PHYSIOLOGICAL AND ANTHROPOMETRIC CORRELATES OF METABOLIC RISK FACTORS AMONG NON-OBESE ADULTS IN ZARIA, NORTHERN NIGERIA

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DECLARATION

I declare that the work in this dissertation entitled 'Physiological and anthropometric correlates of metabolic risk factors among non-obese adults in Zaria, Northern Nigeria' has been carried out by me in the Department of Human Physiology under the supervision of Prof. J.O. Ayo, Department of Veterinary Physiology and Pharmacology, Faculty of Veterinary Medicine, ABU, Dr K.V. Olorunshola of Department of Human Physiology, Faculty of Medicine, ABU, and Prof. C. E. Dikki, Department of Physical and Health Education, Faculty of Education, ABU. No part of this dissertation was previously presented in any application for higher degree at any university. All quotations in this work which have been taken from published works of other investigators were acknowledged and the source of information appropriately referenced.

_____ _____ _____

Name of student **Signature** **Date**

CERTIFICATION

This dissertation entitled 'PHYSIOLOGICAL AND ANTHROPOMETRIC CORRELATES OF METABOLIC RISK FACTORS AMONG NON-OBESE ADULTS IN ZARIA, NORTHERN NIGERIA' by Kolade Oladele SHARAYE, meets the regulations governing the award of the degree of Doctor of Philosophy of Ahmadu Bello University, Zaria, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

To the covenant keeping GOD, for HIS faithfulness is for evermore.

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ABSTRACT

Recent publications on clinical definitions have transformed the metabolic syndrome from a physiological curiosity to a major focus of research, clinical and public health interests on non obese adults. The purpose of this study therefore, was to determine the relationship between anthropometrics and cardiometabolic variables that reflect the existence of metabolic syndrome among non obese adults. One hundred and seventy four (174) adults, with mean age of 47.13 ± 8.10 years (male) and 44.96 ± 9.58 years (female) were recruited for this cross sectional study. Descriptive statistics, partial correlation and multiple regression analysis were used to determine the relationship between anthropometric measurements and cardiometabolic variables, after controlling for age. Anthropometric indices, lipid profile, fasting glucose and blood pressure were among the variables assessed using standard procedures. The best correlation among the anthropometrics ($p \leq 0.05$) was presented between waist circumference and waist-height ratio (male *r*: 0.925, female *r*: 0.916) and percentage body fat and fat mass (male *r*: 0.956, female *r*: 0.944) and they reflected strong and positive correlation among all anthropometric indices including resting energy expenditure and conicity index in male and female groups. Fat mass, waist-height ratio, body mass index and waist-hip ratio in male and waist-height ratio in female were found to have the largest correlation relative to at least 3 risk factors. Combination of three components of cardiometabolic risk factors were significantly more in male than female. Regression analysis also showed that waist-height ratio appears optimal for predicting components of cardiometabolic risk factors among non obese adults, waist-hip ratio ranked second, followed by fat mass. In conclusion, among all obesity measures studied, waist-height ratio, waist-hip ratio and fat mass explained comparatively larger amount of variance of cardiometabolic risk

factors among non-obese adults. Non obese male were significantly more likely to have two or more risk factors than female participants. However, the greater risk of developing metabolic syndrome was associated with increasing waist-height ratio, which could be used as simple and non-invasive method for detecting dyslipidemia among non obese adults and use of this method, was suggested in clinical and epidemiological fields.

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Glossary of Abbreviations and Definition of Terms

ACR – albumin creatinine ratio

AHA- American Heart Association

BMI – Body Mass Index (kg/m^2)

CHD – Coronary Heart Disease

CVD – Cardiovascular Disease

CI - Conicity Index

DBP – Diastolic Blood Pressure (mmHg)

EGIR- European Group for the Study of Insulin Resistance

FFM- Fat Free Mass (kg)

FM – Fat Mass (kg)

HC – Hip Circumference (cm)

HDL – High Density Lipoprotein (mmol/l)

HR – Heart Rate; PR – Pulse Rate (/min)

Ht – Height (cm)

IDF- International Diabetes Federation

LBM – Lean Body Mass (kg)

LDL – Low Density Lipoprotein (mmol/l)

MetS – Metabolic syndrome

MABP – Mean Arterial Blood Pressure

NCEP/ATP- National Cholesterol Education Program/Adult Treatment Plan III

NHLBI- National Heart, Lung, and Blood Institute

REE – Resting Energy Expenditure (kcal/day)

SBP – Systolic Blood Pressure (mmHg)

T2DM- Type 2 diabetes mellitus

TC – Total Cholesterol (mmol/l)

TG – Triglyceride (mmol/l)

UAER- urinary albumin excretion rate

WC – Waist Circumference (cm)

WHO- World Health Organization

WHpR – Waist –to –Hip Ratio

WHtR – Waist-to-Height Ratio

Wt – Body Weight (kg)

% FAT - % Body Fat (%)

∑3SKF: Sum of (3) Skinfolds

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Obesity and its associated metabolic abnormalities have been the focus of many researchers lately, especially physiologists, epidemiologists and geneticists. More so, there are individuals who by standard weight/BMI tables are not obese or even overweight, but who have metabolic abnormalities that are characteristically associated with adult onset obesity. The constellation of these abnormalities also known as metabolic syndrome (MetS) have been widely investigated (Song *et al*., 2006; Opie, 2007; Zhao *et al*., 2010); It was suggested that these metabolically obese normal weight individuals represent one end of the spectrum of obesity and that some of them would be difficult to detect by any criteria. The concept of the metabolically obese normal weight individual is based on the observation that these same characteristics may be found in normal weight individuals with disorders often associated with obesity (St-Onge *et al*., 2004; Tsai, 2009).

MetS is one of the fastest growing health problems worldwide. It is a major risk factor for both diabetes mellitus (DM) and cardiovascular disease (CVD). The etiology is complex, determined by the interplay of both genetic and environmental factors. It is characterized by the clustering of multiple metabolic abnormalities, including abdominal obesity, hypertension, dyslipidemia, insulin resistance, and impaired glucose tolerance. This clustering has been referred to as syndrome X, the deadly quartet, and the insulin resistance syndrome. The term insulin resistance syndrome was widely used until 1998 when the WHO proposed a unifying definition for the syndrome and chose to call it MetS (Song *et al*., 2006).

The concept, definition and criteria for the MetS as a risk factor for CVD have been increasingly discussed. Several expert groups and institutions have proposed different criteria to diagnose the MetS in clinical practice. They include various combinations of central obesity, high blood pressure, high plasma glucose, dyslipidemia and insulin resistance. One of the most recently published definitions takes into account ethnic specific cut points for central obesity. However, European cut-points are still recommended in African populations where specific data are not yet available (Leopold *et al*., 2007). These criteria varied somewhat in specific elements, but in general they include a combination of both underlying and metabolic risk factors (Juan *et al*., 2003).

At present, there are several definitions of the MetS proposed by the WHO (1998, 1999), The European Group for the Study of Insulin Resistance (1999), American Association of Clinical Endocrinology (2000), National Cholesterol Education Program Adult Treatment Panel III (2001, 2004), American Heart Association/ National Heart, Lung, and Blood Institute (2004, 2005), and the International Diabetes Federation (IDF,2005). IDF proposed a definition for MetS for use in epidemiology studies and clinical practice, which would allow for comparison between different population groups and the assessment of its relationship with various health outcomes (Motala *et al*., 2009). Whichever definition used, the presence of MetS is associated with a doubled risk of type 2 diabetes mellitus (T2DM) and CVD, especially stroke (Roberto *et al*., 2009).

The MetS is a clustering of components (abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure and is associated with other co-morbidities including the prothrombotic state, proinflammatory state, non-

alcoholic fatty liver disease, and reproductive disorders) that reflect over-nutrition, sedentary lifestyles, genetic factors and resultant excess adiposity. It describes a constellation of clinical characteristics that are associated with an increase in the risk of developing both atherosclerotic CVD and T2DM (Greenland, 2005; Kelliny *et al*., 2008). The magnitude of the increased risk can vary according to which components of the syndrome are present plus the other non MetS risk factors in a particular person (Zhao *et al*., 2010).

The IDF, (2005) defined a participant as having MetS if he or she had central obesity (Ethnicity specific waist circumference values) plus at least 2 of the following criteria: (1) triglyceride level ≥ 1.7 mmol/L; (2) reduced HDL-C levels of less than 1.03 mmol/L in men, less than 1.29 mmol/l in women; (3) raised systolic or diastolic blood pressure of 130/85 mm Hg or higher or previously diagnosed hypertension; and (4) raised fasting plasma glucose level of 5.6 mmol/L or higher or previously diagnosed T2DM (Cornier *et al*., 2008). A prerequisite in the IDF definition of the MetS is central obesity measured by ethnicity-specific waist circumference and it is recommended that European cut points be used for populations for which such data are not available, e.g. in sub- Saharan Africans (Motala *et al*., 2009). Because risk factors cluster, and because the cardiovascular risk factors for the MetS are linear in their damaging effects, different definitions of the metabolic syndrome make little difference in the prognostic implications (Opie, 2007). Although data in the developing countries and particularly in the sub-Saharan African remain scarce (Okosun *et al*., 2000; Addo *et al*., 2007; Motala *et al*., 2009; Kimani-Murage *et al*., 2010).

Several epidemiological studies from different populations have reported significant association between different anthropometric indicators and blood pressure levels. Some anthropometric measures or indices, such as BMI and other measures of body fatness have been used in most of these studies to analyze the association between adiposity and cardiovascular risk factors. Most of these studies have shown linear relationships between anthropometric measures and the risk of CVD (Williams *et al*., 2000; Duvnjak *et al*., 2008; kjeldsen *et al*., 2008). These associations between body fatness using different indices have been consistently observed, but remain poorly understood and the mechanistic explanations for the phenomenon are still being debated and no biological model of the process has been established (Rufus *et al*., 2008). Anthropometric indices (anthropometrics) are simple, single, safe and most universally applicable, inexpensive, non-invasive method available to assess the size, proportion and composition of human body and to quantify the degree of obesity. In view of the lack of cheap and accurate methods for assessing body composition directly, anthropometrics are often used as surrogates for assessing obesity and body fat distribution (Ahmet *et al*., 2008; Meerjady *et al*., 2009). In addition, the ability of these obesity indicators to predict metabolic risk profiles may differ by ethnicity, age, and sex. For example, among Asian populations, central obesity has been shown to be a more consistent predictor of diabetes than total obesity' while general obesity has been shown to be a better predictor among white US populations and Europeans (Spiegelman *et al*., 1992; Chan *et al*., 1994)**.**

Measurement of waist circumference is recommended by the US National Cholesterol Education Program (NCEP) for the assessment of central obesity, whereas the WHO recommends waist-hip ratio (WHpR) for the same purpose. All

of the mentioned anthropometric indices have been found to be associated with all-cause mortality, diabetes mellitus, cardiovascular morbidity and mortality in prospective studies (WHO, 1997; Ahmet *et al*., 2008). Some authors have proposed waist-height ratio (WHtR) as the best anthropometric index to predict CVD risk and MetS. Hip circumference (HC) has been found to be inversely associated with diabetes, CVD morbidity and mortality in a prospective study (Lissner *et al*., 2001; Hsieh and Muto, 2006). The results of prospective and cross-sectional studies that have attempted to find the best anthropometric index are not uniform, studies from the Eastern Mediterranean area do not agree on the best anthropometric index to predict cardiometabolic risk (Yalcin *et al*., 2005; Ahmet *et al*., 2008). Work in Turkey has suggested that WHpR might better indicate CVD risk than BMI and WC, the same study also showed that both WC and WHpR were strongly associated with BMI, age, diastolic blood pressure and plasma triglyceride (TG); also, WHpR was significantly associated with prevalent CHD only in Turkish women. Fasting glucose, insulin, HDL cholesterol (HDL) and LDL cholesterol (LDL) levels were not ascertained and the association of anthropometric indices with MetS was not reported in that study (Onat *et al*., 1999). On the other hand, Kayode *et al*. (2009), showed in their study that WHtR and abdominal height (measured as the distance from the exam table to the top of the belly when the patient is lying supine) are better predictor of CVD than any other anthropometric measurement including BMI, WC, WHpR and skin-fold thickness.

The Japanese Society of Internal Medicine also announced a definition of the MetS for the Japanese which is now used in Japan. Most of these definitions employ WC as an indicator of central or abdominal obesity. However, several reports have argued that other indices, for example the WHtR and WHpR are

superior to WC for identifying subjects with cardiovascular risk factors. In particular, reports from Japan have proposed using the WHtR (Ishikawa-Takata *et al*., 2002; Masayuki *et al*., 2008).

Use of conicity index (CI) was also advocated by Valdez *et al*. (1993). It has been widely accepted and found to have several advantages (i) It has a theoretical expected range, a person having a CI of 1.25 means he/she has a WC which is 1.25 times larger than the circumference of a cylinder with height and weight of that person. The predicted range of CI is between 1.00 (perfect cylinder) and 1.73 (perfect double cone). It is more variable in women than men. (ii) It includes a built-in adjustment of WC for height and weight, allowing direct comparisons of abdominal adiposity between individuals or even between populations; and (iii) it does not require the HC to assess fat distribution. Conicity is an index of body fat distribution which expresses an individual's WC relative to the circumference of a cylinder generated with that person's weight and height assuming a constant for body density. The more central a person is in fat distribution, the higher the value of CI (Majcher *et al*., 2005; Meerjady *et al*., 2009).

Obesity has become a major worldwide epidemic affecting more than 300 million people. From the clinical perspective, visceral adipose tissue is known to generate diabetogenic substances and, as such, may be more informative than total fat for diagnostic evaluation. Studies using computed tomography and magnetic resonance imaging have provided further evidence to support that central obesity, visceral adipose tissue, and upper-body non visceral fat are the major contributors to the metabolic complications (Wei *et al*., 1997; Ford *et al*.,

2003; Gabriela *et al*., 2007). The standard epidemiologic translation of these important clinical facts uses anthropometric measures (Jensen, 2006).

Little is known about the relationship between the anthropometric indices and various metabolic disorders in Nigeria adult population (Okosun *et al*., 2000; Olatunbosun *et al*., 2000) and there has been paucity of recent literatures relating to local incidence, particularly in Kaduna, Nigeria (Bello-Sani *et al*., 2007). In primary health care settings, it is usually expensive to measure these metabolic disorders. Undoubtedly, if an easily obtained anthropometric index can be found in predicting various metabolic disorders, primary care physicians may develop policies and programs to promote healthy body status and most of these metabolic disorders may be prevented (Olatunbosun *et al*., 2000; Rufus *et al*., 2008). In Sub-Saharan Africa, CVD have been projected to be the possible leading cause of morbidity and mortality by the year 2020 especially considering epidemic expansion (WHO, 1997; Rufus *et al*., 2008).

Reports about cardiovascular risk in relation to anthropometric factors are limited. Secondary data from the developed nations and high income countries are often extrapolated for local use in Africa. Little is known about the anthropometry–blood pressure relationship among resident Nigerian adult population, while very few data are apparently available on the relationship between body-fat distribution and the risk of hypertension in the same population. Although obesity is known to increase the risk of hypertension, few studies have evaluated BMI across various ranges as a primary risk factor (Olatunbosun *et al*., 2000; Salim *et al*., 2005, Rufus *et al*., 2008).

1.2 Statement of research problem

The most effective programme for prevention of MetS is to avoid the development of child-hood obesity. In case of established disease, the effective treatment should address the different components of the syndrome. There is a need for elaboration of these diagnostic criteria as stated in IDF (2005) definition above, national prevalence data, protocols for prevention, early recognition and effective treatment (Salem and Vazirinejad, 2009).

Estimates of disease risk for a given level of an anthropometric indicator may differ in different study populations. The majority of epidemiologic studies examining the relationship between anthropometric measures and incidence of CHD are conducted in the Western society. Therefore, evaluation of these relationships in non-western populations is needed (Molarius and Seidell, 1998; Zhang *et al*., 2004).

The CI, which evaluates WC in relation to height and weight, appears to have a prognostic value similar to that of WHpR in adults (Taylor *et al*., 2000), but its ability to assess truncal adiposity has not been evaluated in Zaria, northern Nigeria. Whether visceral obesity predicts CHD risk above and beyond overall fatness remains unsettled (Carlos *et al*., 2006).

1.3 Research questions

I. Do anthropometric measures that reflect central obesity have greater predictive ability in terms of cardiometabolic risks than those reflecting overall obesity in this target non-obese population?

II. How significant is the relationship between Resting Energy Expenditure and metabolic risk factors?

1.4 Significance of the study

i. This study intends to exploit the requirement for objective test of obesity and health risk factors and to indicate its implication in health and disease.

ii. This study could be a model that modifies the conceptual framework within which the link between obesity and metabolic risk factors may be better understood and suggest a new direction for pathophysiologic research.

iii. The study will also contribute to the international comparative study of anthropometrics and MetS.

iv. This study may contribute to diagnosis, treatment and follow-up treatment of patients suffering from certain health risk complications e.g. diabetes mellitus and CHD.

v. It is hoped that this study will reveal the relationship between anthropometrics and metabolic risk factors and the significance/ implication of cut-off values in predicting the risk factor accumulation among non-obese adults.

1.5 Aim of the Study

The aim of this study is to investigate the interrelationship between anthropometrics and MetS among non-obese adults of Zaria northern Nigeria.

1.5.1 Objectives of the study

1. Test the appropriateness of BMI and WC cut-off points derived in largely white populations (that is, those of European descent) for detecting obesity-related metabolic abnormalities among Nigerian (Zaria) non-obese adults.

2. Compare some anthropometric indices of obesity and identify which among them best discriminates the high metabolic risk.

3. This study intends to measure resting energy expenditure (REE), the energy required to maintain basic physiologic functions and explore their relationship with adiposity and metabolic risk factors.

1.6 Justification of the Study

Obesity is the best described risk factor of MetS. The majority of epidemiologic and clinical studies to date have used indirect anthropometric measures such as BMI and body circumferences to study the association of body mass with MetS, with Bioelectrical Impedance Analysis (BIA) and skinfold being used much less frequently (Williams *et al*., 2000; Duvnjak *et al*., 2008; kjeldsen *et al*., 2008). There is lack of systematic data from studies comparing a wide range of different anthropometric measures in the prediction of MetS and the degree to which these alternate anthropometric indices predict MetS differently by gender and ethnicity has received very limited attention; This is an important issue, considering the ongoing debate regarding the appropriateness of recommended anthropometric measures in MetS definitions and various anthropometric cut-off points across genders and ethnicities. For example, varieties of anthropometric obesity indices are used in MetS definitions: NCEP-ATP III, (2001) uses central adiposity as a component of the definition, requiring subjects to have a WC > 102 cm for men

and > 88 cm for women; IDF, (2005) requires central obesity in its definition and uses ethnic specific WC cut-offs, unless overall obesity (BMI) is > 30 kg/m^2; while the WHO, (2006) uses either central obesity or overall obesity as a component of their definition, defining it as WHpR > 0.85 for women and > 0.90 for men, unless BMI > 30 kg/m^2, in which case obesity is assumed. Varieties of diabetes risk scores use central adiposity measures, such as WC (Wannamethee *et al*., 2005; Gami *et al*., 2007; Mushtaqur *et al*., 2008) while others use overall obesity measures, such as BMI (Isomaa *et al*., 2001; Lindsrom and Toumilehto, 2003; Stern *et al*., 2004). There is no consistency in the obesity requirements for any of these scores and definitions, thus, the utility of anthropometric measures in MetS prediction require additional research. Implications for public health strategy therefore will be framing of appropriate strategies to tackle obesity which should be firmly based on accurate assessments of both the scale of the problem and the populations most at risk, rather than on population-wide approaches coupled with sensationalist claims and unjustified use of terms such as 'epidemic' or 'exponential rise' (Andrea, 2000; Timothy *et al*., 2003; Meigs *et al*., 2008).

1.7 Statements of hypotheses

On the basis of previous research evidences, the following hypotheses were formulated for the purpose of this study:

i There are no significant relationships among anthropometric indices, REE, CI and RFA.

ii Central adiposity does not predict metabolic risk factors better than overall obesity.

1.8 Study delimitations

The study was delimited to healthy, normotensive, non-obese, volunteer male and female adults of Zaria, Northern Nigeria who were aged between 35 and 70

years, having no history of high blood pressure or any other related sickness. Also, they are not actively involved in any form of regular physical or sporting activities.

1.9 Study limitations

This study may have some limitations in data gathering like many cross-sectional studies. Although the researcher has been trained by a standardized protocol of blood pressure and anthropometric measurements and all the estimations were made in one occasion. Also while the results represent the population of non-obese adult male and female of Zaria; without the subjects who were using medication known to influence energy regulation, it is possible that among the study group there were subjects who were not medicated but might be using other life style factors to decrease blood pressure (like daily salt intake and diet moderation, etc.). They were included in the study because of the subjectivity to define some of the lifestyle factors.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Evidence acquisition

Literature search was carried out using the medical subject headings: Obesity, Insulin Resistance, The metabolic syndrome, Diabetes, Dyslipidemia, Nutrition, Resting energy expenditure, Sub-saharan and developing countries, from Medline and Pubmed data base; web sites of Obesity research, clinical practice, Nature.com and Google search engine. The search was restricted to studies in

human beings published between 1996 and 2011 including published documents on the subject matter from the WHO, FAO, ACE/AACE, IDF, EGIR, NCEP-ATPIII and NHLBI/AHA. Bibliographies of retrieved publications were also reviewed to further increase the yield of potential relevant articles.

2.2 Prologue

The health and wellbeing of the rapidly expanding adult population is becoming a major public concern as diseases and disabilities become more prevalent with advancing age. Much of the diseases and disabilities affecting the elderly today have been linked to age related changes in the body composition which in turn may largely be the result of sedentary lifestyle practices and poor nutrition. Consequently the measurement of body composition is becoming increasingly important in the assessment of the older adult population and in monitoring the effectiveness of exercise, diet and medical interventions (Andrea, 2000).

Excess body fat is associated with increased cardiovascular risk even in normotensive individuals, it is an important risk factor for premature mortality and has strong associations with all-cause mortality, CVD and diabetes, and is an important component of the insulin-resistance syndrome. More so, it has become clear that mainly visceral, rather than subcutanuous fat, is associated with cardiovascular risk (Timothy *et al*., 2003; Kotsis *et al*., 2010).

It is still unclear which measure of obesity is the most appropriate for risk stratification; In an attempt to redefined obesity, a correlation study of anthropometrics by Harald, (2005), showed that WHtR, and to some degree WC,

are better predictors of most cardiovascular risk conditions than other parameters, including BMI and WHpR.

The promulgation of BMI by the WHO as the most useful epidemiological measure of obesity is nevertheless a crude index that does not take into account the distribution of body fat, resulting in variability in different individuals and populations. WC alone may be relevant when assessing severely obese subjects whose hip measurements are difficult and unreliable and has been related to the prevalence of diabetes and cardiovascular risk factors. Furthermore, HC is an index of muscle mass and may reflect exercise status and insulin sensitivity. WHpR may prove also to be a more appropriate and universal indicator of risk for ethnically diverse populations (Harald, 2005; Harald *et al*., 2010). Although, other studies are contradictory, differences in study design might play a role in these diverging findings and other diseases might have affected the anthropometric measures, leading to potential bias (Kotsis *et al*., 2010).

2.3 Review of definitions of metabolic syndrome

Just as there are numerous synonyms for MetS that has evolved over time,

	WHO, 1998	WHO, 1999	EGIR, 1999	NCEP/ ATP III, 2001	NHLBI/ AHA, 2004	NHLBI/ AHA , 2005	IDF, 2005

there are also several definitions of MetS beginning with the WHO attempt in 1988 to standardize the criteria (Table 2.1). The WHO viewed insulin resistance as a required component for the diagnosis. In addition, two other risk factors must be present to meet the WHO definition of MetS. These other risk factors include antihypertensive medication and or high blood pressure. One disadvantage of the WHO criteria is that special testing of glucose beyond the routine clinical assessment may be necessary to diagnose MetS (Grundy *et al.*, 2004). The WHO also proposed BMI as a simple measure of obesity. Whereas BMI has great clinical utility, it should be remembered that calculation of a raised BMI does not automatically indicate a high degree of adiposity. This is because BMI does not distinguish between weight due to excess fat, and weight due to a large mass of muscle or bone. Gender and age also have to be considered when evaluating BMI measurements (James, 1998). In a comment by Balkau and Charles (1999) for the EGIR on the WHO criteria for defining MetS, the EGIR proposed their own definition of MetS, but only for non-diabetic individuals. The EGIR stated that there was no simple way at that time to measure insulin resistance in diabetic individuals but that fasting insulin values were a reliable means of determining insulin resistance in non-diabetic persons. The EGIR recommended that MetS include insulin resistance defined as the top 25% of fasting insulin values among non-diabetic individuals plus two or more of other criteria.

Table 2.1: Definitions of metabolic syndrome

Glucose	DM,IGT or IFG As per WHO criteria	DM,IGT or IFG As per WHO criteria	FPG ≥ 110 mg/dl	FPG ≥ 110mg/dl	FPG ≥ 100mg/dl	FPG ≥ 100mg/dl or treatment	FPG ≥ 100mg/dl or Previously diagnosed T2DM
Insulin Resistance	Glucose uptake below Lowest quartile	Glucose uptake below Lowest quartile	IR or Fasting Hyperinsulinemia (top 25%)	----	---	---	---
Blood Pressure	SBP ≥ 160, DBP ≥ 90 mmHg	SBP ≥140, DBP ≥ 90 mmHg	SBP≥140, DBP≥90 mmHg or treatment	SBP≥130 , DBP≥85 mmHg	SBP≥130, DBP≥85 mmHg or treatment	SBP≥130, DBP≥85 mmHg or treatment	SBP≥130, DBP≥85 mmHg or treatment
Dyslipidemia	TG≥150mg/dl and/or HDL□35 mg/dl in men. □39 mg/dl on women	TG≥150mg/dl and/or HDL□35 mg/dl in men. □39 mg/dl on women	TG□177mg/dl or HDL□39 mg/dl or treatment	----	----	----	----
Triglyceride	----	----	----	TG≥150 mg/dl	TG≥150 mg/dl	TG≥150 mg/dl	TG≥150 mg/dl
HDL	----	----	----	HDL □40 mg/dl in men, □50 mg/dl in women	HDL □40 mg/dl in men, □50 mg/dl in women	HDL □40 mg/dl in men, □50 mg/dl in women or treatment	HDLc□40 mg/dl in men, □50 mg/dl in women or treatment
Anthropometry	WHpR □0.90 in men, □0.85 in women and/or BMI□ 30kg/m^2	WHpR□0.90 in men, □0.85 in women and/or BMI□ 30kg/m^2	WC□94cm in men, □80cm in women	WC□102 cm in men, □88cm in women	WC□102cm in men, □88cm in women	WC≥102cm in men, 88cm in women; Asian Americans: ≥90cm in men, ≥80 in women	Central Obesity: Ethnic specific
Microalbuminuria	UAER≥20µg/min or ACR ≥20mg/g	UAER≥20µg/min or ACR ≥30mg/g	----	----	----	----	----
Definition	Glucose intolerance, IGT or DM and/or IR plus ≥2 other components	Glucose intolerance, IGT or DM and/or IR plus ≥2 other components	IR or Fasting hyperinsulinemia plus ≥2 other components	≥3 of 5 components	≥3 of 5 components	≥3 of 5 components	Central Obesity plus ≥2 of another 4 components
Includes people with Diabetes	Yes	Yes	No	Yes	Yes	Yes	Yes

The criteria of American Association of Clinical Endocrinologists are similar, but with some different cut-offs:

- High blood pressure (> =130 mm Hg systolic or > = 85 mm Hg diastolic) or taking blood pressure medication
- Plasma triglycerides > =150 mg/dL (> =1.7 mmol/L)

- HDL cholesterol < 40 mg/dL (< 0.9 mmol/L) in men or < 50 mg/dL (1.0 mmol/L) in women
- BMI greater than 25

Other risk factors considered by this definition include:

- Family history of Type 2 diabetes, high blood pressure, or heart disease.
- Ethnic groups with an increased incidence of Type 2 diabetes, high blood pressure, or heart disease.
- Polycystic ovary syndrome, sedentary lifestyle and advancing age (AACE, 2005).

In 2001, the NCEP/ATP III introduced the concept of MetS into its guidelines to reduce cardiovascular risk. The NCEP/ATP III criteria somewhat overlaps the WHO criteria and a diagnosis is based on having at least three out of five of the criteria. The intent was to include a group of risk factors accompanying T2DM (Reisin and Alpert, 2005). The placement of abdominal obesity as the first risk factor reflects its priority as a contributor to the pathogenesis of MetS, in particular, the development of insulin resistance. According to the NCEP/ATP III criteria, insulin resistance does not need to be demonstrated in order to diagnose MetS, increased fasting glucose suffices (Grundy, 2004). Even though the MetS does not encompass all cardiovascular risk factors, it provides a picture of a predominantly increasing risk for a growing portion of the population. The NCEP/ATP III guidelines were intended to be more user friendly and provided both clinicians and epidemiologists with simple measures that were applicable in both clinical and research settings (Zimmet and Alberti, 2005).

In 2005, the IDF proposed their own definition of MetS intended for global application in clinical practice and represents modifications to the WHO definition and NCEP/ATP III criteria. The IDF places more emphasis on abdominal obesity as the core feature of the syndrome as it is independently associated with each of the other

metabolic syndrome factors including insulin resistance. The IDF took an additional step to develop ethnic specific values for WC cut off points based on various sources of epidemiologic data.

The WHO definition includes those persons with high risk of developing diabetes as well as individuals diagnosed with T2DM. The obesity component can be measured by WHpR or BMI and includes microalbuminuria, which links the syndrome with risk for developing chronic kidney disease. The WHO definition has been criticized for including T2DM in the definition and not reserving the diagnosis of MetS for those who are at risk for developing diabetes. Additionally, the WHO definition includes impaired glucose tolerance measured by oral glucose tolerance test (OGTT) or 2-hour post glucose challenge as part of its criteria, tests considered by some to be less practical and an added cost with a small added value of predicting cardiovascular risk (Grundy *et al*., 2004).

The EGIR excludes diabetics, includes central obesity, dyslipidemia and hypertension as well as individuals treated for these two disorders. However, the determination of those with insulin resistance as being in the top 25% of insulin values for non-diabetics would be cumbersome and not practical in clinical practice. The NCEP/ATP III definition is easy to use and each component is justified by its prevalence, however, this definition does not exclude diabetics, fails to consider treated hypertension or dyslipidemia when defining its criteria and is criticized for the same reasons as the WHO definition (Grundy *et al*., 2004).

The IDF definition emphasizes the presence of abdominal obesity as a core factor in MetS and also provides pragmatic WC criteria for various ethnic groups. IDF also recognizes dyslipidemia or treatment for dyslipidemia, and hypertension or previous

diagnosis for hypertension as risk factors. However, IDF does not exclude diabetics from the definition (Hutley and Prins, 2005).

Resin and Alpert, (2005) have proposed a definition for MetS that attempts to bridge the differences among current definitions and unify the risk factors. They propose that abdominal obesity be the leading component based on its strong association with MetS and the increasing recognition of its biological activity. They also incorporate the IDF determined cut-off-points for various ethnic groups as part of their definition and recognize the risks associated with previous diagnoses of hypertension and dyslipidemia in addition to numerical cut-off values for these two conditions. Additionally, they recommend using the American Diabetes Association cut point for prediabetes as fasting glucose greater than 100 mg/dl since MetS is a condition that may predict the development of T2DM. They included the WHO microalbuminuria criteria in recognition that it is a component that links MetS with the risk of developing chronic kidney disease. In 2009, the IDF Task Force on Epidemiology and Prevention, NHLBI/ AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the study of obesity released a joint statement in an attempt to unify their differing criteria. The risk factors common to all definitions were: reduced HDL, elevated BP, glucose, TG levels and central obesity. The panel recommended that WC be considered a criterion rather than an obligatory component of MetS as previously defined by the IDF. A single set of cut-points (Table 2.2) should be used for all components except WC, where national or regional criteria may be used until further research helps to reach consensus (Hiserote *et al*., 2010).

Measure	Cut-point
Elevated Triglyceride	≥ 150 mg/dl
Reduced High density lipoprotein	≤ 40 mg/dl (male); ≤ 50 mg/dl (female)
Elevated Blood Pressure	≥ 130 mmHg and/or ≥ 85 mmHg
Elevated Fasting Glucose	≥ 100 mg/dl
Waist Circumference	Population and country-specific definition
Current recommended thresholds	

Table 2.2 Diagnostic criteria with ethnicity specific waist circumference

Population	Men	Women
USA and Canada	≥ 102cm	≥ 88cm
European	≥ 102cm	≥ 88cm
Asian	≥ 90cm	≥ 80cm
Middle east, Mediterranean	≥ 94cm	≥ 80cm
Sub-saharan African	≥ 94cm	≥ 80cm
Ethnic Central, South American	≥ 90cm	≥ 80cm
Other Populations		
Caucasian (WHO)	≥ 94cm	≥ 80cm
Europid (IDF)	≥ 94cm	≥ 80cm

(Hiserote *et al*., 2010)

2.4 Utility of definitions

Several researchers have studied the utility of the various definitions of MetS in the identification of various traits of the syndrome and comparing the prevalence of MetS using different definitions. For example, Ford and Giles, (2003) compared the prevalence of MetS using the NCEP/ATP III definition and the WHO definition in a nationally representative sample from the Third National Health and Nutrition Examination Survey (1988-1994). This study found substantial differences in prevalence within specific ethnic groups.

In a research study that compared three different definitions of MetS conducted by the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study Group (2005), disparities were also found in the prevalence of the syndrome depending on the definition used.

It is believed that insulin resistance is the pathological process that underlies the MetS and the associated cardiovascular risk factors and that identifying MetS is a reliable way to also identify persons with insulin resistance. However, several studies have brought into question the ability of the NCEP/ATP III criteria to identify insulin resistant individuals. In a study by Cheal *et al*. (2004) and Liao *et al*. (2004), they found that the NCEP/ATP III criteria for MetS have a low sensitivity for predicting insulin resistance, the poor sensitivity of the NCEP/ATP III criteria to identify insulin resistance means that there are a number of people that are insulin resistant but do not meet the criteria for MetS since it is desirable for screening tools to have a high sensitivity, the value of the NCEP/ATP III criteria as a screening method for those individuals at risk for cardiovascular disease and diabetes is questionable. It was also suggested that NCEP/ATP III criteria exhibit an even lower sensitivity for identifying insulin resistance in African Americans. This may indicate that the cluster of traits identified as MetS may be compositionally different in African Americans.

In a study to assess the capacity of MetS to identify impaired glucose tolerance, Meigs *et al*., (2008) found that MetS specifically defined as impaired fasting glucose, large waist size and elevated triglycerides was an efficient way to identify those with impaired glucose tolerance by oral glucose tolerance test. The purpose of the study was to determine if MetS could be used to screen for individuals likely to fail an oral glucose tolerance test and thus be eligible for T2DM prevention strategies.

In addition, some populations are predisposed to insulin resistance, MetS, and T2DM, with only moderate increases in WC (i.e., populations from South Asia, China, Japan, and other Asian countries). None of these phenotypic features or ethnic differences was included in the NCEP/ATP III diagnostic criteria; but if individuals with such characteristics have only moderate elevations of WC plus at least 2 NCEP/ATP III MetS features, then consideration should be given to managing them similarly to people with three NCEP/ATP III risk factors. The recent IDF definition of metabolic syndrome is similar in practice to the adopted modified NCEP/ATP III definition. Obvious differences are two-fold: IDF requires abdominal obesity as one factor and sets lower thresholds for abdominal obesity than used in the United States (Boyko *et al*., 2000; Scott *et al*., 2005).

A review of normative data published within the last 15 years demonstrated a significant increase in obesity as observed in children and adolescents study groups in many parts of the world, including sub-Saharan African. The WHO has agreed on an international standard for identifying overweight and obesity in adult populations using the BMI. However, increased risk of cardiovascular disease and T2DM has been found in individuals presenting with distribution of excess fat in the abdominal region and at present there is no standard measure of abdominal obesity that is widely accepted; Most studies pointed to WC, WHtR and WHpR as important determinants of metabolic risk factors in obese and nonobese participants, but majority agreed that WC is probably the best indicator (Dobbelstyn *et al*., 2001; Meigs *et al*., 2008; Ford *et al*., 2010).

2.5 Health risk scores and screening

The purpose of screening is to differentiate an asymptomatic individual at high risk from an individual at low risk for Diabetes Mellitus and CHD. Ideally, screening tests should be rapid, simple and safe and can identify patients at an early stage of the disease. The strategy therefore is by designing a questionnaire, to reduce the proportion of

undiagnosed cases through self-reported demographic, behavioural, medical information and anthropometric measurements and to assign a person to a higher or lower risk group which is less expensive than biochemical tests. The aim is to produce a simple risk score calculation that could be conveniently used in primary care and by non medical personnel, easy to assess without laboratory tests and clinical measurements not requiring special skills (Philip, 2005).

MetS represents a useful and simple clinical concept which allows for earlier detection of T2DM and CVD (Duvnjak *et al*., 2008). The Framingham Heart Study (FHS) is a prospective investigation of CVD in a cohort of adult men and women. Framingham Offspring Study (FOS) was also undertaken to expand upon knowledge of CVD, particularly in the area of familial clustering of the disease and its risk factors (Kannel *et al*., 1979). The MetS is not designed to be a competitor to the FRS, which calculates short-term risk over the course of 10 years. Rather, it is formulated to aid the global assessment of lifetime risk; advocates of this approach to the MetS include lipid specialists and cardiologists. First-line treatment for MetS is once again lifestyle intervention; with particular attention to dyslipidemia; the difference in approach has implications for the inclusion of new components in clinical MetS definitions. For example, some have criticized the predictive power of the MetS relative to the FRS and suggested the inclusion of age, sex, or smoking in the syndrome (stern *et al*., 2004). Although these risk factors would certainly improve the syndrome's predictive power, they certainly are not consequences of insulin resistance. Proponents of the pathophysiological perspective would thus reject their inclusion. However, these same scientists may argue for the inclusion of adiponectin, which is highly correlated with insulin resistance, yet is not as well studied as a predictor of cardiovascular events. On the other hand, a risk factor such as C-reactive protein appears both to offer improved

predictive power and to be a consequence of insulin resistance and thus is championed by scientists from both perspectives (Micheal and Tom, 2006).

Since CVD is more common than T2DM, It is not surprising that the FRS is a better predictor of CHD. Prediction criteria based on MetS alone do not include several well-established risk factors for CHD such as serum total cholesterol level and smoking status. However, MetS was a far stronger predictor of T2DM than of CHD, as observed in previous studies, and was a better predictor of T2DM than was FRS. This is likely due to the inclusion of established risk factors for diabetes such as WC, BMI and high blood glucose levels (short of diabetes), which are not included in the FRS (Wannamethee *et al*., 2005; Chamnan *et al*.,2010).

2.6 Epidemiology

The future effect of the demographic and epidemiologic transition in Africa on the prevalence of MetS is unknown and is a matter of concern. From sub-Saharan Africa, the available literature on MetS is limited mainly to small clinical studies in defined high-risk groups of patients, such as those with T2DM, CHD, and rheumatoid arthritis; moreover, synthesizing the results is limited not only by the small numbers but also the variable criteria used for defining MetS (Motala *et al*., 2009).

From the estimates of the IDF for Africa, in adults aged 20–79 years, the regional prevalence of diabetes is projected to increase from 3.1% in 2007 to 3.5% in 2025, with a corresponding 80% increase in numbers from 10.4 million to 18.7 million. In Sub-Saharan Africa, CVD have been projected to be the leading cause of morbidity and mortality by the year 2020 especially considering epidemic expansion (Rufus *et al*., 2008; WHO, 1997).

The prevalence of the MetS is increasing throughout the world. The Prevalence estimates of the MetS however, depend on the geographic location, definition that is used to determine inclusion as well as the composition (*e.g*., sex, age, race, and ethnicity) of the population being studied. Moreover, lifestyle habits and socioeconomic status appear to influence prevalence across sex, age, and race/ethnicity cohorts (Cornier *et al*., 2008).

In a prospective cohort study by Longo-Mbenza *et al*., (2010), it was shown that the risk of incident T2DM was higher for MetS defined by IDF with Europe cut-off of WC than NCEP-III criteria. Moreover, the IDF stated that the cut-off value for WC must be tested among specific ethnic groups because ethnic differences are likely to exist among populations in general and Asians in particular. Africans fulfilling IDF (Local Africa) criteria had the highest risk for developing T2DM and influenced incidence of T2DM from aging.

In many countries there is very little difference between rates of MetS among women and men, there are some countries that have noticeably greater number of women than men that meet the MetS criteria (Harzallah *et al*., 2006) whereas others report greater prevalence in men (Lorenzo *et al*., 2007; Cameron *et al*., 2007). Because sex-related differences in MetS prevalence are not universal, differences between women and men within specific countries may be due, for example, to differing socio-economic status, work-related activities, and cultural views on body fat (Cameron *et al*., 2007). Importantly, the development of the inclusion criteria for each of the definitions was based upon epidemiological data primarily from westernized countries. For example, a WC of more than 88 cm in women from the United States may be a reasonable threshold indicative of higher than normal central adiposity and therefore increased risk of CVD and T2DM, but that same waist threshold in an Arab or Asian nation might be

too high. Indeed, the addition of the ethnicity-specific WC criteria to the IDF, 2005, definition attempted to take this possibility into account, lowering the WC threshold from at least 88 cm to at least 80 cm for women of certain African, Arab, and Asian populations (Cornier *et al*., 2008).

The importance of MetS lies in its ability to predict more significant disease, primarily T2DM and CVD. In addition to T2DM and CVD there have also been studies suggesting that MetS can predict other diseases and outcomes, including chronic kidney disease, sexual dysfunction, hypogonadism, polycystic ovarian syndrome (PCOS), fatty liver and all-cause mortality (Stern *et al*., 2004; Ford *et al*., 2005). it should be noted however that MetS criteria does not include absolute CVD risk factors that are included in standardized risk assessment methods such as age, smoking, and family history; therefore, addressing the limitations and confusion that surrounds MetS, the IDF and AHA have jointly released a new guideline that attempts to unify the MetS criteria (Alberti *et al*., 2009). Other areas of recent research include establishing more evidence to better define the MetS criteria, with a particular focus in different subpopulation and ethnic groups. Also, with the incidence of childhood T2DM on the rise, there is a need to develop standardized criteria for MetS diagnosis in the paediatric population (Ford, 2008).

2.7 Obesity

The prevalence of overweight and obesity have increased dramatically over the past decades in most industrialized countries. More so, many developing countries have undergone economic transition from societies characterized by subsistence agriculture to increased urbanization and industrialization. This transition is typically accompanied by changes in food supply, type of physical activity, level of physical activity, sanitation and access to health care, followed by a relative increase in obesity and its attendant chronic diseases (Amy *et al*., 2002).

The National Institute of Health (NIH) and WHO guidelines defined individuals with BMI ≥25 as overweight and those with BMI ≥30 as obese; measures of abdominal fat distribution such as WC or WHpR are also encouraged. However, the WC has been criticized for not taking into account differences in body height, and the WHtR has been proposed. By these criteria, the prevalence of overweight and obesity are extremely high, approaching epidemic proportions (Wolk *et al*., 2003; Harald *et al*., 2007).

Obesity is characterized by alterations in metabolic functions that result from an increase in total body fat mass as well as an accumulation of visceral adipose tissue. These metabolic alterations are strongly associated with the development of important comorbid diseases like type 2 diabetes, hypertension and dyslipidaemia, as part of the metabolic syndrome. Obesity is now associated very prominently with poverty, and it is believed that abdominal obesity in adults, with its associated enhanced morbidity, occurs particularly in those who had low birth weights and early childhood stunting (Van der Merwe and Pepper, 2006). Amy *et al*., (2002) described obesity in their study as the result of an imbalance between energy intake and energy expenditure, but observed that research about these mechanisms has been hampered by the difficulty in making direct measurement of these quantities.

Frankenfield *et al*., (2001) defined obesity as a BMI of at least 30kg/m^2 or an amount of body fat of at least 25% of total body mass for men and at least 30% for women. They also observed in their study that significant number of people with a BMI below 30kg/m^2 were obese and thus misclassified by BMI. They then suggested that a measurement of body fat is a more appropriate way to assess obesity in people with a BMI, below 30kg/m$^{2.}$

Obesity represents the joint effect of metabolic alterations as well as lifestyle patterns that involve, among others, a high-calorie/high-sodium

intake and reduced physical activity. Also, various regulatory hormones, including insulin and leptin are increased among the obese, and abnormalities in the renin-angiotensin system have been described. A wide range of other metabolic abnormities including rates of ion transport and resting sympathetic tone, have also been reported in obese hypertension compared with the non-obese (Amy *et al*., 2004).

2.8 Etiology of obesity

Obesity is caused by a constellation of factors including excessive energy intake (food), insufficient energy output, genetic predisposition, low fat oxidation rate, low sympathetic activity, low plasma leptin level, environment favouring weight gain, psychologic stressors and lower socioeconomic status. The goal of obesity treatment is to exert a negative energy balance on the system by reducing energy input or increasing energy output, or both and a low REE for a given body mass is a risk factor for weight gain (Ethan and Nancy, 2000; Nina and Murray, 2005).

The balance of food intake and energy expenditure is a complex trait regulated by several peripheral signals such as leptin, ghrelin and insulin, which interact with neuronal circuits in the hypothalamus where a complex array of neuropeptides and neurotransmitters serve as controls of appetite, satiety, basal metabolic rate, food seeking behavior, mood and addictions. In this sense, serotonin and the serotonin transporter seem to play a key role in these vital functions (Silvia and Carlos, 2007).

2.9 Body composition and anthropometrics

Body composition refers to the quantification of the fat and non-fat components of the human body, which is used to provide information on disease risk. The sum of the non-fat (lean body mass) and the fat (fat body mass) components equals the total body weight of the individual (Frankenfield *et al*., 2001). Body composition analysis can be classified according to several models, depending on the purpose of analysis, methods and devices available. These include mainly atomic model,

molecular model, cellular model, tissue system model and whole body model. Most of these models are based on constant relationship between different components inside the model (Jukka, 2003).

The human body stores between 15-25% of its energy as fat (greater in women than men) this is available for the metabolism of endogenous fatty acid during starvation. The remaining FFM is composed of extracellular and intracellular water, the bony skeleton, glycogen and skeletal and visceral protein. Aside from body fat, energy reserves are also provided by intracellular glycogen and protein, which together with intracellular water constitute the body cell mass. Thus, in addition to the enzymes that support the normal metabolic machinery of the body, the Body cell mass provides reserve protein for energy production by gluconeogenesis during the stress response (Charles, 2001).

However, fat patterning is apparently a highly heritable trait, showing ethnic and racial variation. Considering the profoundness of the health problems associated with too much or too little body fat, it is no surprise that the assessment of body composition has become a widespread and meaningful evaluation used by physiologists, clinicians and sport trainers (Mueller and Wohlleb, 1981).

Measures of adiposity reported, vary from study to study as do their relationship to blood pressure. The most commonly reported adiposity measures include weight, WC, subscapular and triceps skinfold measures (as well as their sum), and indices such as BMI, WHpR and various skinfold ratios. A review of studies that examined the association of adiposity measures to blood pressure found the vast majority reported significant relationships (Gregory and Linda, 2001).

The accumulation of fat in visceral and posterior subcutaneous adipose tissue compartment is highly correlated with the metabolic abnormalities that contribute to increase risk of diabetes mellitus and cardiovascular disease. In men, WC is the anthropometric index that most uniformly predicts the distribution of adipose tissue among several fat compartments in the abdominal region and it predicts intraperitoneal adipose tissue mass better than BMI and predicted posterior subcutaneous adipose tissue better than WHpR (Chan *et al*., 2003).

WC is highly correlated with other indices of obesity, unrelated to height, an appropriate index of intra-abdominal fat mass and total body fat and may be a marker of both central and generalized obesity; it is easy to interpret and could be useful in health promotion as an alternative to BMI (Han *et al*., 1997; Lean *et al*., 2001; Lincoln *et al*.,

2002). WHpR has been found to be associated with blood pressure in some studies, but with DBP and not SBP in other studies (Gregory and Linda, 2001). Wang and Hoy (2004) concluded in their study that WC, BMI and HC are associated with cardiovascular outcome, independent of traditional risk factors. However, WC appears to be a better predictor of cardiovascular risk than other parameters.

HC does have a relation to health and disease, but in an inverse way, such that a relatively large HC is associated with lower risks of diabetes and coronary heart disease. This is probably because HC reflects muscle mass, which is reduced in T2DM and inactivity (Lean *et al*., 2001). It is useful, therefore, to be able to distinguish between those at increased risk as a result of abdominal fat deposition or 'android obesity' from those with the less serious 'gynoid' fat distribution, in which fat is more evenly and peripherally distributed around the body (WHO/FAO, 2003).

2.10 Obesity as a "driving force" in the prevalence of metabolic syndrome

The worldwide increase in the prevalence of obesity in the recent decades is startling and is likely a cause of the rising incidence of insulin resistance and the MetS as well as CVD and T2DM (Raeven, 1988; Eckel *et al*., 2005). Although not all overweight or obese individuals are metabolically unhealthy, the majority are insulin resistant (Ruderman *et al*., 1981). Indeed, many experts assert that the MetS would never have been put forth if the obesity epidemic had not become the public health concern that it is today. In particular, the combination of obesity, physical inactivity, and consumption of an atherogenic diet is believed to lead to insulin resistance (Amy *et al*., 2002; Grundy *et al*., 2005). In this state of insulin resistance, normoglycemia is initially maintained by a modest increase in β-cell mass and/or an increase in insulin secretory capacity (Weir and Bonner-Weir, 2007). Although the mechanism for this compensation is unclear, there is recent evidence supporting glucose signalling as a dominant force in this

process (Mittendorfer *et al*., 2009); It is also acknowledged that genetic factors may be involved (Silvia and Carlos, 2007) . However, the loss of insulin secretory capacity in the natural history of T2DM is likely an admixture of β-cell dysfunction in addition to reductions in β-cell mass. If the increasing β-cell function and/or mass is successful long-term as a compensatory mechanism to obesity and insulin resistance, T2DM could be prevented for an undetermined amount of time, despite hyperinsulinemia as a consequence (Cornier *et al*., 2008).

2.11 Patterns of body fat distribution as a risk factor for certain diseases:

The relationship between body mass and increased risk for various diseases is due to the excess fat and not body mass percent. Hence, early recognition and assessment of obesity is important (Hegde and Ahuja, 1996). Not only does excess weight increase the risk of these disorders, but the pattern of fat distribution is important in many of these conditions. Men are more likely to have abdominal or upper-body obesity, whereas women are more likely to have a gluteo-femoral or lower-body pattern of fat distribution. However, as women gain weight, they become more likely to develop abdominal and upper-body fat; this pattern of upper-body fat distribution is independently associated with higher risk of developing diabetes and cardiovascular diseases including hypertension. In a manner similar to their relationship with high BMI or total fat burden (Kunz *et al*., 2000; Xavier, 2002) The highest risk of myocardial infarction or early death has been found in men with high quantity of abdominal fat, which suggested that men, even lean, but with body fat concentrated in the abdomen are those with the highest risk to develop cardiovascular diseases (Francisco and Ines, 2005).

The metabolic risk factors consist of those factors that seemingly have a direct effect on atherosclerotic disease. Among these, as stated earlier, *atherogenic*

dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and ApoB, increased small LDL particles, and a reduced level of HDL. Other metabolic risk factors likewise appear individually to be atherogenic. Among these are *hypertension, elevated plasma glucose*, a *prothrombotic state*, and a *proinflammatory state*. Indeed, 3 of the metabolic risk factors—elevated ApoB containing lipoprotein, low HDL level, and hypertension are well established major risk factors. Each imparts increased risk even when only marginally abnormal, as often observed in the MetS (Grundy *et al*., 2005).

2.11.1 Hypertension

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. It is a very prominent feature of the MetS, present in up to 85% of patients. Insulin resistance and central obesity, recognized as the main factors involved in the pathophysiology of the MetS, contribute to elevated blood pressure, which further promotes vascular damage in cardiac, renal, and brain tissue (Sowers *et al*., 2004; Wang *et al*.,2004) 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 (Wang *et al*., 2004). Therapeutic approach to patients with hypertension and MetS includes modification of unhealthy lifestyle that aggravates the underlying pathology. This treatment includes sodium restriction, alcohol and calorie restriction, smoking cessation, weight reduction, and increased physical activity. Concerning pharmacological agents, emphasis is in particular placed on the RAAS blockade with angiotensin-converting enzyme inhibitors and

angiotensin II receptor blockers, and on central sympatholytic agents that exert additional beneficial effects (Duvnjak *et al*., 2008).

2.11.2 Cardiovascular disease

One of the primary observations regarding the clustering of metabolic disorders was the association of these features with increased CVD risk. The Atherosclerosis Risk in Communities (ARIC) study, which included more minorities found a relative risk of CHD of 1.5 and 2 in men and women with the MetS, respectively (McNeill *et al*., 2005). The presence of the MetS in patients with pre existing CHD is also associated with an increased risk for CVD events and mortality (Malik *et al*., 2004). Obese individuals and those with pre existing diabetes also have a doubling of CVD risk when the MetS is present (Alexander *et al*., 2003). The ability of the MetS to predict the incidence of CVD may differ according to how the MetS is defined. The 10-yr CVD risk in the Hoorn Study was assessed using different definitions of the MetS. The NCEP/ATPIII definition was associated with a 2-fold increase in CVD, whereas the risk was slightly less using the WHO, EGIR, and AACE definitions (Dekker *et al*., 2005). The NCEP/ATPIII definition was also associated with a 2-fold increased risk for CVD compared with the IDF definition when several American and European cohorts were examined (Assmann *et al*., 2007). The meta-analysis by Gami *et al*., 2007, found the WHO definition to be associated with slightly greater risk than the NCEP/ATP III definition. On the other hand, the NCEP, WHO, and IDF MetS definitions showed similar CVD risk in another Study (Lorenzo *et al*., 2007).

2.11.3 Type 2 diabetes mellitus (T2DM)

T2DM is a complex disease caused by both environmental and genetic factors. It is marked by chronically elevated blood glucose concentrations, which result from

defects in insulin production, insulin action, or a combination of both. Although insulin resistance is considered the hallmark of prediabetes, defects in insulin secretion are regarded as the key pathophysiological characteristic of T2DM. In fact, insulin resistance, hyperinsulinemia, dyslipidemia, and obesity precede the progression to T2DM in 75 to 85% of patients (Lebovitz, 1999).

The presence of the MetS increases the risk of T2DM (Grundy *et al*., 2004) and is highly predictive of new-onset T2DM (Laaksonen *et al*., 2002). The risk for incident T2DM is up to five times higher in individuals with the MetS compared with those without the syndrome and the ability of the MetS to predict the incidence of T2DM differs according to how the MetS is defined (Ford *et al*., 2008). The NCEP/ATP III and IDF definitions consider elevated fasting plasma glucose as an essential, but not required, criterion for defining the presence of MetS. The WHO definition, however, requires the presence of Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT). The effect of varying definitions of the MetS on the risk for T2DM may be significant because the risk for T2DM conferred by either IFG or IGT is higher than that conferred by other individual components of the syndrome (Bonora *et al*., 2004). The Insulin Resistance Atherosclerosis Study found that IDF and NCEP/ATPIII MetS definitions predicted incidence of diabetes as well as the WHO definition, despite the first two not requiring the use of an oral glucose tolerance test or a measure of insulin resistance (Hanley *et al*., 2005). The ability of the MetS to predict diabetes risk has also been compared with the Diabetes Predicting Model and the FRS. Stern *et al*., (2004), found that, the MetS was inferior to the diabetes predicting model for determining incidence of diabetes and the FRS, which was developed to

predict the risk of CHD, was inferior to the MetS for predicting incidence of diabetes in men.

The presence of the MetS in women with gestational diabetes mellitus (GDM) substantially increases the risk of developing T2DM. GDM alone significantly increases a woman's risk for subsequently developing T2DM (Jovanovic, 2001). Although there is paucity of data on the prevalence of diabetes in Nigeria and other African countries, available data suggest that diabetes is emerging as a major health problem in Africa, including Nigeria (Nyenwe *et al*., 2003). In Nigeria the prevalence ranges from 1.6% to 5%, depending on the locality, and up to 10% for the adult Population (Fadeniyi *et al*., 2007).

2.12 Associated conditions

There are a number of conditions associated with the MetS and some of these conditions are directly associated with the underlying excess adiposity and insulin resistance associated with the MetS.

2.12.1 Nonalcoholic fatty liver disease (NAFLD)

NAFLD includes a range of pathological features from mild steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis. A presumptive diagnosis of NAFLD can be made in patients with elevated liver enzymes and/or fatty liver by imaging in the absence of other causes of liver disease; although a definitive diagnosis can only be made by liver biopsy (Clark and Diehl, 2003). The prevalence of NAFLD is high in children with obesity and insulin resistance and its presence is a strong predictor of the MetS (Kim *et al*., 2004). In patients with the MetS, liver fat content is significantly increased up to 4-fold higher than those without the MetS and the incidence of NAFLD has shown to be increased 4-fold in men and 11-fold in women with the MetS (Hamaguchi *et al*., 2005). Fat deposition in the liver has been shown to be primarily due to an increased influx of fatty acids to the liver, most likely as a result of the increased lipolysis associated with obesity and insulin resistance and as a result of increased hepatic lipogenesis (Donnelly *et al*., 2005).

2.12.2 Polycystic ovarian syndrome (PCOS)

PCOS is a clinical syndrome that is associated with anovulation, androgen excess, and insulin resistance. Not only do women with PCOS suffer from problems with fertility and clinical stigmata of androgen excess, but they also suffer from consequences of insulin resistance, such as a significant risk for the development of T2DM and CVD risk factors (Cho and Atkin, 2007). There is therefore, significant overlap between PCOS and the MetS. The pathophysiology of the PCOS, like the MetS, is also unclear and highly debated but the ovary, hypothalamic-pituitary axis, and insulin resistance are all thought to have a role in this condition (Legro, 2007). The insulin resistance and obesity that are frequently found in women with PCOS have been implicated in significant risk for CVD and metabolic disorders. Greater than two thirds of women with PCOS have some degree of glucose intolerance and are therefore at high risk for developing diabetes if they do not already have it. Although it is not clear whether women with PCOS have a greater risk for CVD events, they certainly have evidence of greater risk for subclinical CVD (Talbott *et al*., 2000).

2.12.3 Obstructive sleep apnea (OSA)

OSA is a potentially serious consequence of obesity and is associated with increasing BMI. There is also an association between OSA and insulin resistance (Tasali and Van Cauter, 2002), increased inflammation (Peled *et al*., 2007) and reduced adiponectin concentrations (Zhang *et al*., 2006). In addition, disordered sleep in general is associated with weight gain and insulin resistance and it has been suggested that OSA should be considered as a manifestation of the MetS (Vgontzas *et al*., 2005).

2.12.4 Hypogonadism

As women with PCOS are at greater risk for the MetS, there is also a relationship between the MetS and male gonadal and erectile dysfunction. Men with the MetS

appear to have a greater prevalence of hypogonadism. Conversely, hypogonadism is a risk factor for the development of the MetS and T2DM and features of the MetS improve with testosterone replacement (Saad *et al*., 2008). The MetS has also been shown to be independently associated with a greater prevalence of erectile dysfunction (Heidler *et al*., 2007).

2.12.5 Lipodystrophy

Lipodystrophies are inherited or acquired disorders characterized by the loss of selective adipose tissue depots. These patients, especially those with partial and generalized forms of lipodystrophy, generally have severe insulin resistance and often share the features of the MetS, putting these individuals at risk for T2DM, dyslipidemia, NAFLD, and CVD. Highly active antiviral therapy for the treatment of HIV-infected patients has been associated with the development of severe metabolic disturbances and "acquired" lipodystrophy (Falasca *et al*., 2007).

2.12.6 Microvascular disease

The MetS has also been shown to be associated with an increased risk of chronic kidney disease (Rashidi *et al*., 2007) retinopathy (DPPRG, 2007) and microalbuminuria (Klausen *et al*., 2007). Moreover, the MetS has been found to be associated with increased risk for neuropathy (Gordon and Robinson, 2006).

2.13 Pathophysiology of metabolic syndrome

It has been proposed that metabolic complications associated with central obesity, are due to increased body fat mass and by virtue of the enhanced lipolytic activity of abdominal adipose tissue, lead to higher plasma Free Fatty Acid (FFA)

concentrations, which in turn, decrease both hepatic removal of insulin and insulin stimulated glucose uptake by peripheral tissues. The consequences of abdominal obesity are therefore, elevations in circulating FFA and insulin levels as well as insulin resistance. In addition, the accumulation of intracellular fatty acid metabolites stimulates the production of inflammatory proteins, which can also contribute to insulin resistance and atherosclerosis (Golay *et al*., 1990; Mittendorfer *et al*., 2009).

Physiologic increase in plasma FFA levels cause insulin resistance in both diabetic and non-diabetic subjects by producing several metabolic defects: (1) FFA inhibit insulin-stimulated glucose uptake at the level of glucose transport or phosphorylation (or both), (2) FFA inhibit insulin-stimulated glycogen synthesis and (3) FFA inhibit insulin-stimulated glucose oxidation. This last-mentioned defect probably does not contribute to insulin resistance (Boden, 2001). The stimulatory action of FFA on β-cells enables obese individuals who do not have a genetic predisposition to develop T2DM to compensate for their FFA-potentiated insulin resistance with an increase in FFA-mediated insulin secretion (Nina and Murray, 2005). In contrast, subjects who are genetically predisposed to develop T2DM may be unable to secrete sufficient amounts of insulin to compensate for their FFA-induced insulin resistance. This situation will lead to an increase in blood glucose concentration and eventually to T2DM (Campos *et al*., 2010).

Under normal conditions, insulin inhibits adipose tissue lipolysis; however, in the setting of insulin resistance, insulin is unable to properly suppress lipolysis, resulting in relatively more FFA being liberated into the plasma. Although this process is mediated by hormone-sensitive lipase (HSL) evidence points to adipose triglyceride lipase as

playing an additional role which collectively account for 95% of triglyceride hydrolysis. In obese subjects, insulin resistance and hyperinsulinemia are strongly associated with decreased adipose triglyceride lipase and HSL mRNA and protein expression, an effect found to be independent of fat mass (Cornier *et al*., 2008).

Obesity is closely associated with (peripheral as well as hepatic) insulin resistance and with a low grade state of inflammation characterized by elevation of pro-inflammatory cytokines in blood and tissues. Both insulin and inflammation, contribute to the development of T2DM, hypertension, atherogenic dyslipidaemias and disorders of blood coagulation and fibrinolysis. All these disorders are independent risk factors for atherosclerotic vascular disease (ASVD) such as heart attacks, strokes and peripheral arterial disease (Boden, 2001; Boden, 2008).

The associations of obesity and visceral adiposity with elevated cytokine levels suggest the importance of reducing obesity and visceral adiposity to prevent elevations in cytokine levels. Inflammation is thought to play a key role in the pathophysiology of cardiovascular disease as well as in diabetes mellitus. Three of the most important pro-inflammatory cytokines are serum C-reactive protein (CRP), Tumor necrosis factor (TNFα), and interleukin (IL)-6, all of which have been implicated in atherogenesis. CRP has been shown to be an important marker of vascular inflammation and a predictor of atherosclerosis; TNFα activates the transcription factor nuclear factor-kb, which organizes inflammatory changes in vascular tissue and IL-6 has intrinsic pro-inflammatory activity and increases the levels of TNFα. Moreover, the relationship between adiposity and CRP has been reported to differ according to ethnic group (Xavier, 2002; Park *et al*., 2005). Other studies suggest that perivascular adipose tissue may be a source of inflammatory cytokines or adipokines, contributing to a strong

association between obesity and vascular diseases (Ruige *et al*., 2005; Police *et al*., 2009).

The possible role of psychological stress and the major stress-related hormones as etiologic factors in the pathogenesis of these metabolic diseases, as well as atherosclerosis, has been suggested, repeated episodes of acute or chronic psychological stress could induce an acute phase response (APR) and subsequently a chronic inflammatory process such as atherosclerosis. Such stress has been extended to include a chronic inflammatory process(s), characterized by the presence of certain cytokines and acute phase reactants, which is associated with certain metabolic diseases. The fact that stress can activate an APR, which is part of the innate immune inflammatory response, is evidence that the inflammatory response is contained within the stress response and it induces an inflammatory response (Black, 2003).

Evidence also showed that glucocorticoid secretion is associated with this complex phenotype. Continuously changing and sometimes threatening external environment may, when the challenge exceeds a threshold, activate central pathways that stimulate the adrenals to release glucocorticoids which have also been suggested to mediate a pathogenetic role in the MetS (Rosmond, 2005).

2.14 Genetics of obesity and metabolic syndrome:

Obesity results from an interaction of both genetic and environmental factors but their relative contributions to the covariation between MetS and anthropometrics has not been widely studied. A world-wide trend towards positive energy balance, consequent on reduced energy expenditure through lowering of levels of physical work and on increased dietary caloric intake, is expressed in individuals as weight gain to greater or lesser extents depending on genetic predisposition (Gregory and Linda, 2001; Nina and Murray, 2005).

Although insulin resistance has been considered as a common denominator for the different components of metabolic syndrome, there is still debate as to whether it is pathogenically involved in all of the different components of the syndrome. Clustering of the syndrome in families suggests a genetic component. It is plausible that so-called thrifty genes, which have ensured optimal storage of energy during periods of fasting, could contribute to the phenotype of the metabolic syndrome. Common variants in a number of candidate genes influencing fat and glucose metabolism can probably, together with environmental triggers, increase susceptibility to the syndrome. Among these, the genes for beta 3-adrenergic receptor, hormone-sensitive lipase, lipoprotein lipase, skeletal muscle glycogen synthase, etc. appear to increase the risk of the MetS (Groop, 2000; Yamada *et al*., 2008).

The AHA and the NHLBI have issued a scientific statement in 2003, on clinical diagnostic guidelines for metabolic syndrome, providing an opportunity to evaluate this condition using standard criteria that includes family history of T2DM, high blood pressure and heart disease.

Silvia and Carlos, (2007), described MetS as a spectrum of diseases ranging from rare monogenic forms caused by highly penetrant and infrequent mutations in a few genes to more-prevalent polygenic and multifactorial forms, where environmental factors, personal habits and genetic factors conferring resistance or susceptibility to the disease can play an important role. They also suggested that as low birth weight is a strong predictor of MetS in the adult life, other factors participating in the metabolic reprogramming during fetal development, such as epigenetic factors (i.e. DNA methylation and histone acetylation) are attractive new avenues for further research.

Twin and familial aggregation studies have revealed a substantial genetic component for the individual abnormalities that constitute MetS (Yamada *et al*., 2008). Traditional genome-scanning approaches by searching the entire human genome to detect chromosomal regions linked to MetS phenotypes have found several regions linked to hypertension and obesity related phenotypes. In addition, Quantitative Trait Locus (QTL) in Chromosomes 1, 2, 3, 6, 7, 9, 10, and 19 were linked to several metabolic syndrome-related traits, such as weight, WC, leptin, insulin, or insulin resistance in different ethnic populations (Silvia and Carlos, 2007; Yamada *et al*., 2008).

Along with Single Nucleotide Polymorphysm (SNP), the Human Genome Project has also identified a range of other DNA sequence variations, including insertions and deletions of nucleotides and translocations of various segments of a chromosome; Some of these deletions, insertions and duplications have been named collectively as Copy Number Variants (CNVs) and represent a considerable source of human genetic diversity (Silvia and Carlos, 2007)

MetS has been established to be a complex condition of multi factorial etiology. The relative influence of genetic factors is expressed as heritability, which is the proportion of total phenotypic variance in a given trait that is attributable to genetic variation. A number of studies have estimated the heritability of components of MetS but these estimates vary widely. Plasma lipid and lipoprotein concentrations were found to be highly heritable and WC, insulin resistance, plasma glucose and insulin, and blood pressure were found to be at least moderately heritable. WC and plasma glucose were primarily influenced by genetic and environmental factors specific to each phenotype, indicating that these two MetS components may be affected by a variety of

influences in addition to insulin resistance, a proposed underlying MetS pathology. Combined, these suggest that genes play a dominant role in the development of MetS components and that there are common genetic and environmental influences that lead to the development of MetS (Sonya *et al*., 2009).

Although the definition of the phenotype is imprecise, MetS includes a constellation of complex diseases and the genetics of each disease is complex in itself and varies in spectrum from monogenic and syndromic models of inheritance, usually rare, to the most common polygenic and multifactorial forms. In addition, human studies using the candidate-gene approach which has been the traditional approach for identifying the genes involved in the MetS indicate that common genetic variants of several genes are associated with the development of MetS. The candidate genes can be identified according to biological function and/or linkage studies, and association tests for significant differences in their allele frequencies between a patient group and a control population (Roche *et al*., 2005). Genome-wide scans have also provided several chromosomal regions associated with some of the components of MetS. Through comparative genomics, animal models can generate a map for candidate loci in humans and a promising approach is offered by bio-informatic tools for gene prioritization. (The hypothesis of prioritization is that candidate test genes are ranked based on their similarity with a set of known training genes. The similarity measure is in turn calculated by integrating the functional process, gene ontology pathway and sequence similarity information obtained from diverse data source). Moreso, the involvement of genes in the development of MetS whose products are already the targets for approved drugs suggests new avenues for pharmacological treatment (Silvia and Carlos, 2007; Lee-Ming, 2008). However, as yet, only a small fraction of the genetic component is known. Systems-based approaches that integrate genomic, molecular and physiological

data are complementing traditional genetic and biochemical approaches to more fully address the complexity of MetS (Aldons *et al*., 2008).

There is an indication that common genetic variants are associated with the development of this syndrome, although the associations are quite weak and replication of findings has been poor. As with most complex traits, it is premature to propose molecular genetic testing for diagnosis, treatment or both. Unresolved issues include the roles of gene-environment interactions, ethnicity, and sex (Pollex and Hegele, 2006). Given the number of metabolic pathways involved in the MetS, it is immediately apparent that the number of potential candidate genes is tremendous. Overall, there has not been a high extent of success from candidate-gene studies in terms of defining the genetic determinants of the MetS (Roche *et al*., 2005).

Despite research into possible genetic influences for MetS, no consistently reproducible genetic markers have been obtained, partially due to lack of agreement on the definition of the phenotype. Because phenotypic precision is essential for genomic interrogation, the evolving discipline of clinical phenomics, which uses objective and systematic acquisition of phenotypic data (i.e., "deep phenotyping") may help evaluate the genetic influences of MetS (Tisha and Hegele, 2008; Tisha *et al*., 2008). Each of body size, physique, body composition and biological maturation share similarities in genetic influences. Although human stature is mainly determined by genetics, it is also influenced by the environment i.e. maturation. Segmental body length and bone-related mineral mass show a high degree of genetic control. Body weight, skin folds and body circumference show a lesser degree of genetic inheritance due primarily to changes occurring in the environment such as nutritional intake and variation in physical activity (Mueller and Wohlleb, 1981).

2.15 Resting energy expenditure (REE):

Energy expenditure is a fundamental property of living humans and other animals when evaluated over 24 hours; total energy expenditure (TEE) can be described as the sum of five components: REE, physical activity- induced energy expenditure, thermic effect of food, facultative thermogenesis and anabolism/growth. All living organisms expend energy for the maintenance of cellular homeostasis (Zimian *et al*., 2000; Zimian *et al*., 2001; Dohm and Fushiki, 2002). The thermogenic response to food is an increase in REE after ingestion of food (Lopez *et al*., 2000).

The REE is the energy necessary to run the basic process of the body such as the energy to maintain electrochemical gradients, generate heat and synthesize proteins required by body cell to maintain post absorptive homeostatic functions in resting subjects. It is used routinely by clinicians for estimation of energy requirements in patients care as well as by governmental agencies and health organizations in defining population energy requirements. REE is the energy required by an individual to stay alive with no activity, therefore the real energy expenditure is always significantly higher than REE. It accounts for approximately 60% to 70% of the total energy expenditure (Wong *et al*., 1996; Zimian *et al*., 2001; Dohm and Fushiki, 2002; Gonzalez *et al*., 2006). A minor change in REE could lead to a significant energy imbalance and huge change of body weight over a long period and it decreases with muscle wasting not losing fat alone (Huang *et al*., 2004). For an average adult, the REE is fairly close to 1kcal/kg body weight/hr or about 1,680 kcal/ day for an individual weighing 70kg (Dohm and Fushiki, 2002).

REE is a modestly heritable trait and yet virtually nothing is known about the genetic factors that might influence the familial patterns. Wu *et al*., (2004), observed in their study that after adjustment for body size; approximately 11% of the observed variance in REE is due to familial aggregation, suggesting that genetic polymorphisms might influence the level of metabolic activity at rest. One of the primary aims of energy metabolism research is to understand the inherent relations between REE and body composition.

Aging is associated with a decline in whole body REE at a rate of 1-2% per decade after the second decade of life. And the age-related lowering of REE occurs when body weight remains stable over the same time period. The changes in body composition could partly explain the age-related decrease in REE, since FFM is the main contributor to REE (Illner *et al*., 2000; Zimian *et al*., 2005; Gonzalez *et al*., 2006). Poehlman *et al*., (1993) also believed that the age - related decline in the REE is primarily

associated with loss of FFM and the loss is partially related to a decrement in vo_2 max and nutritional factors. Anja *et al*., (2003), agreed that the age-related decline of REE in healthy subjects is not caused by a decreasing organ metabolic rate but is fully accounted for by a reduction in FFM and proportional changes in its metabolically active components. However, change in body composition cannot entirely explain the age-related decrease in REE. Aging has been shown to be associated with a decrease in β-adrenergically stimulated thermogenesis, and sympathetic nervous system activity is a determinant of facultative thermogenesis. Metabolic active organs like heart, liver, kidney or brain and of metabolic less active tissues like muscle, bone or skin could also be responsible for the decline in REE during aging (Gonzalez *et al*., 2006).

REE varies among individuals. Body size, body composition, age, sex, hormones, organ sizes and genetic factors explain most of the variability. It has been suspected that the relative proportion of high and low metabolically active tissues independent of differences in FFM, significantly add to the residual variance in REE (Illner *et al*., 2000; Wu *et al*., 2004). Other factors like puberty (Sun *et al*., 2001), antipsychotic medications (Sharpe *et al*., 2005), menarche (Spadano *et al*., 2004), ethnicity and race (Tershakovec *et al*., 2002), Diabetes (Martins *et al*., 2004), work of breathing, sleep and starvation (Tisha and Bradley, 2003) have also been investigated and they showed significant correlations.

Amy *et al*., (2006), found a positive association between REE and weight gain in a lean adult Nigerian population and noted that the increased REE in this population was the result, rather than cause of weight gain. Amy *et al*., (2004), also suggested that some environmental factors like changes in body temperature in the tropics, increase muscle relaxation induced by the climate, temperature-induced changes to thyroid activity and dietary differences with particular references to protein intake, physiological adaptation to chronic energy restriction or to racial/genetical differences, regulate some components of REE. Kunz *et al*., (2000), also reported the influence of leptin, sympathetic activities, aerobic activity and resistance training, as well as dietary composition; But FFM remains the principal determinant of REE across all age ranges (Cunningham, 1991).

Afghani *et al*., (2005), noted in their study that African- American men and women tend to be more overweight and to have lower REE compared with Caucasian men and women of comparable weight, height, age and FFM. Jones *et al*., (2004), said this observation in those women might be a predisposing risk factor for long term weight gain and obesity. However, Gallagher *et al*., (2006), reported that racial differences in REE were

reduced by >50% and were no longer significant when the mass of specific high-metabolic-rate organ was considered. Differences in FFM composition may be responsible for the reported REE differences.

REE has been shown to be significantly higher in adult men than in women by an average 209kj/day irrespective of differences in body composition and aerobic fitness. It was suggested that the greater thermogenic effect of androgens compared with estrogens might also contribute to the sex difference (Jo *et al*., 2004).

Creatine kinase activity was reported by Brewster and Van Montfrans, (2004), to be a determinant of REE, and high activities of this enzyme are particularly described in black people. Creatine kinase increases the cell's capacity to function under high demands. Thus greater creatine kinase activity in cardiovascular muscle and other tissue with high energy demands could increase cardiovascular contractile reserve, enhance tropic responses and increase renal tubular activity to retain salt; and this could facilitate the development of arterial hypertension.

Sleeping metabolic rate (SMR) was also studied by Zhang *et al*., (2002), they concluded that the rate of decline in metabolic rate during sleep is directly related to body weight, BMI and FFM. Average SMR tends to be lower than REE in obese subjects and higher than REE in non- obese subjects.

The gold standard for measurement of REE is calorimentry (direct or indirect) (Tisha and Badley, 2003). The equipment required to measure respiratory exchange make this procedure time consuming, costly and often unavailable (McDuffie *et al*., 2004). It requires extensive subject cooperation as well as accurate and precise flow and concentration measurement, using sophisticated flow and gas analyzers (Wong *et al*., 1996). Cunningham, (1998), also supported the impractical direct measurement of REE and characterized two perspectives from which a prediction of REE could be approached, namely the clinical and physiologic. The corresponding variables of interest are weight, height and sex for the clinical and FFM for the physiologic perspective.

A number of recognized prediction equations to calculate REE have been developed in clinical practice. It is used to calculate REE of individuals (healthy and non- obese). They are estimates of how many calories an individual will burn if he/she were to do nothing but rest for 24hrs (Laleh *et al*., 2006). These can provide the basis for prescribing an individualized energy intake to attain a desired level of energy deficit and serve as the basis from which daily energy needs are established for the prescription of the diabetic meal plan with computation of macronutrients for weight

control (Huang *et al*., 2004; Gougeon *et al*., 2002). These prediction formulas were originally important in diagnosing thyroid disease, although today their primary role is in estimating subject's energy requirements (Helene *et al*., 2004).

The use of prediction equations have been recommended for calculating energy expenditure (Coss-Bu *et al*., 1998). but the most frequent used formula for predicted energy expenditure are the Harris – Benedict equations which was established in 1919 and took into account gender, age, height and weight (Olympic Games, 2004; Bauer *et al*., 2004).

The comparative studies for accuracy of some of the prediction equations by Wong *et al*., (1996); Tverskaya *et al*., (1998); Cunningham (1998); Amy *et al*., (2000); Martin *et al*., (2004); Gonzalez *et al*., (2006) and Carla *et al*., (2010), showed that the Harris – Benedict equation is the most accurate of all the equations studied, considering the clinical variables, i.e. Age, Sex, Weight and Height. Livinston and Ingrid, (2005), also said that the prediction equations of REE is highly dependent on the methodology employed to compare the various formulas, and supported Harris- Benedict equations to yield reasonable REE predictions for normal sized and obese subjects.

Harris-Benedict equation is correct 80-90% of the time in healthy and normal volunteers. In obese volunteers, the equation predicts resting energy expenditure correctly only 40- 64% of the time. In critically ill patients the equation is correct only 50% of the time. The total energy expenditure of a hospitalized patient can however be calculated by multiplying the resting energy expenditure with the injury or activity factor and the thermic effect (if they are digesting and absorbing food). The activity factor for such patient is simplified to a factor of 1.2 if the patient is confined to bed, or 1.3 if allowed out of bed (Tisha and Bradley, 2003).

2.15.1 Cardiometabolic risks and resting energy expenditure

Obesity-related cardiometabolic risk factors contribute to interindividual variation in REE, with hypertension, insulin resistance and T2DM; been associated with higher REE. REE was moderately heritable, independent of body composition, sex, age, and thyroid function. There were also significant associations of REE with systolic and diastolic blood pressure, FPG, insulin concentrations, and HOMA-IR. Similarly, increase REE is associated with hyperglycemia and glycemic intolerance and positively correlated with

fasting insulin concentrations in non diabetics (Anja *et al*., 2008). Evidence suggests that a low REE may be due to genetic variation involving sympathetic activity, thyroid activity, β-receptor sensitivity, sodium, potassium and adenosine triphosphatase (Na^+, K^+-ATPase) enzyme activity (Ethan and Nancy, 2000; Nina and Murray, 2005).

The etiology of a greater REE in diabetics has been suggested to be the result of abnormal protein metabolism and high insulin resistance. However, the exact mechanism still remains unclear (Huang *et al*., 2004). Studies have also shown linear relationships among T2DM patients, REE, rates of hepatic glucose production and lipid oxidation (franssilla-Kallunki and Groop, 1992; Gougeon *et al*., 2002), urinary albumin loss and anaemia accompanied by diabetic nephropathy (Kiyoko *et al*., 2004).

Ruige *et al*., (2005), reported in their study, a significant link between serum adiponectin concentrations and low REE, It was speculated that protection by adiponectin against obesity-related disorders is especially important for subjects with low REE. Again, subjects with low REE are at increased risk of developing these disorders because larger portion of their daily food intake is stored as fat, in the situation of similar calorie intake. This finding, together with the well-known inverse relation between adiponectin and insulin resistance, fit in the same framework and confirm the important interplay between adiponectin and the pathogenesis of the MetS.

In theory, higher energy expenditure should promote a negative energy balance and thereby weight loss in obese T2DM patients. Together with urinary glucose, this may serve as a defence mechanism against further weight gain. However, T2DM patients are often more resistant than matched nondiabetic individuals to losing weight on weight management programs, independent of whether the intervention is conventional or pharmaceutical assisted (Christain *et al*., 2004).

In contrast, acquired insulin resistance as a consequence of obesity may lead to a higher REE by increasing protein turnover, futile cycling, gluconeogenesis, and the activity of the sympathetic nervous system, as a result an increased REE at an impaired glucose tolerance is a metabolic consequence of obesity that is directed against further weight gain (Anja *et al*., 2008).

2.16 Treatment of obesity and metabolic syndrome

2.16.1 Diet, Exercise and Lifestyle changes

Proper diet, exercise and behavior modification are the foundation of treating obesity. The American Dietetic Association (ADA, 2008) has collected evidence demonstrating that a low-fat diet with 12g to 33g per day of fiber from whole foods or up to 42.5g per day from supplements can help to reduce blood pressure, correct dyslipidemia, reduce indicators of chronic inflammation, and reduce weight. A low-fat/high-fiber diet has also been shown to reduce the risk of developing coronary artery disease. Pharmacologic treatment of obesity should be considered in patients who have comorbid conditions and in whom diet and exercise alone have proved insufficient especially due to lack of discipline. Patients with no comorbid conditions and a BMI of 25.0 to 29.9 should not receive medication for obesity. Patients with a BMI of 30 or greater with no complications and those with a BMI of 27.0 to 29.9 and two comorbid conditions may be candidates for pharmacologic therapy (Nina and Murray, 2005).

2.16.2 Medications

Many different agents are available for the medical management of obesity. They can be classified by their mechanism of action: (a) Drugs that reduce energy intake, examples of these anorectic drugs are noradrenergic and serotonergic agents. (b) Drugs that increase energy expenditure and Nutrient-Partitioning agents e.g. Orlistat (Xenical) is a weight loss medication of novel mechanism. A lipase inhibitor, it acts in the gastrointestinal tract to decrease fat absorption. Although some of these medications show promise, no long-term outcome studies have assessed their effect on overall morbidity and mortality. *Other Drugs:* Leptin, a hormone produced by fat cells, controls food intake and energy expenditure. In obese persons who are losing weight without medications, a decrease in weight is associated with a decrease in circulating levels of leptin, suggesting its role in weight homeostasis (Ethan and Nancy, 2000; Silvia and Carlos, 2007)

2.16.3 Surgical intervention

When medical management and lifestyle changes prove insufficient, surgical intervention may be considered. Vertical banded gastroplasty and Roux-en-Y gastric bypass can result in dramatic weight loss of up to 25 percent (Bloom *et al*., 2008).

Therapeutic options for managing the MetS must be prefaced with the understanding that there are no randomized controlled trials published to help guide specific recommendations for managing the MetS. In addition, because it is unclear whether there is a unifying pathophysiological mechanism resulting in the MetS, it is unclear whether the MetS can be treated in and of itself. Therefore therapeutic attempt should centre on treating the individual components of the MetS, with the overall goals of reducing the risk for or preventing CVD and T2DM (Grundy *et al*., 2005). If the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for

risk factors may be required. It is well established that weight loss is beneficial for treating all of the components of the MetS, including excessive adiposity, dyslipidemia, hypertension, insulin resistance, and hyperglycemia (Pasanisi *et al*., 2001). Regular exercise is the first step in treating the MetS because it increases glucose metabolism by muscle and helps in weight reduction (Opie, 2007), But The magnitude of weight loss need not be drastic; the Finnish Diabetes Prevention Study showed that lifestyle intervention with modest weight loss significantly reduced the prevalence of the MetS compared with the control group (Ilanne-Parikka *et al*., 2008). Recommended principles of management for each of the metabolic risk factors are also considered in the appendix. Nevertheless, concentrating therapeutic efforts on treating the excess adiposity and insulin resistance associated with the MetS may provide the most overall success in attaining these goals (Cornier *et al*., 2008).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Research design

This study is a correlational and quantitative research that cross-sectionally examine the covariation among some physiological and anthropometric indices and assess their predictability as regards to metabolic risk indicators.

3.2 Sampling technique

The subjects for this study were from Zaria, northern Nigeria. The stratified random sampling technique was used to stratify the subjects by wards, and subjects were subsequently constituted by using purposive sampling technique. These were adopted because only subjects who satisfied the predetermined exclusion and inclusion criteria of being healthy, non-obese and aged 35 - 70 years were selected for the research. The criteria for BMI (Lincoln *et al*., 2002) were adopted to assess obese and non-obese subjects.

3.2.1 Sample size determination

This is a correlation study that the primary outcome was the mean of all the values obtained from the measurements.

Least number of participants, $\mathbf{M = [2 \times [(1-\alpha/2) + (1-\beta)]^2] \div \Delta^2}$

Where (1-α/2) and (1-β) represents percentage points of the normal distribution for statistical significance and power, respectively.

α: statistically significant effect : 5% or 0.05.

Adequate power for this study is taken as 95%, also defined as (1-β), where β is false negative rate: 0.5%.

Δ: standardize differences. = (μ1- μ2) ÷ S = δ ÷ S = 5 ÷ 10 = 0.5

δ: clinically significant effect.

μ: mean values.

S: standard deviation (measure of subject to subject variability)

Table 3.1: Typical values for significance levels and power

Significance level			Power			
5%	1%	0.1%	80%	85%	90%	**95%**
1.96	2.5758	3.2905	0.8416	1.0364	1.2816	**1.6449**

(Mark, 1999)

Using the values from the table for a significance level of 5%, $(1-\alpha/2) = 1.96$, and a power of 95%, $(1-\beta) = 1.6449$,

Therefore: M =

$= [2 \times [(1-\alpha/2) + (1-\beta)]^{2}] \div \Delta^{2}$

$= [2 \times [1.96 + 1.6449]^{2}] \div 0.5^{2}$

$= [2 \times [3.6049]^{2}] \div 0.25$

$= [2 \times 12.9953] \div 0.25$

= 103.96 = **104** **(This means that 104 is the least number of subjects that can participate in this study)**

3.3 Study population

The participants for this study were 174 male and female adults in Zaria; northern Nigeria; aged between 35 and 70 years (Although, the calculated least number of subjects that can participate was 104). The subjects were not obese, not on any special diet and not hypertensive or diabetic. Participants were not engaged in any weight loss practices and not on any medication known to influence energy regulation. The subjects were certified fit by a physician at the ABUTH, Family Medicine Out-Patient Department, and were adequately informed about the rationale behind this study and their consent sought before the commencement of the study. In addition, participating adult female subjects were ensured not to have been pregnant or had a laparotomy procedure in the past 2 years.

3.4 Study site

This study was carried out between May and October, 2011 in Zaria, Kaduna state, Northern Nigeria. Zaria is a cosmopolitan city, inhabited by about 408,198 people as stated by the 2006 census report and is the second largest city in Kaduna state. It is

located at latitude 11^0 3'N and longitude 7^0 42'N. The city lies on the high plains of Northern Nigeria, in the Sub-Saharan Africa. It is about 643.7 kilometres from the coast of Nigeria. Different tribes and ethnic groups could be found in Zaria, the three major ethnic groups: Hausa, Yoruba and Igbo and minorities grouped together as others. Zaria has many tertiary institutions of learning and research, including Ahmadu Bello University, Zaria. The climate is savannah with annual rainfall ranging from 0.0 – 816.0 mm/month and minimum and maximum temperature of 15.3 and 36.25^0C, respectively (Avidime *et al*., 2011).

3.5 *Flowchart of the study procedure*:

Appointment

Made by the researcher with the subject

↓

Arrival of subject at the physiology department

as arranged with the researcher

↓

Informed consent and Brief consultation by the researcher

↓

Anthropometric measurements,

Prediction equations and Body composition analysis.

Blood sample collection by the

assisting Chem. Path. Lab. Scientist

↓

Biochemical analysis at the Department of

Chemical Pathology

TG, FPG, HDL, LDL, TC

↓

Recording of data by the researcher

↓

Statistical analysis at the Department of

Biostatistics,Ahmadu Bello University,

Zaria

↓

Documentation of data

By the researcher

3.6 Instruments

The equipment for this study included:

a) Stadiometer: (By SECA; Vogel and Halke; Made in Germany) was used for height measurements (cm).

b) Weighing Scale: (By SECA; Vogel and Halke; Made in Germany) was used for weight measurements (kg).

c) Sphygmomanometer: (Dekamet Accoson Mercury Sphygmomanometer, Made in England). Calibrated in mmHg from 0 – 300 mmHg; arm cuff size 22 – 32(cm); was used for blood pressure measurements (mmHg).

d) Tape rule measure: Flexible, non-stretchable tape measure (NEWEY, Made in Germany). Calibrated in (cm), from 0 – 150, was used for WC and HC measurements.

e) Skinfold caliper: (Jamar; Sammons Preston Ability One, Bolingbrook, IL. 60440, USA) calibrated in (mm) from 0 – 70, was used for skinfold measurements.

f) Stopwatch: (Heuer Trackstar Stopwatch; Made in England) was used to monitor the pulse rate.

g) Spectrophotometer: (Infinity™, TECO diagnostics U.S.A.). Where *k* is a new constant, *c* is concentration of the colored compound, and *T* is the transmittance of the solution. There is a logarithmic relationship between transmittance and the concentration of the colored compound. Thus,

-**Log T = Log 1/T = *kc* = optical density (OD).** The OD is directly proportional to the concentration of the colored compound which it reads at 540nm after blanking (TECO Diagnostic operational manual, 2008).

3.7 Prediction equations

(1.) Body density (BD), defined by Jackson and Pollock, (1978; 1980), as

Male (BD) = 1.10938 – (0.0008267 x ∑3SKF*) + (0.0000016 x 2 [∑3SKF*]) - (0.0002574 x Age)

Female (BD) = 1.0994921 – (0.0009929 x ∑3SKF*) + (0.0000023 x 2 [∑3SKF*]) – (0.0001392 x Age). Age in years; 3SKF* = Sum of 3 skinfold measurements

(2.) % Body fat (% FAT) = [(4.95 ÷ BD) - 4.5] x 100 (Siri, 1961).

(3.) Fat mass (FM) = %Body fat x Body Wt

(4.) Body mass index (BMI) = Weight ÷ (Height) ^{2} (kg/m^2) (Lincoln *et al*., 2002)

(5.) FFM = Body weight – FM (Jackson and Pollock, 1978)

(6.) Resting Energy Expenditure (REE)

In male = 66.437 + (13.752 x Wt) + (5.003 x Ht) – (6.755 x Age) kcal/day.

In female = 655.096 + (9.563 x Wt) + (1.85 x Ht) – (4.676 x Age) kcal/day.

Weight (Wt) in kg; Height (Ht) in cm and Age in (years) (Martin *et al*., 2004).

(7.) The mean arterial Blood pressure (MABP) is defined by Sabri, (2003), as the average arterial pressure throughout the cardiac cycle and it is calculated as follows:

MABP = Diastolic Blood Pressure + 1/3 Pulse Pressure (mm/Hg)

Pulse Pressure = Difference between Systolic and Diastolic Blood Pressure.

(8.) Conicity Index (CI) is defined by Meerjady *et al*., (2009), as:

$$\text{Waist Circumference (m)} / [0.109 \times \sqrt{\{\text{Body Weight (kg)} / \text{Height (m)}\}}].$$

(9.) Atherogenic index = total cholesterol ÷ high density lipoprotein (Goh *et al*., 2004).

The IDF, 2005 guideline of the MetS with ethnic specific WC for Sub-Sahara Africans was used as the main outcome measures. Normal-weight BMI was defined as a range of 18.5 - 24.9 kg/m^2 according to NIH/NHLBI, 1998 criteria and overweight BMI $\leq$ 27 kg/m^2 was considered because BMI $\geq$ 28 kg/m^2 has been shown to be a significant prognostic factor for all-cause and cardiovascular mortality among adults (Asefeh *et al*., 2001; Zhou, 2002; Ofei, 2005).

3.8 Ethical committee approval

The research proposal was submitted to the Joint Institutional Scientific and Ethical Committee of the Ahmadu Bello University Teaching Hospital, Shika- Zaria; for review, screening and approval. The written consent of the subjects was sought before they were included in the study and confidentiality was maintained in accordance with standard medical practice.

3.9 Format of testing:

All the readings and measurements were carried out in the Department of Human Physiology Laboratory, Faculty of Medicine, Ahmadu Bello University, Zaria. Each subject in their gymnasium kits made a total of two visits to this same venue for the purpose of this study.

3.9.1 First visit:

The first visit was basically familiarization and screening of subjects to ensure their fitness for the study. All the exclusion and inclusion criteria

(as stated in 3.3) were strictly observed. A routine BMI check for obese subjects was also carried out and consent forms signed.

3.9.2 Second visit:

The actual readings and measurements were taken on this day by the researcher with the assistance of the Laboratory scientist who specifically assisted in blood sample collection and biochemical analysis of the lipid profile and fasting blood sugar. The subjects reported at 09.00hrs in their gymnasium kits to the same venue in the morning of the appointed day (expected to have fasted for at least 12 hours). They were allowed to rest for about 30 minutes after which the readings and measurements was taken as follows:

3.10 Anthropometric measurements:

They were used for body composition assessments. The methodology is based on the assumption that body fat is distributed at various sites on the body specifically chest, abdomen and thigh in men; triceps, suprailiac and thigh in women (Gallagher *et al*., 1996). With the use of a skinfold caliper, the skinfold thickness in (mm) at these sites was taken twice, and the average at each site recorded.

The measurements taken from each individual included 3 skinfold measures from the body trunk and extremities as follows:

Chest: Axilla and nipple diagonal fold was taken half the distance between the anterior axillary line and nipple on the right side.

Abdomen: Abdominal umbilicus vertical fold was taken vertically, 2 cm, lateral to the umbilicus on the right side. Subjects with umbilical hernia were not included.

Thigh: Inguinal crease and patella vertical fold was taken on the anterior aspect of thigh, midway between inguinal crease and proximal border of patella on the right side (body weight shifted to the left leg) (Chan *et al*., 2003; Wang and Hoy, 2004).

Triceps: Triceps skinfold thickness was measured on the back of the arm, directly over the muscle at the midpoint of the arm. The midpoint of the arm was located by measuring the distance between the olecranon process and acromial process while the arm was flexed at a right angle, and the midpoint was marked. The measurement was taken with the arm hanging at the subjects' side with the skinfold pinched and measured vertically (Pi-Sunyer, 1998).

Suprailiac: A diagonal pinch just above the front forward protrusion of the hip bone (iliac crest). The fold was directed anteriorly and downward in line with the natural fold of the skin. The right arm held across the body to keep it away from the measurement area with the subject standing and relaxed (Pi-Sunyer, 1998). The readings were then computed into the prediction equations stated above.

3.10.1 Waist circumference (WC): This was measured at the narrowest point below the ribs, half way between the lowest rib and the iliac crest (Wang and Hoy, 2004).

3.10.2 Hip circumference (HC): This was measured at the level of the anterior superior iliac spine, where this could be felt, otherwise at the broadest circumference below the waist (Wang and Hoy, 2004).

3.10.3 Waist-to-hip ratio (WHpR): This was calculated as the WC divided by the HC in cm (Chan *et al*., 2003; Wang and Hoy, 2004).

3.10.4 Waist-to-height ratio (WHtR): This was calculated as the WC divided by the Ht in cm (Chan *et al*., 2003).

3.10.5 Height measurement: The height of each subject was measured with the subject barefooted and standing with the back against the stadiometer placed vertically along a smooth wall touching the ground. The height was obtained by a flat ruler indicator attached to the vertical stadiometer, pressing down horizontally in contact with the vertex of the head.

3.10.6 Weight measurement: The weight was measured with the subject barefooted, wearing light clothing and standing erect on the weighing scale.

3.10.7 Resting energy expenditure (REE): The REE was computed using the age, weight and height parameters into the 'Harris and Benedict' equation as shown in prediction equations above.

3.11 Physiological parameters

3.11.1 Blood pressure: Resting blood pressure was determined by auscultation in the right arm after a five minutes resting period. Using the sphygmomanometer and a stethoscope, the onset of the first tapping sound taken to indicate the SBP, while the point of complete disappearance of the sound (5^{th} diastolic phase) indicate the DBP as recommended by Korotkoff. For each subject, two measurements were taken and average of the two readings recorded (Danladi *et al*., 2002).

3.11.2 Heart rate: The pulse rate was counted by palpating the radial artery with the tip of index and the middle fingers just below the radial

styloid process. The pulses in 30 second were recorded and multiplied by 2 to get pulse/min (Sembulingam and Sembulingam, 2002)**.**

3.11.3 Blood sample analysis: The blood sample for the lipid profile analysis was taken and all the test and analysis were carried out at the Chemical Pathology Laboratory of ABUTH, Shika- Zaria. After cleaning with methylated spirit, Blood was drawn from a vein (venipuncture), in the ante-cubital fossa. A needle inserted into the vein, and the blood (5 ml) was collected in an air-tight vial or a syringe. Blood was then allowed to clot and separated within an hour of collection to get the serum.

3.11.3.1 Total cholesterol (TC): This is by cholesterol-oxidase-peroxidase reaction. Free and esterified cholesterol in the sample originate, by means of the coupled reactions described below, a coloured complex that can be measured by spectrophotometry.

Cholesterol ester + H_2O $\xrightarrow{cholesterase}$ cholesterol + fatty acid

Cholesterol + ½O_2 + H_2O $\xrightarrow{choloxidase}$ cholasterone + H_2O_2

$2H_2O_2$ + 4-Aminoantipyrine + Phenol $\xrightarrow{peroxidase}$ Quinoneimine +$4H_2O$

Reagent: The reagents and standards are provided ready to use.

Reagent-sample ratio: 1 ml: 10 µl; Sample: Serum; Incubation time @ 37^0C: 5 min.

Linearity: 500 mg/dl

Reference value: The following uniform cut off points have been established by the U.S National Cholesterol Education program and have been adopted in many other countries for the evaluation of health risk factors.

Up to 200 mg/dl = 5.2 mmol/dl desirable

200-239 mg/dl = 5.2-6.21 mmol/dl border-line high

>240 mg/dl = >6.24 mmol/dl high. (WHO, 2006)

3.11.3.2 Triglyceride (TG): The TG is determined after enzymatic hydrolysis with lipase. The indicator is a quinoneimine formed from hydrogen peroxide, 4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase.

Triglyceride + H_2O $\xrightarrow{lipase}$ glycerol + fatty acid

Glycerol + ATP $\xrightarrow{glycerol\ kinase}$ glycerol-3-phosphate + ADP

Glycerol-3-phosphate + O_2 $\xrightarrow{glycerol\text{-}3\text{-}phosphate\ oxidase}$ dihydroxyacetone + phosphate + H_2O_2

$2H_2O$ + 4-aminophenazone + 4-chlorophenol $\xrightarrow{peroxidase}$ quinoneimine + HCl +$4H_2O$

Reagent: The reagents and standards are provided ready to use.
Reagent-sample ratio: 1 ml: 10 µl; Sample: Serum; Incubation time @ 37^0C: 5 min. Linearity: 1000 mg/dl

Reference value: The following upper limits are recommended for the determination of the risk factor hypertriglyceridaemia: Suspected from 1.71 mmol/l (150 mg/dl); increased from 2.29 mmol/l (200 mg/dl). (<150 mg/dl normal, 150-199 mg/dl borderline, 200-499 mg/dl high, □500 mg/dl very high) (WHO, 2006)

3.11.3.3 High density lipoprotein (HDL): Lipoproteins other than HDL (i.e LDL, VLDL and chylomicrons) are first removed via selective reaction with cholesterol esterase and cholesterol oxidase that is coupled to a non coloured endpoint via catalase reduction of the peroxidase byproduct. In the second step, catalase is inhibited and the remaining HDL-C is specifically reacted with cholesterol esterase and cholesterol oxidase. In the presence of peroxidase, the peroxidase byproduct now react with 4-aminoantipyrine and HDAOS [N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline] to form a coloured quinine dye, which is measured spectrophotometrically at 600 nm.

Reagent: Two reagents (R1 &R2) and standards will be provided ready to use.
Reagent-sample ratio: R1-33: R2-100: 1µl; Sample: Serum;
Incubation time @ 37^0C: 5 + 5 min.

Linearity: 150 mg/dl

Reference value: < 40 mg/dl (1.03 mmol/ dl) in males; < 50 mg/dl (1.29 mmol/ dl) in females (WHO, 2006).

3.11.3.4 Low density lipoprotein (LDL): The values for LDL was calculated using the Friedewald´s formula: LDL = TC-HDL-(TG/2.17) mmol/l (Provided TG values are less than 4.52mmol/l)

Reference value: < 100 mg/dl optimal 2.59mmol/l
100-129 mg/dl near optimal 2.59-3.34mmol/l
130-159 mg/dl borderline high 3.36-4.11mmol/l
160-189 mg/dl high 4.14-4.89mmol/l
□ 190 mg/dl very high 4.9mmol/l (Warnick *et al*., 1990).

3.11.3.5 Fasting plasma glucose (FPG): This was by glucose oxidase method. The glucose present in the plasma is oxidized by the enzyme glucose oxidase to gluconic acid with libration of hydrogen peroxide, which is converted to water and oxygen by the enzyme peroxidase. 4-Aminophenazone, an oxygen acceptor, takes up the oxygen and together with phenol forms a pink coloured chromogen which can be measured at

515 nm. ***Reference value:*** 80 mg/dl—110 mg/dl (4.4 — 6.1 mmol/dl) (WHO, 2006).

3.12 Data analysis:

Data was analyzed using statistical package for social sciences (SPSS Inc, version 16. 0; Chicago). Descriptive statistics of mean and standard deviation was computed for the purpose of data interpretation. Partial correlation analysis was used to identify the significance and trend of relationships among the variables. Correlations were considered significant at $P \leq 0.05$ with critical values located at 0.2050 (male), 0.2172 (female) (Thomas and Nelson, 1996).

The accuracy of simple and derived anthropometrics was assessed further by stepwise multiple regression analysis in which the data included the predictive variables that correlated with the RFA as dependent variables. Differences were considered significant at $P \leq 0.05$.

CHARPTER FOUR

4.0 RESULTS

4.1 Anthropometric characteristics of the study participants

Participants were within the BMI class of normal weight (male: 23.13 ±2.73, female: 23.78 ±2.42). The physical and anthropometric characteristics of study participants are summarized in Table 4.1. The mean age of study participants was 47.13 years for male and 44.96 years for female. Using statistical t-test of equality of means at $P \leq 0.05$; Male were significantly taller (173.32 ±6.42), narrower hips (93.37 ±6.12), smaller fat mass (14.40 ±5.47) and higher resting energy expenditure (1571 ±166.85) as compared to female (162.58 ±6.09, 99.27 ±6.48, 22.14 ±6.55 and 1.347.17 ±97.38) respectively. The waist-height ratio (0.535 ±0.05) and % fat (34.682 ±7.65) were higher in female than in male (0.508 ±0.048, 20.20 ±5.89) respectively. No significant difference was observed between males and females with respect to conicity index (male: 1.28 ±0.066, female: 1.283 ±0.07), waist circumference (male: 87.90 ±8.17, female: 86.87 ±7.70) and BMI (male: 23.13 ±2.73, female: 23.78 ±2.42).

TABLE 4.1 Anthropometric characteristics of the study participants

Variables	Male (n= 91)	Female (n= 83)	P values
	Mean ± SD	Mean ± SD	
Age (years)	47.13 ±8.10	44.96 ±9.58	0.111
Weight (kg)	69.55 ±9.60	62.90 ±7.96	0.001**
Height (cm)	173.32 ±6.42	162.58 ±6.09	0.001**
Waist circumference (cm)	87.90 ± 8.17	86.87 ±7.70	0.391*
Hip circumference (cm)	93.37 ±6.12	99.27 ±6.48	0.001**
∑SKF (mm)	53.84 ±15.59	72.54 ±16.33	0.001**
Body mass index (kg/m^2)	23.13 ±2.73	23.78 ±2.42	0.098
Waist-hip ratio	0.94 ±0.05	0.88 ±0.06	0.001**
Waist-height ratio	0.51 ±0.05	0.54 ±0.05	0.001**
Conicity index	1.28 ±0.07	1.28 ±0.07	0.468
Body density (kg/l^3)*	1.05 ±0.013	1.02 ±0.02	0.001**
Resting energy expenditure (kcal/day)	157.65 ±17.85	135.17 ±97.38	0.001**
Percentage body fat (%)	20.20 ±5.89	34.68 ±7.65	0.001**
Fat mass (kg)	14.40 ±5.47	22.14 ±6.55	0.001**
Fat free mass (kg)*	55.15 ±6.03	40.76 ±4.68	0.001**

*P ≤ 0.05; **P ≤ 0.01

4.2 Blood pressure and lipid profile of the study participants

Table 4.2 Show the blood pressure and lipid profile of study participants. Only pulse rate showed significant difference between males and females (0.00**), no significant differences were observed in the lipid profiles between male and female. Also, male and female groups showed minimal values for atherogenic index and statistical t-test of equality of means at P ≤0.05 did not show any significant difference between male and female.

TABLE 4.2 Blood pressure and lipid profile of the study participants

Variables values	Male (n= 91) Mean ± SD	Female (n= 83) Mean ± SD	P
Systolic blood pressure (mmHg)	127.03 ± 20.14	132.77 ± 26.05	0.109
Diastolic blood pressure (mmHg)	79.01 ± 10.76	82.71 ± 14.74	0.063
Pulse rate (beats/min)	68.73 ± 8.92	75.81 ± 11.79	0.001**
Mean Arterial Blood Pressure (mmHg)	95.02 ± 12.76	99.398 ± 17.94	0.068
Total cholesterol (mmol/dl)	3.13 ± 1.12	3.017 ± 0.83	0.448
Triglyceride (mmol/dl)	1.37 ± 1.11	1.150 ± 0.82	0.137
High density Lipoprotein (mmol/dl)	0.944 ± 0.325	0.955 ± 0.37	0.835
Low density lipoprotein (mmol/dl)	1.63 ± 0.904	1.581 ± 0.71	0.683
Fasting plasma glucose (mmol/dl)	3.997 ± 1.40	4.174 ± 1.32	0.393
LDL/HDL	1.787 ± 0.92	2.055 ± 1.97	0.260
TC/HDL	3.421 ± 1.02	3.640 ± 2.21	0.409

* $P \leq 0.05$; **$P \leq 0.01$

4.3 Relationships among measures of adiposity

Tables 4.3 and 4.4 show the relationships among all anthropometric variables that were examined in this study ($P \leq 0.05$). In male, waist circumference exhibited the strongest correlation among the anthropometric variables studied (weight *r*= 0.797**, BMI *r*= 0.851**, waist-height ratio *r*=0.925**, waist-hip ratio *r*= 0.727**, fat mass *r*=0.956**), followed by waist-height ratio (weight *r*=0.580**, BMI *r*=0.840**, waist circumference *r*= 0.925**, waist-hip ratio *r*= 0.807**, fat mass *r*= 0.776**) as shown in Table 4.3. Similarly in female, waist circumference exhibited the strongest correlation among the anthropometric variables studied (weight *r*= 0.721**, BMI *r*= 0.774**, waist-height ratio *r*=0.916**, waist-hip ratio *r*= 0.692**, fat mass *r*=0.689**), followed by waist-height ratio (weight *r*=0.474**, BMI *r*=0.775**, waist circumference *r*= 0.916**, waist-hip ratio *r*= 0.666**, fat mass *r*= 0.553**) as shown in Table 4.4. Comparatively, male group had higher values of correlation coefficient and the strength of correlation was more than that of the female group. The pattern of correlation was also similar for waist circumference, waist-height ratio and BMI; with waist circumference showing the strongest attitude in both groups.

Despite considering non obese subjects in this study, FM showed some interesting trend and strength with other variables in male (weight *r*=0.816**, waist circumference *r*= 0.890** and BMI *r*= 0.800**) and (weight *r*=0.793**, waist circumference *r*= 0.689** and BMI *r*= 0.751**) in female group; and a strong but negative relationship with body density was obtained in male (*r*=-0.955**) and female (*r*= -0.943**). Resting energy expenditure and conicity index also exhibited strong correlation with most variables, but not with each other. Fat free mass (*r*= 0.898** in male, 0.539** in female) and weight (*r*= 0.930** in male, 0.877** in female) were the most influencing factors on REE, and no correlation was found between resting energy expenditure and

waist-hip ratio. Conicity index also showed no correlation with height and fat free mass in both groups.

Skinfold measure also shows some remarkable strength of relationship with other anthropometric variables in both groups (Table 4.5 and 4.6), but little or none with age, height and fat free mass. The correlation of abdominal skinfold (weight *r*= 0.629**, waist circumference *r*= 0.763**, BMI *r*= 0.675** and waist-height ratio *r*= 0.718**) in male (Table 4.5) and suprailiac skin fold (weight *r*= 0.544**, waist circumference *r*= 0.636**, BMI *r*= 0.565** and waist-height ratio *r*= 0.565**) in female (Table 4.6) with other variables were strongest among the skin fold measures investigated. However, both groups presented best correlation between % fat and fat mass: *r*= 0.956 in male, *r*= 0.944 in female followed by waist circumference and waist-height ratio: *r*= 0.925 in male, *r*= 0.916 in female.

Table 4.3 Correlation matrix for measures of adiposity in male participants

	AGE	WT	HT	WC	HC	BMI	WHpR	WHtR	CI	BD	REE	%FAT	FM	FFM
AGE	1.00													
WT	-0.12	1.00												
HT	-0.07	0.51**	1.00											
WC	0.15	0.80**	0.12	1.00										
HC	-0.04**	0.88**	0.39**	0.84**	1.00									
BMI	-0.10	0.84**	-0.03	0.85**	0.78**	1.00								
WHpR	0.31**	0.31**	-0.26*	0.73**	0.21*	0.53**	1.00							
WHtR	0.18	0.58**	-0.26*	0.93**	0.65**	0.84**	0.81**	1.00						
CI	0.43**	0.28**	-0.090	0.78**	0.45**	0.39**	0.79**	0.73**	1.000					
BD	-0.25*	-0.63**	-0.05	-0.83**	-0.74**	-0.69**	-0.54**	-0.78**	-0.671**	1.00				
REE	-0.44**	0.93**	0.62**	0.61**	0.78**	0.69**	0.10	0.35**	0.067	-0.42**	1.00			
%FAT	0.25*	0.62**	0.05	0.83**	0.73**	0.69**	0.54**	0.78**	0.671**	-1.00	0.42**	1.00		
FM	0.15	0.82**	0.23*	0.89**	0.85**	0.80**	0.51**	0.78**	0.595**	-0.96**	0.64**	0.96**	1.00	
FFM	-0.33**	0.85**	0.60**	0.46**	0.63**	0.62**	0.04	0.22*	-0.090	-0.13	0.90**	0.13	0.39**	1.00

*P ≤ 0.05, ** P ≤ 0.01

Table 4.4: Correlation matrix for measures of adiposity in female participants

	AGE	WT	HT	WC	HC	BMI	WHpR	WHtR	CI	BD	REE	%FAT	FM	FFM
AGE	1.00													
WT	-0.14	1.00												
HT	-0.21	0.55**	1.00											
WC	0.07	0.72**	0.13	1.00										
HC	-0.15	0.74**	0.16	0.65**	1.00									
BMI	-0.02	0.80**	-0.07	0.77**	0.76**	1.00								
WHpR	0.23*	0.25*	0.02	0.69**	-1.00	0.30*	1.00							
WHtR	0.15	0.47**	-0.28*	0.92**	0.56**	0.78**	0.67**	1.00						
CI	0.20	0.25*	-0.05	-0.83**	0.28*	0.34**	0.81**	0.83**	1.00					
BD	-0.04	-0.57**	-0.09	-0.59**	-0.55**	-0.62**	-0.26*	-0.54**	-0.35**	1.00				
REE	-0.59**	0.88**	0.62**	0.52**	0.64**	0.60**	0.08	0.25*	0.09	-0.42**	1.00			
%FAT	0.04	0.56**	0.09	0.59**	0.55**	0.62**	0.26*	0.53**	0.35**	-1.00	0.41**	1.00		
FM	-0.02	0.79**	0.27*	0.69**	0.68**	0.75**	0.26*	0.55**	0.33**	-0.94**	0.64**	0.94**	1.00	
FFM	-0.20	0.52**	0.51**	0.23	0.25*	0.25*	0.04	-0.00	-0.06	0.40**	0.54**	-0.40**	-0.11	1.00

* P ≤ 0.05
** P: ≤0.01

Table 4.5: Correlation between skinfold measure and other measures of adiposity in male participants

	AGE	WT	HT	WC	HC	BMI	WHpR	WHtR	CI	BD	REE	%FAT
	FM	FFM										
Axil	0.17	0.55**	0.01	0.74**	0.61**	0.63**	0.54**	0.72**	0.60**	-0.83**	0.38**	0.83**	0.81**
Abdominal	0.14												
Thigh	0.08	0.63**	0.07	0.76**	0.68**	0.68**	0.50**	0.72**	0.58**	-0.90**	0.48**	0.90**	0.87**
∑SKF	0.20												
	0.01	0.53**	0.08	0.63**	0.67**	0.57**	0.27**	0.58**	0.44**	-0.82**	0.43**	0.82**	0.79**
	0.13												
	0.09	0.66**	0.07	0.82**	0.76**	0.73**	0.50**	0.78**	0.62**	-0.99**	0.51**	0.99**	0.96**
	0.19												

∑SKF = sum of skinfold measures; * P ≤ 0.05; ** P ≤ 0.01.

Table 4.6: Correlation between skinfold measure and other measures of adiposity in female participants

	AGE	WT	HT	WC	HC	BMI	WHpR	WHtR	CI	BD	REE	%FAT	
	FM	FFM											
Triceps	-0.06	0.45**	0.09	0.43**	0.44**	0.48**	0.15	0.38**	0.22*	-0.89**	0.38**	0.89**	0.83**	-
Suprailiac	0.42**													
Thigh	0.02	0.54**	0.12	0.64**	0.43**	0.57**	0.43**	0.57**	0.45**	-0.69**	0.41**	0.69**	0.70**	-
∑SKF	0.10													
	-0.05	0.46**	0.06	0.43**	0.52**	0.51**	0.08	0.39**	0.21	-0.87**	0.37**	0.87**	0.80**	-
	0.38**													
	0.04	0.58**	0.10	0.59**	0.56**	0.62**	0.25*	0.53**	0.34**	-1.00**	0.46**	1.00**	0.95**	-
	0.38**													

∑SKF = sum of skinfold measures; * $P \leq 0.05$, ** $P \leq 0.01$

4.4 Correlation between measures of adiposity and cardiometabolic risk factors

Tables 4.7 and 4.8 show the correlation between anthropometrics and cardiometabolic risk factors ($P \leq 0.05$), Among male subjects, higher values of waist-height ratio and waist-hip ratio were associated with increasing cardiometabolic risk factors (mean arterial blood pressure r=0.286** and 0.222*; triglyceride r=0.0.318** and 0.352**; waist circumference r=0.925** and 0.727**) respectively, and overall association did not vary substantially among the indices. Associations were somewhat weaker in the female group with only waist-height ratio showing association with mean arterial blood pressure (r=0.257*) and waist circumference (r=0.916**). Sex differences in the correlation of obesity pattern with metabolic risk factors were further confirmed. Among the male group, waist-height ratio demonstrated the strongest gradient in association with risk factors, followed by waist-hip ratio. Though, the correlation of risk factors with waist-height ratio among female was weaker, the existence of waist-height ratio in both groups was phenomenal and no correlation existed with fasting plasma glucose in both groups.

Also, there were significant correlations between Conicity idex and cardiometabolic risk factors (mean arterial blood pressure r= 0.214*, triglyceride r=0.297** and waist circumference r=-0.779**) in male and waist circumference (r=0.828**) in female. Resting energy expenditure showed correlations with diastolic blood pressure (r=0.229*) and waist circumference (r= 0.605**) in male, and systolic blood pressure (r= -0.288**) and waist circumference (r= 0.522**) in female. Correlation of weight, resting energy expenditure and fat free mass with atherogenic indices: low density lipoprotein-high density lipoprotein ratio and total cholesterol-high density lipoprotein ratio respectively, was also obtained in male but not in female subjects.

Table 4.7 Correlation between measures of adiposity and cardiometabolic risk factors in male participants

	SBP	DBP	PULSE	MAP	TC	TG	HDL	LDL	FPG	LDL/HDL	TC/HDL
AGE	0.23*	0.05	0.06	0.15	-0.09	0.11	-0.04	-0.06	-0.10	-0.08	-0.12
WT	0.12	0.28*	0.18	0.23*	0.34**	0.10	0.09	0.33**	0.16	0.30**	0.31**
HT	-0.17	0.11	-0.09	0.03	0.25*	-0.13	-0.00	0.29**	0.07	0.35**	0.33**
WC	0.26*	0.27**	0.27**	0.29**	0.30**	0.27**	0.14	0.25*	0.13	0.17	0.18
HC	0.13	0.27**	0.20	0.22*	0.42**	0.10	0.17	0.39**	0.17	0.28**	0.27*
axil	0.23*	0.26**	0.26*	0.27*	0.26*	0.29**	0.22*	0.15	0.18	0.02	0.05
abdominal	0.27*	0.22*	0.28**	0.23*	0.18	0.14	0.05	0.15	0.08	0.12	0.17
thigh	0.09	0.07	0.15	0.09	0.15	0.06	-0.14	0.18	-0.08	0.14	0.14
∑SKF	0.23*	0.21*	0.27*	0.24*	0.22*	0.17	0.08	0.18	0.06	0.12	0.15
BMI	0.24*	0.25*	0.26*	0.27*	0.24*	0.20	0.11	0.20	0.15	0.13	0.15
WHpR	0.28**	0.13	0.23*	0.22*	0.01	0.35**	0.04	-0.04	0.03	-0.05	0.02
WHtR	0.31**	0.22*	0.30**	0.29**	0.19	0.32**	0.14	0.14	0.10	0.03	0.05
CI	0.24*	0.15	0.21*	0.21*	0.17	0.30**	0.13	0.12	0.03	0.02	0.02
BD	-0.26*	-0.21*	-0.27**	-0.26*	-0.20	-0.18	-0.07	-0.17	-0.04	-0.10	-0.13
REE	-0.01	0.23*	0.11	0.12	0.35**	0.02	0.09	0.33**	0.17	0.33**	0.35**
%FAT	-0.26*	0.21*	0.27**	0.26*	0.20	0.18	0.07	0.17	0.04	0.11	0.13
FM	0.25*	0.27**	0.26**	0.28**	0.27*	0.16	0.08	0.25*	0.09	0.19	0.21*
FFM	0.03	0.21*	0.05	0.10	0.30**	0.02	0.08	0.30**	0.17	0.30**	0.30**

*P ≤ 0.05, **P ≤ 0.05

Table 4.8 Correlation between measures of adiposity and cardiometabolic risk factors in female participants

AGE	0.46**	0.27*	-0.07	0.37**	0.17	0.18	0.03	0.13	0.07	0.10	0.10
WT	-0.05	0.01	0.04	-0.03	-0.04	-0.11	0.00	0.06	-0.06	0.08	0.04
HT	-0.31**	-0.27*	-0.11	-0.30**	0.05	-0.13	0.06	0.09	-0.06	-0.03	-0.06
WC	0.15	0.13	-0.00	0.14	0.04	0.07	0.07	0.06	0.001	0.03	0.01
HC	0.07	0.18	0.20	0.13	0.08	-0.16	0.08	0.12	0.02	0.04	0.00
Triceps	-0.02	0.03	-0.01	0.01	0.19	-0.15	0.04	0.20	-0.19	0.15	0.15
Suprailiac	0.02	0.02	-0.07	0.02	0.01	0.16	0.09	0.01	0.12	-0.05	-0.07
thigh	-0.05	0.01	-0.07	-0.02	0.30*	-0.14	0.10	0.30*	-0.10	0.14	0.12
∑SKF	-0.03	0.02	-0.05	0.00	0.22	-0.06	0.09	0.22	-0.09	0.11	0.09
BMI	0.16	0.19	0.12	0.18	-0.07	-0.03	-0.03	-0.01	-0.02	0.12	0.09
WHpR	0.12	-0.02	-0.20	0.05	-0.03	-0.25*	0.01	-0.04	-0.02	0.00	0.00
WHtR	0.27*	0.23*	0.04	0.26*	0.02	-0.11	0.04	-0.02	0.03	0.04	0.03
CI	0.17	0.11	-0.09	0.14	0.12	0.17	0.12	0.05	0.05	-0.05	-0.05
BD	-0.01	-0.05	0.06	-0.03	-0.23*	0.05	-0.09	-0.22*	0.08	-0.12	-0.10
REE	-0.29**	-0.16	0.05	-0.23*	-0.10	-0.18	-0.00	- 0.01	-0.08	0.01	0.02
%FAT	0.01	0.04	-0.06	0.03	0.23*	-0.05	0.09	0.22*	-0.08	0.12	0.10
FM	0.02	0.03	-0.03	0.00	0.15	-0.09	0.06	0.19	-0.08	0.12	0.09
FFM	-0.06	-0.05	0.10	-0.05	-0.27*	-0.04	0.09	-0.17	0.02	-0.03	-0.06

** P ≤ 0.01 , * P ≤ 0.05.

4.5 Multivariate correlation of risk factors accumulation with measures of adiposity

Multivariate correlation of risk factor accumulations with various measures of adiposity ($P \leq 0.05$) is presented in tables 4.9 and 4.10. The tables show the relationships of various measures of adiposity with risk factors accumulation. Waist-height ratio showed the strongest relationship with risk factors accumulation in male (waist circumference r= 0.80**, systolic blood pressure r= 0.31**, diastolic blood pressure r= 0.22* and triglyceride r= 0.32**) (Table 4.9). Other measures of adiposity, that is, waist-hip ratio and conicity index also showed relationships with risk factors accumulation, but not as strong as waist-height ratio in the male group, and no relationship was found in the female group (Table 4.10). The common combination of risk factors accumulation was the existence of large waist circumference, high blood pressure and hypertriglyceridemia. Risk factors accumulation was present in male group not in female group.

Table 4.9: Multivariate correlations of measures of adiposity and risk factor accumulations in male participants

	Wt	HC	WHtR	WHpR	BMI	% fat	FM	REE	CI
WC	0.80**	0.84**	0.93**	0.73**	0.85**	0.83**	0.89**	0.61**	0.78**
SBP	0.12	0.13	0.31**	0.28*	0.24*	-0.26*	0.25*	0.01	0.24*
DBP	0.28*	0.27*	0.22*	0.13	0.25*	0.21*	0.27*	0.23*	0.15
TG	0.10	0.10	0.32**	0.35**	0.20	0.18	0.16	0.02	0.30**
HDL	0.09	0.17	0.14	0.04	0.11	0.07	0.08	0.09	0.13

*P ≤ 0.05, ** P: ≤0.01

Table 4.10: Multivariate correlations of measures of adiposity and risk factor accumulations in female participants

CI	Wt	HC	WHtR	WHpR	BMI	% fat	FM	REE
WC	0.72**	0.65**	0.92**	0.69**	0.77**	0.59**	0.69**	0.52**	-0.83**
SBP	-0.05	0.07	0.27*	0.12	0.16	0.01	0.02	0.29**	0.17
DBP	0.01	0.18	0.23*	-0.02	0.19	0.04	0.03	-0.16	0.12
TG	-0.11	-0.16	0.17	-0.25*	-0.03	-0.05	-0.09	-0.18	0.17
HDL	0.00	0.08	0.04	0.01	-0.03	0.09	0.06	-0.00	0.12
FPG	-0.06	0.02	0.03	-0.02	-0.02	-0.08	-0.08	084	0.05

*P ≤ 0.05, ** P: ≤0.01

4.6 Logistic regression analysis of measures of adiposity and cardiometabolic risk factors

Logistic regression analyses were used to investigate the independent relation between the obesity indices and cardiometabolic risk factors after adjusting for age P: ≤ 0.05. In the male group (Table 4.11), only waist-height ratio predicted the existence of large waist circumference (0.00**) and at least two other components of metabolic syndrome, that is, elevated triglycerides (0.01**), systolic blood pressure (0.01**) and diastolic blood pressure (0.00**). None of the obesity measures predicted elevated fasting blood glucose. No prediction of these combinations of cardiometabolic risk factors existed in the female group.

Similarly, regression graph in figures i, ii, iii and iv further showed the strength of waist-height ratio in predicting existence of risk factors accumulation in the male group (waist circumference y = 0.006 x +0.03, systolic blood pressure y = 0.0033 x +0, diastolic blood pressure y = 0.004 x -0.02 and triglyceride y = 0.0286 x -0.0429). Other measures of adiposity did not exhibit predictions with risk factors accumulation. No prediction was found for risk factors accumulation in female participants. Measures of adiposity did not show relationships with fasting plasma glucose, and no prediction was exhibited in both male and female groups.

Table 4.11 Regression analysis of obesity measures and cardiometabolic risk factors in male participants

Predictors	Dependent variables	R^2	P values
WHtR	WC	0.52	0.001**
	SBP	0.09	0.007**
	DBP	0.11	0.003**
	TG	0.08	0.014**
	HDL	5.81E	0.834
	FBG	0.01	0.555
WHpR	WC	0.85	0.001**
	SBP	0.12	0.001**
	DBP	0.09	0.005**
	TG	0.04	0.686
	HDL	8.99E	0.784
	FBG	0.01	0.545
BMI	WC	0.69	0.001**
	SBP	0.00	0.739
	DBP	8.86E	0.993
	TG	0.01	0.471
	HDL	0.00	0.572
	FBG	0.01	0.601
FM	WC	0.78	0.001**
	SBP	9.00E	0.993
	DBP	0.00	0.635
	TG	0.03	0.618
	HDL	0.01	0.384
	FBG	4.68E	0.843

*P ≤ 0.05, ** P: ≤0.01

Table 4.12

Predictors	Dependent variables	R^2	P values

Regression analysis of obesity measures and cardiometabolic risk factors in female participants

WHtR	WC	0.50	0.001**
	SBP	0.08	0.001**
	DBP	0.06	0.028**
	TG	0.07	0.553
	HDL	0.01	0.585
	FBG	0.02	0.622
WHpR	WC	0.85	0.001**
	SBP	0.12	0.001**
	DBP	0.09	0.005**
	TG	0.04	0.086
	HDL	8.99E	0.784
	FBG	0.01	0.545
BMI	WC	0.61	0.001**
	SBP	0.01	0.426
	DBP	0.02	0.193
	TG	0.01	0.605
	HDL	0.02	0.842
	FBG	8.72E	0.601
FM	WC	0.51	0.001**
	SBP	0.04	0.092
	DBP	0.02	0.261
	TG	0.02	0.609
	HDL	0.00	0.741
	FBG	0.01	0.562

*P ≤ 0.05,
** P: ≤ 0.01

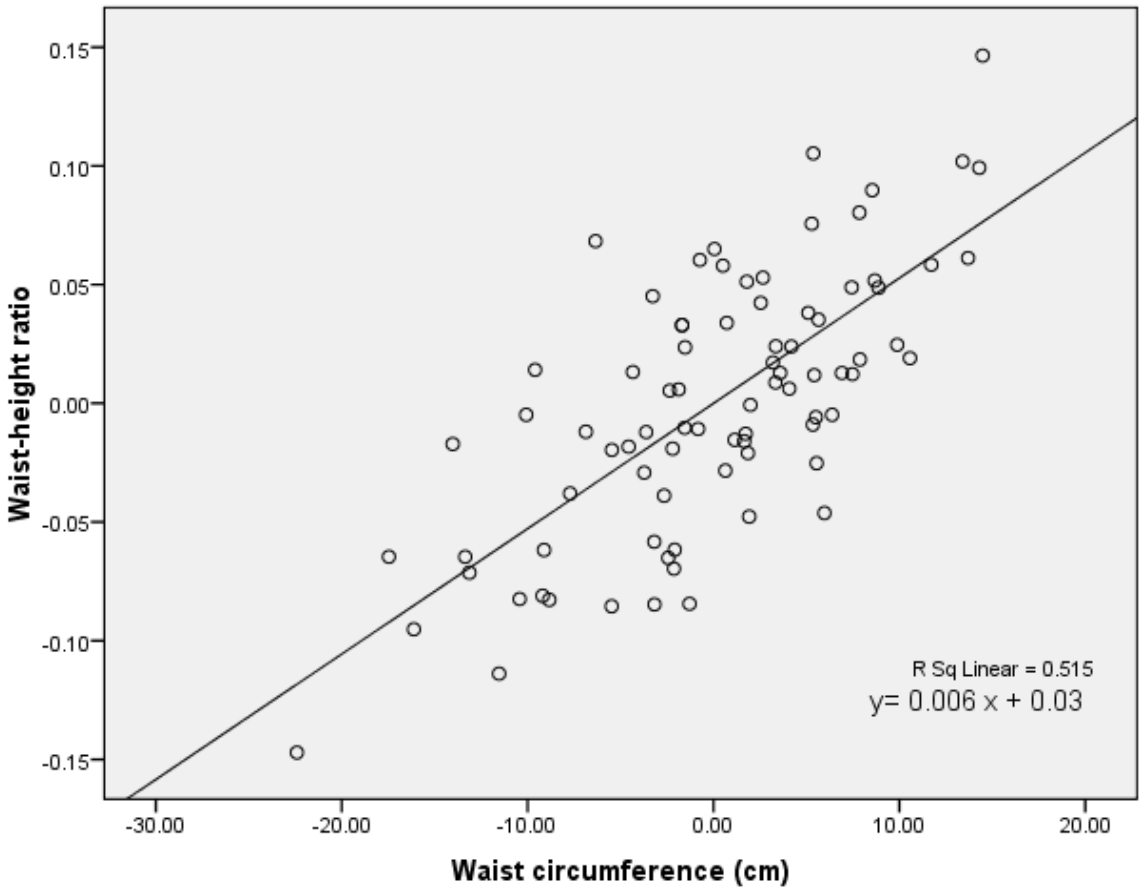

Figure 4.1: Partial regression graph of relationship between waist-height ratio and waist circumference in male

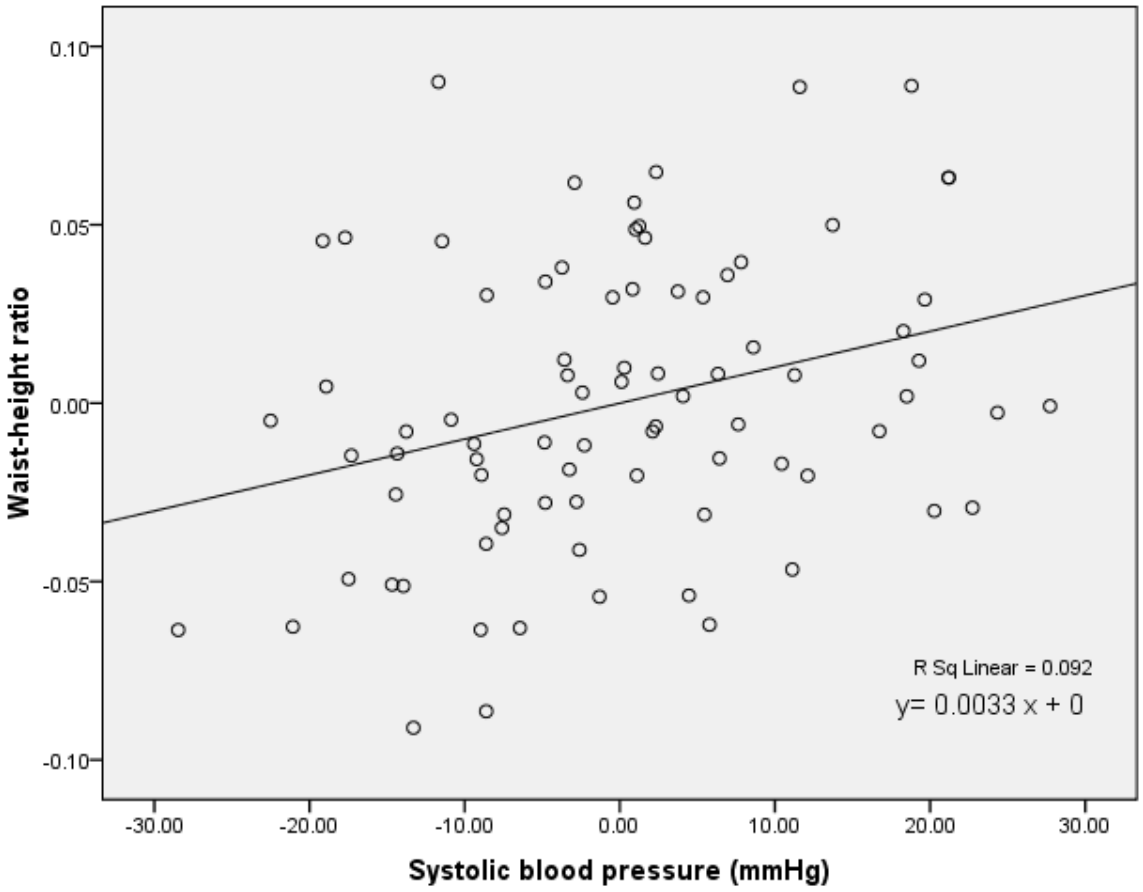

Figure 4.2: Partial regression graph of relationship between waist-height ratio and systolic blood pressure in male

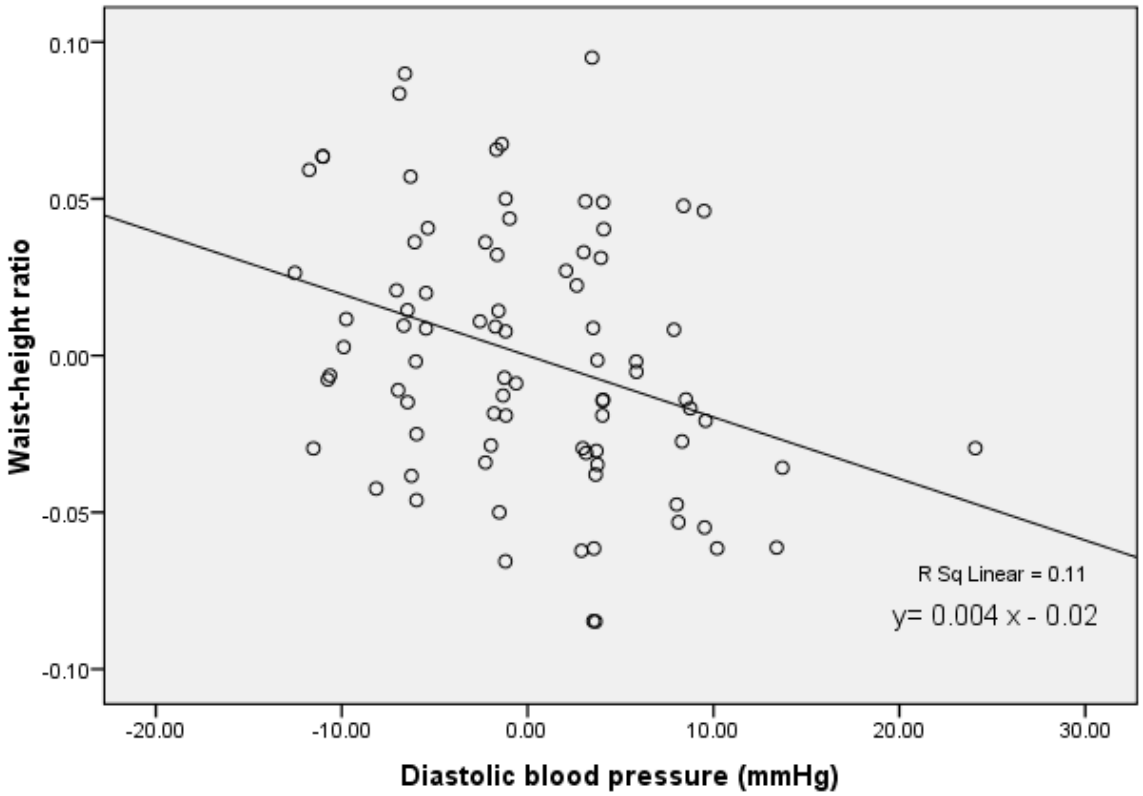

Figure 4.3: Partial regression graph of relationship between waist-height ratio and diastolic blood pressure in male

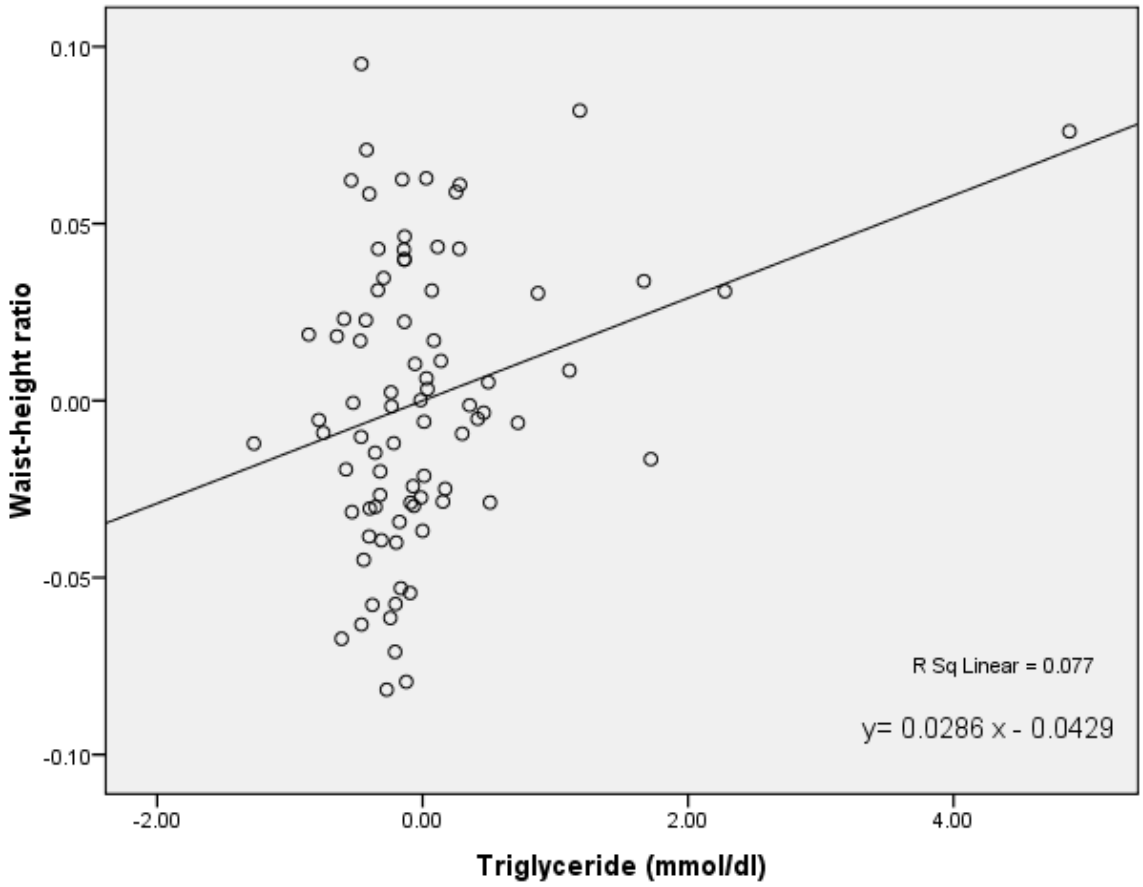

Figure 4.4: Partial regression graph of relationship between waist-height ratio and triglyceride in male

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5.0 DISCUSSION

Metabolically obese normal weight (MONW) individuals who despite having a normal weight BMI present with metabolic disturbances typical of obese individuals and the associated metabolic disorders among non obese are often ignored relatively to obesity (Ruderman *et al*., 1998; Succuro *et al*., 2008). The main findings of this study suggested that waist-height ratio provides a marginally superior tool for discriminating high cardiometabolic risks among non-obese adults compared with Fat mass, BMI and waist-hip ratio and that discrimination is more precise, on average, in male. Linear correlation analyses also showed that measures of adiposity were positively and significantly associated with cardiometabolic risk factors in both sexes, with the exception of fasting plasma glucose.

5.1 Relationship between anthropometrics and cardiometabolic risk factors

The results from this study showed that WC, WHtR, %Fat and FM were the strength of correlation between anthropometrics and cardiometabolic risk factors. In addition, WHtR, HC and WC had a greater influence on cardiometabolic risk factors and the influence was more conspicuous among the male group of non-obese adults investigated. The correlation among the anthropometric indices observed in this study however shows that they carry same information of adiposity and the associated health risk factors among non obese adults. The results are in agreement with the findings of other investigators, who earlier showed that the concept of the metabolically obese normal weight individual is based on the observation that these same characteristics may be found in normal weight individuals with disorders often associated with obesity (St-Onge *et al*., 2004; Tsai, 2009).

Also in this study, the strong association of Skinfold thickness with other anthropometric indices and cardiometabolic risk factors, particularly axillary skinfold in male group, is consistent with report from Hafner *et al*., (1987), who showed a reasonably

strong association of skinfold thickness with increased body fat percentage and associated morbidity but this association is still considered to be of limited clinical utility.

5.2 Correlation and prediction of cardiometabolic risk factors exhibited by WHtR

Palacios *et al*., (2011), showed in their study that general and abdominal adiposity were both associated with cardiometabolic risks, and that WC, WHpR and WHtR appear to be slightly better predictors than BMI among the population studied. Although several anthropometric indices serve as simple clinical tools for the measurement of central adiposity, it is not particularly clear which surrogate marker is the most reliable predictor of metabolic risk factor accumulation. BMI measurements in childhood are associated with abnormal metabolic clustering in adulthood, but the usefulness of BMI is limited for the following reasons: (1) its inability to distinguish fat from muscle mass; (2) its tendency to under-represent body fat distribution; and (3) its inability to measure central adiposity in a direct fashion, and for WC, there are currently no agreements about a health-related classification, varying percentile has been considered as a cut-off point for high wc; Both of these measures are also age and-sex dependent (Vasan *et al*., 2011).

WHtR takes into account the distribution of body fat in the abdominal region which has been shown to be more associated with cardiovascular risks than body weight. WHtR adds significantly to cardiometabolic risk prediction over BMI and waist circumference in men, and it is an important index of central obesity, which is free from any bias due to hip width changes along with waist circumference of short and tall subjects (Dhall *et al*., 2011). The significant correlation and strength of prediction exhibited by WHtR in this study could then mean that it carries the burden of cardiometabolic risks among non obese individuals

investigated in this study; so much so that the recommended optimal cut-off point of 0.5 for men and women (Browning *et al*., 2010), is higher in this study (0.508 in men and 0.535 in female). This is in agreement with the findings of Park *et al*., (2009), Nambiar *et al*., (2010), who showed WHtR to be a better predictor of cardiovascular diseases than other anthropometric measurements, including BMI, WC, WHpR and skinfold thickness.

This observation was also reflected in recent studies on non obese adults by Gomes-ambrosi *et al*., (2011), Knowels *et al*., (2011) and Vasan *et al*.,(2011), who proved that WHtR was the best predictor of both hypertension and dyslipidaemia for both male and female, and that BMI was the least accurate predictor of hypertension. Similar observation was also noted in this study, but more pronounced in male than female. The heterogeneity in findings across studies that have assessed cardiometabolic risk factors in relation to indices of adiposity may be attributable to difference in race, ethnicity, age and gender distribution of participants across study population (Duncan *et al*., 1995; Deurenberg *et al*., 1998).

WHtR is a recently introduced index to assess central fat distribution; an increase circumference is most likely associated with elevated risk factors because of its relation with visceral fat accumulation and the mechanism may involve excess exposure of the liver to fatty acid. The combination of WC and Height; that is, WHtR could manifest better, the morphology of an enlarged abdomen with inappropriate short stature (Lin *et al*., 2002, Kayode *et al*., 2009).

As was also observed by Kayode *et al*., (2009), Wint *et al*., (2011), HC assessment in non-obese is more relevant than in obese individuals. This is particularly so, because BMI does not reflect body fat distribution. Indeed, other anthropomeric indices such as WC, HC, WHtR and WHpR have been used as alternatives.

This study also showed that both HC and WHpR were significantly correlated with various cardiometabolic risk factors, but in a smaller degree than WC and WHtR. This means that the use of Ht rather than HC adjusted for WC better indicates the clustering of cardiometabolic risk factors. Generally, incorporating either HC or Ht may provide more information on cardiometabolic risk than WC alone, the universally use of WC therefore may cause overestimation of risk factors in tall persons and underestimation in short persons (Ahmet *et al*., 2008).

Hypertension is now recognised globally as a major public health problem in terms of well-known risk factors for cardiometabolic diseases (Nobukazu *et al*., 2005, Ghosh and Bandyopadhyay, 2007). In this study, WHtR showed strong and consistent correlation with SBP>DBP>MABP in both male and female groups, followed by WC and FM. This fact could then mean that WHtR, WC and abdominal skinfold carry same information of visceral obesity. Therefore, the significant correlations with SBP, DBP and MABP observed also in this study could suggest that a decrease in intra-abdominal fat could reduce blood pressure and shows consistence with previous studies (Ilse and Luc, 2000; Wang and Hoy, 2004; Roopakala *et al*., 2009).

5.3 Metabolic syndrome among non-obese adults

Noteworthy, obesity is defined as an excess accumulation of body fat with the amount of this excess fat being responsible for most obesity associated health risks (Vasan *et al*., 2011). In this study, BMI cut off values, even at the highest quintile (27.0 in male and 26.60 in female) did not show strong associated risk of MetS compared to WC, WHtR and % fat. The findings signify that although BMI may help in categorising obesity, it is not a reliable predictor for MetS in this study and may not reflect cardiometabolic risks clustering among non obese adults.

Since the correlation between BMI and central obesity can vary considerably from one individual to another, it has been suggested that what causes normal weight individuals to have MetS is having a greater body fat or abdominal obesity at a normal BMI range (Hadaegh *et al*., 2007).

Insulin resistance, not obesity (Baba *et al*., 2010), non alcoholic fatty liver disease (Kim *et al*., 2004) and independent role of leptin concentration (Esteghamati *et al*., 2011) have also been found to be significantly associated with MetS according to IDF definition and is independent of overall and central obesity among obese and non-obese subjects. This could also, in combination with familial and genetic background, explain the non correlation or prediction for FPG found in male and female of this study. Although mean fasting blood glucose was higher in female compared to male, none of the study population had fasting blood sugar greater than 5.6mmol/L. Dietary intake might be an important factor in determining blood glucose (Parillo and Riccardi, 2004). Moebus *et al*., (2011), also observed that the carbohydrate content and metabolic demands of last meal before the time of fasting blood glucose measurement, coupled with observed fasting state by subjects might be another contributing factors. Infections (Ugwu *et al*., 2008) and stress (Wing *et al*., 1985) have also been mentioned.

5.4 Sex differences and prevalence of metabolic syndrome

Studies on sex differences and prevalence by sex of MetS among non-obese supported results from this study, which showed high prevalence of 20.4 % in men and 15.3 % in women (Hwang *et al*., 2007) and 15.5 % in men and 10.5 % in women (Lin *et al*., 2006). The most common component was hypertension and abdominal obesity. More so, the sex difference in the development of MetS among non-obese has been attributed to low serum sex-hormone-binding-globulin, low total testosterone and symptomatic androgen

deficiency and may provide early warning signs for cardiovascular risk and consequently an opportunity for early intervention in non-obese men (Varant *et al*., 2006). Generally, the hormonal environment plays a key role in determining body fat distribution. This is because sex hormones are known to affect regional fat deposition; the changing hormonal environment during puberty may contribute to the development of sex differences and large individual changes in fat distribution (Goran and Gower, 1999).

Sex specificity has also been attributed to the heterogeneity of two different anthropometric indices in prediction of cardiometabolic risk factors among non-obese males and females in this study. Sex-related differences in MetS prevalence are not universal; the differences within specific countries may also be due, for example, to differing socio-economic Status, work-related activities, and cultural views on body fat (Cameron *et al*., 2007).

5.5 Resting energy expenditure, Conicity index and cardiometabolic risk factors

The determinants of REE are well established in adults, but FFM remains the principal determinant of REE across all age range (Goran *et al*., 1994; Jo *et al*., 2004). The present results (in Table 4.3a and 4.3b) are in agreement with the above findings as they showed a strong positive correlation between REE and FFM: r = 0.898** (male) and 0.539** (female) (P≤0.05). This strong relationship has also been explained by the significant relationship with muscularity or lean body mass (Viitasalo *et al*., 1979). Besides, the effects of FFM, WC, FM, Wt and Ht on REE as observed in this study suggest that male sex hormones cannot entirely influence REE among male adults.

The relationship between REE and WC found in this study was also observed by Jia *et al*., (2005), who similarly showed that the relationship was more pronounced in men and can be used as an index in the evaluation of pathophysiology of intra abdominal obesity. The association may also point to protection by adiponectin against obesity-related disorders, particularly when low REE is present (Wang *et al*., 2004).

CI was also shown to correlate significantly with most abdominal adiposity indices (WC and WHtR), and this finding is in agreement with those of other investigators (Mueller *et al*., 1998; Meerjady *et al*., 2009), but cannot be used to predict cardiometabolic risks in this study, apparently due to the non-obese subjects used in this study.

5.6 Atherogenic index as a risk indicator

The highest variable for metabolic risk factors for non-obese adults in this study was shown for low HDL, which is the same as in previous studies on normal weight individuals (Hadaegh *et al*., 2007; Succuro *et al*., 2008). The strong relationship between cholesterol esterification rate in HDL and lipoprotein particle sizes have been identified as a functional risk marker for metabolic diseases (Nwagha *et al*., 2010). Low density lipoprotein (LDL) concentration has been the prime index of cardiovascular disease risk and the main target for therapy. Beyond LDL lowering, other strategies that might reduce the residual risk include the optional secondary targets which include reducing the TC/HDL ratio, high-sensitivity C-reactive protein and triglycerides, although there are no clinical trial data to support such strategies (Leiter et al., 2011). However, the use of atherogenic index (TC/HDL and LDL/HDL) has been suggested to be a risk indicator with greater predictive values than isolated parameters used independently, particularly LDL. The strong correlation of Wt, Ht, HC, FFM and REE with TC/HDL and LDL/HDL found in men, not in women, is an obvious indication of lower HDL in men than in women as observed in this study. This could mean that the non-obese men in this study are more responsive and at higher risk than women. It should however be noted that Individuals with a high TC/HDL or LDL/HDL ratio have greater cardiovascular risk, owing to the imbalance between the cholesterol carried by atherogenic and protective lipoproteins. This may be

due to an increase in the atherogenic component contained in the numerator, a decrease in the anti-atherosclerotic trait of the denominator, or both (Milan *et al*., 2009).

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMMENDATION

6.1 SUMMARY:

This study was conducted in Zaria; Kaduna state Nigeria; to elucidate the effectiveness of various anthropometric indices as cardiovascular risk and determine which anthropometric index best predicts common cardiovascular risk factors among non obese adults. To achieve this, a purposive and stratified random sampling technique was adopted and 174 subjects were purposively sampled and participated in this cross-sectional study (91 males, mean age = 47.13yr) (83 females, mean age = 44.96yr). Various anthropometric and physiological measurements were taken on each subject using standard process, and their correlated classification was evaluated by descriptive statistics, partial correlation and step-wise multiple regression analysis. A correlation matrix was used to display the behaviours of the variables in relation to one another.

In this study, of all the anthropometric indices measured, axillarry skinfold, FM, WHtR and WC in male and WHtR in female were found to have the strongest correlation relative to at least three risk factors. Combination of three components of cardiometabolic risk factors and atherogenic index were significantly more in male than female. WHtR was found to be most closely related to cardiometabolic risk factors, although not as strong a measure as WC for quantifying abdominal adipose tissue, and not as highly correlated with BMI as WC was, WHtR could add to the strength of BMI and WC in its relationship with cardiometabolic variables in non-obese adults.

In this study, the correlation coefficients between WC and BMI was significant at (r: 0.851 male; r: 0.774 female) and those between WC and WHtR was also significant at (r: 0.925 male; r: 0.916 female); Thus, it is not surprising that both WC and WHtR had a significant relationship with the same variables in male and female groups, and both were better predictors of variables that make up metabolic syndrome than BMI.

This study clearly revealed the sex specificity and relative effectiveness of anthropometric indices in prediction of cardiovascular health among non-obese adults (WC and WHtR in males; WHtR in females). It also showed that the high prevalence of lipid profiles, as cardiovascular risk factors among non-obese adults with men at more risk than women, need special attention, intervention and appropriate treatment. Consistent with other reports, WHtR is a better discriminator of cardiovascular risk factors compared with other anthropometric indices.

Since this anthropometric index is relatively quick, easy, and inexpensive to perform, clinicians should take the time to routinely measure WHtR in the assessment of health risks, especially among non-obese adults. Further research, including collection of longitudinal data is needed before reaching an internationally acceptable simple and appropriate measure that could be effectively used in the clinical and epidemiological fields for non-obese adults.

6.2 CONCLUSION:

Based on the findings of this study and in view of its limitations, the following conclusions were drawn:

1. Same anthropometric indices, which were correlated in obese individuals, were also correlated among non-obese adults in this study.
2. This study clearly revealed the sex specificity and relative effectiveness of anthropometric indices in the relationship and prediction of cardiometabolic risks among non-obese adults.

3. WC and WHtR mediate the correlation between cardiometabolic risk factors and anthropometrics among non-obese adults, with men being at greater risk than women.
4. Of all the anthropometric indices investigated, Waist-height ratio and axillary skin-fold in male group, and waist-height ratio in the female group appear to be better predictors of cardiometabolic risk factors among non-obese adults
5. The most common combination of three components in men was arterial hypertension (SBP/DBP) + abdominal obesity (WC) + hypertriglyceridaemia; and in women - SBP/DBP + WC + high low density lipoprotein.
6. The energy expenditure at rest is strongly associated with adiposity among non-obese adults, and it is a recognized predictor of cardiometabolic risk factors and weight gain.
7. CI shows association with adiposity and not cardiometabolic risks, and might not be a strong factor in health risks study among non-obese adults.

6.2.1 The gains and contributions of this study

1. The association between the measures of adiposity and the clustering of metabolic risk factors among non-obese adults has not been studied in this population.
2. This study will add to the body of research by comparing side-by-side the associations of body mass index, waist circumference and waist-to-height ratio to different cardiometabolic outcomes and using more than one type of analysis, the study suggests optimal cut-off values in screening for increased cardiometabolic risk.
3. The waist-height ratio and axillary skin fold thickness measurements in male and waist-height ratio in female are important predictors of the metabolic abnormalities in non-

obese adults. These simple clinical tools in a clinical setting will be meaningful to diagnose and predict future risk.

4. Body mass index is not a reliable predictor of cardiometabolic risk clustering among non-obese adults.

6.3 RECOMMENDATIONS:

Based on the findings of this study, the following recommendations are proposed:

1. Optimal intervention strategies should be directed towards prevention of fat accumulation and improving fitness by a regular, coordinated and supervised exercise programme and dietary modifications. A three day national exercise and health programme can also be introduced as a means of sensitizing the populace.
2. WHtR, as shown in this study, should be used by physicians as screening tool for metabolic abnormalities in persons with a BMI at the upper end of the normal weight and lower end of the overweight spectrum, since the early detection of Metabolic obese normal weight individuals may be beneficial in the prevention of diabetes and cardiovascular disease.
3. Future longitudinal studies are needed to compare the anthropometrical markers in larger non-obese cohorts, incorporating resting energy expenditure, conicity index, different age groups and ethnic backgrounds.

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Appendix ii

CONSENT LETTER AND FORM

Dear Sir/Ma;

Sharaye, Kolade Oladele , a PhD student of the Department of Human Physiology, A.B.U., Zaria; is conducting research to determine the Physiological and Anthropometric Correlates of Metabolic risk factors among non- obese adults in Zaria, Northern Nigeria. This study will help to improve on the preventive strategies and treatment of metabolic risk complications, specifically cardiovascular diseases and Type II Diabetes Mellitus.

You are therefore being asked to partake in this study where blood samples will be drawn and body measurements will be taken. The information obtained from you will remain confidential and results of your participation will be readily available on request. If you feel you do not want to participate in the study, please feel free to say so.

Thank you for your co-operation.

Yours sincerely,

Kolade Oladele SHARAYE

I ……..... willingly agree to participate in the study and give permission for my results to be used in the study confidentially and results of my participation will be readily available to me on request.

Signature..... Date.....

Appendix iii:
Therapeutic goals and recommendations for clinical management of metabolic syndrome

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Abdominal obesity Reduce body weight by 7% to 10% during year 1 of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI <25 kg/m^2)	Consistently encourage weight maintenance/ reduction through appropriate balance of physical activity, caloric intake, and formal behavior-modification programs when indicated to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of 7% to 10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably 60 min) 5 dys/ wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking, preferably daily, supplemented by increase in daily lifestyle activities (e.g., pedometer step tracking, walking breaks at work, gardening, housework). Longer exercise times can be achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet Reduced intake of saturated fat, *trans*fat and cholesterol	Recommendations: saturated fat <7% of total calories; reduce *trans* fat; dietary cholesterol <200 mg/dL; total fat 25% to 35% of total calories. Most dietary fat should be unsaturated; simple sugars should be limited.
Metabolic risk factors *Atherogenic dyslipidemia* Primary target: elevated LDL Secondary target: elevated non-HDL. High-risk patients*: <130 mg/dL (3.4mmol/L) (optional: <100 mg/dL [2.6 mmol/L] for very high-risk patients) Moderately high-risk patients: <160 mg/dL (4.1 mmol/L). Therapeutic option: <130 mg/dL (3.4 mmol/L) Moderate-risk patients: <160 mg/dL (4.1 mmol/L) Lower-risk patients: <190 mg/dL (4.9 mmol/L)	*Options:* Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD in people with metabolic syndrome. The VA-HIT showed that raising HDL concentrations using a fibrate in patients with well-established CHD and both a low HDL and a low LDL-c level will significantly reduce the incidence of major coronary events. Statins to reduce all ApoB-containing lipoproteins and to achieve ATP III goals for LDL as well as for non-HDL (ATP III, 2001). Fibrates in combination with statins but may be complicated by side effects.
Elevated BP Reduce BP to at least achieve BP of	For BP 120/80 mm Hg: Initiate or maintain lifestyle modification in all patients with metabolic syndrome: weight control, increased

<140/90 mm Hg (or <130/80 mm Hg if diabetes present). Reduce BP further to extent possible through lifestyle changes.	physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. For BP 140/90 mm Hg (or 130/80 mm Hg for individuals with chronic kidney disease or diabetes): As tolerated, add BP medication as needed to achieve goal BP. Examples are IACE and ARA. But no particular agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.
Elevated glucose For IFG, delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A1C <7.0%	For IFG, encourage weight reduction and increased physical activity. For type 2 diabetes mellitus, lifestyle therapy, and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C (<7%). Modify other risk factors and behaviors (e.g., abdominal obesity, physical inactivity, elevated BP, lipid abnormalities). Some Insulin sensitizers have also been identified: Glitazones, Metformines and Thiazolidionediones
Reduce thrombotic and fibrinolytic risk factors	High-risk patients: Initiate and continue low-dose aspirin therapy; in patients with ASCVD, consider clopidogrel if aspirin is contraindicated. Moderately high-risk patients: Consider low-dose aspirin prophylaxis
Proinflammatory state	Recommendations: no specific therapy beyond lifestyle modifications but Aspirin has been considered.

Abbreviations: TG: Triglycerides; BP: Blood Pressure; CVD: Cardiovascular Disease; CHF: Congestive Heart Failure; BMI: Body Mass Index; IFG: Impaired Fasting Glucose; ASCVD: Atherosclerotic Cardiovascular Disease, IACE: Inhibitors of Angiotensine Converting Enzyme, ARA: Angiotensine Receptor Antagonists, VA-HIT: Veterans Affairs High-Density Lipoprotein Intervention Trial.

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes TIA or stroke of carotid origin or >50% carotid stenosis. Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome. Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%. Factors that favour therapeutic option of non-HDL-C <100 mg/dL are those that can raise individuals to upper range of moderately high risk: multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex). Moderate-risk patients are those with 2 plus major risk factors and 10-year risk <10%. (Grundy *et al*., 2005; IDF, 2005; Fulop *et al*., 2006).