTAL</b>	102(68%)	48(32%)	0.0005*

n:number; %: percentage/proportion; 0: no MetS; 1: one MetS component; 2: two MetS components; ≥3 : at least MetS components present.

\*Significant.

#### 4.4 Prevalence of MetS in the Study Participants

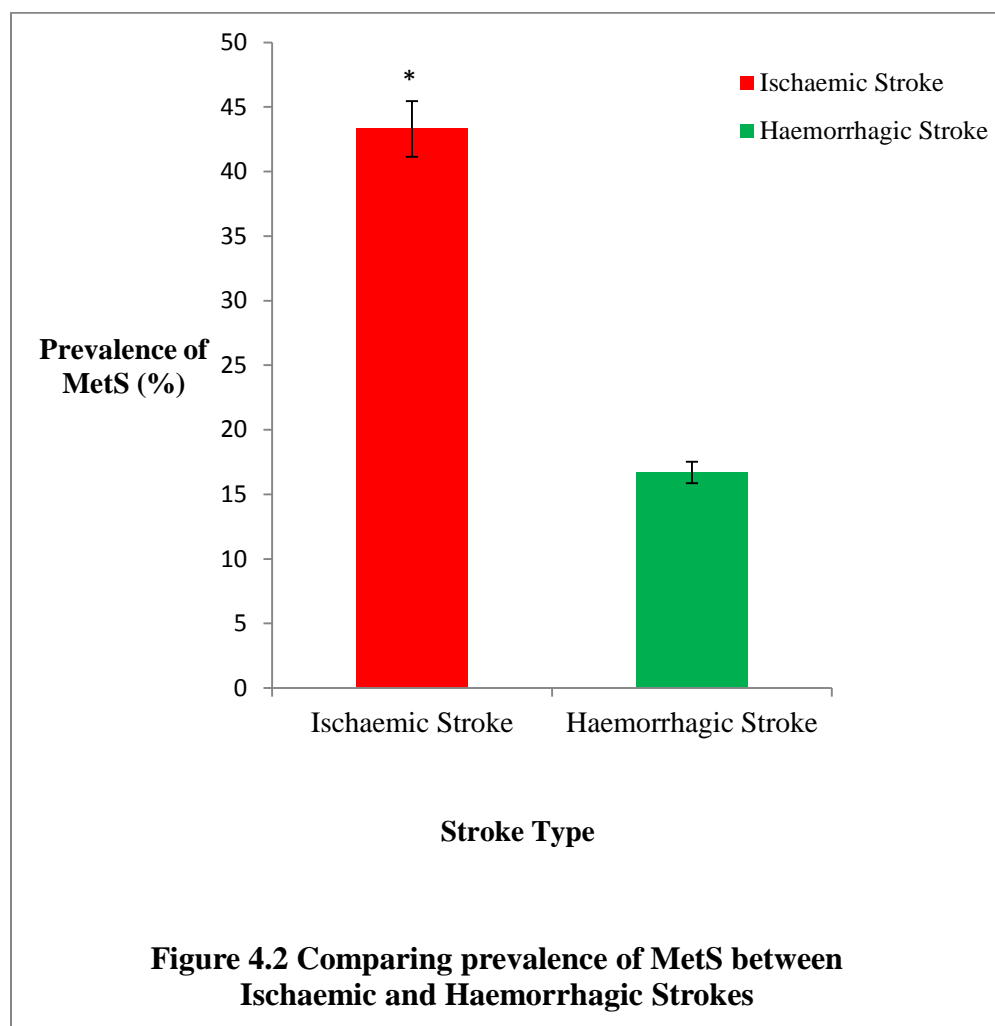
Figure 4.1 shows the distribution of MetS in the study participants. Sixty percent (60%) of the participants had MetS whereas 40% did not have MetS according to NCEP ATP III criteria. The differences between proportion with and without MetS was significant ( $p=0.016$ ).



**\*Significant.**

#### 4.5 Comparing Prevalence of MetS between ischaemic and haemorrhagic strokes.

Figure 4.2 shows a comparison of prevalence MetS between Ischaemic and Haemorrhagic strokes. Out of the 60% with MetS, 43.3% were ischaemic whereas 16.7% were haemorrhagic stroke participants. The difference in proportions of MetS between ischaemic and haemorrhagic strokes was significant ( $p=0.0185$ ).



**\*Significant.**

#### 4.6 Comparisons of Proportions of MetS Scores between Genders

The results showed that the proportions of MetS scores between male and female participants were not significant ( $p>0.05$ ) as shown in table 4.4. Out of the 60% with MetS, 34.7% were female stroke survivors whereas 25.3% were male stroke survivors. The differences between the proportion of female stroke survivors with MetS and male stroke survivors with MetS was not significant ( $p=0.1691$ ). Out of the 40% without MetS, 16.7% were female stroke survivors whereas 23.3% were male stroke survivors. The differences between the proportion of female stroke survivors without MetS and male stroke survivors without MetS was significant ( $p=0.047$ ).

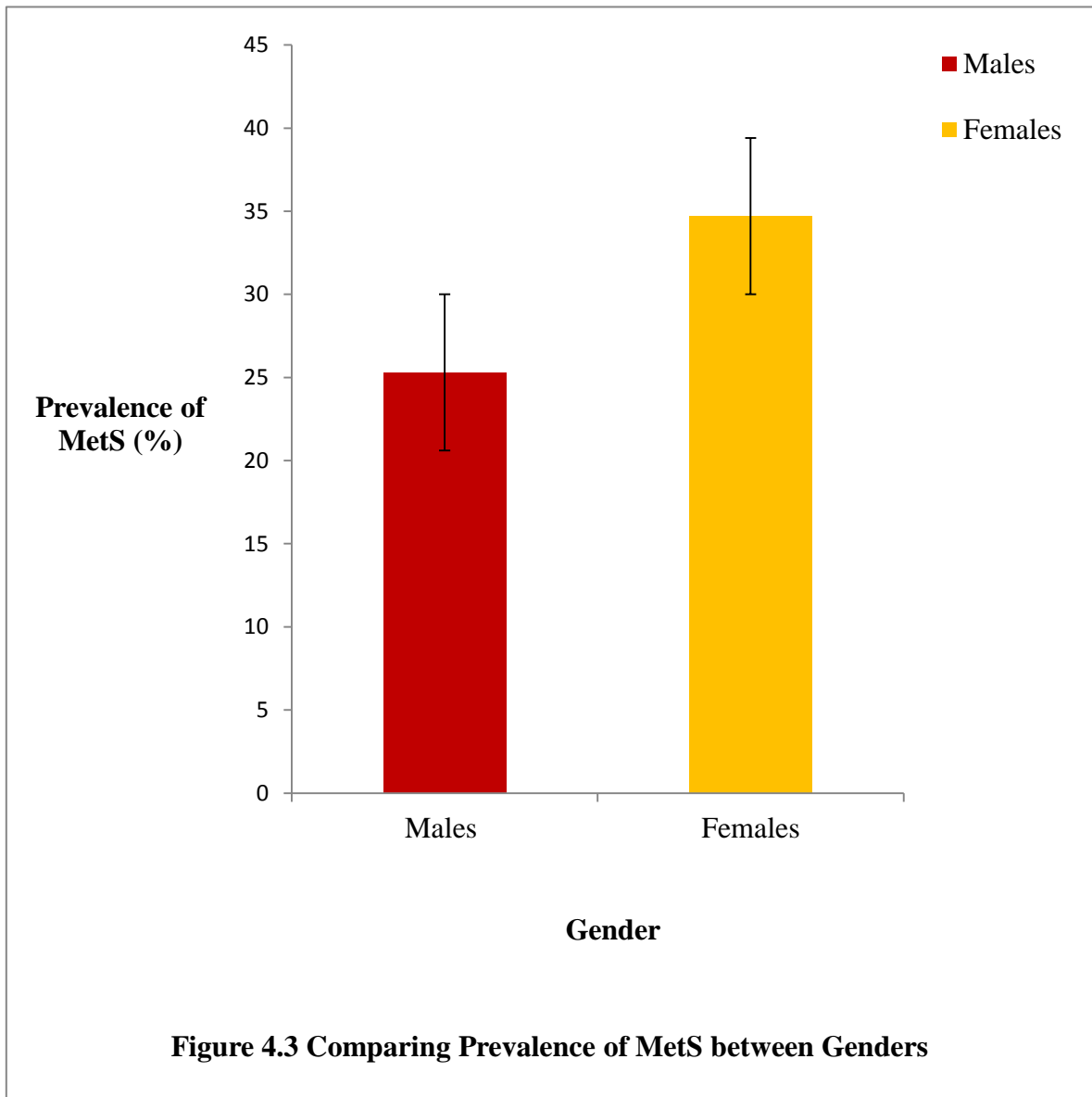
**Table 4.4 Comparing Prevalence of MetS score between male and female stroke survivors.**

Number of MetS Indicators	Male n(%)	Female n(%)	P-value
0	2(1.3%)	2(1.3%)	1.0000
1	9(6%)	10(6.7%)	0.9503
2	24(16%)	13(8.7%)	0.5342
≥3	38(25.3%)	52(34.7%)	0.1691
<b>TOTAL</b>	73(48.7%)	77(51.3%)	0.7502

**n: number; %: percentage/proportion; 0: no MetS; 1: one MetS component; 2: two MetS components; ≥3 : at least MetS components present.**

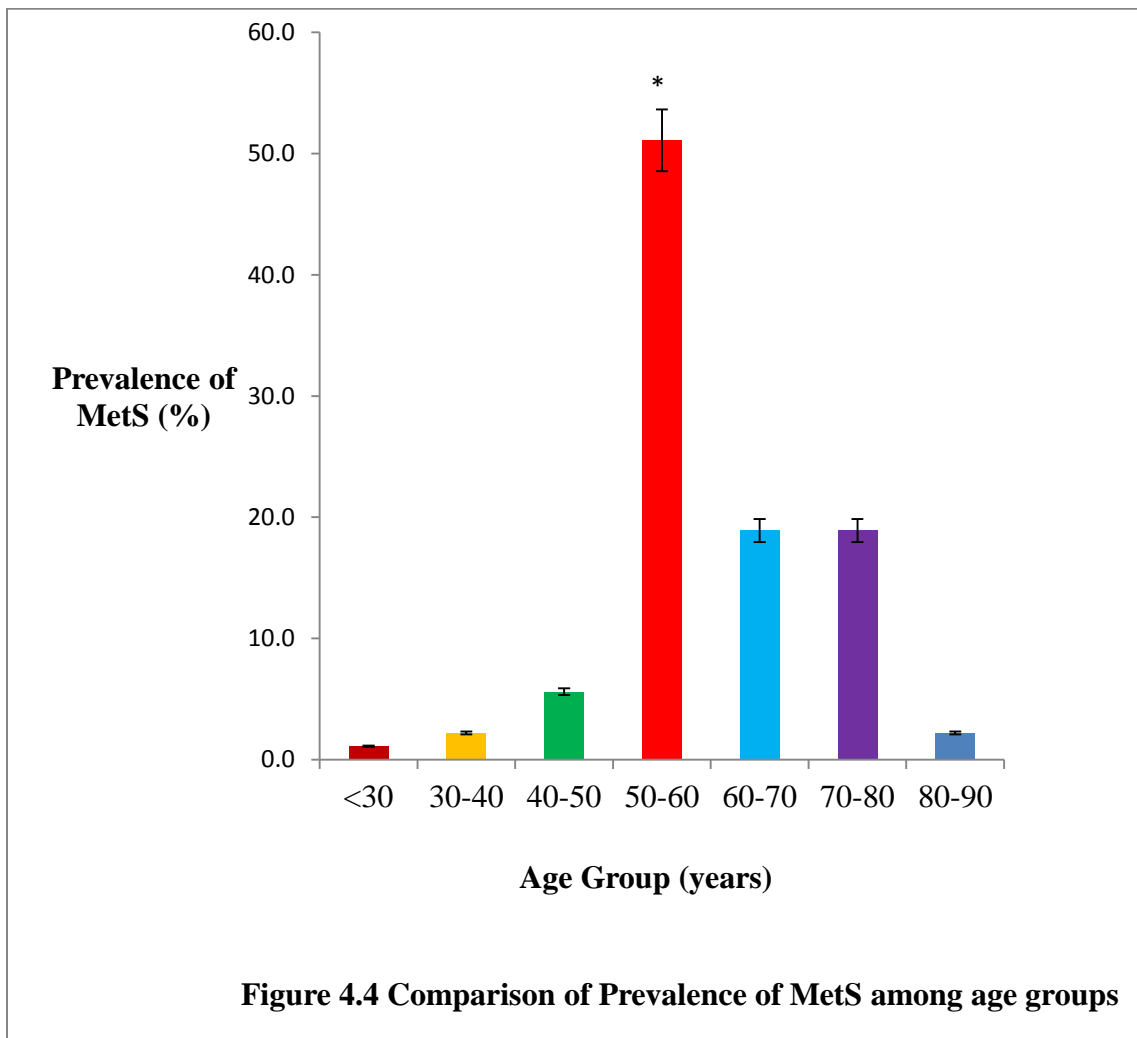
#### 4.7 Comparing Prevalence of MetS between Genders

The analysis showed that 25.3% and 34.7% of the male and female participants respectively had MetS. However, the mean difference between the proportions was not significant ( $p=0.1691$ ) as shown in Figure 4.3 below.



#### 4.8 Comparing Prevalence of MetS among Age Groups

There were significant differences in prevalence of MetS among the age groups ( $p < 0.05$ ) as shown in Figure 4.4 below. 51.1% of patients with MetS were within 50-60 years with 18.9% each within 60-70years and 70-80years respectively. 5.6% of patients with MetS were within 40-50 years with 2.2% of patients with MetS each within 30-40years and 80-90years respectively. The age group less than 30years had the least patients with MetS of 1.1%.



**\*Significant**

#### 4.9 Comparing Proportions of MetS individual Components in the Study Participants.

The result showed that 64% of patients with MetS had high fasting blood glucose (HFBG) whereas 36% had normal levels of FBG and the difference in the proportions was significant ( $p=0.001$ ). Also, 61% of the patients with MetS had high blood pressure (HBP) and the difference in the proportions was significant ( $p=0.0086$ ). Waist circumference (WC), decreased high density lipoprotein (DHDL) and raised triglycerides (RTGL) were found in 58%, 57% and 56% of the study participants respectively; however, the mean differences in the proportions between those with and without MetS components were not significant ( $p>0.05$ ) as shown in Table 4.5

**Table 4.5 Comparing proportions of MetS individual components in the Study Participants.**

MetS components	Participants with MetS n(%)	Participants without MetS n(%)	P-value
<b>HFBG (mmol/l)</b>	96(64%)	54(36%)	0.0010*
<b>DHDL(mmol/l)</b>	85(57%)	65(43%)	0.0892
<b>HBP(mmHg)</b>	92(61%)	58(39%)	0.0086*
<b>RTGL(mmol/l)</b>	84(56%)	66(44%)	0.1445
<b>OBESITY (waist circumference) (cm)</b>	87(58%)	63(42%)	0.0530

n: number of participants; %: percentages; HFBG: high fasting blood glucose; DHDL: decreased high density lipoprotein; HBP: high blood pressure; RTGL: raised triglycerides; WC: waist circumference; mmol/l: millimole per litre; cm: centimetre. \*Significant.

#### 4.10 Comparing Proportions of MetS Components between Ischaemic and Haemorrhagic Stroke.

The analyses showed no significant differences in the proportions of MetS components between ischaemic and haemorrhagic strokes: high fasting blood glucose (HFBG), high blood pressure (HBP), raised triglycerides (RTGL), decreased high density lipoprotein (DHDL) and obesity ( $p>0.05$ ) as shown in Table 4.6.

**Table 4.6 Comparing MetS components/Indicators between Ischaemic and Haemorrhagic Stroke participants.**

MetS components	Ischaemic stroke	Haemorrhagic Stroke	p-value
	n(%)	n(%)	
<b>HFBG ≥6.1mmol/l</b>	60(40%)	36(24%)	0.1091
<b>HBP ≥130/85</b>	55(36.6%)	37(24.7%)	0.2295
<b>RTGL ≥1.7</b>	51(34%)	33(22%)	0.2379
<b>DHDL &lt;0.9(men)/&lt;1.0(women)</b>	47(31.4%)	38(25.3%)	0.5364
<b>HWC &gt;102cm(men)/&gt;88cm(women)</b>	51(34%)	36(24%)	0.3155

n: number of participants; %: percentages; HFBG: high fasting blood glucose; DHDL: decreased high density lipoprotein; HBP: high blood pressure; RTGL: raised triglycerides; WC: waist circumference; millimole per litre; cm: centimetre.

#### 4.11 Comparison of Proportions of MetS Components between Male and Female

##### Participants

There were no significant differences in means of FBG, BP, TGL and HDL ( $p>0.05$ ); however, there was a significant difference in WC between males and females ( $p=0.04$ ) as shown in Table 4.7.

**Table 4.7 Comparing MetS components between Gender in the Study Participants**

MetS components	Male	Female	p-value
	n(%)	n(%)	
<b>HFBG</b> <b>≥6.1mmol/l</b>	52(34.7%)	42(28%)	0.38
<b>HBP</b> <b>≥130/85mmHg</b>	55(38%)	57(36.7%)	0.40
<b>RTGL</b> <b>≥1.7mmol/l</b>	51(34%)	48(32%)	0.29
<b>DHDL</b> <b>&lt;0.9(men)/&lt;1.0(women)</b> <b>mmol/l</b>	38(25.3%)	44(29.4%)	0.09
<b>WC</b> <b>&gt;102cm(men)/&gt;88cm(women)</b>	51(34%)	57(38%)	0.04*

n: number of participants; %: percentages; HFBG: high fasting blood glucose; DHDL: decreased high density lipoprotein; HBP: high blood pressure; RTGL: raised triglycerides; WC: waist circumference; millimole per litre; cm: centimetre.

#### 4.12 Comparison of proportions of male and female participants between haemorrhagic and Ischaemic strokes.

There were no significant differences in the MetS component of male and female participants between haemorrhagic and Ischaemic strokes ( $p>0.05$ ) as shown in Table 4.8 below:

**Table 4.8 Comparing proportions MetS components between male and female Ischaemic and Haemorrhagic stroke participants.**

MetS components	Ischaemic stroke n(%)	Haemorrhagic Stroke n(%)	p-value
<b>HFBG(mmol/l)</b>			
Male	25(26.0%)	12(12.5%)	0.3504
Female	35(36.5%)	24(25%)	0.3515
<b>DHDL(mmol/l)</b>			
Male	21(24.7%)	13(15.2%)	0.5092
Female	26(30.5%)	25(29.6%)	0.9441
<b>RTGL(mmol/l)</b>			
Male	21(25%)	13(15.5%)	0.5114
Female	30(35.7%)	20(23.8%)	0.3725
<b>HBP(mmHg)</b>			
Male	35(38%)	20(21.7%)	0.2128
Female	20(21.7%)	17(18.6%)	0.8152
<b>WC(cm)</b>			
Male	20(23%)	16(18.4%)	0.7361
Female	31(35.6%)	20(23%)	0.3407

n: number of participants; %: percentages; HFBG: high fasting blood glucose; DHDL: decreased high density lipoprotein; HBP: high blood pressure; RTGL: raised triglycerides; WC: waist circumference; millimole per litre; cm: centimetre.

#### 4.13 Comparison of the association between stroke and MetS.

There were significant associations between stroke and MetS as well as selected components of MetS ( $P < 0.05$ ) as shown in Table 4.9 below:

**Table 4.9 Associations of Stroke with MetS and Components**

Variables	Chi-square test	p-value
Stroke with MetS	4.54	0.0331
Stroke with HFBG	8.96	0.0028
Stroke with HBP	4.32	0.0377
Stroke with WC	5.70	0.0170

HFBG: high fasting blood glucose; HDL: decreased high density lipoprotein; HBP: high blood pressure

## CHAPTER FIVE

### 5.0 DISCUSSION

#### 5.1 Introduction

Metabolic syndrome has been found as an independent risk factor of cardiovascular diseases such as coronary artery disease and stroke (Cortez-Dias *et al.*, 2011). Stroke is characterised by high rates of recurrence and mortality (Mohan *et al.*, 2011). Since the presence of MetS has been associated with an increased risk of stroke (Juan *et al.*, 2007), assessing the coexistence of MetS with stroke in a population of stroke survivors is an important step in reducing the menace of MetS as possible risk factor for stroke recurrence.

#### 5.2 Characteristics of Participants

The mean age of the study participants was 57 years. The age difference between ischaemic and haemorrhagic stroke participants was not significant. This result is consistent with studies where participants had similar age distributions (Ashtari *et al.*, 2012; Iqbal *et al.*, 2010). Age is one important risk factor for stroke (Cubriilo-Turek, 2004). The average age at which people suffer haemorrhagic stroke tends to be lower than for ischaemic stroke (Tanne *et al.*, 2001); however, in this study the mean age of the haemorrhagic stroke patients was not significantly lower than that of ischaemic stroke patients. Feigin *et al.* (2003) and Lemogoum *et al.*, (2005) further reported that stroke also occurs at much earlier ages in Sub-Saharan Africa, resulting in a greater number of years of prospective life lost. Thus, given that age is comparable between both groups, other factors may be essential in the pathogenesis of stroke. This is because several unhealthy lifestyle behaviours such as smoking or drug use can cause stroke rather than the effects of aging (Dearle, 2010; Mohammad, 2014). Cubriilo-Turek (2004) reported that, the risk of stroke

increases with age such that each decade after 55 years doubles stroke rate in both men and women.

The results of the present study showed that there were more female (53.3%) stroke patients than males (46.7%). This result was inconsistent with that of other studies. In a systematic review on sex differences in stroke epidemiology, it was found that worldwide, stroke is more common among men; but women are more severely ill (Appelros *et al.*, 2009). In addition, other previous studies have consistently reported that there was a significantly higher proportion of smokers and heavy drinkers in male than in female patients (Reeves *et al.*, 2009; Reeves *et al.*, 2008) resulting in higher prevalence and incidence. These probably underscore the need for changing unhealthy lifestyle and adopt prudent ones that can positively modify the risk of stroke. In contrast, Foerch *et al.* (2013) explored gender distribution in patients with acute stroke through a multi-national approach and reported that, gender distribution of acute stroke patients is highly variable and differs among countries. Physiologically, the positive effect of estrogen on cerebral circulation has been postulated to mitigate the incidence of stroke in women (Krause *et al.*, 2006), a mechanism that seems to cease with menopause (Murphy *et al.*, 2004) has been speculated to explain the reason why women do have lower stroke incidence than men. Therefore, given the mean age in this study the result obtained regarding gender distribution could be expected.

### 5.3 Metabolic Syndrome in Study Participants

The results of the present study showed that the prevalence of ischaemic stroke (68%) was significantly higher than haemorrhagic stroke (32%). This result is in agreement with other research findings (Ashtari *et al.*, 2012; Beal, 2010; Iqbal *et al.*, 2010). Iqbal *et al.* (2010) found that, out of 50 patients 27 (54%) had ischaemic and 23 (46%) haemorrhagic strokes. In a case-control study, Ashtari *et al.* (2012) found 50% of the study participant having ischaemic stroke and the other half being haemorrhagic stroke. In contrast, Akpalu *et al.* (2011) found a higher proportion of haemorrhagic stroke (31%) than ischaemic stroke (29%), although the difference in the proportions was not significant. It is well documented that ischaemic stroke accounts for 80-85% of all strokes, whereas haemorrhagic stroke accounts for 15-20% (Beal, 2010). There is a disproportionate distribution of ischaemic and haemorrhagic strokes with ischaemic stroke being 10 times more prevalent than haemorrhagic stroke, moreover, absolute numbers of haemorrhagic stroke are relatively lower compared to ischaemic stroke (Lavados *et al.*, 2005). This observation has been speculated to be partly due to the severity of haemorrhagic stroke which results in higher mortality compared to ischaemic stroke (Lavados *et al.*, 2005). About 8% to 12% of ischaemic strokes and 37% to 38% of haemorrhagic strokes result in death within 30 days (Roger *et al.*, 2012). This is because many of the risk factors of haemorrhagic stroke are related to unhealthy behaviours, such as smoking or drug use, rather than the effects on the body of aging. The fatality rate for haemorrhagic strokes is higher than for ischaemic strokes and overall prognosis is poorer (Liu *et al.*, 2007).

The cut points of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) were used in determining metabolic syndrome in the study participants. Thus, in this study, at least three (3) MetS scores criteria per the NCEP ATP III were used to define metabolic

syndrome. The results showed that, prevalence of metabolic syndrome among study participants was 60% using the NCEP ATP III criteria. This was significantly higher than in patients without metabolic syndrome. This result is consistent with several other studies (Ashtari *et al.*, 2012; Mi *et al.*, 2012; Liu *et al.*, 2011; Iqbal *et al.*, 2010; Boden-Albala *et al.*, 2008; Kabir *et al.*, 2008; Najarian *et al.*, 2006; Ovbiagele *et al.*, 2006). These studies recorded relatively higher proportions of patients with MetS. Mi *et al.* (2012) found metabolic syndrome in 50% in a cohort of study participants with hazard ratio for stroke recurrence (metabolic syndrome versus no metabolic syndrome) approaching two. In another study, Iqbal *et al.* (2010) reported that 46% of stroke patients had metabolic syndrome. Ashtari *et al.* (2012) also found about 62% of the patients and 34% of controls had metabolic syndrome per NCEP ATP III criteria. The Framingham Offspring Study conducted by Najarian *et al.* (2006) which determined the risk for stroke in 2097 participants yielded 22% prevalence of metabolic syndrome.

In this study, it has been shown that 51.1% of patients with MetS are within 50-60 years with 18.9% each within 60-70 years and 70-80 years. These observations support other research finding given that the highest prevalence of MetS was found in the modal age group. Similarly, Jia *et al.* (2011) showed that metabolic syndrome was associated with first-ever stroke in middle-aged and the elderly. In Ghana, Akpalu *et al.* (2011) found the prevalence of metabolic syndrome among a group of patients with cardiovascular diseases and healthy controls to be 54% and 18% respectively, with the prevalence increasing with increasing age. Thus, this study supports the assertion that metabolic syndrome increases with age and tend to be common among the middle-aged group especially, in patients with first time stroke (Akpalu *et al.*, 2011; Jia *et al.*, 2011). The prevalence and incidence of metabolic syndrome are increasing and a large number of people worldwide are at risk of cardiovascular diseases such as stroke and ischaemic heart

diseases (Khang *et al.*, 2010). Therefore, the relatively high prevalence of MetS in this study could be due to high prevalence of MetS components especially, high fasting blood glucose, high blood pressure and high waist circumference or obesity.

When adjusted for type of stroke, the results of the present study showed that, 43.3% of the participants with MetS (60%) were ischaemic stroke patients whereas 16.7% were haemorrhagic stroke patients. The difference in proportions was significantly higher in ischaemic stroke than haemorrhagic stroke. This finding supports other studies using the NCEP ATP III criteria (Ashtari *et al.*, 2012; Mi *et al.*, 2012; Iqbal *et al.*, 2010). Ashtari *et al.* (2012) found 62% of the study participants with metabolic syndrome being ischaemic stroke patients. Iqbal *et al.* (2010) reported that 65.2% of the ischaemic stroke had metabolic syndrome compared to haemorrhagic stroke. Also, Mi *et al.* (2012) found 51.4% of the ischaemic stroke participants having metabolic syndrome. It has been reported that more than 50% of ischaemic stroke patients are suffering from metabolic syndrome (Iqbal *et al.*, 2010). The current study concurs with this finding in literature. The frequency of MetS has been reported to be significantly higher in patients with a history of atherothrombotic or non-embolic ischaemic stroke (Milionis *et al.*, 2005; Ninomiya *et al.*, 2004; Suk *et al.*, 2003). Broła *et al.* (2015) recently studied metabolic syndrome in Polish ischaemic stroke patients and estimated over 60% of Polish Ischaemic stroke patients with MetS and concluded that MetS may be a risk factor for Ischaemic stroke. The National Health and Nutrition Examination Survey (NHNES) among 10 357 subjects, the prevalence of MetS was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of vascular disease (22.8%) (Ninomiya *et al.*, 2004). Metabolic syndrome increases atherosclerosis and that can predispose an individual to higher risk for stroke (Ashtari *et al.*, 2012). The association between MetS and atherosclerosis with subsequent ischaemic

stroke is because the risk factors are similar. Ovbiagele *et al.* (2006) reported 50% patients with symptomatic intracranial atherosclerosis had metabolic syndrome. Moreover, frequency of brain ischaemic lesions increases with MetS, independent of other risk factors (Park and Yasuda, 2009; Yamaguchi *et al.*, 2008). Notwithstanding the fact that the actual mechanism of MetS causing cardiovascular diseases is unclear, it has been found as an independent risk factor for ischaemic stroke (Ashtari *et al.*, 2012). Therefore, metabolic syndrome is associated with an increased risk of cardiovascular events and ischaemic stroke (Li *et al.*, 2008).

To compare metabolic syndrome by gender, the NCEP ATP III criteria was used. The result showed that, 25.3% and 34.7% of male and female participants respectively had MetS. Thus, the frequency of MetS was higher in females than males; however, the difference between these proportions was not significant. This result is similar to that of stroke and metabolic syndrome studies in different populations (Ashtari *et al.*, 2012; Mi *et al.*, 2012). Ashtari *et al.* (2012) observed that the prevalence of MetS in women (52%) was more than males (44%); although the difference was not significant. Also, Mi *et al.* (2012) found that patients with metabolic syndrome were more likely to be female, slightly younger, nonsmokers and were less likely to have a previous history of atrial fibrillation than subjects without metabolic syndrome. There are gender differences in the syndrome (Ford, 2005). The prevalence of metabolic syndrome has been increasing at a steeper rate in women during the last decade; this may be contributing to the increased rate of CVD such as stroke in postmenopausal women who are more prone to central obesity (Regitz-Zagrosek *et al.*, 2006). Thus, further buttressing the gender distribution of participants in this study, given that, 46.7% of the participants were males and 53.3% females with mean age of 57 years.

#### 5.4 Components of Metabolic Syndrome in Participants

Comparisons were made with the components or indicators of metabolic syndrome between patients with and without MetS, ischaemic and haemorrhagic stroke as well as both sexes. In this study, per the NCEP ATP III criteria, 64% and 61% of the participants had high fasting blood glucose (HFBG) and high blood pressure (HBP) respectively, and the differences in the proportions were significantly higher than patients with normal glycaemia and normal blood pressure. Also, waist circumference (WC), decreased high density lipoprotein (DHDL) and raised triglycerides (RTGL) were found in 58%, 57% and 56% of the participants respectively. These findings correlate with recent studies (Ashtari *et al.*, 2012; Mi *et al.*, 2012; Akpalu *et al.*, 2011; Iqbal *et al.*, 2010). Mi *et al.* (2012) reported higher prevalence of high fasting blood glucose (51.1%) and high blood pressure (74.3%). Also, Ashtari *et al.* (2012) reported higher proportions of their study participants with high fasting blood glucose (57%) and high blood pressure (68%). Similarly, Iqbal *et al.* (2010) found decreased high density lipoprotein (DHDL) and raised triglyceride levels in 68% and 64% in their study participants respectively. Again, Ashtari *et al.* (2012) found high waist circumference in 85% of their study participants. In this study, the most prevalent or common indicators of MetS were high fasting blood glucose and elevated hypertension. The next frequent components were high waist circumference or central obesity, decreased high density lipoprotein and raised triglycerides. The high prevalence of MetS components observed in this study may have accounted for the high prevalence of MetS in the study participants. Liu *et al.* (2011) reported that, hypertension and hyperglycemia were independent risk factors for cardiovascular diseases. Hwang *et al.* (2011) showed that high fasting blood glucose and/or metabolic syndrome were the highest predicting factors of cardiovascular diseases. Impaired fasting glucose and hypertension were found to be the

strongest predictors of first stroke or transient ischaemic attack (Koren-Morag *et al.*, 2005). Moreover, Mozaffarian *et al.* (2008) demonstrated that MetS is associated with higher risk of stroke and that the risk is higher in the presence of elevated fasting blood glucose alone or hypertension alone.

In the patients with MetS, when adjusted for type of stroke (ischaemic or haemorrhagic), MetS components were relatively higher in ischaemic stroke patients than haemorrhagic patients. However, differences in proportions and mean values were not significant. Iqbal *et al.* (2010) reported higher prevalence of high fasting blood glucose, decreased high density lipoprotein, raised triglycerides and high waist circumference in ischaemic stroke than haemorrhagic stroke. Generally, the differences in proportions of individual components of MetS between male and female participants were not significant. Moreover, when proportions of MetS components compared between ischaemic and haemorrhagic stroke by gender, no significant differences were observed. This finding is similar to that of Ashtari *et al.* (2012) where MetS component frequency was similar between males and females.

The findings of this study show an association between stroke and MetS as well as the most prevalent MetS components namely: high fasting blood glucose, high blood pressure and high waist circumference. The MetS is associated with different kind of diseases such as development of myocardial ischemia, ischaemic stroke, extra and intracranial atherosclerotic, and asymptomatic carotid atherosclerotic (Aoki and Uchino, 2011). Mi *et al.* (2012) found association between stroke risk and MetS and concluded that high fasting plasma glucose was an independent predictor for stroke recurrence. Metabolic syndrome has been found to be a risk factor for a secondary stroke or future cerebral lesion (Boden-Albala *et al.*, 2008). A dose-

response relationship has been speculated between MetS components and risk of cardiovascular events (Liu *et al.*, 2011). Thus, the more the components of MetS, the more likely for an individual to develop stroke, since MetS has been found to be an independent risk factor for cardiovascular diseases especially, ischaemic stroke. This study demonstrates that there is high prevalence of MetS in Ghanaian acute stroke survivors especially, ischaemic stroke. The prevalence of MetS increases with age and the middle-age group tends to be frequent with stroke and MetS prevalence. Metabolic syndrome is more prevalent in female than male stroke patients. Also, high fasting blood glucose, high blood pressure and high waist circumference or obesity were the most prevalent MetS components among the study participants.

## **5.5 Conclusion**

Metabolic syndrome is high in acute stroke patients in Ghana. There is higher prevalence of metabolic syndrome in ischaemic stroke than haemorrhagic stroke. Metabolic syndrome and stroke tend to peak between 50 and 60 years. Female stroke patients have higher frequency of metabolic syndrome than males. High fasting blood glucose, high blood pressure and high waist circumference (obesity) are the most prevalent MetS components. Therefore, fasting blood glucose, blood pressure and body weight should be well controlled to reduce risk of recurrent stroke in patients with history of stroke especially, acute stroke and also, to prevent stroke in individuals without history of stroke.

## **5.6 Limitations of the Study**

The main limitations of this study were the high cost of analyses of the indicators of metabolic syndrome. This necessitated recruitment with relatively small number of participants.

## **5.7 Recommendations**

From the findings of this study, the following recommendations are made:

The individual components of metabolic syndrome should be monitored and treated meticulously in patients with acute stroke or history of stroke.

Routine checking and/or treatment of MetS components must be encouraged in Ghanaian apparently healthy individuals especially, those from 50-60 years and over.

Lifestyle modification such as increased physical activity and improved diet is highly recommended for stroke patients and the apparently healthy to prevent MetS and risk of stroke especially, in postmenopausal women.

Further study should be conducted with large sample size comparing acute and chronic strokes in rural and urban dwellers of different ethnic descent in Ghana.

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## **APPENDIX II**

### **7.0 Ethical Issues**

#### **7.1 Approval**

The proposal of this study was submitted to the Research Protocol and Ethical Review Committee of the University of Ghana Medical School for review and approval.

#### **7.2 Confidentiality**

Subjects were made to complete informed consent forms and laboratory sheets and were signed by the supervisors of this study. The data gathered from the subjects will be used only for the purpose of the study and the subjects will be assured of complete confidentiality of any information obtained from them.

#### **7.3 Voluntary Written Informed Consent**

As part of the requirements for ethical considerations, a written informed consent was obtained from the Stroke Unit of the Korle-Bu Hospital, and the Biochemistry Department of the University of Ghana Medical School in order to use their laboratories for the sample collections and analyses respectfully. A detailed written informed consent stating the title and the purpose of the study was given to the subjects for their consents. In addition, detailed explanations on the need to participate in this study will be emphasized. The consent form was attached to this proposal for approval by the Research Protocol and Ethical Review Committee of the University of Ghana Medical School.

#### **7.4 Potential Risks**

The most probable potential risks which was associated with this study was the pains that subjects experienced as a result of blood sample collections which was made at baseline.

#### **7.5 Safety Precautions**

The standard protocol for conducting a study of this nature was duly followed. Subjects will undergo a thorough medical screening and health history questionnaire. Subjects was taken through a familiarization section to get themselves acquainted to the procedure. In addition, heart rates and blood pressures was monitored during the procedure.

## 7.6 Benefits

The results of this study will be useful to the subjects, entire stroke population, college of health sciences, and clinicians as well as the general public. Subjects having successfully gone through the study will appreciate the impact of metabolic syndrome in stroke survivors and as well as its potential effect in recurrent stroke in Stroke survivors in Ghana. Clinicians especially, those in medicine and exercise prescription and supervisions such as Physicians, Exercise Physiologists and Physiotherapists will be guided on how to design planned structured treatment programme for their stroke patients or clients. In terms of research, this will stimulate more work in this area in Ghana.

## 7.7 Informed Consent

**Subject's Name:** .....

**Date:** .....

### Introductions

The title for this study is “Metabolic Syndrome among Stroke Survivors in Ghana”. The aim of this study is to assess metabolic syndrome in major types of stroke in Ghana. Your role in this study will be: as a stroke survivor being recruited into either ischaemic or haemorrhagic stroke survivor. Blood pressure, height, weight and waist circumference will be taken and recorded. About 10mls of blood samples will be drawn and used for analyses.

### Risk and Discomfort

Participating in this study will not be detrimental to your health. Potential risks and safety precautions have been taken care of. However, you reserve the right to withdraw from the study at any point in the study. Nevertheless, you will experience some discomfort from the parameters that will be measured and discomfort from venupuncture.

### Confidentiality

Your confidentiality concerning any information given towards this study will be purposely used for this study alone and these data will be kept as confidential as possible. Your identity will be

kept anonymous when the results are presented or published. All participants involved in the study will be referred to as “Subjects”.

### **Problems or Questions**

If you have any problem or question about this study, you can contact the investigator: Edward Ababio (0246734198) in the Department of Physiology, University of Ghana Medical School.

### **Consent**

I have read or have had someone read to me, the entire explanation of this study and have been given the opportunity to discuss any questions. I understand the nature, risk and benefits of this study and that I may withdraw at any time from the study. Likewise, I have received a copy of this informed consent document. I hereby consent to take part in this study.

**Subject’s Signature:**.....

**Date Signed**.....

**Investigator’s Signature**.....

**Date Signed**.....