UNIVERSITY FOR DEVELOPMENT STUDIES

INSULIN RESISTANCE IN RELATION TO OBESITY, NON-ALCOHOLIC FATTY LIVER DISEASE, SEXUAL DYSFUNCTION AND DYSLIPIDAEMIA AMONG MEN CLINICALLY DIAGNOSED WITH TYPE 2 DIABETES

BY

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DECLARATION

I hereby declare that this thesis is the result of my original work and that no part of it has been presented for another degree in this University or elsewhere.

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I hereby declare that the preparation and presentation of the thesis was supervised following the guidelines on supervision of thesis laid down by the University for Development studies.

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ABSTRACT

From a pathophysiological standpoint, type 2 diabetes can result from insulin resistance or insulin insufficiency alone. It is unclear which of the two is linked to adverse health outcomes. Therefore, the objective of this study was to evaluate the relationship between insulin resistance (IR) and obesity, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), and sexual dysfunction (SD) in men with type 2 diabetes mellitus as well as the interaction between IR and obesity on adverse cardiometabolic outcomes. One hundred twenty-one (121) type 2 diabetic men participated in this cross-sectional study, which was conducted between September 2018 and September 2019. To collect sociodemographic information, a self-made questionnaire was used. Anthropometric measures were also taken and blood samples collected for measurement of insulin, glucose and other biochemical parameters. Sexual dysfunction was assessed using a GRISS questionnaire and non-alcoholic fatty liver disease, using the fatty liver index. HOMA-IR was calculated from the fasting insulin and glucose values and a HOMA-IR ≥2 was considered as insulin resistance. Of the 121 participants, 39.7% were classified as insulin resistant. Anthropometric markers of obesity and prevalence of obesity were higher in the insulin resistant group, whiles adiponectin was lower in the insulin resistant group. Similarly, LDL-c and total cholesterol were higher in the insulin resistance group with LDL but were not independently associated with insulin resistance. Fatty liver index and AST were higher and independently associated with insulin resistance. Even though the sexual dysfunction score was higher in the insulin resistance, only non-communication and infrequency were independently associated with insulin resistance. BMI, LDL-c, AST and stanine score for infrequency of sex, were found to better classify subjects as insulin resistance and may prove useful in risk stratification. A comorbidity of obesity and insulin resistance were seen to reflect higher levels total cholesterol, LDL-cholesterol, fatty liver index and testosterone levels than in isolated cases of the two abnormalities. Insulin resistance among type two diabetics is thus independently associated with obesity, low adiponectin levels, high risk of non-alcoholic fatty liver disease and higher testosterone. Estimation of c-peptide instead of insulin in the assessment of insulin resistance may prove useful in future studies.

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LIST OF ABBREVIATIONS

4-AAP	-	4-Aminoantipyrine
5HMF	-	5- hydroxymethylfurfural
AACE	-	American Association of Clinical Endocrinologists
Ach	-	Acetylcholine
ADA	-	American Diabetes Association
AHA/NHLBI	-	America Heart Association/National Heart, Lungs, And Blood Institute
AV	-	Avoidance
BMI	-	Body Mass Index
CDC	-	Center for Disease Control
cGMP	-	Cyclic Guanosine Monophosphate
CHD	-	Coranary Heart Disease
CHS	-	Cardiovascular Health Survey
CVD	-	Cardiovascular Disease
DAP	-	Dihydroxyacetone Phosphate
DIS	-	Dissatisfaction
DM	-	Diabetes Mellitus
DOD	-	Duration of Disease
ED	-	Erectile Dysfunction
EDTA	-	Ethylene Diamine Tetraacetic Acid
EGIR	-	European Group for The Study of Insulin Resistance
eNO(S)	-	Endothelial Nitric Oxide (Synthase)
FBG	-	Fasting Blood Glucose
FFA	-	Free Fatty Acids
GPO	-	Glycerophosphate Oxidase
GRISS	-	Golombok-Rust Inventory for Sexual Satisfaction-M
GRISS-M	-	Golombuk-Rust Inventory for Sexual Saisfaction-Male
HbA1c	-	Haemoglobi A1c
HC	-	Hip Circumference
HDL-C	-	High Density Lipoprotein Cholesterol
HPG-axis	-	Hypothalamic Pituitary Gonadal- axis
HRP	-	Horseradish Peroxidase
IDF	-	International Diabetes Federation
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
IL	-	Interleukin

IMP	-	Impotence
INF	-	Infrequency
IR	-	Insulin Resistance
LDL	-	Low Density Lipoprotein
LH	-	Luteinizing Hormone
MAPK	-	Mitogen-Activated Protein Kinase
METS	-	Metabolic Syndrome
MMAS	-	Massachusetts Male Aging Study
NAFLD	-	Non-Alcoholic Fatty Liver Disease
NHANES	-	National Health and Nutritional Examination Survey
NO	-	Nitric Oxide
NS	-	Non-sensuality
PAI	-	Plasminogen Activator Inhibitor
PCOS	-	Polycystic Ovarian Syndrome
PDEF	-	Phosphodiesterase 5
PE	-	Premature Ejaculation
RBCs	-	Red Blood Cells
RMR	-	Resting Metabolic Rate
ROS	-	Reactive Oxygen Species
SAT	-	Subcutaneous Adipose Tissue
SD	-	Sexual Dysfunction
SHBG	-	Sex Hormone Binding Globulin
T2DM	-	Type 2 Diabetes Mellitus
TG	-	Triglycerides
TNF-a	-	Tumor Necrosis Factor Alpha
VAT	-	Visceral Adipose Tissue
VLDL	-	Very Low-Density Lipoproteins
WC	-	Waist Circumference
WHO	-	World Health Organisation
WHR	-	Waist to Hip Ratio

Chapter 1
INTRODUCTION

1.1 Background

Diabetes Mellitus is a chronic illness which occurs either when the pancreatic beta (β)-cells are unable to synthesise adequate insulin or the body is unable to utilise the insulin that is produced. Uncontrolled diabetes usually leads to hyperglycaemia (increased blood glucose), which eventually causes major harm to numerous bodily systems, particularly the heart, blood vessels, and neurons (World Health Organization, 2015). Two major forms of diabetes mellitus have been explained; type 1 and type 2.

Type one (1) diabetes mellitus (previously referred to as juvenile or childhood onset, insulin dependent, diabetes) is characterized by inadequate insulin synthesis and necessitates insulin therapy. The pathophysiology of type 1 diabetes involves a number of functional flaws in the immune system, β-cells, bone marrow and the thymus (Atkinson *et al.*, 2014). Type two (2) diabetes (formerly called adult onset or non-insulin dependent) is linked to β-cell dysfunction and insulin resistance, (especially hepatic insulin resistance) (Ferrannini and Mari, 2014) and makes up 90% of individuals with diabetes around the globe (World Health Organization, 2015).

It is abundantly clear from extensive research on the pathophysiology of type 2 diabetes before hyperglycaemia manifests, reductions in both beta-cell function and insulin sensitivity have already occurred (Reaven, 1988). According to various studies, insulin resistance is the initial defect and β-cell dysfunction is a late occurrence that results from the sustained, increased secretory demand that insulin resistance places on the β-cell. (DeFronzo, 1992; Kruszynska and Olefsky, 1996). On the other hand, other researchers believe that the shift from normal glucose tolerance to hyperglycaemia requires diminished β-cell function, which manifests as lower insulin release (Porte Jr, 1991; Mitrakou *et al.*, 1992; Kahn, 2001).

Insulin resistance (IR) is a disorder where the body's ability to respond to the hormone's normal functions, which include delivering circulating glucose to cells, is compromised. This contributes to the emergence of type 2 diabetes and hyperglycaemia (T2DM). Pancreatic β-cells ultimately, produce more insulin, which tends to cause hyperinsulinaemia (DeFronzo, 2009). The β-cells of

the pancreas produce the anabolic hormone insulin, which plays a variety of roles in the control of protein, lipid, and carbohydrate metabolism. In addition to controlling the transport of glucose into muscles, insulin lowers hepatic glucose synthesis. When insulin resistance occurs, too much glucose is generated, which contributes to hyperglycaemia (Saltiel and Kahn, 2001).

Insulin slows the breakdown of triglycerides that have been accumulated while increasing the uptake of circulating lipoproteins from circulation. Thus, lower absorption and increased lipid mobilization brought on by insulin resistance result in higher blood levels of free fatty acids. Extra glucose is stored as glycogen in the liver and muscle cells and as triglycerides in fat cells after it has been delivered into the cells where it is utilized to produce energy. In light of this, decreased muscle glucose absorption, higher hepatic glucose synthesis, and increased blood fatty-acid content all contribute to elevated blood glucose levels (Saltiel and Kahn, 2001). When β-cells detect hyperglycaemia, more insulin is released, resulting in hyperinsulinaemia. When the pancreas is unable to produce enough insulin to counteract the high blood glucose and insulin resistance, blood glucose concentrations rise even higher, resulting in T2DM (Saltiel and Kahn, 2001).

Several techniques have been developed over time to evaluate insulin resistance (Singh and Saxena, 2010). The gold standard approach, the hyperinsulinemic euglycemic glucose clamp, has limitations due to its invasiveness, complexity, high cost, and rigorous restrictions. The homeostasis model assessment of insulin resistance (HOMA-IR), on the other hand, offers a practical and affordable method of assessing insulin resistance, and the results have been proven to closely match those from the euglycemic clamp (Bonora *et al.*, 2000; Wallace *et al.*, 2004).

The HOMA-IR assumes a feedback loop between hepatic glucose release and pancreatic insulin secretion in the fasting state (Turner *et al.*, 1971). While HOMA-IR calculates fasting IR using standard laboratory data, its correlation with physiologic approaches is only moderate, with published results between 0.6 and 0.9 (Bonora *et al.*, 2000; Yeni-Komshian *et al.*, 2000; Einhorn, 2003; Wallace *et al.*, 2004). Despite not optimally reflecting the physiology, HOMA-IR has been used in a variety of scenarios and can offer reasonable population estimates of future CVD and diabetes complications (Wallace *et al.*, 2004).

There are a number of metabolic disorders that have been linked to hyperinsulinaemia and underlying insulin resistance with several studies finding that a number of common non-communicable diseases in men, like dyslipidaemia, obesity, non-alcoholic fatty liver disease, hypertension, cardiovascular disease, sleep apnoea, and sexual and erectile dysfunction, are largely pathophysiologically influenced by insulin resistance (Kelly, 2000; Tsai *et al.*, 2004; Krentz, 2008; Chen *et al.*, 2013; Li *et al.*, 2015; Ormazabal *et al.*, 2018).

1.2 Justification/Problem Statement

Previously believed to be a disease of the wealthy and high-income nations, diabetes is now prevalent around the globe, including rural areas of low- and middle-income nations. In 2014, the WHO predicts that 422 million people worldwide will have diabetes. Age-adjusted prevalence increased from 4.7% in 1980 to 8.5% in 2014, with low- and middle-income nations experiencing the largest increases (World Health Organization, 2015).

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance (IR) (hyperinsulinaemia) and beta-cell dysfunction (relative insulin deficiency), however it is unknown how much each contributes to the pathogenesis of Type 2 diabetes (O'Rahilly *et al.*, 1988; Temple *et al.*, 1989; DeFronzo, 1992). This discrepancy between the relative importance of beta-cell dysfunction and insulin resistance during diagnosis is partially brought on by the fact that these parameters are typically not evaluated during diagnosis or are frequently evaluated in isolation. Once the existence of a carefully controlled feedback mechanism including beta-cells and insulin-sensitive tissues is taken into account, it becomes abundantly obvious that early in the course of the development of T2DM, both impairments in insulin sensitivity and beta-cell activity may be present (Reaven, 1988).

Clinically, type 2 diabetes is identified by elevated plasma glucose levels that are controllable without the use of exogenous insulin (no other substrate or hormone is taken into consideration) (World Health Organisation, 1985). Such a broad definition pigeonholes a wide range of conditions such as people with a relative insulin deficiency (Zimmet, 1995). Also, a considerable number of people who develop diabetes after 40 years do not have insulin resistance (Naseem *et al.*, 2012).

Many type-2 diabetics may be presumed to be insulin resistant to some extent and, by description, each diabetic person produces less insulin than required for their level of insulin sensitivity (Ferrannini, 1998). Additionally, each patient's combination of insulin resistance and insulin shortage may be unique, and in any subject, it may change over the course of the disease. Clinically, it is more of a matter of preference than a conclusion based on facts to view relative insulin deficiency or insulin resistance as the primary factor affecting each individual patient with type 2 diabetes.

Pathophysiologically, plasma glucose levels can change due to insulin resistance or insulin insufficiency alone (Thow *et al.*, 1988; Taylor *et al.*, 1994). However, despite the possibility of type two diabetics being insulin resistant or a relatively insulin deficient, it is still unclear which category of type 2 diabetics, whether those with marked insulin resistance or relative insulin deficiency are more prone to adverse cardiometabolic outcomes. Additionally, studies which include both men and women may lack statistical power to detect meaningful results for men. Therefore, an assessment of IR and its associated metabolic outcomes among diabetic men, is necessary in the risk stratification, evaluation, and monitoring of treatment of DM.

1.3 Aim

The aim of this study is to assess the interplay of insulin resistance (IR), with obesity, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD) and sexual dysfunction (SD) among men clinically diagnosed with type 2 diabetes mellitus.

1.3.1 Specific objectives

1. To assess the association between HOMA-IR and markers of obesity (BMI, WHR and WC) as well adipokines (adiponectin and leptin) among male T2DM subjects
2. To assess the association between HOMA-IR, dyslipidaemia and hypertension among male T2DM subjects.
3. To evaluate the relation between HOMA-IR and NAFLD as well as liver function in male T2DM subjects.
4. To evaluate the relation between HOMA-IR, SD, SD domains and testosterone levels among male T2DM subjects.

5. To assess the effect of insulin resistance and obesity comorbidity on dyslipidaemia, hypertension, NAFLD and SD among male T2DM subjects.

Chapter 2

LITERATURE REVIEW

2.1 Diabetes Mellitus

Diabetes is a disease in which the body's capacity to handle glucose is compromised. According to MacCracken *et al.* (1997) this illness is likewise marked by a "too great emptying of urine," as recorded in ancient Egyptian texts from 1500 BC. Indian doctors gave the illness the original name of *madhumeha*, which translates as "honey urine," because of how insects were drawn to it. Sushruta, an Indian surgeon, and Charaka, a physician, both discovered the types of diabetes. Later, type 1 and type 2 were used to describe these types (Frank, 1957; Tipton, 2008).

According to several research, Aretaeus the Cappadocian, who later coined the name diabetes, provided the first comprehensive description of this illness. No important component of the liquid is absorbed by the body while large quantities of flesh are dissolved into urine, according to Aretaeus (Ahmed, 2002; Sanders, 2002; Sattley, 2008). Additionally, the great Persian physician Avicenna was the first to describe diabetic gangrene and an aberrant hunger connected with the disease (Dobson, 1776). British General Surgeon created the word "*mellitus*" in 1798 to assist distinguish one form of diabetes from the other (*Insipidus*), whose urine is not honey-like (MacCracken *et al.*, 1997).

Paul Langerhans discovered the insulin-producing cells for the first time in 1869; they were thereafter known as islets of Langerhans (Sakula, 1988). The name "insulin" was first used to describe the hormone generated by the Islets of Langerhans that was found to lower blood glucose levels in two experiments conducted by Mayer and Schaefer in 1909 and 1910, respectively (De Mayer, 1909; Sharpey-Schäfer, 1914).

2.2 Types of Diabetes Mellitus

The categorisation of diabetes is crucial to the treatment plan. Numerous studies have highlighted the difficulty in categorizing diabetes because many patients, notably younger ones, fit into multiple categorises (Rosenbloom *et al.*, 2009; Thunander *et al.*, 2012; American Diabetes Association, 2014). The American Diabetes Association's (ADA) classification from 1997, which divides diabetes into types 1 and 2, as well as other forms including monogenic diabetes

and gestational diabetes, is the most frequently acknowledged and utilized classification system for diabetes (American Diabetes Association, 2014).

2.3 Type 1 Diabetes Mellitus (T1DM)

The principal cause of T1DM is autoimmune destruction of the pancreatic beta cells. Insulin is an anabolic hormone that is synthesized by these β-cells. Insulin is known to have effects on the metabolism of proteins, lipids, carbohydrates, and minerals, which has an impact on growth. Insulin works by promoting glucose transport into adipose and muscle cells and by encouraging hepatocytes to store glucose as glycogen. It also facilitates the uptake of potassium into cells, the production of fatty acids, the inhibition of fatty acid catabolism, and the uptake of amino acids. Most TIDM patients are prescribed lifelong insulin treatment (Yue *et al.*, 2018; Saxby *et al.*, 2020).

2.3.1 Prevalence of Type 1 Diabetes Mellitus

Several studies have shown that the prevalence of type 1 diabetes are rising by an average of 2-3% annually on a global scale (Maahs *et al.*, 2010; Mayer-Davis *et al.*, 2017). Type 1 diabetes prevalence and incidence were projected to be 9,004,610 and 234,710, respectively, in 2017 (Green *et al.*, 2021). Green and his team also noted that the global prevalence and incidence were, respectively, 52% and 49% higher in high income nations. Additionally, 31 and 32% of the global prevalence and occurrence were linked to Asia, which is home to nearly 60% of the world's population. According to the same study, there were 6%, 35%, 43%, and 16% prevalence instances in the age ranges of 0 to 14, 15 to 39, 40 to 64, and 65 years and over, respectively.

According to International Diabetes Federation (2021) , sub-Saharan Africa is seeing a sharp rise in the prevalence of diabetes in accordance with the global trend. According to several research, sub-Saharan Africa is anticipated to have the highest incidence of diabetes in relation to the rest of the globe. About 5–15% of diabetes cases in Africa are type 1 diabetes and other uncommon forms of the disease (Mbanya *et al.*, 2010; Hall *et al.*, 2011).

Sarfo-Kantanka *et al.* (2020) studies at the Komfo Anokye Teaching Hospital in Ghana, found out that women are more likely than men to develop type 1 diabetes. According to the same study, there was a diminution in the number of subjects with T1DM in the 10–19 age range between 1992 and 1994, followed by an increase in the medical condition in the same age range from 1995

to 2018. On the other hand, the incidence of T1DM in patients aged 0 to 9 years decreased between 1992 and 2018 (Sarfo-Kantanka *et al.*, 2020).

2.4 Type 2 Diabetes Mellitus (T2DM)

Diabetes mellitus, according to the WHO, is a metabolic disorder that causes damage to the kidneys, eyes, heart, nerves, and other body organs as a result of high blood sugar levels. T2DM accounts for more than 90% of diabetes cases worldwide. T2DM is distinguished by tissue insulin resistance (IR), a decrease in insulin secretion, and a lack of compensatory responses to insulin secretion (Weyer *et al.*, 1999; Stumvoll *et al.*, 2005). As T2DM worsens, the body's ability to maintain glucose homeostasis is compromised due to the beta cells' reduced sensitivity to insulin. Additionally, T2DM patients have increased levels of body fat in their abdomens, making them obese. These lipids promote the metabolism of free fatty acids and adipokines, which both contribute to insulin resistance (Galicia-Garcia *et al.*, 2020). According to Schwartz *et al.* (2016), alterations in the body's microbiota, immune system dysregulation, and dysregulation of adipokines are important causes of T2DM. T2DM has been linked to several main organs, including those in the brain, small intestine, kidneys, skeletal muscle, pancreas, liver, and adipose tissue (DeFronzo, 2009).

2.4.1 Prevalence of T2DM

According to studies by Khan *et al.* (2020), there were 462 million people with T2DM worldwide in 2017. This amount roughly corresponds to 6.28% of the global population. The study's findings led to an estimated global prevalence rate of 6059 cases per 100,000 people. The authors also noted that diabetes may contribute to more than 1 million deaths annually. This ranked diabetes as the ninth most common cause of mortality worldwide. T2DM has been observed to affect both sexes equally. If precautions are not taken, it is predicted that by 2030, 7079 out of every 100,000 people will have T2DM (Khan *et al.*, 2020).

According to the International Diabetes Federation, 4.2 million deaths worldwide in 2019 were caused by diabetes (International Diabetes Federation, 2021). Globally, it is predicted that the prevalence of diabetes will increase by about 2.5% annually. In addition, between the ages of 20 and 79, an estimated 463 million people are said to have T2DM. In 2019, it is anticipated that spending on diabetes would total around 720 billion USD. Furthermore, given that 232 million

people have T2DM that was not properly identified, this figure might not be a genuine depiction of the situation. This number equates to one out of every three diabetic patients.

Many T2DM patients are between the ages of 40 and 59, according to several studies. The number of patients with T2DM varies greatly between countries. The estimated burden of T2DM among people with low and middle incomes is roughly 4/5 of all cases worldwide. The way T2DM is treated is significantly impacted by this result. Cardiovascular disease is the leading cause of death in people with type 2 diabetes, therefore their risk of passing away is 15% higher than that of people in general health (Gæde *et al.*, 2003). Sedentary behaviour, a high caloric diet, obesity, and an aging population are the major factors behind the worldwide rise in type 2 diabetes (Zhou *et al.*, 2016; Chatterjee *et al.*, 2017).

2.4.2 Prevalence of T2DM in Sub-Saharan Africa

According to IDF estimates from 2019, Africa is home to the greatest number of T2DM cases that have never been properly diagnosed. These unidentified incidents affected people between the ages of 20 and 79 (Saeedi *et al.*, 2019; International Diabetes Federation, 2021). As more data from Tanzania, South Africa, and Tanzania reached a consensus, there has been an rise in the incidence of T2DM in Sub-Saharan Africa during the past ten years (Mbanya *et al.*, 2010; Peer *et al.*, 2012; Hird *et al.*, 2016). Studies conducted in Durban between 1984 and 2014 revealed a 2.4-fold increase, and studies conducted in Cape town between 1993 and 2012 revealed a 1.5-fold increase (Omar *et al.*, 1993; Peer *et al.*, 2012). These findings are in agreement with trends of studies in west African regions over the last ten years.

2.4.3 Prevalence of T2DM in Ghana

A previous meta-analysis research in Ghana found that diabetes prevalence among adults was 6.5%. According to the survey, the southern belt and people over 40 years old had the highest incidence rates (Asamoah-Boaheng *et al.*, 2019). According to earlier research published in 2007, the incidence in some regions of the country will exceed the global prevalence (Aikins, 2007). A recent study comprising 202 people in Ho, Ghana, revealed prevalence rates for T2DM and prediabetes of 6.9% and 17.3%, respectively. According to the same study, the prevalence rates for the age ranges of 30-39, 40-49, 50-59, 60-69, and above 70 years were 0%, 42%, 21.4%, 21.4%, and 14.3%, respectively. The investigators also noted that hypertensives had a greater

frequency of T2DM than normotensives, and that T2DM was more common among drinkers than non-alcoholics (Bawah *et al.*, 2021). The results of another study conducted in the Ashanti region of Ghana showed a greater prevalence of T2DM, with the incidence occurring predominantly in females and those living in urban centres (Katey *et al.*, 2022).

2.4.4 Pathophysiology of T2DM

According to Stumvoll *et al.* (2005), hyperglycaemia results from aberrant feedback loops between insulin's activity and its secretion. When the pancreatic beta cells malfunction, less glucose is released, which reduces the body's capacity to keep normal blood glucose levels. On the other hand, the adipocytes, hepatocytes, and muscle cells are unable to ingest as much glucose as they would otherwise because of the liver's increased synthesis of glucose as a result of insulin resistance.

Even though both mechanisms are present in the early phases of the aetiology of T2DM, the effects of cells not operating correctly are more profound compared to those of insulin resistance (IR). When both IR and insufficient B-cell function are the underlying causes of T2DM, blood glucose levels are amplified, according to several studies. The T2DM gets worse when these two processes happen at the same time (Cerf, 2013; Zheng *et al.*, 2018).

2.4.5 Risk Factors for T2DM

In sub-Saharan Africa, Motala *et al.* (2022) identified a number of factors as key risk factors for T2DM, including physical activity, diet, urbanization, migration, age, sex, obesity, family history, ethnicity, diet, and others.

2.4.5.1 Ethnicity and Family History/Genetic Predisposition

Numerous researches have shown that there is an increased likelihood of T2DM worldwide for Japanese, Hispanics, and Native Americans. This lends credence to the idea that T2DM differs between different geographic regions and racial/ethnic groupings (Chan *et al.*, 1993; Liu *et al.*, 2009). In addition, several researches have shown that Asians are more likely than White Americans and UK nationals to suffer from type 2 diabetes. It is augmented reality that black people are more likely to have T2DM (Haines *et al.*, 2007; Shah *et al.*, 2015). There is no better explanation for this phenomenon, although some scholars agree that sedentary lifestyles, socioeconomic conditions, and genetic predispositions may contribute to these results.

Over last ten years, a number of research have demonstrated the influence of multiple genes on T2DM. These genes are hypothesized to primarily influence one's vulnerability to T2DM through the secretion of insulin. Several investigations have also revealed that other genes reduce the action of insulin (McCarthy, 2010; Fuchsberger *et al.*, 2016). Dimas *et al.* (2014) were able to categorize these gene variations according to how they affect T2DM. Several researches shows that one polymorphism was linked to altered insulin processing fits the insulin resistance pathway, decreases insulin production with normal fasting blood sugar levels, and decreases insulin production with fasting high blood glucose levels (Stumvoll *et al.*, 2005; Chatterjee *et al.*, 2017).

Furthermore, it was found in the same study that T2DM is highly polygenic, hence further linkage studies are important to identify other T2DM loci (Flannick and Florez, 2016) . Clinical trials and a few observational studies have suggested that there may be an unexplained hereditary component to T2DM that links environmental influences with gene loci's propensity. This mechanism explains the control of genetic variations by environmental variables (Franks *et al.*, 2013)

2.4.5.2 Obesity, Unhealthy Diet and Low Physical Activity

Obesity has been associated to metabolic disturbances that result in IR, and two studies have found that it doubles the chance of developing type 2 diabetes (T2DM) (Carey *et al.*, 1997; Bellou *et al.*, 2018). The age of T2DM diagnosis and BMI was discovered to be negatively correlated, according to Hillier and Pedula (2003). Obesity hasn't been fully described as the cause of T2DM and IR. Numerous elements have been observed to be crucial in the development of this disease. All of these entail processes for inter-organ and cell-autonomous communication. According to several studies, walking for 2 to 3 hours per week or for at least 20 to an hour per week reduces the risk of getting T2DM by 34% and 56%, accordingly. This result confirms the hypothesis that a sedentary lifestyle contributes to the occurrence of type 2 diabetes (Lynch *et al.*, 1996; Weinstein *et al.*, 2004).

In the delayed start of T2DM, physical activity is well established to be crucial. When one exercises, glucose absorption is enhanced because blood supply to the muscle is improved as a result of the contraction of the skeletal muscle cells. Additionally, it is well recognized that exercise reduces the aberrant fat deposits in the abdomen that promotes IR. Furthermore, it has been found that light exercise increases glucose absorption by roughly 40% (Ross, 2003; Strasser,

2013). Exercise can help reverse oxidative stress and inflammation because it improves insulin sensitivity and glucose absorption (Venkatasamy *et al.*, 2013).

2.4.6 Clinical Presentation of T2DM

The clinical profile of T2DM in both children and adults does not follow any specific patterns. According to a number of studies, roughly one-third of T2DM individuals do not initially exhibit any diabetes-related symptoms. These people are frequently in their mid-adolescence, are obese, and have one or more diabetes risk factors. They may also have glucosuria. Additionally, these people could exhibit Metabolic Syndrome (MetS) symptoms as hypertension, dyslipidaemia, and others (Reinehr, 2005).

About 50% of adolescents with T2DM have common hyperglycaemic symptoms as nocturia, polydipsia, and polyuria (Scott *et al.*, 1997). Patients with T2DM may also experience weight loss. According to Curran *et al.* (2011), teenage girls can get vulvovaginitis or fungal skin infections. Few people with T2DM experience ketonuria, acidosis, or hyperglycaemia, which are symptoms of diabetic ketoacidosis. Hyperosmolar hyperglycaemia is one of the rarest clinical manifestations in children with T2DM. Severe dehydration, an increase in serum osmolality exceeding 330mOsm/kg, hyperglycaemia with plasma glucose above 33mmol/L, and slight or non-existent ketonuria are its defining features (Zeitler *et al.*, 2011)

2.4.7 Diagnosis of T2DM

There are primarily two phases involved in the confidential diagnosis of a patient with T2DM. In order to identify T2DM from the other types of diabetes, particularly T1DM, it is first necessary to determine that a person has diabetes. Diabetes diagnosis techniques have already been covered in the section on T1DM diagnosis. To be able to differentiate between T2DM and T1DM, the clinical presentation, history, and various test data are taken into consideration. Early in the course of the disease, differentiation is practically impossible. Age, ethnicity, family history, body weight, clinical results, and other variables are among those taken into account. According to studies by Dabelea *et al.* (2007), T2DM often manifests after puberty, while roughly half of T1DM individuals arrive before the age of 10. According to Copeland *et al.* (2011) reports, more T2DM patients than T1DM patients already had family members who had the illness.

Type 2 DM is more common in African Americans, Pacific Islanders, and Native Americans than it is in Caucasians, according to studies by Dabelea *et al.* (2014). Furthermore, compared to

T1DM, T2DM is more frequently observed in obese people (Liu *et al.*, 2010). Additionally, compared to T1DM, T2DM is more likely to have hypertension, acanthosis nigricans, polycystic ovarian syndrome, dyslipidaemia, and other characteristics of the metabolic syndrome (Dabelea *et al.*, 2011). Further, T1DM is more likely to have pancreatic autoantibodies than T2DM, such as anti-glutamic acid decarboxylase, islet cell antibody, and tyrosine phosphatase (Klingensmith *et al.*, 2010). Additionally, observing ketoacidosis can help differentiate between T1DM and T2DM. Measurements of urine ketones and venous pH are used for this. C-peptide and insulin levels can help distinguish between T1DM and T2DM. Lower C-peptide levels are indicative of T1DM (Ludvigsson *et al.*, 2012).

Moreover, autoantibodies of the pancreas such as anti-glutamic acid decarboxylase, islet cell antibody, tyrosine phosphatase are usually seen in T1DM than T2DM (50). Additionally, the observation of ketoacidosis can aid in the differential diagnoses of T1DM from T2DM. This is done by taking measurement venous pH and urinary ketones. The quantity of C-peptide and insulin can aid in distinguishing T1DM from T2DM. low levels of C-peptide suggest T1DM (Ludvigsson *et al.*, 2012).

2.5 Insulin

Wilcox (2005) claims that Insulin is a peptide hormone made by the pancreatic beta cells that helps control blood sugar levels by promoting cellular glucose uptake, modifying protein, carbohydrate, and lipid metabolism, and stimulating cell division and growth through mitogenic actions. German scientists Vonmering and Minkowski's pancreatomy animal tests in 1889 led to the discovery of the hormone insulin. Belgian researcher de Meyer suggested the term insulin in 1909 for isolates he had taken from the pancreas. After certain experiments were presented to the Association of Americans physicians later in 1922, the term "insulin" was coined (Bliss, 1993).

2.5.1 Structure and Chemical Properties of Insulin

Research indicates that the amino acid sequence of insulin and its identification as a polypeptide occurred in 1928 and 1952, respectively. It is a dipeptide hormone because of the chains that make up its structure. These chains were joined together via disulphide bridges. According to Dodson and Steiner (1998), it has a molecular weight of 5802 and is made up of 51 amino acids. The hormone's isoelectric point is pH 5.5. The core helical segment of the chain is connected to the N-terminal of the α-chain by an anti-parallel C terminal helix. It was found that in proinsulin,

the N-terminal of the β-chain is connected to the C-terminal of the chain (Dodson and Steiner, 1998).

2.5.2 Physiological Role of Insulin

According to Burks and White (2001), in a fed condition, the human insulin is involved in the modulation of cellular energy supply and balance of micronutrient. The hormone plays a key role in the uptake of glucose into muscles, liver, adipose tissues and other tissues where are insulin dependent. Lipid's synthesis is enhanced and lipolysis is suppressed in a state of high body energy levels, which prompts the secretion of insulin. The entry of glucose into the myocytes enhanced the glycogenesis and storage of glycogen. This prevents the myocytes from using amino acids or fatty acids for muscle contraction. According to research by Masharani and German (2011), insulin obstruct gluconeogenesis and lipolysis in the muscular tissues whiles enhancing glycogenesis and lipid synthesis. If there is abundance of amino acids, insulin acts as anabolic hormone in the muscular tissue.

2.5.3 Role Of Insulin Pathology

2.5.3.1 Insulin Deficiency

The availability of nutrients has a significant impact on the secretion and functional regulation of insulin. Consuming fatty foods alters the physiology of the mitochondria. This promotes the excessive production of reactive oxidant species, which hinders insulin's ability to work (ROS). According to Ruegsegger *et al.* (2018), aerobic exercise improves insulin activity and increases mitochondrial biogenesis in people who are insulin resistant. Additionally, Thomas *et al.* (2019a) investigations found that T1DM patients over 30 with insulin insufficiency exhibit the same biochemical and clinical symptoms as those who are younger. In these people, insulin insufficiency is difficult to diagnose. According to Bazotte *et al.* (2014), hyperglycaemia build-up should always be expected in obese and IR patients. Santoleri and Titchenell (2019) asserts that both extrahepatic and intrahepatic pathways are involved in the control of lipid and glucose metabolism by glucose. The interaction between these pathways is thought to have an impact on the regulation of insulin signalling.

According to Titchenell *et al.* (2016), lipogenesis, not gluconeogenesis, is the primary function of direct insulin signalling on the hepatocytes. Research has revealed that the actions of insulin insufficiency and IR alone can change plasma glucose levels in a disease state (Ferrannini, 1998).

According to research by Woo (2015), limiting fast-acting insulin peaks and prolonging the basal insulin's action period are crucial for diabetic patients. The use of multiple systems for delivering insulin was found to be one method of improving control of high blood sugar levels, according to the same study. The adoption of an artificial pancreas or closed loop system, in addition, has further advantages for glycaemic management (Majeed and Thabit, 2018).

According to Ramzy *et al.* (2018), persons with the cell phenotype benefit somewhat from short-term insulin glargine use, but long-term insulin replacement with isogenic transplants enhances the production of numerous mature cells. Additional research by Nathan *et al.* (2009) shown that due to microvasculature, IR and other variables are implicated in issues related to diabetes. Cerasi (1995) has demonstrated that the presence of both sustained high glucose levels and an increase in insulin levels indicates the existence of insulin dysfunction. When the first-stage response of insulin to glucose administration by intravenous is absent, it is a warning sign that the cells are malfunctioning. The absence is essential to understanding how diabetes will develop in the future (Groop *et al.*, 1993).

2.5.3.2 Hyperinsulinemia

Hyperinsulinemia is characterized by an elevated level of insulin in the plasma compared to normal. Hyperinsulinemia patients frequently exhibit mitochondrial dysfunction, destruction of myocardial insulin signalling, changes in calcium homeostasis, ER stress, abnormal immune response, abnormalities in coronary microcirculation, stimulation of the renin-angiotensin-aldosterone system, and sympathetic nervous system injury. The manipulation of these processes leads to an increase in fibrosis, oxidative stress, cardiac diastolic dysfunction, hypertrophy, and ultimately failure of systolic function of the heart (Rahman *et al.*, 2021).

Bazotte *et al.* (2014) suggests that hyperinsulinemia may be the primary cause of the link between T2DM and obesity. For the purpose of diagnosing hyperinsulinemia, the fasting blood glucose levels are utilized as a standard. According to Kuzuya and Matsuda (1997), T2DM and obesity are the two classic IR conditions. As noted by Moghetti and Tosi (2021), the regulation of insulin production by IR leads to hyperinsulinemia. According to a number of studies, hyperinsulinemia is a factor in the increased morbidity and mortality of obese patients due to cardiovascular problems (Thomas *et al.*, 2019a; Thomas *et al.*, 2019b).

Hyperinsulinemia is primarily brought on by IR. In IR, the pancreas produces more insulin in an effort to return things to normal. Rarely, insulinoma, a pancreatic cell tumour, or nesidioblastosis, an abnormal β cell growth, can lead to hyperinsulinemia. This condition is known to result in hypoglycaemia (Coimbra *et al.*, 2010). T2DM, Alzheimer's disease, chronic inflammation, hypertriglyceridemia, and obesity are all direct results of hyperinsulinemia, according to research by Kopp (2019). Furthermore, fatty acids are important in the development of diabetic hyperinsulinemia. This is because a spike in dietary fatty acids stimulated gut enterocyte secretion, which in turn led to a rise in GSIS.

According to studies, diabetic cardiomyopathy exhibited in hyperinsulinemia is classified by mitochondrial dysfunction, ER stress, destruction of myocardial insulin signalling, stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, improper immunological response, deterioration of myocardial insulin signalling, coronary microcirculation derangements, and disturbed homeostasis of calcium (Jia *et al.*, 2018). According to Otto-Buczkowska *et al.* (2018), hyperinsulinemia in women with polycystic ovarian syndrome is a predictive factor for later-life health problems like infertility, cardiovascular disease, and diabetes. According to studies, if a person is hyperinsulinemia, their risk of developing atherosclerosis is significant. This might be because of hyperinsulinemia's overexpression of triglyceride-rich lipoproteins (Alves-Bezerra and Cohen, 2017).

2.6 Insulin Resistance

Insulin resistance (IR) is the lack of an insulin-responsive cell's ability to react to an increase in blood glucose or the decline in the blood glucose's reaction to circulation insulin (Czech, 2017). IR or insulin deficiency conditions can be divided into three categories, according to Pearson *et al.* (2016), First, pancreatic beta cells only produce a small amount of insulin. Second, the existence of insulin antagonist molecules in the plasma, which are caused by either hormones that act as counter-modulators or by molecules other than hormones that block insulin signalling or receptors. Lastly, preventing target tissues from responding to insulin.

It is known that substances such as growth hormone and insulin-like growth factor 1 (IGF-1) have an effect on how insulin works when a person has eaten. Glucocorticoids, catecholamines, and glucagon all reduce the effect of insulin in order to prevent insulin-induced hypoglycaemia in a

fasting state. Several studies have demonstrated that the ratio of insulin to glucagon, which measures the phosphorylation of enzymes downstream in controlling the signalling pathway, is crucial in modifying this process. Additionally, catecholamines speed up both glycogenolysis and lipolysis. Glucocorticoids help to accelerate lipolysis, gluconeogenesis, and muscle breakdown; as a result, an increase in these hormones is linked to IR (Nussey and Whitehead, 2001; Wilcox, 2005). The principal extra-pancreatic-sensitive organs that are essential in the aforementioned pathways are the liver, skeletal muscle, and adipose tissue. The dysfunction of insulin in this tissue brought on by systemic IR is believed to be the root of T2DM.

2.6.1 Insulin Resistance in Skeletal Muscles

Skeletal muscle IR is the key extra-pancreatic component involved in the development of T2DM, claims by Petersen and Shulman (2002b). By promoting glycogenesis, insulin helps a healthy person's skeletal muscles absorb glucose. Glycogenesis and glucose uptake are primarily constrained by hexokinase, glycogen synthase, and glucose transporter 4 (GLUT4) (Petersen and Shulman, 2002a). The fusion of insulin and the insulin receptor (INSR) in muscle cells causes GLUT4 to move from the intracellular compartment to the plasma membrane, limiting the amount of glucose that is accessible in the circulation (Satoh, 2014).

Numerous investigations have found that a hyperglycaemic state is known to happen when there is a mutation that reduces the expression of GLUT 4 or INSR. Furthermore, any mutation that affects the downstream or upstream signalling pathway results in this condition. The stimulation of INSR's tyrosine kinase activity is a key factor in how insulin affects glucose levels. Insulin-mediated signalling occurs when the INSR's tyrosine residues on the β-subunit are phosphorylated. When insulin binds to the α subunit of INSR, this phosphorylation is started. Therefore, any mutation that alters the phosphorylation sites on INSR may result in a restriction of insulin's actions on skeletal muscles. Additionally, it reduces INSR's tyrosine kinase activity (Abdul-Ghani and DeFronzo, 2010).

As was already mentioned, any mutation in key proteins like phosphoinositide 3-kinase (P13K), IRS-1, and IRS-2 that are involved in the signalling pathway impede the action of insulin. Environmental factors have also been noted to influence the muscle's ability to absorb glucose. For instance, physical exercise enhances blood circulation to the cells of the skeletal muscle, which increases glucose use (Venkatasamy *et al.*, 2013). Obesity, which is brought on by chronic

inflammation, contributes to IR and T2DM. Several studies have demonstrated how obesity can lead to skeletal muscle inflammation. The increase in immune system cells and proinflammatory cytokines in perimuscular and intermyocellular adipose tissue may be the cause of this phenomenon. This result causes the muscle cells to become inflamed and their metabolism to be destroyed, which causes IR (Wu and Ballantyne, 2017).

2.6.2 Insulin Resistance in Adipose Tissues

Adipose tissue has the capacity to produce a wide range of biologically active chemicals that are in charge of regulating metabolic homeostasis, according to studies by Coelho *et al.* (2013). The adipose tissue is also said to play a role in bodily functions like lipid metabolism, body weight homeostasis, glucose metabolism, angiogenesis, immunity, vascular tone, appetite modulation, fibrinolysis, reproduction, and control of vascular tone, according to Rosen and Spiegelman (2006).

According to Gastaldelli *et al.* (2017), insulin's effects on adipose tissue have been seen to include accelerating triglyceride synthesis, glucose uptake, glycerol uptake, free fatty acid (FFA) uptake, and reducing triglyceride hydrolysis. When the person is fed, GLUT4 helps in the transfer of glucose into the adipose tissue cells. Glycerol-3-phosphate, which is generated from the commencement of glycolysis, is absorbed into the mechanism that results in lipogenesis during this step. According to studies, glycerol-3-phosphate and free fatty acids from VLDLs are esterified to produce triacylglycerol (TGA). These TGA are kept as lipid droplets in storage. These TGA droplets are catabolized to produce FFA, which is employed as an energy source in some tissues when the body is experiencing metabolic stress. Adipose-IR refers to the failure of the adipose tissue to response to insulin stimulation. According to Czech (2020), among of the effects of adipose-IR include the impairment of glucose uptake, downplaying of lipolysis, and stimulation of FFA production from the adipocytes, which results in a rise in insulin levels.

Adipose-IR is connected to glucose tolerance and an increase in FFA release from the liver or muscle. If the process takes place in the liver, it has been discovered that this mechanism causes the onset of T2DM. This happens when there is an excessive build-up of FFA in the liver, which impairs insulin signalling that helps the hepatocytes increase gluconeogenesis and impairs the glucose-enhanced response to insulin. According to research by Scherer (2019), there is a

connection between hypoxia, pathologic vascularization, fibrosis, inflammation caused by macrophages, and the aberrant increase in adipose tissue bulk and adipocyte size.

Studies by Roden and Shulman (2019) have shown that the activation of saturated FFA in an obese or diet high in fats, which subsequently stimulates the mitochondrial protein adenine nucleotide translocase 2 (ANT2), which produces hypoxia in the adipocytes and stimulates the transcription factor hypoxia-inducible factor-1(HIF-1), might result in adipose tissue malfunctioning and inflammation. The immune cells that live in adipose tissue and the hypertrophied adipocytes contribute to the rise of circulating proinflammatory chemicals. The localized cytokines TNF, IL-1, and IL-6, along with the circulatory pro-inflammatory cytokines, contribute to the development of metabolic inflammation. Also, according to Maki *et al.* (2011) studies, chronic inflammation plays a major role in the pathogenesis of IR and T2DM.

2.6.3 Insulin Resistance in the Liver

Insulin typically influences liver glucose production and utilization as well as lipid metabolism. When blood glucose levels are high, the cells of the pancreas generate insulin, which fuses with the INSR, causing autophosphorylation of the liver INSR to occur. The recruitment of insulin receptor substrates is followed by phosphorylation. After phosphatidylinositol-3,4,5-triphosphate activates PDK1, this mechanism results in the phosphorylation of AKT (PIP3) (Galicia-Garcia *et al.*, 2020). PIP3 is formed phosphatidylinositol (4,5)-bisphosphate (PIP2) phosphorylation, which takes place after IRSs have activated PIK3. In addition, mTORC2 can phosphorylate AKT. According to Titchenell *et al.* (2017), activated AKT has been observed to control a variety of pathways, including lipid synthesis, glycolysis, glycogenesis, and gluconeogenesis.

Cherrington *et al.* (2007) noted that the actions of both glucagon and insulin have an impact on how the hepatic glucose production is modulated in a healthy person. When blood glucose levels are high, insulin is known to suppress gluconeogenesis whereas glucagon promotes it. Insulin's impact on hepatic gluconeogenesis has been seen in both indirect and direct pathways. According to Edgerton *et al.* (2006), this process does not have a distinct value.

Insulin limits the generation of glucose by promoting the synthesis of glycogen and by activating FOXO1, which is another method by which it does so. Numerous investigations have found that the genes for phosphoenolpyruvate carboxykinase and glucose-6-phosphate contain insulin

response elements (IREs), which are critical for maintaining blood glucose levels in the fasting state (Van Schaftingen and Gerin, 2002; Montal *et al.*, 2015). Then, via the suppression of FOXO1, insulin increases glycogenesis by inhibiting gluconeogenesis and hepatic glucose production.

As seen by Meshkani and Adeli (2009), an IR situation limits the amount of active insulin in blood circulation that can start the correct insulin response in the hepatocytes. When IR occurs, the liver produces more CRP and other proinflammatory chemicals, produces more lipogenesis, has trouble making glycogen, and is unable to stop gluconeogenesis. According to Leclercq *et al.* (2007), the addition of proinflammatory chemicals like adipocytokines and circumstances like oxidative stress may be responsible for the alterations in the hepatocytes' responsiveness to insulin caused by inflammation.

2.6.4 Assessment of Insulin Resistance

The hyper insulinemic euglycemic clamp was regarded as the gold standard for determining insulin sensitivity. Researchers created more practical methods for measuring insulin sensitivity because this method's time and financial requirements made it limited. In the last 20 years, the oral glucose tolerance test (OGTT) has been used to measure insulin sensitivity or resistance. Two groups of insulin sensitivity indicators have been identified. First, those markers that are determined by the levels of glucose, triglycerides, and insulin in fasting plasma. Finally, indications derived from plasma insulin and glucose concentrations following a 2-hour OGTT. Examples of the former category include Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), QUICKI, and McAuley index, while the latter group includes Belfiore, Cederholm, Stumvoll Avignon, and Matsuda index (Gutch *et al.*, 2015).

The use of these indicators to forecast the rise of diabetes in the non-diabetic population has been proven in epidemiological and clinical research to be accurate. Their use in clinical practice is constrained by the lack of reference values for both normal and abnormal insulin sensitivity. In contrast to HOMA-IR, Matsuda, and QUICKI, which are more desired for clinical use, Belfiore, Cederholm, HES, McAuley, Stumvoll, and Avignom are more sought for research studies (Gutch *et al.*, 2015).

2.6.4.1 Homeostasis Model Assessment-Insulin Resistance (HOMA-IR)

The homeostasis model index was devised in 1985 by Matthew and his colleagues. This approach evaluates IR and beta-cell task. This process checks the levels of basal (fasting) glucose and insulin (C-peptide). The relationship between the dynamics of glucose and insulin is used in the model to predict the concentration of insulin and glucose in the fasting state in the broadest range that is compatible with IR and the combined function of beta cells.

This model has shown to be quite helpful in epidemiological and clinical assessments of IR. Homeostasis of glucose and insulin is defined by HOMA using a set of simple nonlinear equations. The fasting blood sample is used in the streamlined version of this model for IR. It results from dividing the insulin-glucose product by a fixed number. According to Matthews *et al.* (1985), the combination of FPG and FPI results in the liver IR index. If variables for fasting glucose and insulin are the only ones available, it is generally advised to adopt this model in large epidemiological research.

2.6.4.2 Quantitative Insulin Sensitivity Check Index (QUICKI)

The Quantitative Insulin Sensitivity Check Index is a fasting plasma concentration of insulin and glucose conversion that has experimental origins. According to studies, QUICKI has a significantly higher positive prediction ability and also offers unwavering and exact ISI. The inverse and logarithm of the product of glucose and insulin are used to translate data in this derivative of the HOMA equation. Most of the time, there is very little skewing of the fasting insulin readings in the distribution. Due to their stronger associations with glucose clamp, this index performs better than minimal model predictions in determining insulin sensitivity in diabetic and obese people.

As in the HOMA model, fasting insulin and glucose measurements are used. Every aspect is comparable to the HOMA model, with the exception of the log transformation of the product of insulin and glucose. According to Chen *et al.* (2003), QUICKI can be used by determining the concentration of fasting glucose (mg/dl) and insulin (mIU/L).

2.6.4.3 McAuley Index

The majority of the time, this indicator is advised for use in predicting IR in people with normal blood sugar levels. According to McAuley *et al.* (2001), the index uses regression analysis to estimate the IR references. Also, the same methodology is used to assess basal metabolic rate (BMI), waist circumference, insulin, aspartate aminotransferase and triglycerides concentration. The bootstrap technique was used to find an index that has a good correlation with the sensitivity to insulin index, corrected for fat-free mass acquired by HEC (Mffm/I).

$Mffm/I = e\ (2{,}63–0{,}28\ \ln(I_0) – 0{,}31\ \ln(TAG_0)$

2.6.4.4 Matsuda Index

Matsuda and Defronzo's Matsuda index is an ISI marker. This index uses a straightforward method to estimate insulin sensitivity from an OGTT and delivers a better estimate. The ISI computation makes use of the 2hr and 3hr OGTT results. DeFronzo and Matsuda's multifactorial whole-body insulin sensitivity index (WBISI) is based on values of insulin in microunits per milliter (U/mL) and glucose in milligrams per decilitre (mg/dl) obtained from OGTT and its parallel fasting levels. WBISI can detect the merging of hepatic and peripheral tissue insulin sensitivity.

2.6.4.5 Belfiore Index

The Belfiore index is mostly utilized in calculations employing Belfiore formulas. The formulas aid in describing the mean, basal, and glucose concentrations during an oral glucose tolerance test. According to Belfiore *et al.* (1998), the main goal of the Belfiore formula has been to compare the recorded levels of insulin and glucose (measured during fasting, 0–12 h, or 0–2 h regions) with a reference range of normal values.

2.6.4.6 Cederholm Index

Wibell, Cederholm, and CEDERHOLM, according to Cederholm and Wibell (1990), identified this ISI. The index assessed glucose uptake into the myocytes and peripheral ISI. This indicator primarily uses the release of glucose by peripheral tissues following an oral glucose load.

2.6.4.7 Stumvoll Index

Stumvoll and Gerich (2001) recommended using demographic indicators and values to measure the IS and insulin secretion during the OGTT. Age, BMI, sex, and glucose response during the OGTT were used to predict beta cell activity and insulin sensitivity. According to Stumvoll and Gerich (2001), the equations were created using multiple regression analysis.

2.6.5 Measuring Beta Cell Function

Several investigations have found that glucose acts as the primary regulator of insulin production. ADP/ATP ratios are changed together with glucose uptake in the route that promotes insulin production. Changes in the conductance of potassium across membranes also take place. According to O'Meara *et al.* (1993) and Polonsky *et al.* (1988), this ultimately results in the migration of insulin-containing granules, which creates the oscillatory and pulsatile form of insulin secretion.

Furthermore, according to two investigations, incretin also stimulates beta cells to secrete insulin via cAMP. This procedure will make glucose work more effectively. Additional research by Ward *et al.* (1984) found that fatty acids, monobasic amino acids, and beta-adrenergic agonist can all stimulate the synthesis of insulin through a separate mechanism unrelated to glucose. The aforementioned mechanism is what drives the numerous methods for evaluating beta cell functioning.

2.6.5.1 Hyperglycemic Clamp

In this technique, exogenous glucose is infused into the patient to raise their blood sugar levels above fasting levels or to a specific concentration. The frequency and strength of the stimulant for high blood sugar levels can be adjusted. Precision and repetition of the C-peptide/insulin secretion are made possible by this regulation. Additionally, this modulation has the effect of clearly differentiating the phase 1 and phase 2 responses to intravenous glucose (DeFronzo *et al.*, 1979; Elahi, 1996).

Despite the method's benefits, some of its limitations include the need for two intravenous lines, the difficulty of performing accurate glucose measurements every 5 to 10 minutes, the need for quick glucose measurements after initial infusions, and the need for specialized knowledge to regulate the rate of infusion of glucose to reach target levels.

2.6.5.2 Intravenous Glucose Tolerance Test (IVGTT)

In the IVGTT, dextrose is administered intravenously, and within 10 minutes, immediate sampling is performed to estimate the glucose and insulin concentrations and determine the first phase responses to insulin and C-peptide. The remaining test measurements are used to determine second phase responses. In order to successfully adjust insulin sensitivity at this time, exogenous insulin has taken the position of dextrose. Several studies employing the IVGTT have provided

clear explanations for the progression of beta cell function deterioration in diabetes, the physiology of people at high risk of developing the disease, and the treatment response that follows (Buchanan *et al.*, 2002; Bonadonna *et al.*, 2003; Nijpels *et al.*, 2008).

2.6.5.3 Glucose-Potentiated Arginine Stimulation Test

L-arginine is infused into patients who have high blood sugar levels of 450 mg/dl (25 mmol/L) or higher in order to stimulate an insulin response that is at its highest during this technique. The pancreatic beta cells' capacity to function is predicted by this approach (Ward *et al.*, 1984; Haeften *et al.*, 1989). Kahn *et al.* (2008) asserts that people with dull or missing phase 1 insulin/C-peptide exhibit strong sensitivity to intravenous glucose. The arginine response is seen to be attenuated in these people.

2.6.5.4 Oral Glucose Tolerance Test (OGTT)

One test used to assess beta cell function is the OGTT. The relative lag in the release of glucose into the bloodstream makes it difficult to categorize the insulin response strictly into the first and second stages. Thus, it is preferable to use both early and late responses to insulin. According to Phillips *et al.* (1994), the rise of C-peptide/insulin quantities over basal levels following the start of glucose ingestion between time 0 and 30 minutes is how the early response is measured. The insulinogenic index is calculated by dividing the increase above basal insulin/C-peptide levels by the increase in glucose over the same time period. OGTT can be used to determine insulinogenic index.

2.6.5.5 Mixed Meal Tolerance Test (MMTT)

OGTT and MITT are related. In MMTT, oral administration of a solid or liquid booster including carbohydrates and other macronutrients is followed by the collection of blood for glucose and insulin. Incretin impact on the overall response to a meal can also be evaluated using this approach, according to Jiménez *et al.* (2014). According to reports, this method promotes human meal consumption more effectively than the isolated glucose load (Rijkelijkhuizen *et al.*, 2010).

2.6.5.6 Fasting Proinsulin to Insulin (or C-Peptide) Ratio

According to several studies, the molar ratio of proinsulin to insulin in non-diabetic people is estimated to be 15% in an unfed state (Ward *et al.*, 1987; Kahn *et al.*, 1995). As beta cell activity begins to decline, there is a 2-3-fold rise in the percentage of fasting proinsulin to insulin in those

with T2DM. This is a result of the proinsulin's inability to be converted into insulin and C-peptide. Surprisingly, IGT participants have not noticed any appreciable increases in this ratio, according to Saad (1990). This suggests that the ratio's increase may be a sign of either beta cell malfunction or increased demand for beta cells. Additionally, beta cell function can be evaluated using the homeostatic model evaluation.

2.7 Obesity

A third of the world's population is believed to be obese or overweight, according to Ataey *et al.* (2020), and the incidence of obesity has increased globally since 1980 by a factor of two. World Health Organisation (2000) studies have revealed that women over the age of 50 are more likely than men to be fat. In both sexes and in all age groups, obesity is becoming more and more prevalent.

The incidence rate varies between different continents and racial groups. The socioeconomic status has an impact on the incidence rate as well. So, it has been observed that the BMI has been gradually increasing in some middle-income and high-income countries. The prevalence of obesity in children from high-income nations including the United States, France, Australia, Denmark, Norway, and Sweden have decreased, according to recent studies by Abarca-Gómez *et al.* (2017). At first, obesity was thought to be a problem for industrialized nations.

2.7.1 Prevalence of obesity

The prevalence of obesity is escalating, according to research, in metropolitan areas of low- and middle-income countries. According to Wariri *et al.* (2021), the frequency of overweight among African children under the age of five has surged by 24% since 2000. In 2019, it was noted that about 50% of Asian children were obese. According to studies by Tydeman-Edwards *et al.* (2018), the prevalence of adult obesity and overweight as well as childhood undernutrition and wasting in sub-Saharan Africa are negatively correlated.

The elevation in the incidence of obesity or overweight in Africa have been on the increased since 1990.The severity of the incidence varies amongst the various geographical areas. Accordingly, the incidence rates of overweight in West Africa, Middle Africa, Eastern Africa, Southern Africa, and Northern Africa in 1990 were 2.6%, 3.7%, 4.5%, 6.4%, and 7.5%. After 1990, there has been a remarkable increase in the prevalence of overweight people in the Southern African region; in

2015, a 21% incidence rate was noted. In the same vein, prevalence in Northern Africa increased to 13% in 2015. The incidence rate has only slightly increased in the remaining regions (Agyemang *et al.*, 2016).

According to studies by Amoah (2003), the prevalence rates of overweight and obesity among individuals over 25 in Ghana were 23.4% and 14.1%, respectively. Biritwum *et al.* (2005) studies found a 5.5% prevalence of obesity. The occurrence rate was larger in girls (7.4%) than in males (2.8%), according to the researchers. In the same study, the majority of the obese participants were married and in the workforce. Greater Accra had the greatest prevalence rate, whereas the Upper West and Upper regions of Ghana have the lowest incidence rates. Additionally, these studies note that the Ga Adangbes, Ewes, and AKans had the highest incidence of obesity, with rates of occurrence of 14.6%, 6.6%, and 6.0%, correspondingly. Participants in the study who had previously been diagnosed with diabetes or who were taking medication to decrease hyperglycaemia also showed signs of obesity (Biritwum *et al.*, 2005)

2.7.2 Indices for classifying obesity

There are several indices used for assessing obesity, some of which are covered below.

2.7.2.1 Body Mass Index

It is the most often used index to measure obesity. It is largely regarded as the best predictor of obesity by several organizations. It measures relative height. It was computed by dividing the body mass (in kilograms) by the square of the height (in metres). BMI is divided into three categories: normal, overweight, and obesity. The ranges are as follows: 18.5-24.9kg/m^2, 25-29.9kg/m^2, and above 30kg/m^2. However, underweight is defined as a BMI of less than 18.5 kg/m^2 (Yanovski and Yanovski, 2002; Bray, 2016). Numerous studies have utilized various reference ranges, particularly for age and sex, to categorize juvenile obesity and overweight (Deurenberg *et al.*, 1991; Cole *et al.*, 2007).

The BMI index assesses excess weight gain rather than extra body fat. The limitation of BMI is that it cannot evaluate aspects of body composition like visceral fat or the distribution of fat (Britton *et al.*, 2013). Due to the elderly population's redistribution of fat to the area of the belly, this index does not serve as a better predictor of obesity (Seidell and Visscher, 2000). Additionally, there is variance in the morbidity associated with excess body weight in individuals with the same BMI and belonging to distinct racial groups (World Health Organisation, 2004).

BMI is unreliable for classifying sportsmen and bodybuilders because these individuals are always known to be obese. Furthermore, because the index is based on age and height, it is impossible to classify prepubescent and puberty populations using the adult BMI reference range (Rolland-Cachera, 1982).

2.7.2.2 Waist Circumference

It is one of the straightforward and useful anthropometric indices for determining adult visceral fat. BFP and this index go hand in hand fairly well (Lemieux *et al.*, 1996; Heo *et al.*, 2013). It refers to the circumference of the human waist. The methodology for measuring it has numerous variations. For this index, no agreement has been reached (Ross *et al.*, 2008). According to the WHO, IDF, ASTM, ISO 7250, and ISAK, the level of the waist is situated at about the midpoint between the top of the iliac crest and the lower edge of the last perceptible rib. The top of the iliac crest, according to NHANES III, NCEP, and ATP III, and the navel, according to MESA study.

The classification of metabolic syndrome has been suggested using a number of reference ranges. Within sexes and ethnic groupings, the WC cut-off points vary (Alberti 2006). The minimum height requirements for men and women in Europe are 94 cm and 80 cm of WC, respectively. Additionally, WC cut-offs of 90 cm and 80 cm have been suggested for men and women who are South Asian, Japanese, and Chinese, respectively (Tan *et al.*, 2004; Wildman *et al.*, 2004). Alberti *et al.* (2006) notes that whereas central and south Americans utilize the Asian classification, sub-Saharan Africans use the European criteria. In order to be applied to youngsters and the elderly, the WC criteria is also adjusted.

2.7.2.3 Waist-To-Hip Ratio (WHR)

This index is recognized as a visceral fat measure. It is computed by dividing the waist diameter by the hip circumference (HC). According to the WHO, IDF ASTM, NHANES, and other organizations, the level of the buttocks is the measurement of HC. According to the World Health Organization's recommendation for central obesity, 0.8 and 1, respectively, are the cut-off points for men and women (World Health Organisation, 2000). The likelihood of developing T2DM, CVD, and mortality are all increased by an increment in WHR (Ross *et al.*, 2020). Van Der Kooy *et al.* (1993) asserts that the loss of data makes WHR unsuitable for evaluating feelings. When

the BMI exceeds 35kg/m2, the result is unreliable. Gender has an impact on WHR, and children cannot be classified.

2.7.2.4 Waist-To-Height Ratio (WHtR)

This score also serves as a measure of central adiposity (ICO). It evaluated the body fat distribution. It is computed using the WC to height ratio. According to Ashwell *et al.* (2012), the cut-off point for metabolic risk in a number of adult populations is 0.5. Numerous studies have demonstrated that this indicator is more accurate at predicting metabolic risk than BMI and WC (Browning *et al.*, 2010; Ashwell *et al.*, 2012) (Browning 2012, Ashwell 2012). Increased levels of WHtR have been linked to conditions such as diabetes, hypertension, CVD, and dyslipidaemia (Song *et al.*, 2015). The usage of this index among kids is not documented.

2.7.2.5 Conicity Index

It is a metric for measuring central adiposity. It is incredibly straightforward and precise (Roriz *et al.*, 2014).

$$\text{Conicity index } (CI) = \frac{WC(m)}{0.1109\sqrt{\frac{Weigh\,(Kg)}{Height\,(m)}}}$$

In various populations, according to Filgueiras *et al.* (2019), different cut-offs have been employed. This score is a superb predictor of metabolic syndrome in children and the elderly population, according to numerous research (Ceolin *et al.*, 2019; Silva *et al.*, 2020). Additionally, several researches have demonstrated that this score is a superior diabetes predictor (Wang *et al.*, 2019; Escobedo-de la Peña *et al.*, 2020) (Wang 2019, Hernandez 2020). There are no accessible reference ranges for the conicity index in clinical settings.

2.7.3 ***Endocrine Changes in Obesity***

Adipose tissues' main purpose is to store energy, but they also undertake other tasks that are made possible by the hormones and molecules they generate as well as the exocytosis of their own cells. Adipokines, which mediate activity in an autocrine, paracrine, or endocrine way, are the name for these substances produced by adipocytes (Schulz and Tseng, 2013). Below are a few of these compounds produced by white fat;

2.7.3.1 Leptin

It is a hormone that white adipose cells generate. It is a 167-amino-acid peptide hormone that was first found in 1994. The *ob* (obesity) gene contains the genetic coding for leptin. With the help of this hormone, humans now have a better knowledge of how the central nervous system and adipose tissue communicate (Zhang *et al.*, 1994; Friedman and Halaas, 1998). According to Vong *et al.* (2011), this hormone is known to control hunger and energy expenditure by fusing with presynaptic GABAergic neurons of the hypothalamus after crossing the blood brain barrier.

Leptin continues to play a crucial role in alerting the body when there is starvation or less food intake. Numerous investigations have found that leptin levels are reduced during uncontrolled T1DM, fasting, or low-calorie dieting (Klok *et al.*, 2007; Cooper *et al.*, 2009). In these circumstances, leptin levels are declining, which causes hunger while, on the other hand, reducing body energy consumption. It subsequently triggers other bodily adjustments that help the body replenish its fat reserves. In contrast, the increase in adiposity and the rise in serum leptin levels are related. This serum concentration of leptin rises in healthy individuals, enhancing expenditure and minimizing food intake. However, people who are overweight or obese do not experience this effect. This illustrates how leptin resistance manifests in these people.

Leptin is connected to many bodily parts besides the CNS, too. Leptin receptors have been found in various human organs, including adipose tissue, skeletal muscles, liver, and pancreatic beta cells. This shows that leptin has endocrine, paracrine, and autocrine effects on energy metabolism. Leptin levels are thought to influence metabolism in several tissues. Leptin's impact on the metabolism of lipids and glucose has been documented in two investigations. It works by making insulin more sensitive (Sirotkin *et al.*, 2008; Paz-Filho *et al.*, 2012). Ahima and Flier (2000) asserts that leptin increases insulin intake to the hepatocytes while reducing hepatic glucogenesis, glucagon secretion, and synthesis. Additionally, it is linked to increased lipolysis and diminishing lipogenesis.

2.7.3.2 Adiponectin

Another adipocytokine that influences insulin sensitivity and atherogenesis is adiponectin. According to Kadowaki *et al.* (2006), adiponectin works by attaching to adipoR1 and adipoR2

receptors, which activates adenosine monophosphate dependent kinase, or PPAR-. Reduced adiponectin levels have been linked in several human studies to dyslipidaemia, IR, and atherosclerosis (Kantartzis *et al.*, 2005; Sattar *et al.*, 2006). According to Yang *et al.* (2001), when people lose weight, their insulin sensitivity improves, which is highly correlated with an increase in adiponectin levels.

Numerous studies have demonstrated how adiponectin controls the activity of natural killer cells, inhibits the effect of various inflammatory molecules like TNF-α, and more. Additionally, it helps to reduce dyslipidaemia and other CVD risk factors (Goldstein and Scalia, 2004; Karbowska and Kochan, 2006). Adiponectin has also been connected to anti-tumour properties. By preventing leptin-stimulated cancer cell proliferation, it serves as an anti-tumour molecule (Fenton *et al.*, 2008). The capacity of cancer cells to spread is known to be constrained by adiponectin. Further research has shown that those with hypoadiponectinemia have a higher likelihood of developing stomach, breast, prostate, and lung cancer (Mantzoros *et al.*, 2004; Michalakis *et al.*, 2007).

2.7.3.3 Chemerin

It is a freshly discovered adipokine. Retinoic Acid Receptor Responder Protein 2 is another name for chemerin. This chemical, which is produced by fully developed adipocytes, is essential for controlling adipogenesis. Additionally, it facilitates macrophage penetration into adipose tissue (Bozaoglu *et al.*, 2010).

2.7.3.4 Retinol Binding Protein-4 (RBP-4)

Adipocytokine RBP-4 is mostly produced by adipocytes and the liver. It conveys hydrophobic small molecules as a member of the lipocalin family (Okuno *et al.*, 1995). In humans, it is unclear if obesity and serum concentration of RBP-4 are related. However, numerous studies have found a direct link between glucose levels, BMI, and RBP-4 expression (Janke *et al.*, 2006). According to two studies, a healthy diet, weight loss, and physical activity that improves insulin sensitivity can result in a drop in RPB-4 serum levels.

2.7.4 Obesity and Insulin Resistance

Majority of metabolic problems are primarily influenced by obesity. Leptin, pro-inflammatory cytokines, adiponectin, NEFAs and glycerol, are all released by adipose tissue to influence metabolism (Wellen, 2005; Scherer, 2006; Shoelson *et al.*, 2006). By decreasing phosphatidylinositol-3-OH kinase (PI(3)K) signaling in muscle and boosting the synthesis of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver via a retinol-dependent pathway, Retinol-binding Protein-4 (RBP4) promotes insulin resistance (Yang *et al.*, 2005). Contrarily, adiponectin stimulates fatty acid oxidation through acting as an insulin sensitizer, which is dependent on peroxisome proliferator activated receptor-α (PPAR-α) and AMP-activated protein kinase (AMPK) (Kadowaki *et al.*, 2006; Scherer, 2006).

Higher release of monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and other byproducts of macrophages and other cells that are found in adipose tissues may also play a role in the emergence of insulin resistance in addition to adipocyte-derived substances (Fain *et al.*, 2004; Wellen and Hotamisligil, 2005). TNF-α and IL-6 increase the activity of possible inflammatory mediators that can result in insulin resistance by activating the the c-Jun aminoterminal kinase (JNK) and IκB kinase-β (IKK-β)/nuclear factor-κB (NF-κB) pathways through classical receptor-mediated mechanisms.

Molecular processes that result in the expression of SOCS (suppression of cytokine signaling) proteins (Mooney *et al.*, 2001) and inducible nitric oxide synthase (iNOS) (Perreault and Marette, 2001) could play a role in facilitating cytokine-induced insulin resistance. Endothelial cells, adipocytes, and monocytes secrete these proinflammatory proteins, particularly MCP-1, which encourages the recruitment of macrophages and resulting in a feedforward loop (Weisberg *et al.*, 2003; Xu *et al.*, 2003). The single most important component in altering insulin sensitivity may be the release of NEFAs. Type 2 diabetes and obesity are both accompanied by elevated NEFA levels, which are linked to both conditions' insulin resistance (Reaven, 1988; Boden, 1997). Within hours following a sudden spike in plasma NEFA in people, insulin resistance appears (Roden *et al.*, 1996).

However, after administration of the antilipolytic medication acipimox, insulin-facilitated glucose uptake and glucose tolerance increase, along with a sharp decrease in NEFA levels (Santomauro *et al.*, 1999). Hexokinase II, phosphofructokinase, and pyruvate dehydrogenase

activity may be successively suppressed as a result of increased intracellular NEFAs competing with glucose for substrate oxidation (Randle *et al.*, 1963). It has also been proposed that perhaps an increase in NEFA delivery or a decrease in cellular fatty acid metabolism results in an increase in the cellular content of fatty acid molecules like diacylglycerol (DAG), fatty acyl-coenzyme A (fatty acyl-CoA), and ceramides, which activate a serine/threonine kinase cascade and cause the serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2), and a lowered capacity to activate PI(3)K (Shulman, 2000). Consequently, events which occur after insulin-receptor signalling are reduced.

2.7.5 Obesity And Androgens in Men

Various studies have reported that low testosterone (T) induces the development of hypogonadism and elevates body fat levels. According to two studies, obesity in men is linked to a drop in sex hormone binding globulin (SHBG) and a low total T level. The decrease in SHBG brought on by obesity may help to partially explain the dip in T levels. In addition, a rise in BMI is related to low levels of measured or calculated bioavailable and free testosterone. More than 40% of obese men with BMIs higher than 40 kg/m^2 were found to have reduced free testosterone, according to studies by Hofstra *et al.* (2008).

Numerous studies have connected secondary hypogonadism to obesity, despite the fact that the aetiology of this process is exceedingly complicated and poorly understood. Additionally, obesity has been linked to some primary hypogonadism, such as testicular failure. Multiple factors have been linked to secondary hypogonadism in men who are obese. Some of these include high blood pressure, type 2 diabetes, sleep apnoea, obesity, and the various adipokines it produces (Dandona *et al.*, 2004; Saboor Aftab *et al.*, 2013).

Additionally, Wagner *et al.* (2016) claims that long-term obesity is linked to a decline in the number of T-producing Leydig cells. This decrease occurs as a result of obesity triggering an increase in proinflammatory cytokines and related cells, such as macrophages and TNF-, which worsen the state of pre-existing cells. The declining in intra testicular concentration of T as seen by Wagner *et al.* (2016) is caused by the rise in serum leptin and oestradiol concentrations as well as the restriction of the production of the cytochrome P450 gene of the cholesterol side chain cleavage enzyme (Cyp11a1). Men's hypogonadism is believed to accelerate the increase in body

fat mass, which ultimately causes the hypogonadal condition to worsen. Studies have shown that a fall in serum T concentration results in a reduction in muscle mass and a gain in adipose tissue, particularly visceral adipose tissue. It is possible to treat the illness with testosterone therapy (Mårin *et al.*, 1992; Kapoor *et al.*, 2006).

Additionally, Strain *et al.* (1988) studies found that with an increase in adiposity, aromatase activity increases. Following the increase in aromatase, there is an increase in the conversion of testosterone to oestradiol, which results in a decrease in GnRH secretion. The preferred fat deposition within the abdominal depots advances when T levels subsequently decline (Belanger *et al.*, 2002; Mammi *et al.*, 2012). T-level normalization happens following weight loss, according to a number of studies (Hammoud *et al.*, 2009; Corona *et al.*, 2013b).

2.8 Dyslipidemia

Dyslipidaemia is the name for the disorder that results from aberrations in plasma lipids. Reduce Low-density lipoprotein cholesterol concentrations, a decrease in high-density cholesterol (HDL) and an increase in triglycerides are the main components of the aberrant lipid profile (De Backer *et al.*, 2019; Tilahun *et al.*, 2021). It has been demonstrated by numerous studies that dyslipidaemia manifests as an increase in one, two, or more circulating lipids.

2.8.1 Prevalence of dyslipidemia

In healthy population genetics, dyslipidaemia has been connected with between 43–83% of circulating plasma protein variations (Chang *et al.*, 2010; Ríos-González *et al.*, 2011). Thompson *et al.* (2015) claims that the LDL receptor gene mutation responsible for this disorder is an autosomal dominant inherited disorder. As a result of the LDL cell surface receptor being damaged, this causes a rise in the amounts of LDL and TC in the blood, which in turn causes an increase in their circulating levels.

According to numerous researches, those who are healthy have a two times lower chance of having CVD than people who have dyslipidaemia (Thompson *et al.*, 2015). Tripathy *et al.* (2017) estimates that dyslipidaemia is responsible for around 50% of ischemic heart disease nationwide and more than 4 million annual fatalities. One of the most important public health problems nowadays is dyslipidaemia. Dyslipidaemia has been linked to an incidence rate in Africa ranging from 5.2% to 89.9%. According to studies by Tripathy *et al.* (2017), abnormalities in plasma

lipids have been linked to the rise in unhealthy lifestyles, urbanization, and economic expansion. These aberrations are frequently found in people with IR, T2DM, MetS, central obesity, and other conditions (Bays *et al.*, 2013).

Hypertriglyceridemia, elevated LDL, and decreased TC are the most frequent dyslipidaemia patterns seen in T2DM (Daya *et al.*, 2017; Hirano, 2018). Dyslipidaemia in T2DM is brought on by IR and an increase in free FFA flux that results from IR. According to two studies, IR and high blood glucose levels contribute to the pathogenesis of high TGs in T2DM. As a result, the hepatocytes produce an excessive amount of TG-rich lipoprotein, and these lipoproteins are less easily cleared from the body. Postprandial lipid metabolism has been seen to be modified in some T2DM patients (Sugden and Holness, 2011; Wu and Parhofer, 2014).

Research has indicated that the rise in the consumption of unhealthy foods, urbanization, obesity, and inactivity have all contributed to an increase in the burden of dyslipidaemia in diabetic patients worldwide (Goldberg, 2001; Kiplagat *et al.*, 2017). In China, Nepal, Thailand, and Jordan, respectively, the prevalence rates for dyslipidaemia in T2DM were reported to be 59.3%, 63.1%, 88.9%, and 90% (Li *et al.*, 2018; Mehta *et al.*, 2021). In addition, a number of studies from Ethiopia, Nigeria, and South Africa have indicated that dyslipidaemia in T2DM is prevalent at rates of 68.1%, 69.3%, and 89%, accordingly (Bello-Ovosi *et al.*, 2019; Haile and Timerga, 2020; Omodanisi *et al.*, 2020).

A 53% prevalence incidence of dyslipidaemia was found in a cross-sectional investigation at Tema port in Ghana. According to the same study, females were more likely to be affected than males (Ofori *et al.*, 2019). In Kumasi, Ghana, among T2DM outpatients, there was an incidence rate of 63.8%, 15.8%, and 1.3% for single, combination, and mixed dyslipidaemia, respectively. Dyslipidaemia, which causes CVD, was responsible for around 68% of mortality in T2DM (Asamoah-Boakye *et al.*, 2017). Another study in the Tema metropolitan, using a large population sample of 246, found that the prevalence of hypercholesterolemia was 46.2% for men and 48.3% for women among T2DM patients, respectively (Alidu *et al.*, 2022).

2.8.2 Classification of Dyslipidaemia

According to two investigations, the primary and secondary classifications of dyslipidaemia are primarily employed in clinical settings. Additionally, dyslipidaemia can be further divided based

on the changes that accompany it. For example, a single increase in total cholesterol (TC) or triglycerides (TG), a decline in HDL cholesterol levels, or a concomitant elevation in TG and TC coupled with a drop in HDL cholesterol is referred to as mixed or combined dyslipidaemia (Mann *et al.*, 2017; Mosca *et al.*, 2022). Sometimes hyperlipidaemia might mimic dyslipidaemia. Additionally, abetalipoproteinemia, errors in sterol synthesis, and familial hypobetalipoproteinemia can develop when the TC is below normal (Saudubray and Garcia-Cazorla, 2016; Mosca *et al.*, 2022).

2.8.2.1 Primary Dyslipidaemia

According to numerous researches, primary dyslipidaemias are caused by various combinations of a certain group of illnesses. The pronounced rise in TG, cholesterol, and especially LDL distinguishes primary dyslipidaemia from other types. LDL cholesterol and TG can occasionally both increase at the same time (Stanton *et al.*, 2007; Saudubray and Garcia-Cazorla, 2016).

2.8.2.2 Hypertriglyceridemia

Most of the time, familial hypertriglyceridemia is driven by alteration in VLDL and CM use. Approximately 95% of these cases are the result of insufficient LPL activity. Rarely, it may also arise as a consequence of mutations in the APOC2, LMF1, APOA5, and GPIHBP1 genes. Patni *et al.* (2016) claims that a sign of LPL deficiency is an increase in fasting TG of more than 1000 mg/dl. Without any connection to atherosclerosis or an elevated risk of cardiovascular disease, the LPL deficiency can result in significant pancreatitis and other gastrointestinal disorders.

According to Stewart *et al.* (2020), most commonly observed complications include disorientation, paraesthesia, dyspnoea, and retinal vein damage when the TG rises above 2000mg/dl. Several investigations have found that the abhorrence and self-avoidance of calorie-dense diets is the cause of the lag in the clinical symptom of this disorder from infancy till adulthood (Elkins *et al.*, 2019; Stewart *et al.*, 2020). Although it is known that hypertriglyceridemia is autosomal dominantly inherited, its genetic basis is elusive.

2.8.2.3 Hypercholesterolemia.

According to studies by Sturm *et al.* (2018), an attribute of familial hypercholesterolemia is an elevation in LDL cholesterol levels. An alteration in the hepatic LDR-R, a modification in the apolipoprotein B100 receptor on the surface of LDL, or an increase in kexin type 9 activity, which

is engaged in LDL-R disintegration, are all possible causes of this increase in LDL. The scope of this disorder has been noted in numerous researches. Hypercholesterolemia can occur either heterozygous or homozygous. Usually uncommon yet quite severe is the homozygous variant (Lobstein *et al.*, 2004; Mann *et al.*, 2017). Both kinds are related to an increase in CVD. Sitosterolemia is brought on by enhanced plant sterol intestinal absorption.

2.8.2.4 HDL Decrease

Saudubray and Garcia-Cazorla (2016) asserts that there are erratic modifications connected to HDL metabolism. Among these alterations are Tangier disease, familial hypoalphalipoproteinemia, LCAT deficiency, apolipoprotein A-1 deficiency, and protein deficiencies that prevent the transfer of cholesterol esters. Bibbins-Domingo *et al.* (2016) research revealed a connection between changes in HDL metabolism and the early onset of nephropathy, atherosclerosis, corneal opacity, and neuropathy.

2.8.2.5 Combined Dyslipidaemia.

Multiple investigations have found that mixed dyslipidaemia is frequently present in children. A moderate to severe TG rise and a reduction in HDL cholesterol levels characterize the illness. According to De Ferranti and Jane (2016), this kind of dyslipidaemia is caused by environmental and epigenetic variables. It develops as a result of extrinsic stimuli including alcohol, hypothyroidism, calorie-dense diets, diabetes mellitus, renal illness, or obesity combined with genetic variations and polymorphisms. According to the findings of two investigations, between 30 and 60 percent of obese teenagers have this kind of dyslipidaemia (Elmaoğulları *et al.*, 2015; Drozdz *et al.*, 2021). The aetiology of mixed dyslipidaemia is caused by the coexistence of familial hyperlipidaemia and complex genes with attributes such as reduced HDL levels and elevated TG and LDL that are frequently associated to a family history of early onset of CVD.

Many studies have revealed that polygenic hypercholesterolemia is the primary factor in the development of increased LDL with a family pattern but without any discernible hereditary vulnerability. Sharing the same environment with others who have the disorder already increases your risk of having polygenic hypercholesterolemia (Sturm *et al.*, 2018).

2.8.3 Secondary Dyslipidaemia

According to Tam *et al.* (2010) and Hegele and Tonstad (2014), environmental influences on the metabolism of lipids result in this form of dyslipidaemia. Genetics may also play a role at other times. When compared to outside influences, genetics has a minor impact on the genesis of this particular kind of dyslipidaemia. Depending on the variance they increase, secondary dyslipidaemia can be categorized into Hypercholesterolemia: they promote cholestasis, anorexia nervosa, hypothyroidism, nephrotic syndrome, progesterone, thiazide diuretics, cyclosporine and carbamazepine; Hypertriglyceridemia: promote alcohol consumption, kidney failure, stress, T2DM, obesity, HIV, Cushings syndrome, pregnancy and others; Low HDL levels: promotes obesity, T2DM, smoking, malnutrition, steroids, sedentary life style and β-blockers.

2.8.4 Dyslipidaemia in T2DM

Hepatic triglyceride levels have been found to increase in T2DM patients in several investigations. This led to an increase in the liver's synthesis of VLDL, LDL-C, and sdLDLs (Ginsberg, 1991; Vergès, 2015). Insulin's inability to stop hormone-sensitive lipase's (HSL) activity in IR affects the ability of adipose tissues to store fat. The process culminates in the adipocytes' intracellular TG storage secreting FFA on a continuous basis. The freed FFAs are taken up by the liver cells and may go through β-oxidation in the mitochondria. It is subsequently assembled into a new VLDL particle through the reassimilation of TG. This can result in the storage of TG, which causes liver steatosis, or it can be switched to undergo gluconeogenesis, which raises blood sugar levels. The primary features of diabetic dyslipidaemia include an increase in the rate of VLDL-apoB100 production, particularly VLDL1. In accordance with Adiels *et al.* (2005), this represents a marker of insulin sensitivity.

According to Vergès (2010), it is believed that insulin has a substantial impact on how the hepatocytes assemble and secrete VLDL. Insulin is observed to suppress the transcription of the protein Mttp. According to what Lin *et al.* (1995) found, Mttp assembles TG with apoB100. Additionally, this protein aids in lipidation, apoB100 folding in the ER lumen, and lipid transfer. MTP affects the amount of apoB100's active pool (Blasiole *et al.*, 2007). The rate-limiting process for the stability of apoB100 mRNA is apoB100 lipidation. As a result, the apoB100 breakdown commences when there is a low TG supply. This occurrence also co-translates. Vesicles carrying Sar2/COPII transport the emerging VLDL that results from the interaction of TG with apoB100

and GA. VLDL development within GA is facilitated by phospholipase D1 (PLD1) (203). MTP expression and activity are elevated, which improve apoB100 lipidation and hasten its breakdown as shown in IR patients. According to Blasiole *et al.* (2007), loss in IR is a characteristic of insulin's mediation of apoB100 inhibition.

According to Chapman *et al.* (2011), the amount of TG present in the hepatocytes affects how much VLDL is produced. According to observations made by 207, extra-hepatic FFAs and de novo FFAs serve as the substrate for the liver's production of TG. When a person is well fed, sterol regulatory element-binding protein (SREBP) regulates the lipogenic genes, leading to the production of de novo lipids. 208 discovered that the isoform of SREBP-1 up-regulates practically all of the enzymes involved in the synthesis of FA and acetyl-CoA supply enzymes. The regulating function of insulin on SREBP-1c provides an explanation for the lipogenic impact on chronic inflammation. FFAs from adipose tissue are the primary source of the TGs and VLDL that are produced by hepatocytes. According to research by Choi and Ginsberg (2011), the adipocytes' ability to synthesize FFAs is heightened in T2DM patients. Thus, adipocytes from IR patients are showing an increase in TG lipolysis. The FFAs produced by lipolysis may be another method for the liver to obtain lipids.

In the IR environment, there is an increase in apo-CIII synthesis and a decrease in the availability of apo-CII. This is due to the limits of insulin's capacity to stop the production of VLDL in a fed state. Due to the liver's decreased ability to remove TRLs as a result of the aforementioned mechanism, VLDL remnants and IDL start to build up. In addition, IR of the liver hinders the translocation of LRP1 from intracellular vesicles to the plasma membrane of the hepatocytes. This contributes to the clearing of TRLs being hampered (Laatsch *et al.*, 2009; Gordts *et al.*, 2016).

2.8.5 Diagnostic Approach

For the screening of dyslipidaemia, postprandial and fasting samples might be employed. According to research, TG levels rose in post-meal samples more than in fasting samples. Two independent fasting samples, with a minimum fast of 12 hours, are used for the confirmatory diagnosis. The two tests should be spaced apart by two to three weeks. The mean of the two tests must be taken into account for both diagnoses and treatments (Lobstein *et al.*, 2004). According

to Di Bonito *et al.* (2015), subtracting HDL cholesterol from TC in a postprandial sample is how non-HDL cholesterol is computed.

Several studies have noted a notable increase in TG levels in an infection-related inflammation. It is advised avoiding running a lipid profile in these situations three weeks following the illness. Apolipoprotein A-1 or apolipoprotein B are not specified; the initial stage quantifies the main components of the lipids TC, HDL, and TG. Lobstein *et al.* (2004) claims that when TG is less than 400 mg/dl, the Friedewald formula, LDL = TC-HDL-TG/5, is employed to calculate LDL. The optimum option is direct measurement of LDL if the TG is greater than 400mg/dl.

2.8.5.1 Differential Diagnosis of Dyslipidaemia

It is crucial to distinguish monogenic primary dyslipidaemia from mixed type for therapeutic purposes, according to Alves *et al.* (2016) and Burton *et al.* (2015), because the various types of dyslipidaemias present similarly. Family history of dyslipidaemia, recurring or early-onset pancreatitis, tendon xanthomas, premature CVD, and cutaneous xanthomas are a few factors to be used during the differentiation. Additionally, the majority of cases of monogenic dyslipidaemia occur when TG or LDL surpass 500 mg/dl or 1000 mg/dl, respectively.

2.9 Non-Alcoholic Fatty liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD), which is marked by cryptogenic cirrhosis, liver failure, and eventually hepatocellular carcinoma, includes pure steatosis (simple fatty liver) and non-alcoholic steatohepatitis (NASH), which is characterized by hepatocellular injury/inflammation with or without fibrosis (Angulo, 2002). Physiopathologic factors, laboratory research, clinical connection, and understanding of its etiology all point to the major role that insulin resistance (IR) plays. According to numerous research, NAFLD is now believed to be the hepatic indication of the metabolic syndrome (MetS) linked to IR and its clinical characteristics, including obesity, type 2 diabetes (T2DM), dyslipidaemia, and hypertension (Marchesini *et al.*, 2003).

2.9.1 Prevalence of NAFLD in T2DM

According to Younossi *et al.* (2019b), NAFLD affects almost one-fourth of the global population. The incidence rate of non alcoholic steatohepatitis (NASH) occurs in about 3-5% of people, according to research by Younossi *et al.* (2019a). The incidence rate of NASH among people

with diabetes was observed to be 3.7% according to current meta-analysis by Younossi *et al.* (2019b). The same study also revealed that a significantly higher percentage of people with T2DM and NAFLD had advanced NASH fibrosis. The global prevalence of progressive fibrosis among T2DM patients was later estimated by the authors to be 4.8%. Ye *et al.* (2020) claims that these findings are relevant since the fibrosis stage of NAFLD is thought to be the primary indicator of mortality linked to liver diseases. The authors also suggest that individuals with lean NAFLD, who make up 20% of the total population and have a higher risk of developing T2DM, should receive special care (Sinn *et al.*, 2019; Wei *et al.*, 2021).

There have not been many investigations on the prevalence of NAFLD among T2DM patients in sub-Saharan Africa. According to a prediction based on data from 1990 to 2017, the age-standardised prevalence of NAFLD in sub-Saharan Africa ranged from 5.0 to 7.5% and 10.1 to 12.5% in Mauritius. Ghana and Benin were given credit for the biggest annual percentage change (Ge *et al.*, 2020). In Nigeria, NAFLD patients with T2DM and those without diabetes, respectively, had prevalence rates of 9.5-16.7% and 1.2-4.5% (Olusanya *et al.*, 2016; Onyekwere *et al.*, 2016).

2.9.2 Diagnosis of NAFLD

Neuman *et al.* (2015) contends that severe fat build-up in the liver is required for the diagnosis of NAFLD. Histological or imaging methods may be used to achieve this proof. Additionally, it is required that all alcohol consumption connected to that is excluded. Neuman *et al.* (2015) states it's important to rule out conditions like Wilsons's disease, severe malnutrition, lipodystrophy, environmental toxins, metabolic syndrome conditions like obesity and diabetes, chronic liver conditions including hemochromatosis and chronic viral hepatitis, fatty liver in pregnancy, tyrosinemia, and parenteral nutrition before diagnosing NASH. In order to diagnose NAFLD, percutaneous liver biopsy continues to be the gold standard. Despite being the most accurate procedure, neither doctors nor patients enjoy it.

Histological indications of both NAFLD and alcoholic liver disease have been reported to follow identical continuums. Some unique manifestations, such as mild liver steatosis or more severe hepatic steatosis along with inflammation or the progression of liver fibrosis in the midst of liver cirrhosis, may occur. A liver biopsy is used to stage and grade any liver conditions. A few of the criteria for diagnosing steatohepatitis include the presence of more than 5% vesicular steatosis,

inflammation, and liver ballooning with a specific distribution that is primarily centrilobular. The NAFLD activity score is made up of the steatosis, inflammation, and ballooning scores (NAS). Brunt *et al.* (1999) research indicates that the NAS can be used to measure the disease's activity; for example, a score of 5 or higher is associated with a higher likelihood of having NASH. However, when the score is below 5, the diagnosis of NASH is debatable.

The most obvious signs of NASH are elevated serum TG levels and decreased HDL levels. NAFLD is linked to a modest increase in alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) up to three times the upper limit without any known cause. ALT levels are significantly higher in NASH than AST levels (Neuman *et al.*, 2015).

2.9.2.1 Imaging Methods for Liver Fibrosis

The procedure is non-invasive as well. Due to the fact that the majority of patients are unwilling to endure a liver biopsy, liver enzymes and ultrasonography are the most commonly used procedures in the general population to evaluate liver problems. According to Poynard *et al.* (2006), magnetic resonance elastography and US-based transient elastography are few of the techniques that assessed the solidity as biological indicator of fibrosis of the liver. According to studies, a wide range of chronic liver infections can be evaluated using transient elastography to determine the extent of liver fibrosis (Neuman *et al.*, 2014). It is a practical method for determining hepatic steatosis in diabetics (Sporea *et al.*, 2016).

2.9.3 NAFLD and Insulin Resistance

According to research by Lomonaco *et al.* (2016), obesity-related hepatic steatosis is the root cause of NAFLD. Hepatocytes become dysfunctional as a result of this. In comparison to patients without NAFLD, obese people with T2DM and NAFLD had more extreme dyslipidaemia and hyperinsulinemia. Adipose tissue and the liver are examples of peripheral tissues where surplus fatty acids may accumulate and cause IR. The rise in fatty acid production, lipogenesis, and β - oxidation of fatty acids are the causes of the extra fatty acids (Méndez-Sánchez *et al.*, 2007). Adipose tissue can serve as an endocrine organ or as a storage tissue. In its storage function, it aids the body in storing systemic fats while secreting endocrine hormones like leptin and other molecules referred to as adipokines. Adipokines include substances like adiponectin, vaspin, retinol binding protein-4, among others (Siiteri, 1987).

Adiponectin modifies fatty acid oxidation and suppresses lipid deposition in adipose tissue and the liver, claims Angulo (2006). By enhancing sensitivity to hepatic insulin, adiponectin has also been shown to have a role in maintaining glucose homeostasis (Berg *et al.*, 2001). NAFLD patients' serum adiponectin concentrations were found to be lower than those of non-NAFLD patients in Masarone *et al.* (2014) research. Hypoadiponectinemia aids in the progression of NAFLD or T2DM by fostering chronic inflammation and hindering fatty acid metabolism in hepatocytes (Bugianesi *et al.*, 2005; Pagano *et al.*, 2005). As a result, preserving adiponectin levels in NAFLD can delay the onset of inflammation and fibrosis.

Obesity is unquestionably the feature that causes NAFLD most frequently, is most likely the primary contributor in IR, and can serve as a clinical signal for IR. Adipose tissue affects increased IR and free fatty acid (FFA) turnover. Due to the fact that visceral adipocytes are more sensitive to catecholamine-stimulated lipolysis than subcutaneous adipocytes, this pathophysiological process seems to be more active when there is an increase in visceral adipose tissue (Arner, 1998). Since the portal system receives direct venous drainage from visceral adipose tissue, IR in visceral obesity may be a direct result of free fatty acid overflow into the liver (portal theory) (Bergman *et al.*, 2007). Also, a build up of visceral fat has also been directly linked to hepatic fat (Kelly, 2000; Nguyen-Duy *et al.*, 2003) and hepatic IR in both sexes (Miyazaki *et al.*, 2002). However, there is data that suggests liver fat may be linked with IR, in the absence of abdominal fat (Kelly, 2000; Seppälä-Lindroos *et al.*, 2002).

2.10 Male Sexual dysfunction

Desire disorders, erectile dysfunction (arousal), and orgasm (premature/delayed ejaculation) are three kinds of male sexual dysfunctions. Despite this, there are situations when two or more of these illnesses coexist ((Rösing *et al.*, 2009).

2.10.1 Desire Disorders

Most often, men who are seeking medical treatment for their sexual issues tend to have this disorder. These males frequently lament their inability to get an erection. However, various sexual challenges like tiredness, interpersonal difficulties, and uncommonly sexual preference disorder can be easily concealed by erectile dysfunction. A few factors that contribute to desire disorders include testosterone insufficiency, hyperprolactinemia, adverse drug reactions, and others ((Rösing *et al.*, 2009).

2.10.2 Erectile Dysfunction

NIH consensus conference (1993) claims that ED can be described as the continuous failure to keep or sustain an erection of the penis during effective sexual intercourse, which diminishes the quality of life for men. Two studies have observed that ED is a familiar male sexual dysfunction which heightens as one ages (Laumann *et al.*, 1999; De Berardis *et al.*, 2002). The incidence rate of 1-10%, 2-9%, 60-69% and 50-100% have been associated ED in men between the ages of 18-39years, 40-49years, 60-69 years and above 70 years respectively according to international consultation committee for sexual medicine report on the Definitions/ Epidemiology/Risk Factors for Sexual Dysfunction (Lewis *et al.*, 2010). The study found that older people were more likely than younger people to experience erectile dysfunction.

Diabetic men had a three times higher probability of having erectile dysfunction than people without the disease, according to studies on the association of erectile dysfunction with diabetes and non-diabetics among aging men in Massachusetts. Similarly, after correcting for age, those with diabetes had an ED rate that was 2 times greater than that of those without diabetes (Johannes *et al.*, 2000). According to several studies by 2025, 322 million more people around the world are expected to develop ED. Several longitudinal and cross-sectional studies have revealed a connection between ED and cardiovascular risk factors such diabetes, depression, MetS, smoking, hypertension, and others (Feldman *et al.*, 1994; Ponholzer *et al.*, 2005).

2.10.3 Orgasmic Dysfunction

A wide range of anomalies play a role in men's orgasmic dysfunction. Retrograde ejaculation, anejaculation, and delayed ejaculation are among the possible symptoms. It describes a person's failure to experience orgasm. There is prominently reduced intensity of sensation of orgasm or clearly slowdown of orgasm from any kind of stimulant for sex (Hatzimouratidis and Hatzichristou, 2007).

2.10.4 Premature Ejaculation

The most well-known male sexual problem is premature ejaculation. It describes recurring or ongoing ejaculation that occurs before, during, or right after penetration and over which the person has little to no control or that is unattended by an orgasmic feeling. Mathers *et al.* (2007) claims that, on average, 20 to 25 percent of men in developed nations attribute their premature ejaculation to distress. The inability to find reliable incidence rate information for

this condition has been linked to two difficulties. The normal time interval between permeation and ejaculation is first affected by individual and cultural differences. Last but not least, there is a distinct difference between the problem that requires therapeutic intervention and that of biological malfunction in this part of studies (Althof, 2006).

2.10.5 Erectile Function and Sexual Hormones

The control of sexual function is handled by a number of systems. The neurological system, vascular system, and others are a few of these systems (Andersson and Wagner, 1995; Hotta *et al.*, 2011; Musicki *et al.*, 2018). The key chemical involved in erectile dysfunction is nitric oxide. After NO is released, the smooth muscles relax, but as NO release declines, erectile function begins to wane, culminating in ED. The relaxant system is crucially important for a healthy erection to happen.

The endothelium and nervous systems are engaged in controlling the relaxant system. It is well known that ED develops when the smooth muscle relaxant system's upper region begins to diminish. Conversely, constrictors like noradrenaline influence the contraction of the body's smooth muscle while it is in a flaccid mode. In some circumstances, an upregulation of the contraction leads to ED.

Additionally, it has been shown in numerous studies that the equilibrium between smooth muscle contraction and relaxation is disrupted by aberrant activation of signalling pathways that entail contracting, such as adrenergic modulation. In several ED-causing disorders like MetS or diabetes mellitus, it has been seen that smooth muscle contraction is enhanced (Wingard *et al.*, 2007; Wingard *et al.*, 2009).

2.10.6 Testosterone Deficiency and Erectile Dysfunction

The connection between ED and TT deficiency has been the subject of numerous studies (Kataoka *et al.*, 2014; Kataoka *et al.*, 2017). According to Mills *et al.* (1998), ED has been attributed to TT deficiency in research using castrated animals. Once more, the framework for talking about erectile function is the neuronal NOS (nNOS) and endothelial NO synthase (eNOS) pathways. After TT treatment, investigations have shown that NOS expression is upregulated and erectile function is recovered (Armagan *et al.*, 2006).

The decline in the activities eNOS and drop in the upregulation of ROS have been reported by Li *et al.* (2016). The authors also claimed that the loss in eNOS activity is responsible for the lowered stimulated cGMP concentrations in the penis. TT concentrations have been linked with the modification of phosphodiesterase type 5 (PDE-5) expression in the penis. In rabbit models, fall in PDE-5 activities have been positively correlated with deficit of serum TT concentration (Traish *et al.*, 1999).

Furthermore, it is known that TT influences the corpus cavernosum smooth muscles. Castrated rats' smooth muscle developed fewer -adrenergic-1 receptors, which was linked to a decrease in serum TT concentration (Reilly, 1997). According to Reilly *et al.* (1997), TT regulates the adrenergic response of the corpus cavernosum's vascular smooth muscle. The findings from the research stated above imply that a fall in the smooth muscle's ability to contract is directly related to a dip in the serum TT concentration.

Conversely, according to Sopko *et al.* (2014), there is increment in RhoA and Rho-kinase proteins corpus cavernosum of castrated rats. This denotes that rise in contractile ability of the smooth muscles in TT insufficiency, hence resulting in drop in erectile function and hypertension. In-depth research is required to properly comprehend how TT affects the contraction of the corpus cavernosum's smooth muscle. Unexpectedly, testosterone also has a direct impact on how smooth muscles relax. According to Yue *et al.* (1995), TT caused the smooth muscle in rabbits' coronary arteries and aorta to relax. Isometric tension analysis was employed by the researchers.

Traish *et al.* (2005) claims that a TT shortage is related to the deposition of fat-holding cells, particularly fibroblasts in the penis. Surprisingly, the absence of TT has been linked to the discovery of increased collagen in the rat penis' corporal cavernosum via reducing autophagy and promoting apoptosis of the smooth muscle myocytes as well as the decline in erectile performance (Wang *et al.*, 2015). The crucial role of TT controlling the morphological integrity of the corpus cavernosum and erectile function was highlighted, although there were a number of flaws in these reports. This is the outcome of TT regulating the interaction between Bcl-2 and BECN1 by adjusting the balance between apoptosis and autophagy (Lian *et al.*, 2010; Kang *et al.*, 2011).

2.10.7 ED and Diabetes

Giuliano *et al.* (2004) and Thorve *et al.* (2011) investigations found that around half of all males with diabetes experience erectile dysfunction. This finding validates numerous epidemiological research that hypothesized a link between higher ED risk and both T1DM and T2DM. In research pertaining to the epidemiology of ED in diabetes, the majority of authors do not segregate T1DM from T2DM. When compared to patients with T2DM, those with T1DM had an increased risk of acquiring ED, according to studies by Fedele *et al.* (1998), while T2DM and T1DM patients have comparable chances of developing ED, according to several other studies (Bacon *et al.*, 2002; Kalter-Leibovici *et al.*, 2005).

According to Feldman *et al.* (1994), males who have diabetes experience ED 10 to 15 years earlier than guys who don't have the condition. Furthermore, it has been found that diabetes is tied with a harder time responding to oral ED medications and a more severe ED when compared to non-diabetes (Penson *et al.*, 2003; Corona *et al.*, 2013a). Moreover, aging and having diabetes for a longer period of time have both been linked to a greater chance of developing ED in diabetic patients, according to various research (Fedele *et al.*, 1998; Giugliano *et al.*, 2010).

The link between elevated circulating plasma glucose and ED in diabetic males has not been sufficiently established. The question of whether hyperglycaemia is a risk factor for ED has been the subject of conflicting research. For instance, studies by Siu *et al.* (2001) and (Al-Hunayan *et al.*, 2007) found no significant link between poor glycaemic control and ED in diabetic men, whereas research by Penson *et al.* (2003) and Giugliano *et al.* (2010) revealed that patients with poor glycaemic control had elevated incidence of erectile dysfunction as shown by rising HbA1c levels. The variations in research methodology utilized in these studies may be responsible for the findings' discrepancies.

Further, related risk factors for both ED and diabetes include hypertension, overweight, obesity, MetS, smoking, autonomic neuropathy, and hyperlipidaemia (Nicolosi *et al.*, 2003; Ponholzer *et al.*, 2005). Additionally, a number of studies have connected the increased risk of ED in people with diabetes to certain comorbidities such microvascular and macrovascular issues (Heruti *et al.*, 2007; Chew *et al.*, 2013). Moreover, various studies have shown that using certain fibrates and diabetic medications has a detrimental effect on ED in diabetics. Spironolactone, thiazide diuretics, psychiatric drugs, and other antihypertensive drugs are a few of these medications

(Rosen, 1997; Foresta *et al.*, 2009). According to Nicolosi *et al.* (2003) and Kalter-Leibovici *et al.* (2005), a preventive effect of ED in the general population and diabetic men has been connected to average alcohol use.

2.10.8 Erectile Dysfunction and Obesity

Several studies have connected men's obesity to a drop in coital frequency. According to these authors, a possible reason of infertility is a fall in coital frequency. Studies conducted by Goldbeck-Wood (2010) found a 1.3-fold relative risk of ED to be linked to obesity. Additionally, Da Silva *et al.* (2017) study found that 79% of males with clinically evident ED were obese or overweight. Obesity and a number of vascular risk factors have been linked (Theleritis *et al.*, 2017). In addition, according to Ramalingam and Monga (2015), there are a variety of lifestyle factors with heightened incidence of CVD and diabetes, both of which are internal risk factors for ED, and these factors have a fiercely independent epidemiologic correlation to ED.

According to Silva *et al.* (2013), there are not many studies that back up the theory that men who are obese may have less coital encounters. Further research along males who are obese in the examination and fail to address this problem could support the conclusion of diminished fecund capacity in couples (Chen *et al.*, 2019). If the link between obesity and decreased coital frequency is established, extensive research will need to be done to determine whether changes in the endocrine system, erectile dysfunction symptoms, or psychosocial characteristics of obesity are to blame.

2.10.9 Assessment of Male Sexual Function

Male sexuality can be evaluated via a straightforward doctor-patient conversation. The shortcoming of this technique is the potential for underestimating sexual dysfunction. It is crucial for the doctor to make a clear distinction between loss of erection, loss of libido, and ejaculatory issues while utilizing this method so the patient can comprehend. In addition, a self-administered questionnaire and a personal interview can be used to examine sexuality. The majority of the questionnaires have been authenticated by reputable organizations. When constructing these questionnaires, it is important to take into account both the qualitative and quantitative aspects of sexuality because there is no linear relationship between measured results and quality that is perceptible to the patient (Lukacs, 2001).

2.10.9.1The Brief Male Sexual Function Inventory (BMSFI)

The BMSFI system, according to Donovan *et al.* (1996), was designed to assess solely males' sexual function. There are 11 questionnaire scales included in it that assess different facets of male sexuality. Erection, sexual drive, ejaculation, total satisfaction, and problem evaluation were all assessed by the BMSFI. The principal benefits of this method are adequate differentiation of erectile function, issue, and overall satisfaction, test-retest reliability, an increase in magnitude of internal consistency, ease of useability, and appropriate test-retest reliability. Potential limitations of BMFI include the limited evaluation of orgasmic and erectile function and the lack of information about sensitivity and therapeutic responses (Lukacs, 2001).

2.10.9.2The Danish Prostatic Symptom Score (DAN-PSS)

The presence and seriousness of 12 symptoms related to voiding and bladder storage, according to Hansen *et al.* (1995), are what this technique relies on. It is also known as a symptom score. Each question about the scope and intensity of the illness presents the study participants with four options from which to choose. This method is more trustworthy, responsive, and valid, according to studies. Median test-retest reliability of this instrument was connected with a score of 83.5%. When assessing the severity of symptoms among individuals who exhibit LUTS associated with BPH and their therapy follow-up, it is the most prudent strategy to apply.

2.10.9.3International Index of Erectile Function (IIEF)

According to Rosen *et al.* (1997), this measure is primarily employed to evaluate sexuality in therapeutic trials. The method uses 15 items to evaluate five key facets of sexual function. The five domains of assessment by this technique are orgasmic satisfaction, intercourse satisfaction, erectile function, sexual desire, and total satisfaction. The severity algorithm is used to compute the mean score from each main section and to interpret the values clinically. Regarding the psychometric assessment of this instrument in both clinical and non-clinical settings, various studies have indicated a very excellent measure of reliability. Excellent sensitivity and specificity for this approach in clinical trials have been observed in two investigations (Meuleman *et al.*, 2001; Wagner *et al.*, 2001).

This approach has been tested in a number of studies and has been translated into about 23 different languages. The main benefits of this method are its usage's clarity and simplicity.

Additionally, it has a high psychometric profile and involves a number of sexual function domains. One or more of this tool's constraints include the limited time frame, reduced examination of certain aspects of sexual dysfunction, such as desire and orgasmic function, and the validity of some populations, such as mental patients, which is not always reliable.

2.10.9.4 The International Continence Society Sex (ICSsex)

ICSsex is a part of the lengthy ICSBPH questionnaire, according to Donovan *et al.* (1996). The ICS-Benign Prostatic Hyperplasia investigation gave rise to the ICSBPH. There are 22 questions in the ICS-BPH study, and 20 of them are about urine symptoms. A large percentage of the questions ask about how much discomfort the symptoms produce. In order to assess issues pertaining to quality of life, the ICS-BPH additionally includes the ICSQoL. According to two studies, ICSmale and ICSQoL are very trustworthy in terms of psychometric evaluation (Donovan *et al.*, 1996; Donovan *et al.*, 1997). The ICSex approach includes four questions about how LUTS has affected the patients' sex lives, including if they have erections or ejaculations and whether they have felt any discomfort while ejaculating. This instrument also assesses the degree of discomfort the patient has in relation to the symptoms.

Chapter 3

MATERIALS AND METHODS

3.1 Study Population and Design

This study was a cross-sectional study conducted at the diabetic clinic of the Tamale Teaching Hospital, among male diabetic subjects from September, 2018 to September, 2019. Male subjects with diabetes who were sexually active, at least 18 years old, of sound mind, and who were married or had recently been in a committed heterosexual relationship made up the target group. A convenieint sampling technique was used and each respondent provided informed, written consent prior to participating on a voluntary basis.

3.1.1 Sample Size

From the assumption that 6.5% of the general adult population is diabetic, the minimal sample size for this study was estimated to be 93 adult male diabetics (Asamoah-Boaheng *et al.*, 2019), Considering a type I error (α) of 0.05 and an anticipated difference between the sample and the overall population of 5%.

$$n = \frac{z^2 p(1-p)}{d^2}$$

Where n = minimum sample size; d=Absolute standard error=0.05; p=prevalence=6.5%; Z = standard normal variance=1.96 to give a power of 95% CI (β=5%) and a type 1 error probability of 5%.

The sample size was recalculated in this study, restricted to only adult male diabetics who responded to not less than 80% of the questionnaire items, to account for any potential loss of respondents. The sample size was computed with a response rate of 80% as follows: 93/0.80. The estimated sample size was roughly 116 using the formula above. One hundred and twenty-one (121) individuals were therefore included in this study.

3.2 Data Collection.

3.2.1 Socio-Demographic and Anthropometric Data

Participants in the study who provided their assent were given a self-designed semi-structured questionnaire to fill out regarding socio-demographic data such as age, highest educational level,

occupation, smoking, alcohol consumption, marital status, level of exercise, income, and duration of diabetes. Any action lasting more than 30 minutes that caused light perspiration, a slight to moderate increase in respiration, or an increase in heart rate was considered to be exercise. Having a weekly intake of at least one bottle of alcohol was deemed to constitute alcohol usage. Whether a person had the habit of smoking at least one cigarette each day determined whether they were considered a smoker. Education was divided into four levels: primary/elementary, secondary/technical, and tertiary.

Weight and height measurements were taken while wearing light clothing and were performed to the nearest 0.1 kg and 1 cm, respectively, on digital flat floor weighing scales made by SECA (Hamburg, Germany) (measurement range: 0 cm to 220 cm). Halfway between the suprailiac crest and the inferior angle of the ribs, the waist circumference was measured (to the nearest centimeter) with a Gulick II spring-loaded measuring tape (Gay Mill, WI). Hip circumference was estimated using the largest circumference over the buttocks. Waist to Hip Ratio was calculated as waist circumference (cm) divided by hip circumference (cm), and Body Mass Index was computed as body weight in kg/height in m^2. Overweight and obesity were defined as BMIs of 25 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively, whereas a WHR of ≥0.90 and WC of ≥94 cm were considered obese.

3.2.2 Blood Pressure

Using a sphygmomanometer cuff and a stethoscope, blood pressure was taken while the subject was seated at the level of the heart. According to the American Heart Association's recommendation, measurements were collected from the left brachial artery after patients had been seated for at least five (5) minutes (Kirkendall et al., 1976). The diastolic value was calculated using the fifth Korotkoff sound, phase V (lack of sound), rather than phase IV (muffling). The mean reading was recorded to the closest 2.0 mm Hg in triplicate measurements with a five (5) minute rest period in between observations.

3.2.3 Sample Collection, Preparation and Analysis

Following an overnight fast, each subject had ten milliliters of venous blood taken from them into a fluoride oxalate tube and Serum Seperator Tubes (SST) under strict aseptic conditions (Becton Dickinson, Rutherford, NJ). When it was time for the biochemical investigations, samples in SSTs were centrifuged at 3000 g for 5 minutes, and the serum was aliquoted and kept in cryovials

at a temperature of -70 °C. On the other hand, samples in fluoride oxalate tubes were used for fasting blood glucose measurement. The Mindray BS-240 Chemistry Analyser (Mindray, China) was used to measure the lipid profile, liver function tests, and fasting blood glucose levels. MedSource Diagnostics reagents were utilized in each of these assays. The AxSYM analyzer was used to conduct the hormonal assays. Micro-particle Enzyme Immunoassay is used by the AxSYM to measure the levels of testosterone, adiponectin, leptin, SHBG, and insulin. All of the hormonal assays were performed using the Elabscience® reagent kits. The automated equipment used procedures that followed the reagent makers' directions to determine biochemical and hormonal parameters.

3.3 Biochemical Assays

3.3.1 Total Cholesterol

By hydrolyzing esters, cholesterol esterase is able to release fatty acids and cholesterol. The preformed cholesterol and the free cholesterol produced are both oxidized in the presence of cholesterol oxidase to produce cholest-4-en-3-one and hydrogen peroxide. In the presence of peroxidase and hydrogen peroxide, phenol is oxidatively bonded to 4-aminophenazone to produce the quinoneimine chromogen, which has a maximum absorption wavelength of 500 nm. The intensity of the final red hue varies directly with the concentration of total cholesterol.

$$\boldsymbol{Cholesterol\ Esters \xrightarrow{cholesterol\ esterase} Cholesterol\ + Fatty\ Acids}$$

$$\boldsymbol{Cholesterol\ +\ O_2 \xrightarrow{Cholesterol\ oxidase} Cholest-4-en-3-one\ +\ H_2O}$$

$$\boldsymbol{2H_2O_2 + 4-aminophenazone + Phenol \xrightarrow{Peroxidase} Quinoneimine\ +\ 4H_2O}$$

3.3.2 Fasting Blood Glucose (FBG)

The hexokinase method, which is connected to the generation of NADH, was used to measure the glucose concentration. Glucose-6-phosphate is created when the enzyme hexokinase phosphorylates glucose with ATP.

$$\boldsymbol{Glucose + ATP \rightarrow Glucose\text{-}6\text{-}phosphate + ADP}$$

Afterwards, the enzyme glucose-6-phosphate dehydrogenase oxidizes 6-phosphogluconate to glucose-6-phosphate with a conversion of NAD to NADH

$$\textit{Glucose-6-phosphate} + \textit{NAD} \rightarrow \textit{6-Phosphogluconate} + \textit{NADH}$$

The amount of NADH generated during this reaction is precisely proportional to the initial sample's glucose content. The quantity of glucose in the sample was evaluated by measuring the absorbance of NADH at 340 nm.

3.3.3 Triglycerides

Lipase hydrolyzes the sample's triglycerides into glycerol and fatty acids. Glycerol kinase then catalyzes the phosphorylation of glycerol by adenosine 5-triphosphate (ATP), resulting in glycerol-3-phosphate and adenosine 5-diphosphate (ADP). Glycerophosphate oxidase then breaks down glycerol-3-phosphate into dihydroxyacetone phosphate (DHAP) and hydrogen peroxide (H_2O_2). In a subsequent process facilitated by peroxidase, the hydrogen peroxide reacts with 4-aminoantipyrine and 3, 5-dichloro-2-hydroxybenzene (Chlorophenol) to produce a red quinoneimine color. The concentration of triglycerides present in the sample directly correlates with the intensity of the color produced.

$$\textbf{Triglycerides} + \textbf{H}_2\textbf{O} \xrightarrow{\textbf{Lipase}} \textbf{Glycerol} + \textbf{Fatty Acids}$$

$$\textbf{Glycerol} + \textbf{ATP} \xrightarrow{\textbf{Glycerol kinase}} \textbf{G3P} + \textbf{ADP}$$

$$\textbf{Glycerol} - \textbf{3} - \textbf{Phosphate} \xrightarrow{\textbf{Glycerolphosphate oxidase}} \textbf{DHAP} + \textbf{H}_2\textbf{O}_2$$

$$2\textbf{H}_2\textbf{O}_2 + \textbf{4} - \textbf{aminophenazone} + \textbf{Chlorophenol} \xrightarrow{\textbf{Peroxidase}} \textbf{Quinoneimine} + 2\textbf{H}_2\textbf{O}$$

3.3.4 HDL-Cholesterol

Low-density lipoproteins (LDL and VLDL) and chylomicron fractions quantitatively precipitate out when phosphotungstic acid is added to a sample in the presence of Mg^{2+} ions. The amount of cholesterol in the HDL is then measured.

3.3.5 LDL- cholesterol

The following formula was used to calculate LDL cholesterol from triglycerides(TG), HDL cholesterol (HDL-c), and total cholesterol (TC) (Friedewald *et al.*, 1972);

$$\mathbf{LDL-Cholesterol\ (mmol\ L^{-1})} = \mathbf{TC\ (mmol\ L^{-1})} - \frac{\mathbf{TG(mmol\ L^{-1})}}{\mathbf{2.2}} - \mathbf{HDL(mmol\ L^{-1})}$$

3.3.6 Total Protein

The estimation of total protein was performed using the Biuret method. In this procedure, a violet-colored chelate is created when cupric ions (Cu^{2+}) in the biuret reagent combine with peptide bonds in the presence of alkaline conditions, i.e., 3% NaOH and at least two peptide bonds. Additionally, the sodium potassium tartrate in biuret aids in the production of Cu^{2+} complexes and hinders their precipitation in an alkaline solution. At 540 nm, the colored chelate's absorbance is measured.

3.3.7 Albumin

Albumin forms blue green coloured complex with Bromocresol green in acidic medium. The colour formed is directly proportional to the concentration of albumin present in the sample, intensity of colour is measured at 620nm.

3.3.8 Gamma Glutamyl Transferase (GGT)

According to the following reaction, gamma-glutamyl transferase (γ-GT) catalyzes the transfer of the γ-glutamyl group from γ-glutamyl-p-nitroanilide to acceptor glycylglycine.

$$\boldsymbol{\gamma - L - Glutamyl - 3 - Carboxy - 4 - nitroanilide + Glycylglycine} \xrightarrow{\boldsymbol{\gamma-glutamyl\ transferase}} \boldsymbol{\gamma - L - Glutamyl - glycylglycine + 2 - Nitro - 5 - aminobenzoic\ acid}$$

The photometrically determined rate of 2-nitro-5-aminobenzoic acid synthesis is proportional to the amount of γ-GT that is catalytically active in the sample.

3.3.9 Alanine Transaminase (ALT)

The reversible transfer of an amino group from alanine to α-ketoglutarate, creating glutamate and pyruvate, is catalyzed by the enzyme alanine aminotransferase (ALT). When pyruvate is created, lactate dehydrogenase (LDH) and NADH convert it to lactate.

$$\alpha - ketoglutarate + L - Alanine \xrightarrow{ALT(GPT)} L - Glutamate + Pyruvate$$

$$Pyruvate + NADH + H^{+} \xrightarrow{Lactate\ Dehydrogenase} L - Lactate + NAD$$

The catalytic concentration of ALT present in the sample determines how quickly the concentration of NADH decreases when evaluated photometrically.

3.3.10 Aspartate Transaminase (AST)

In order to create glutamate and oxaloacetate, aspartate aminotransferase (AST) catalyzes the reversible transfer of an amino group from aspartate to α-ketoglutarate. Malate dehydrogenase (MDH) and NADH convert the oxaloacetate into malate:

$$\alpha - Ketoglutarate + L - Aspartate \xrightarrow{AST\ (GOT)} L - Glutamate + Oxaloacetate$$

$$Oxaloacetate + NADH + H^{+} \xrightarrow{Malate\ dehydrogenase\ (MDH)} Malate + NAD$$

The catalytic concentration of AST present in the sample determines the rate of decline in NADH concentration, which is assessed photometrically.

3.3.11 Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP) catalyses the hydrolysis of p-nitrophenyl phosphate at pH 10.4, liberating p-nitrophenol and phosphate, according to the following reaction:

$$p - Nitrophenylphosphate + H_2O \xrightarrow{ALP} p - Nitrophenol + Phosphate$$

The rate of p-Nitrophenol formation, measured photometrically, is proportional to the catalytic concentration of alkaline phosphatase present in the sample.

3.3.12 Bilirubin Estimation

By using diazotized sulfanilic acid, bilirubin is transformed into colored azobilirubin, which is then photometrically measured. Only the former of the two fractions present in serum—bilirubin-

glucuronide and free bilirubin loosely linked to albumin—reacts in aqueous solution directly (bilirubin direct); free bilirubin must first be solubilized in dimethylsulfoxide (DMSO) before it can react (bilirubin indirect). The sum of both the direct and indirect bilirubins is the total bilirubin. The amount of bilirubin present in the sample determines how intense the color will be.

3.3.13 Hormones and Adipokines

The Elabscience reagent kit was used in the assay of insulin, testosterone, sex hormone binding globulin, adiponectin and leptin levels in all the samples. The ELISA kit for insulin and testosterone, use the competitive-ELISA method whiles those of sex hormone binding globulin, adiponectin and leptin use the Sandwich-ELISA method.

3.3.13.1 Insulin

The Elabscience reagent kit was used in the assay of insulin levels in all the samples. This ELISA kit uses the competitive-ELISA method. The microtitre plate provided was precoated with Insulin. Fifty microlitres (50 ul) of sample is added to the wells. Fifty microlitres of biotinylated detection antibody was immediately added. During the reaction, human insulin in the added sample or standard competes with a fixed amount of insulin on the solid phase supporter for sites on the biotinylated detection antibody which is specific to human insulin, this was incubated for 45 minutes at 37 ^{0}C. Excess conjugate and unbound sample or standard were then washed off the plate using wash buffer in three repeated washes. Hundred microlitres (100 ul) of Avidin conjugated to horseradish peroxidase (HRP) was then added to each microplate well and incubated at 37 ^{0}C for 30 minutes. Ninety microlitres (90 ul) of a Tetramethylbencidine (TMB) substrate solution was then added and incubated at 37 ^{0}C for 15 minutes. The enzyme substrate reaction was then stopped by the addition of 50 ul of sulphuric acid solution to each well. The colour change was then measured at 450 nm ± 2 nm. The concentration of insulin in the sample was then calculated by comparing the optical density obtained from the samples to the standard curve.

3.3.13.2 Leptin

The Elabscience reagent kit was used in the assay of SHBG level in all the samples. This ELISA kit uses the Sandwich-ELISA method. The microtitre plate provided was been precoated with antibody specific to leptin. Samples and standards were added (100 ul) to the microplate wells

and they combine with the specific antibody. This is incubated at 37 ^{0}C for 90 minutes. Hundred microlitres (100 ul) of a biotinylated detection antibody which is specific to leptin and Avidin-Horseradish Peroxidase (HRP) conjugate is then added to each microplate. This was incubated for at 37 ^{0}C for 1 hour. Excess biotinylated antibody and unbound sample or standard were then washed off the plate using wash buffer in three repeated washes. Hundred microlitres (100 ul) of Avidin conjugated to horseradish peroxidase (HRP) was then added to each microplate well and incubated at 37 ^{0}C for 30 minutes. Excess conjugate was then washed off using wash buffer in three repeated washes. Ninety microlitres (90 ul) of a Tetramethylbencidine (TMB) substrate solution was then added and incubated at 37 ^{0}C for 15 minutes. The reaction was then stopped by the addition of 50 ul of sulphuric acid solution to each well. The colour change was then measured at 450 nm ± 2 nm. The concentration of leptin in the sample was then calculated by comparing the optical density obtained from the samples to the standard curve.

3.3.13.3 Adiponectin

The Elabscience reagent kit was used in the assay of adiponectin levels in all the samples. This ELISA kit uses the Sandwich-ELISA method. The microtitre plate provided was precoated with antibody specific to adiponectin. Samples and standards were added (100 ul) to the microplate wells and they combine with the specific antibody. This was incubated at 37 ^{0}C for 90 minutes. Hundred microlitres (100 ul) of a biotinylated detection antibody which is specific to SHBG and Avidin-Horseradish Peroxidase (HRP) conjugate was then added to each microplate. This was incubated for at 37 ^{0}C for 1 hour. Excess biotinylated antibody and unbound sample or standard were then washed off the plate using wash buffer in three repeated washes. Hundred microlitres (100 ul) of Avidin conjugated to horseradish peroxidase (HRP) was then added to each microplate well and incubated at 37 ^{0}C for 30 minutes. Excess conjugate was then washed off using wash buffer in three repeated washes. Ninety microlitres (90 ul) of a Tetramethylbencidine (TMB) substrate solution was then added and incubated at 37 ^{0}C for 15 minutes. The reaction was then stopped by the addition of 50 ul of sulphuric acid solution to each well. The colour change was then measured at 450 nm ± 2 nm. The concentration of adiponectin in the sample was then calculated by comparing the optical density obtained from the samples to the standard curve.

3.3.13.4 Testosterone

The Elabscience reagent kit was used in the assay of total testosterone level in all the samples. This ELISA kit uses the competitive-ELISA method. The microtitre plate provided was precoated with testosterone. Fifty microlitres (50 ul) 0f sample was added to the wells. Fifty microlitres of biotinylated detection antibody was immediately added. During the reaction, human testosterone in the added sample or standard competes with a fixed amount of testosterone on the solid phase supporter for sites on the biotinylated detection antibody which is specific to human testosterone, this is incubated for 45 minutes at 37 ^{0}C. Excess conjugate and unbound sample or standard are then washed off the plate using wash buffer in three repeated washes. Hundred microlitres (100 ul) of Avidin conjugated to horseradish peroxidase (HRP) is then added to each microplate well and incubated at 37 ^{0}C for 30 minutes. Ninety microlitres (90 ul) of a Tetramethylbencidine (TMB) substrate solution was then added and incubated at 37 ^{0}C for 15 minutes. The enzyme substrate reaction was then stopped by the addition of 50 ul of sulphuric acid solution to each well. The colour change is then measured at 450 nm ± 2 nm. The concentration of testosterone in the sample was then calculated by comparing the optical density obtained from the samples to the standard curve.

Free testosterone was calculated from total testosterone, SHBG, and albumin using the Vermeulen (1999) equation whiles bioavailable testosterone was calculated using the formular bioavailable testosterone = 23.43 x Free testosterone.

3.3.13.5 Sex Hormone Binding Globulin (SHBG)

The Elabscience reagent kit was used in the assay of SHBG level in all the samples. This ELISA kit uses the Sandwich-ELISA method. The microtitre plate provided was precoated with antibody specific to SHBG. Samples and standards were added (100 ul) to the microplate wells and they combined with the specific antibody. This was incubated at 37 ^{0}C for 90 minutes. Hundred microlitres (100 ul) of a biotinylated detection antibody which is specific to SHBG and Avidin-Horseradish Peroxidase (HRP) conjugate was then added to each microplate. This was incubated at 37 ^{0}C for 1 hour. Excess biotinylated antibody and unbound sample or standard were then washed off the plate using wash buffer in three repeated washes. Hundred microlitres (100 ul) of Avidin conjugated to horseradish peroxidase (HRP) was then added to each microplate well and incubated at 37 ^{0}C for 30 minutes. Excess conjugate was then washed off using wash buffer in

three repeated washes. Ninety microlitres (90 ul) of a Tetramethylbencidine (TMB) substrate solution is then added and incubated at 37 ^{0}C for 15 minutes. The reaction was then stopped by the addition of 50 ul of sulphuric acid solution to each well. The colour change was then measured at 450 nm ± 2 nm. The concentration of SHBG in the sample was then calculated by comparing the optical density obtained from the samples to the standard curve.

3.4 The Golombok Rust Inventory of Sexual Satisfaction

The male version of the Golombok Rust Inventory of Sexual Satisfaction (GRISS-M) was used to assess each subject's sexual function. The purpose of the 28-item GRISS-M questionnaire is to assess the presence and intensity of sexual problems in heterosexual relationships or in heterosexual couples or individuals. Answers to each of the 28 questions range from "always" to "usually," "occasionally," "hardly ever," and "never" on a five-point (Likert type) scale. It offers general rankings of a relationship's sexual functioning quality. Additionally, profiles can be created using the subscale scores of impotence, premature ejaculation, infrequency, non-communication, dissatisfaction, non-sensuality, and avoidance. High scores indicate more serious issues. The total score and subscale scores are transformed using a standard nine-point scale. Scores of five or higher are regarded as representing SD. The GRISS was used because it is simple to use, standardized, less expensive and generally inconspicuous.

3.5 Definitions of Terms

3.5.1 Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

HOMR-IR was estimated based on the mathematical formula: (fasting insulin [mlU/L] x fasting glucose [mmol/L]) / 22.5 (Matthews *et al.*, 1985). Values ≥ 2 were considered as insulin resistance (Lee *et al.*, 2016).

3.5.2 Quantitative Insulin Sensitivity Check Index (QUICKI)

QUICKI was calculated using the mathematical formula: 1/ (log (fasting Insulin [mU/L]) + Log (Fasting Blood Sugar [mg/dL])). Lower values indicate greater insulin resistance and values below 0.34 were considered as insulin resistance (Katz *et al.*, 2000).

3.5.3 Homeostatic Model Assessment of β-cell function (HOMA-B)

HOMA-B was calculated based on the formula: 20 × fasting insulin (mU/L)/ fasting glucose (mmol/ml) − 3.5 (Matthews *et al.*, 1985).

3.5.4 Fatty Liver Index (FLI)

The validated Fatty Liver Index developed by Bedogni *et al.* (2006) was used to evaluate Non-Alcoholic Fatty Liver Disease (NAFLD). Based on TG, WC, BMI, GGT, and natural logarithm (ln), the approximated equation for fatty liver is as follows: FLI = exp [0.953 x ln (TG) + 0.139 x BMI + 0.718 x ln (GGT) + 0.053*WC - 15.745] / (1+ exp [0.953 x ln (TG) + 0.139 x BMI + 0.718 x ln (GGT) + 0.053 x WC - 15.745]) x 100. Values > 60 are classified as higher risk of NAFLD.

3.6 Statistical Analysis

All analyses were conducted using MedCalc® version 10.2.0.0 (www.medcalc.be), GraphPad® version 9.0 (San Diego, California, USA), and the Statistical Package for Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp). Indicators of data included mean, standard deviation, and percentages. When comparing continuous variables, the unpaired T-test and Mann-Whitney tests were used, and when comparing categorical variables, the Chi-square test was used. The correlation between the variables was assessed using Pearson's correlation. Receiver Operator Features (ROC) were used to evaluate the relative propensities of various characteristics to predict the dependent variable. All statistical analyses were considered significant at a value of <0.05.

Chapter 4

RESULTS

4.1 General Characteristics of Studied Population

One hundred and thirty (130) questionnaires were administered in total, of which 125 (96%) followed through to the end of the data collection. 121 completed and evaluable questionnaires, representing a response rate of 93%, were left after the set of questionnaires from 4 people were rejected because they were insufficiently completed. Following stratification based on a HOMA-IR ≥2, forty-eight (48) participants representing 39.7% had insulin resistance.

4.1.1 Sociodemographic Characteristics of Study Population Stratified by HOMA-IR

Table 4.1 summarises the general and sociodemographic characteristics of the studied population. The average age of the study population was 63.0±10.8 years with majority (95%) of them being married. About half (48%) of the participants had attained at least secondary education whiles very few (16%) took alcohol. The mean FBG, insulin, HOMA-IR were 9.0±2.7 mmol/L, 114.1±174.7 pg/mL and 1.5±2.3 respectively.

When the population was stratified based on HOMA-IR, the proportion of subjects with at least secondary education (60%) was significantly higher in HOMA-IR <2 group than in their counterparts with a HOMA-IR ≥2. FBG, insulin levels, HOMA-IR and HOMA-B were significantly higher among subjects with HOMA-IR ≥ 2 compared to their counterparts. However, QUICKI was significantly lower in the HOMA-IR ≥ 2 subjects compared to the HOMA-IR <2 group as shown in Table 4.1.

Table 4.1: General and sociodemographic characteristics stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Age	63.0±10.8	63.1±11.48	62.8±9.8	0.872
Marital Status				
Married	115(95%)	69(94.5%)	46(95.8%)	0.745
Single	6(5%)	4(5.5%)	2(4.2%)	
Highest Education				
Basic	63(52%)	30(41.1%)	33(68.8%)	0.005
Secondary	52(43%)	37(50.7%)	15(31.3%)	
Tertiary	6(5%)	6(8.2%)	0(0%)	
Alcohol Intake				
No	102(84.3%)	62(84.9%)	40(83.3%)	0.813
Yes	19(15.7%)	11(15.1%)	8(16.7%)	
Exercise per week	1.8±0.9	1.9±0.9	1.7±1.0	0.382
Duration of Diabetes	8.3±6.2	7.55±6.1	9.5±6.3	0.096
Fasting Blood Glucose (mmol/L)	9±2.7	8.0±2.6	10.5±2.2	<0.0001
Insulin (pg/mL)	114.1±174.7	3.24±7.6	282.6±172.4	<0.0001
Insulin (mU/L)	3.31±5.1	0.1±0.2	8.2±5.0	<0.0001
HOMA-IR	1.51±2.34	0.03±0.08	3.76±2.32	<0.0001
QUICKI	0.82±0.44	1.14±0.24	0.32±0.03	<0.0001
HOMA-B	11.24±20.2	0.52±0.93	27.54±24.30	<0.0001

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test.

4.2 Anthropometric Characteristics of Study Population

Table 4.2 summarises the anthropometry and adipokine levels of the study population stratified by HOMA-IR. The average weight and height for the studied population were 83.9±32.7 kg and 1.69±0.1 m respectively. The mean BMI, WC and WHR were 29.48±12.3 kg/m^2, 94.92±10.7 cm and 0.93±0.04. The hormones adiponectin, leptin and the leptin to adiponectin ratio were 150.8±111.7 ng/mL, 2.59±2.4 ng/mL and 0.04±0.05 respectively.

When the population was stratified based on their HOMA-IR, weight, BMI, WC, HC, WHR as well as the leptin to adiponectin ratio were significantly higher among the HOMA-IR ≥2 group compared to their counterparts with HOMA-IR <2. Conversely, Adiponectin levels were significantly reduced in the HOMA-IR ≥2 group, as shown in Table 4.2

Table 4.2: Anthropometric and adipokine levels stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Weight (kg)	83.9±32.71	71.82±9.79	102.3±44.88	<0.0001
Height (m)	1.69±0.07	1.69±0.07	1.69±0.07	0.877
Body Mass Index (kg/m^2)	29.48±12.34	25.06±3.15	36.21±17.23	<0.0001
Hip Circumference (cm)	101.6±9.3	99.58±6.78	104.7±11.58	0.003
Waist Circumference (cm)	94.92±10.66	91.92±9.08	99.48±11.35	<0.0001
Waist to Hip Ratio	0.93±0.04	0.92±0.04	0.95±0.04	<0.0001
Adiponectin (ng/mL)	150.8±111.7	206.4±93.93	66.31±79.17	<0.0001
Leptin (ng/mL)	2.59±2.41	2.61±2.43	2.57±2.41	0.930
Leptin/Adiponectin	0.04±0.05	0.03±0.04	0.07±0.06	<0.0001

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test

4.2.1 Prevalence of Obesity among Study Population

Figure 4.1 shows the proportions of obesity based on different criteria, among the studied population. More than half (59%) of the studied population were obese, using BMI as a criterion, with a similar proportion being obese when WC (55%) and WHR (54%) were used as the criteria for classification of obesity.

When the population was stratified based on HOMA-IR, the proportion of subjects with general obesity (BMI), central obesity (WC) and abdominal obesity (WHR) were significantly higher in the HOMA-IR ≥2 group (72.9%, p=0.010; 66.7%, p=0.043; 70.8%, p=0.002 respectively) compared to their counterparts with HOMA-IR <2 (49.3%, 47.9%, 42.5% respectively), as shown in Figure 4.1.

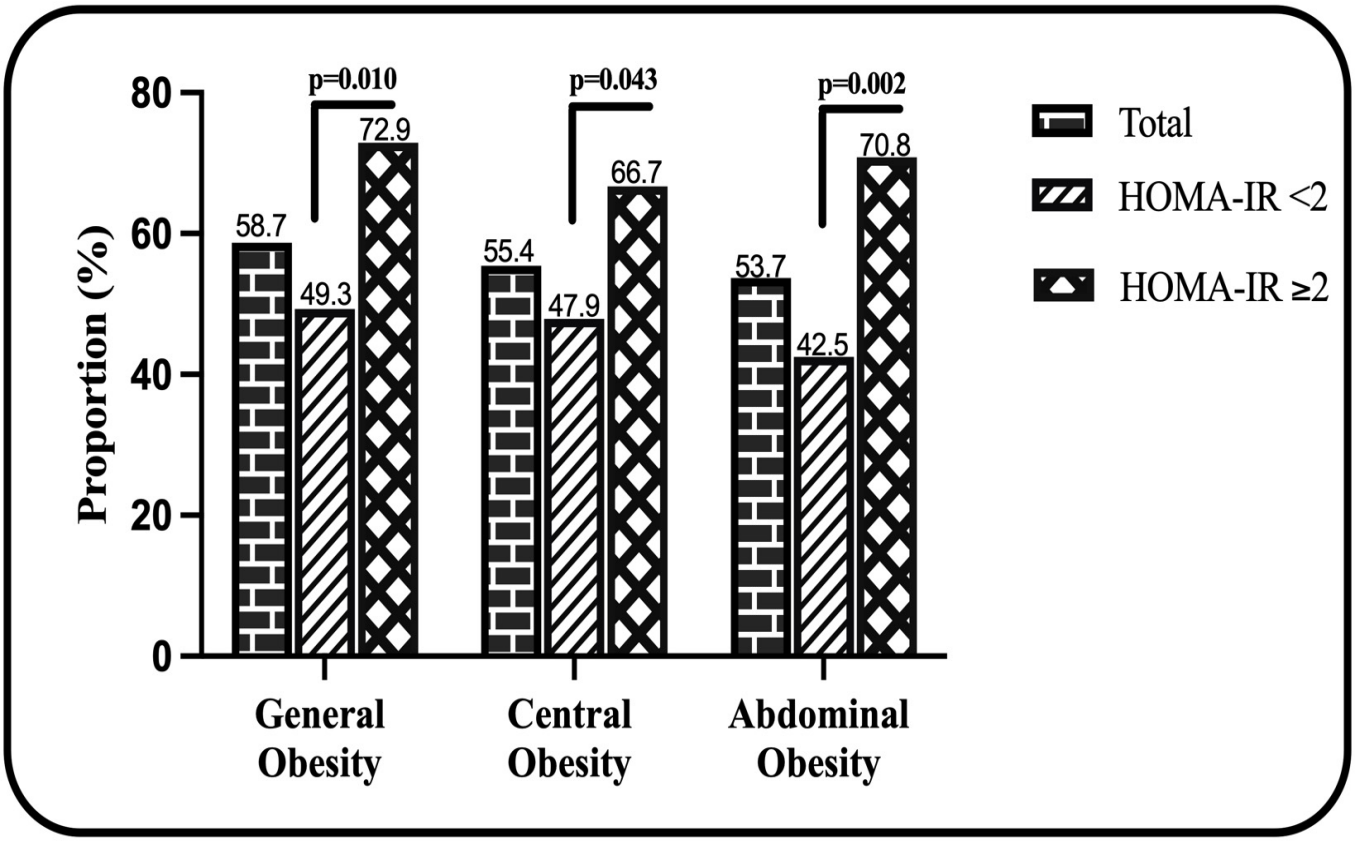

Figure 4.1: Distribution of general obesity (BMI), central obesity (WC) and Abdominal obesity (WHR) among study population stratified by HOMA-IR

4.2.2 Anthropometric and Adipokines as Determinants of Insulin Resistance

The impact of various anthropometries and adipose hormones on the occurrence of insulin resistance are shown in Table 4.3. Being overweight or obese (BMI ≥ 25kg/m^2) [OR=2.8, p=0.011], central obesity (WC>94cm) [OR=2.2, p=0.044], abdominal obesity (WHR ≥0.90) [OR=3.3, p=0.003] and low adiponectin levels (OR=0.9, p<0.0001) were found to significantly affect the occurrence of insulin resistance (HOMA-IR ≥2). After adjusting for confounding variables, abdominal obesity (WHR ≥0.90) [aOR=9.1, p=0.003] and low adiponectin levels (aOR=0.9, p<0.0001) were found to be independent risk factors for occurrence of insulin resistance, as show in Table 4.3.

Table 4.3: Effects of anthropometry and adipokines on insulin resistance

Parameter	OR (95%CI)	P Value	aOR (95%CI)	P-value
Body Mass Index				
Normal Weight	1.0	-	1.0	-
Overweight/Obese	2.8(1.26-6.07)	0.011	3.1(0.65-14.57)	0.159
Waist Circumference				
Normal	1.0	-	1.0	-
Obese	2.2(1.02-4.62)	0.044	0.3(0.06-1.62)	0.169
Waist to Hip Ratio				
Normal	1.0	-	1.0	-
Obese	3.3(1.51-7.15)	0.003	9.1(2.15-38.03)	0.003
Adiponectin	0.9(0.98-0.99)	<0.0001	0.9(0.98-0.99)	<0.0001
Leptin	0.9(0.85-1.16)	0.929	1.1(0.86-1.28)	0.628

4.2.3 Correlation of Insulin, Indices of Insulin resistance against Anthropometric Markers of Obesity and Adipokines

Pearson's correlation was done to assess the association between insulin, insulin resistance indices (HOMA-IR and QUICKI), index of pancreatic beta function (HOMA-B) and markers of obesity and adipokines as shown in Table 4.4. Insulin and HOMA-IR showed significant positive correlations with weight, BMI, WC, WHR and leptin to adiponectin ratio but showed a significant inverse relation with adiponectin levels. QUICKI conversely showed significant inverse relations with weight, BMI, HC, WC, WHR and Leptin to adiponectin ratio and a significant positive correlation with adiponectin levels. HOMA-B was significantly positively related with WC, WHR and leptin to adiponectin ratio but showed a negative correlation with adiponectin levels. The association between insulin levels (r = -0.52), HOMA-IR (r = -0.50), QUICKI (r = 0.58) and HOMA-B (r = -0.47) and adiponectin levels were the strongest and, in all cases, QUICKI showed the strongest association with the anthropometric parameters compared to the other insulin resistance indices.

Table 4.4: Partial correlation of insulin resistance indices against anthropometry and adipokines

Parameter	Insulin	HOMA-IR	QUICKI	HOMA-B
	r	r	r	r
Weight (kg)	0.27**	0.30**	-0.43***	0.17
Height (m)	0.01	0.01	-0.02	0.03
Body Mass Index (kg/m^2)	0.26**	0.30**	-0.41***	0.16
Hip Circumference (cm)	0.17	0.16	-0.29**	0.16
Waist Circumference (cm)	0.23*	0.22*	-0.36***	0.22*
Waist to Hip Ratio	0.24**	0.22*	-0.33***	0.22*
Adiponectin (ng/mL)	-0.52***	-0.50***	0.58***	-0.47***
Leptin (ng/mL)	-0.05	-0.01	-0.01	-0.07
Leptin/Adiponectin	0.35***	0.41***	-0.40***	0.28**

Significant correlation at the 0.05 level, ** Significant correlation at the 0.01 level, ***Significant correlation at the 0.001 level.

4.2.4 Receiver Operator Characteristics (ROC) for Anthropometries and Adipokines

The ROC curves and the area under curve (AUC) showing the predictive abilities of anthropometric and adipokines to predict insulin resistance are shown in Figure 4.2 whiles their respective cut-off points for classification insulin resistance are also shown in Table 4.5. With the exception of leptin levels, all other parameters significantly classified subjects as insulin resistant or not, with adiponectin levels showing the highest AUC for the classification of insulin resistance.

A higher Youden index indicates higher diagnostic value as evaluated by a balance between the sensitivity and specificity of a marker. From Table 4.5, adiponectin levels gave the highest Youden index (0.66) at a diagnostic cut-off of ≤ 148ng/mL (Sensitivity = 85.4 and Specificity = 80.8).

Table 4.5: Cut-offs, sensitivity and specificity of anthropometry and adipokines

Parameter	Youden Index	Cut-off	Sensitivity	Specificity
Weight (kg)	0.43	>85.2	45.8	97.3
Body Mass Index (kg/m^2)	0.43	>28.8	54.2	89.0
Hip Circumference (cm)	0.24	>108.5	29.2	94.5
Waist Circumference (cm)	0.28	>91	79.2	49.3
Waist to Hip Ratio	0.36	>0.91	91.7	43.8
Adiponectin (ng/mL)	0.66	≤148	85.4	80.8
Leptin (ng/mL)	0.17	>1.73	58.3	58.9
Leptin/Adiponectin	0.49	>0.05	62.5	86.3

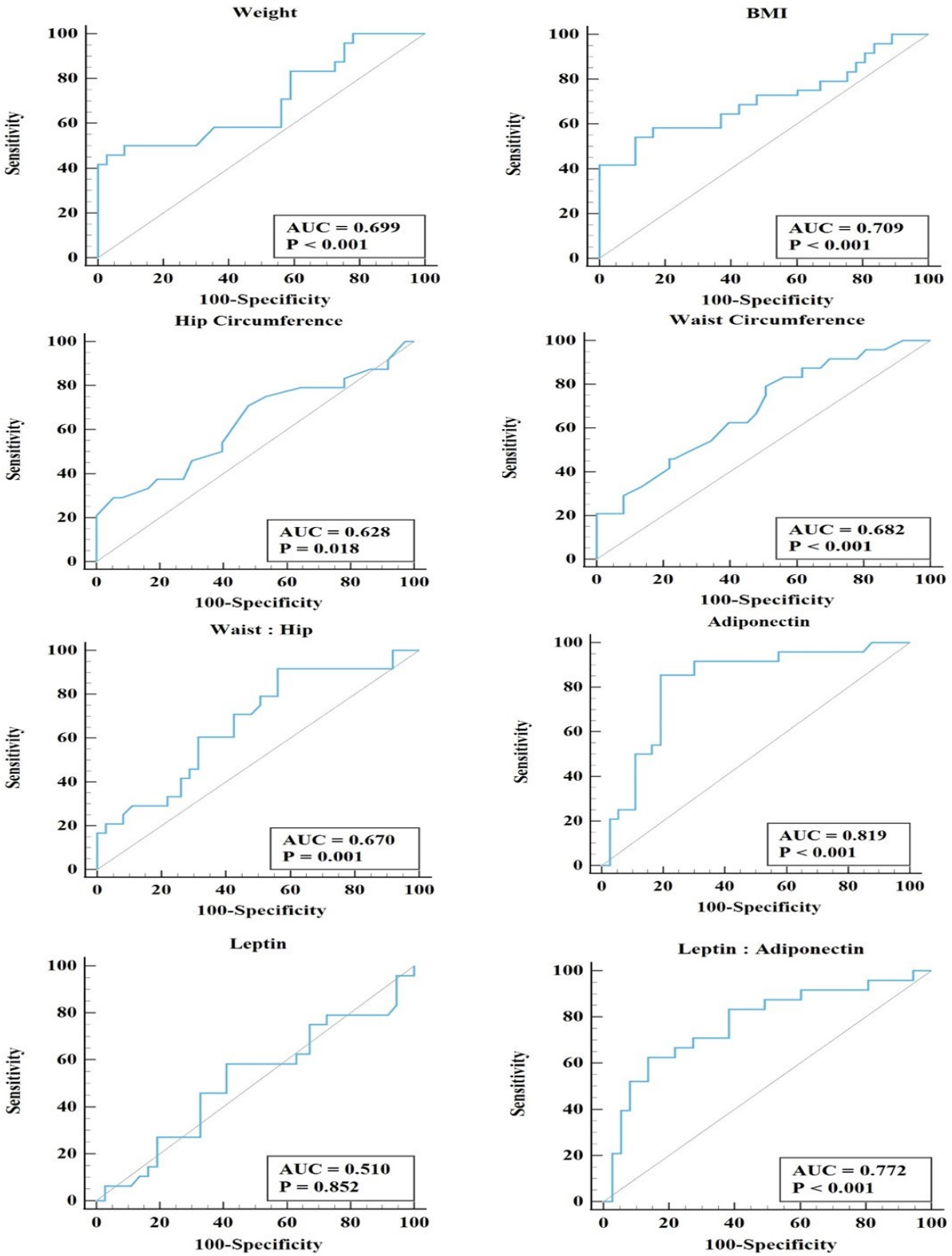

Figure 4.2: ROC curves for anthropometry and adipokines in classifying insulin resistance.

4.3 Haemodynamic and Lipid Profile of Study Population

Table 4.6 summarises the haemodynamic and lipid parameters of the study population stratified by HOMA-IR. The average SBP and DBP were 158.1±25.8 mmHg and 100.9±13.5 mmHg respectively. The mean total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol were 4.47±1.2 mmol/L, 0.9±0.4 mmol/L 1.27±0.4 mmol/L and 2.78±0.9 mmol/L respectively. The TC/HDL ratio and TG/HDL ratio of the studied population were 3.72±0.9 and 1.76±0.9 respectively.

When the population was stratified based on their HOMA-IR, total cholesterol, LDL-cholesterol and TC/HDL ratio were higher among the HOMA-IR ≥2 (4.82±1.2 mmol/L, p=0.007; 3.17±0.9 mmol/L, p=0.001; 3.93±0.9, p=0.042 respectively) group compared to their counterparts with HOMA-IR <2 (4.25±1.1 mmol/L, 2.52±0.8 mmol/L, 3.58±0.9) as shown in Table 4.6

Table 4.6: Haemodynamic and lipid profile of study population stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Systolic Blood Pressure (mmHg)	158.1±25.8	154.6±25.4	163.3±25.8	0.069
Diastolic Blood Pressure (mmHg)	100.9±13.5	99.19±12.2	103.6±15.1	0.082
Pulse (beats/min)	84.71±14.1	85.68±13.4	83.23±14.9	0.349
Total Cholesterol (mmol/L)	4.47±1.2	4.25±1.1	4.82±1.2	0.007
Triglyceride (mmol/L)	0.9±0.4	0.86±0.4	0.97±0.4	0.158
HDL-Cholesterol (mmol/L)	1.27±0.4	1.29±0.5	1.26±0.3	0.712
LDL-Cholesterol (mmol/L)	2.78±0.9	2.52±0.8	3.17±0.9	0.001
Atherogenic Index of Plasma	0.19±0.2	0.17±0.2	0.22±0.2	0.242
TC/HDL	3.72±0.9	3.58±0.9	3.93±0.9	0.042
TG/HDL	1.76±0.9	1.72±0.9	1.83±0.7	0.513

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test

4.3.1 Prevalence Hypertension and Dyslipidemia

Table 4.7 shows the proportions of study population with elevated blood pressure and abnormal lipid parameters. Most (73.6%) of the studied participants had elevated blood pressure, most (78.5%) of whom indicated having hypertension on diagnosis of their diabetes. Majority of the population had normal total cholesterol (71%), triglyceride (91%), HDL-cholesterol (68%) and LDL-cholesterol (93%). However, more than half (63%) had at least one abnormal lipid (dyslipidemia) parameter.

When the population was stratified based on HOMA-IR, the proportions of subjects with elevated blood pressure, and high LDL-cholesterol were significantly higher in the HOMA-IR ≥2 (83.3%, p=0.048 and 14.6%, p=0.015) group compared to their counterparts with HOMA-IR < 2 (67.1% and 2.7% respectively), as shown in Table 4.7

Table 4.7: Distribution of elevated blood pressure and abnormal lipid parameters stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Systolic Blood Pressure				
Normal	30(24.8%)	22(30.1%)	8(16.7%)	0.093
Elevated	91(75.2%)	51(69.9%)	40(83.3%)	
Diastolic Blood Pressure				
Normal	20(16.5%)	14(19.2%)	6(12.5%)	0.333
Elevated	101(83.5%)	59(80.8%)	42(87.5%)	
Blood Pressure				
Normal	32(26.4%)	24(32.9%)	8(16.7%)	0.048
Elevated	89(73.6%)	49(67.1%)	40(83.3%)	
Hypertension on Diagnosis				
No	26(21.5%)	14(19.2%)	12(25%)	0.446
Yes	95(78.5%)	59(80.8%)	36(75%)	
Total Cholesterol				
Normal	86(71.1%)	55(75.3%)	31(64.6%)	0.202
High	35(28.9%)	18(24.7%)	17(35.4%)	
Triglyceride				
Normal	110(90.9%)	67(91.8%)	43(89.6%)	0.681
High	11(9.1%)	6(8.2%)	5(10.4%)	
HDL-Cholesterol				
Normal	82(67.8%)	48(65.8%)	34(70.8%)	0.559
Low	39(32.2%)	25(34.2%)	14(29.2%)	
LDL-Cholesterol				
Normal	112(92.6%)	71(97.3%)	41(85.4%)	0.015
High	9(7.4%)	2(2.7%)	7(14.6%)	
Dyslipidaemia				
No	45(37.2%)	28(38.4%)	17(35.4%)	0.743
Yes	76(62.8%)	45(61.6%)	31(64.6%)	
Atherogenic Index				
Normal	62(51.2%)	40(54.8%)	22(45.8%)	0.335
Abnormal	59(48.8%)	33(45.2%)	26(54.2%)	

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test

4.3.2 Haemodynamic and Lipid Determinants of Insulin Resistance

The impact of hemodynamic and lipid parameters on the occurrence of insulin resistance are shown in Table 4.8. A high LDL-cholesterol (OR=6.1, p=0.029) was found to significantly affect the occurrence of insulin resistance (HOMA-IR ≥2). After adjusting for confounding variables, none of the variables could independently predict the occurrence of insulin resistance as shown in Table 4.8.

Table 4.8: Effects of blood pressure and lipid parameters on insulin resistance

Parameter	OR (95%CI)	P-value	aOR (95%CI)	P-value
Systolic Blood Pressure				
Normal	1.0	-	1.0	-
Elevated	2.2(0.87-5.35)	0.097	0.9(0.24-3.05)	0.818
Diastolic Blood Pressure				
Normal	1.0	-	1.0	-
Elevated	1.7(0.59-4.68)	0.337	1.1(0.26-4.4)	0.930
Blood Pressure				
Normal	1.0	-	1.0	-
Elevated	2.5(0.99-6.04)	0.052	0.7(0.22-2.52)	0.631
Hypertension on Diagnosis				
No	1.0	-	1.0	-
Yes	0.7(0.3-1.71)	0.447	0.3(0.09-1.26)	0.106
Total Cholesterol				
Normal	1.0	-	1.0	-
High	1.7(0.76-3.71)	0.204	1.1(0.42-2.85)	0.844
Triglyceride				
Normal	1.0	-	1.0	-
High	1.3(0.37-4.52)	0.681	0.9(0.22-3.49)	0.852
HDL-Cholesterol				
Normal	1.0	-	1.0	-
Low	0.8(0.36-1.74)	0.559	0.9(0.42-2.29)	0.956
LDL-Cholesterol				
Normal	1.0	-	1.0	-
High	6.1(1.2-30.56)	0.029	5.8(0.96-35.03)	0.056
Dyslipidemia				
No	1.0	-	1.0	-
Yes	1.1(0.53-2.42)	0.744	1.1(0.50-2.40)	0.831

4.3.3 Correlation of Insulin, Indices of Insulin Resistance against Haemodynamic and Lipid Parameters

Pearson's correlation was done to assess the association between insulin, insulin resistance indices (HOMA-IR and QUICKI), index of pancreatic beta function (HOMA-B) and haemodynamic and lipid parameters as shown in Table 4.9. HOMA-IR showed significant positive correlations with atherogenic index of plasma ($r = 0.18$, $p < 0.05$). QUICKI showed significant inverse relations with systolic blood pressure ($r = -0.20$, $p<0.05$), total cholesterol ($r = -0.18$, $p < 0.05$) and LDL-cholesterol ($r = -0.25$, $p < 0.01$) as shown in Table 4.9

Table 4.9: Partial correlation of indices of insulin resistance against blood pressure and lipid parameters

Parameter	Insulin	HOMA-IR	QUICKI	HOMA-B
	r	r	r	r
Systolic Blood Pressure (mmHg)	0.16	0.14	-0.20*	0.14
Diastolic Blood Pressure (mmHg)	0.17	0.14	-0.17	0.17
Pulse (beats/min)	-0.07	-0.07	0.21	-0.05
Total Cholesterol (mmol/L)	0.12	0.10	-0.18*	0.11
Triglyceride (mmol/L)	0.14	0.15	-0.15	0.12
HDL-Cholesterol (mmol/L)	-0.07	-0.08	0.02	-0.06
LDL-Cholesterol (mmol/L)	0.17	0.15	-0.25**	0.15
Atherogenic Index of Plasma	0.17	0.18*	-0.14	0.16
TC/HDL	0.15	0.15	-0.14	0.14
TG/HDL	0.12	0.13	-0.06	0.12

Significant correlation at the 0.05 level, ** Significant correlation at the 0.01 level, ***Significant correlation at the 0.001 level.

4.3.4 Receiver Operator Characteristics (ROC) for Haemodynamic and Lipid parameters

The ROC curves and the area under curve (AUC) showing the comparable abilities of haemodynamic and lipid parameters to classify insulin resistance are shown in Figure 4.3 and their respective cut-off points for classification of insulin resistance are shown in Table 4.10. Total cholesterol (AUC=0.626, p=0.013), LDL-cholesterol (AUC=0.670, p=0.001) and TC/HDL (AUC= 0.620, p=0.019) significantly classified subjects as insulin resistant, with LDL-cholesterol showing the highest AUC for the classification of insulin resistance.

A higher Youden index indicates higher diagnostic value as evaluated by a balance between the sensitivity and specificity of a marker. From Table 4.10, LDL-cholesterol (0.34) and TC/HDL ratio (0.34) showed the highest Youden indices at diagnostic cut-offs of >2.3mmol/L (Sensitivity =83.3 and Specificity =50.7) and >3.12 (Sensitivity =87.5 and Specificity =46.6) respectively.

Table 4.10: Cut-offs, sensitivity and specificity of lipid and blood pressure parameters

Parameter	Youden Index	Cut-off	Sensitivity	Specificity
Systolic Blood Pressure (mmHg)	0.31	>150	79.2	52.1
Diastolic Blood Pressure (mmHg)	0.14	>99	54.2	60.3
Total Cholesterol (mmol/L)	0.23	>3.3	100.0	23.3
Triglyceride (mmol/L)	0.30	>0.77	66.7	63.0
HDL-Cholesterol (mmol/L)	0.30	≤1.7	100.0	30.1
LDL-Cholesterol (mmol/L)	0.34	>2.3	83.3	50.7
TC/HDL	0.34	>3.12	87.5	46.6
TG/HDL	0.26	>1.4	70.8	54.8

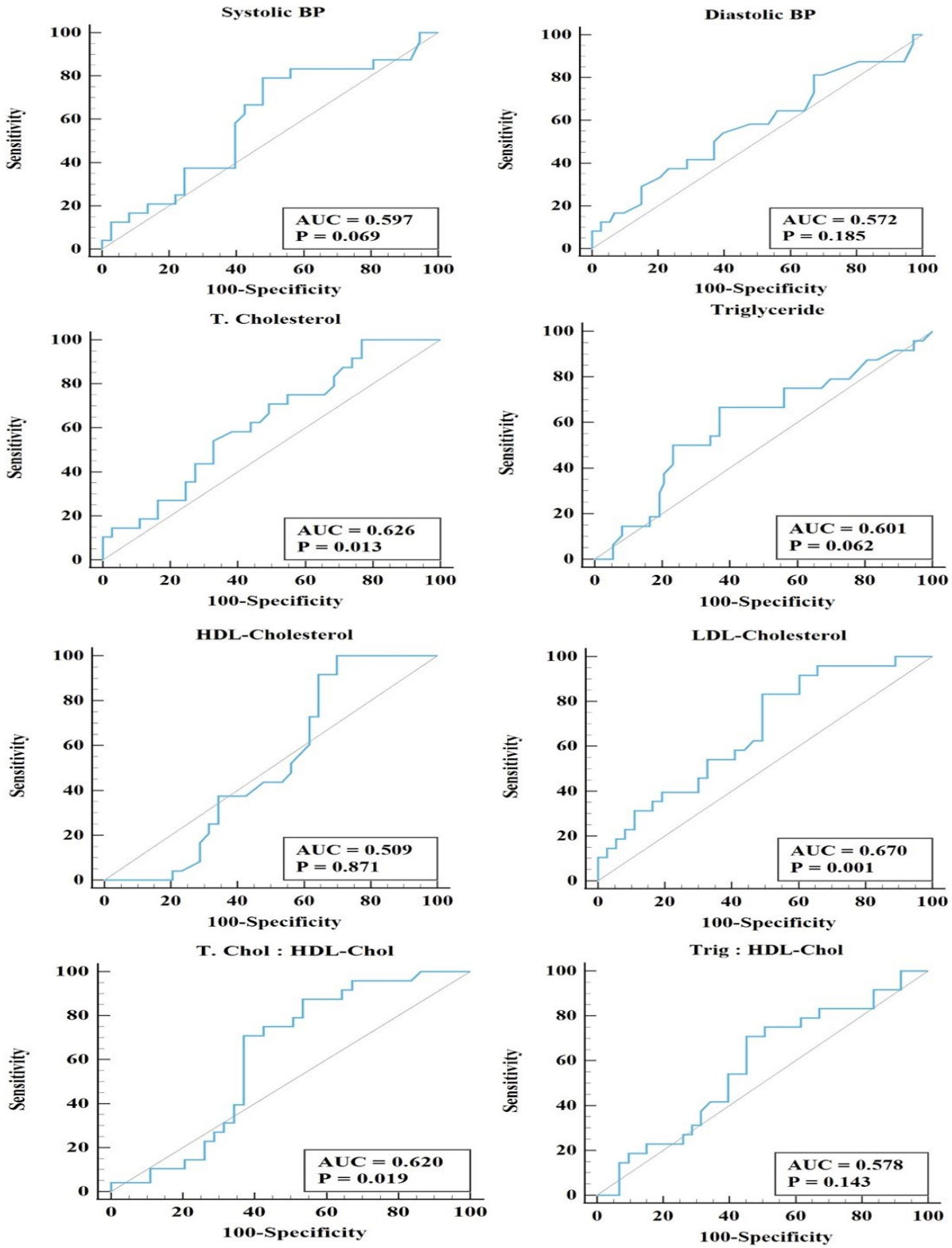

Figure 4.3: ROC curves for blood pressure and lipid parameters in classifying insulin resistance

4.4 Fatty Liver Index and Liver Function Parameters of Study Population

Table 4.11 shows the liver function parameters and fatty liver index of the study population stratified by HOMA-IR. The average total protein, AST, ALT and GGT were 7.73±0.8 g/dL, 13.05±9.3 IU/L, 29.11±16.6 IU/L and 23.18±17.76 IU/L respectively whiles the fatty liver index of the studied population was 48.43±28.2.

When the population was stratified based on their HOMA-IR, AST (40.25±16.1 IU/L, p<0.0001) and fatty liver index (65.3±29.9, p<0.0001) were higher among the HOMA-IR ≥2 group compared to their counterparts with HOMA-IR <2 (21.78±12.3 IU/L and 37.34±20.8 respectively) as shown in Table 4.11

Table 4.11: Liver function parameters and fatty liver index of study population stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Total Protein (g/dl)	7.73±0.8	7.76±0.9	7.68±0.6	0.620
Albumin (g/dl)	4.11±0.5	4.11±0.5	4.11±0.4	0.960
Globulin (g/dl)	3.62±0.7	3.65±0.8	3.58±0.6	0.560
A/G	1.18±0.3	1.18±0.3	1.18±0.2	0.905
Alkaline Phosphatase (IU/L)	84.03±33.9	84.34±30.9	83.56±38.4	0.902
Alanine Transaminase (IU/L)	13.05±9.3	12.78±10.9	13.46±5.9	0.696
Aspartate Transaminase (IU/L)	29.11±16.6	21.78±12.3	40.25±16.1	<0.0001
γ-Glutamyl Transferase (IU/L)	23.18±17.8	22.16±18.5	24.73±16.6	0.439
Total Bilirubin (µmol/L)	1.34±0.7	1.34±0.5	1.35±0.8	0.969
Direct Bilirubin (µmol/L)	0.47±0.2	0.47±0.2	0.48±0.3	0.933
Indirect Bilirubin (µmol/L)	0.87±0.4	0.87±0.3	0.87±0.6	0.990
Fatty Liver Index	48.43±28.2	37.34±20.8	65.3±29.9	<0.0001

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test

4.4.1 Prevalence Non-Alcoholic Fatty Liver Disease

Figure 4.4 shows the proportion of subjects with high risk of non-alcoholic fatty liver disease (NAFLD) among the studied population. About a third (35%) of the studied participants had a high risk of NAFLD, with the proportion in the insulin resitant subjects (62.5%, p<0.0001) being higher than that in their counterparts with HOMA-IR <2 (16.4%).

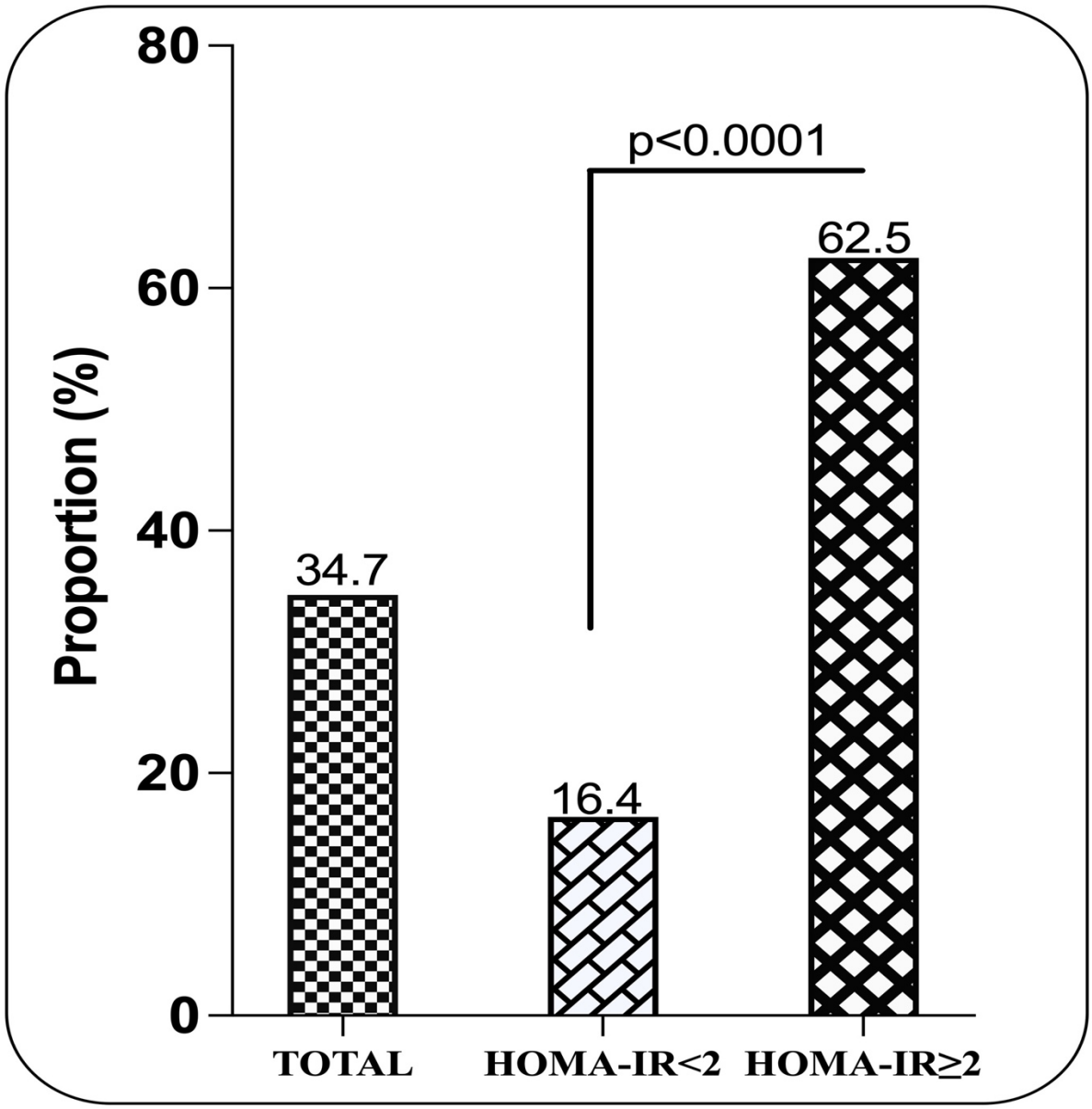

Figure 4.4: Distribution of high risk of NAFLD among the study population stratified by HOMA-IR

4.4.2 Haemodynamic and Lipid Determinants of Insulin Resistance

The impact of fatty liver index and liver function parameters on the occurrence of insulin resistance are shown in Table 4.12. A high AST concentration (OR=1.1, p<0.0001) and high risk of NAFLD (OR=8.5, p<0.0001) were found to significantly affect the occurrence of insulin resistance (HOMA-IR ≥2). After adjusting for confounding variables, A high AST concentration (OR=1.1, p<0.0001) and high risk of NAFLD (OR=9.7, p=0.001) were found to independently predict the occurrence of insulin resistance as shown in Table 4.12.

Table 4.12: Effect of liver function parameters and fatty liver index on insulin resistance

Variable	OR (95%CI)	P-value	aOR (95%CI)	P-value
Total Protein (g/dl)	0.99(0.57-1.4)	0.617	1.7(0.95-3.1)	0.073
Albumin (g/dl)	1.01(0.46-2.28)	0.960	2.5(0.86-7.37)	0.094
Alkaline Phosphatase (IU/L)	0.99(0.98-1.01)	0.901	0.99(0.98-1.01)	0.676
Alanine Transaminase (IU/L)	1.01(0.97-1.05)	0.694	1.03(0.97-1.09)	0.325
Aspartate Transaminase (IU/L)	1.1(1.05-1.12)	<0.0001	1.1(1.05-1.13)	<0.0001
γ-Glutamyl Transferase (IU/L)	1.01(0.99-1.03)	0.437	0.98(0.95-1.01)	0.125
NAFLD				
No	1.0	-	1.0	-
Yes	8.5(3.62-19.85)	<0.0001	9.7(2.43-38.52)	0.001

4.4.3 Correlation of Insulin, Indices of Insulin Resistance against Haemodynamic and Lipid Parameters

Pearson's correlation was done to assess the association between insulin, insulin resistance indices (HOMA-IR and QUICKI), index of pancreatic beta function (HOMA-B) and fatty liver index (FLI) as well as liver function parameters as shown in Table 4.13. Insulin, HOMA-IR and HOMA-B showed significant positive correlations with AST, ALT, GGT, bilirubin and Fatty liver index. Whiles QUICKI showed significantly stronger inverse relations with AST concentration (r=-0.51, p<0.0001) and FLI (r=-0.47, p<0.0001) as shown in Table 4.13.

Table 4.13: Partial correlation of insulin resistance indices against lipids parameters and fatty liver index

Parameter	Insulin	HOMA-IR	QUICKI	HOMA-B
	r	r	r	r
Total Protein (g/dl)	-0.06	-0.09	0.04	-0.04
Albumin (g/dl)	-0.02	-0.05	0.05	0.00
Globulin (g/dl)	-0.05	-0.07	0.01	-0.03
A/G	-0.05	-0.03	0.07	-0.06
Alkaline Phosphatase (IU/L)	-0.07	-0.07	0.05	-0.09
Alanine Transaminase (IU/L)	-0.01	-0.01	0.05	-0.02
Aspartate Transaminase (IU/L)	0.47***	0.43***	-0.51***	0.42***
γ-Glutamyl Transferase (IU/L)	0.22*	0.20*	-0.10	0.18*
Total Bilirubin (µmol/L)	0.23*	0.26**	-0.05	0.23*
Direct Bilirubin (µmol/L)	0.19*	0.21*	-0.05	0.20*
Indirect Bilirubin (µmol/L)	0.24**	0.27**	-0.05	0.24**
AST/ALT	0.06	0.04	-0.09	0.07
Fatty Liver Index	0.40***	0.38***	-0.47***	0.36***

Significant correlation at the 0.05 level, ** Significant correlation at the 0.01 level, ***Significant correlation at the 0.001 level.

4.4.4 Receiver Operator Characteristics (ROC) for Haemodynamic and Lipid Parameters

The ROC curves and the area under curve (AUC) showing the comparable abilities of fatty liver index and liver function parameters to classify insulin resistance are shown in Figure 4.5 and their respective cut-off points for classification of insulin resistance are shown in Table 4.14. ALT concentration (AUC=0.636, p=0.007), AST concentration (AUC=0.808, p<0.001) and fatty liver index (AUC=0.765, p<0.001) significantly classified subjects as insulin resistant, with AST showing the highest AUC for the classification of insulin resistance.

A higher Youden index indicates higher diagnostic value as evaluated by a balance between the sensitivity and specificity of a marker. From Table 4.14, AST (0.57) showed the highest Youden index at diagnostic cut-off of >24 IU/L (Sensitivity =81.3 and Specificity =75.3).

Table 4.14: Cut-offs, sensitivity and specificity for liver function parameters and fatty liver index

Parameter	Youden Index	Cut-off	Sensitivity	Specificity
Total Protein (g/dl)	0.19	≤7.9	68.8	50.7
Albumin (g/dl)	0.20	>3.7	95.8	24.7
Alkaline Phosphatase (IU/L)	0.22	≤100	83.3	38.4
Alanine Transaminase (IU/L)	0.40	>6	100.0	39.7
Aspartate Transaminase (IU/L)	0.57	>24	81.3	75.3
γ-Glutamyl Transferase (IU/L)	0.26	>9	100.0	26.0
AST/ALT	0.32	>1.5	85.4	46.6
Fatty Liver Index	0.47	>55.2	66.7	80.8

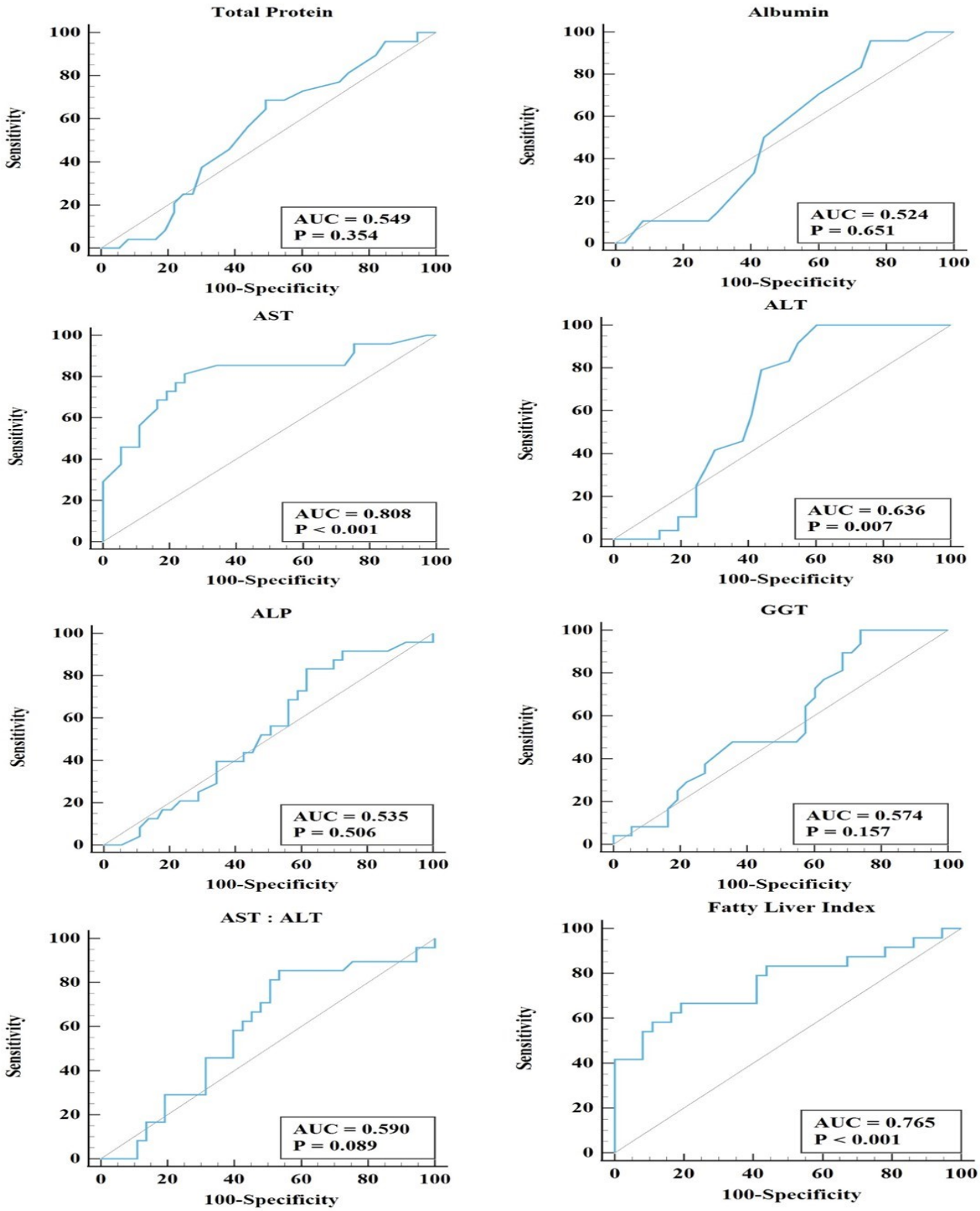

Figure 4.5: ROC curves for liver parameters and fatty liver index in classifying insulin resistance

4.5 Sexual Dysfunction (SD), SD Domains and Sex hormones in the Study Population

Table 4.15 shows the raw and stanine scores for sexual dysfunction and its domains as well as hormone levels of the study population stratified by HOMA-IR. On average the stanine scores for sexual dysfunction (SD), impotence (IM), premature ejaculation (PE), non-communication (NC) and infrequency (IF) were 5.1±1.81, 5.08±2.05, 4.78±1.69, 5.24±1.83 and 4.73±1.58 respectively. The median (IQR) for total testosterone, bioavailable testosterone and the sex hormone binding globulin concentration for the studied population were 36.0 ng/dL (12.0-95.0), 1.1 ng/dL (0.5-3.0), 24.50 ng/dL (10.6-69.8), 3.6 nmol/l (0.5-6.8).

When the population was stratified based on their HOMA-IR, both raw scores and stanine scores for SD, PE, NC and IF were higher among the HOMA-IR ≥2 group compared to their counterparts with HOMA-IR <2 as shown in Table 4.15. Similarly, concentrations of total testosterone, free and bioavailable testosterone were significantly higher in the insulin resistant group. However, there were no significant differences in sex hormone binding globulin between the two groups.

Table 4.15: Raw, stanine scores for SD domains and hormone levels of study population stratified by HOMA-IR

Parameter	Total (n=121)	HOMA-IR < 2 (n=73)	HOMA- IR ≥ 2 (n=48)	P-value
Raw Score				
Sexual Dysfunction	77.83±3.5	77.25±4.0	78.73±2.4	0.023
Impotence	12.02±1.6	12.22±1.6	11.71±1.4	0.078
Premature Ejaculation	8.79±1.7	8.51±1.9	9.23±1.3	0.025
Non-Sensuality	11.29±1.3	11.37±1.3	11.17±1.2	0.391
Avoidance	10.75±2.2	10.58±2.2	11.02±2.2	0.272
Dissatisfaction	10.83±1.0	10.77±0.9	10.94±1.1	0.378
Non-Communication	5.2±0.8	4.99±0.8	5.52±0.7	<0.0001
Infrequency	5.86±0.8	5.62±0.6	6.23±0.9	<0.0001
Stanine Score				
Sexual Dysfunction	5.1±1.8	4.82±2.1	5.52±1.3	0.026
Impotence	5.08±2.1	5.33±2.1	4.71±1.9	0.078
Premature Ejaculation	4.78±1.7	4.48±1.8	5.23±1.3	0.015
Non-Sensuality	5.14±1.9	5.26±2.1	4.96±1.8	0.391
Avoidance	4.94±1.9	4.78±1.9	5.19±1.9	0.272
Dissatisfaction	4.7±1.9	4.53±1.9	4.96±2.1	0.276
Non-Communication	5.24±1.8	4.77±1.8	5.96±1.6	<0.0001
Infrequency	4.73±1.6	4.26±1.5	5.44±1.5	<0.0001
Sex Hormones				
Testosterone (ng/dL)	36.0 (12.0-95.0)	20.0 (8.5-54)	48.0 (24-119)	0.005
Free Testosterone (ng/dL)	1.1 (0.5-3.0)	0.7 (0.27-2.23)	1.8 (1.04-4.68)	0.005
Bioavailable Testosterone (ng/dL)	24.50 (10.6-69.8)	15.8 (6.0-47.6)	38.6 (22.8-102.0)	0.007
Sex Hormone Binding Globulin (nmol/l)	3.6 (0.5-6.8)	2.7 (0.7-5.8)	3.9 (0.34-7.03)	0.793

Data is presented as as proportions and mean±SD where appropriate. Categorical variables were compared using Chi-square test and continuous variables, using unpaired T-test. Non-parametric data were summarised as medians (Interquartile Range) and compared using the Mann-Whitney test.

4.5.1 Prevalence of Sexual Dysfunction and Its Domains

Figure 4.6 shows the proportions of study subjects with sexual dysfunction and its domains. About two-thirds of the studied subjects had SD (69%), and this was mainly contributed to by high proportions of non-sensuality (73.6%), dissatisfaction (60%), non-communication (83%) and infrequency (72%), as shown in Figure 4.6.

When the studied population was stratified based on HOMA-IR, the proportions of study subjects with HOMA-IR ≥2 who had SD (79.2%, p=0.42), premature ejaculation (66.7%, p=0.009), non-communication (91.7%, p=0.034) and infrequency (91.7%, p<0.0001) were significantly higher than in those with HOMA-IR <2 (61.6%, 42.5%, 76.7% and 58.9% respectively) (Figure 4.6).

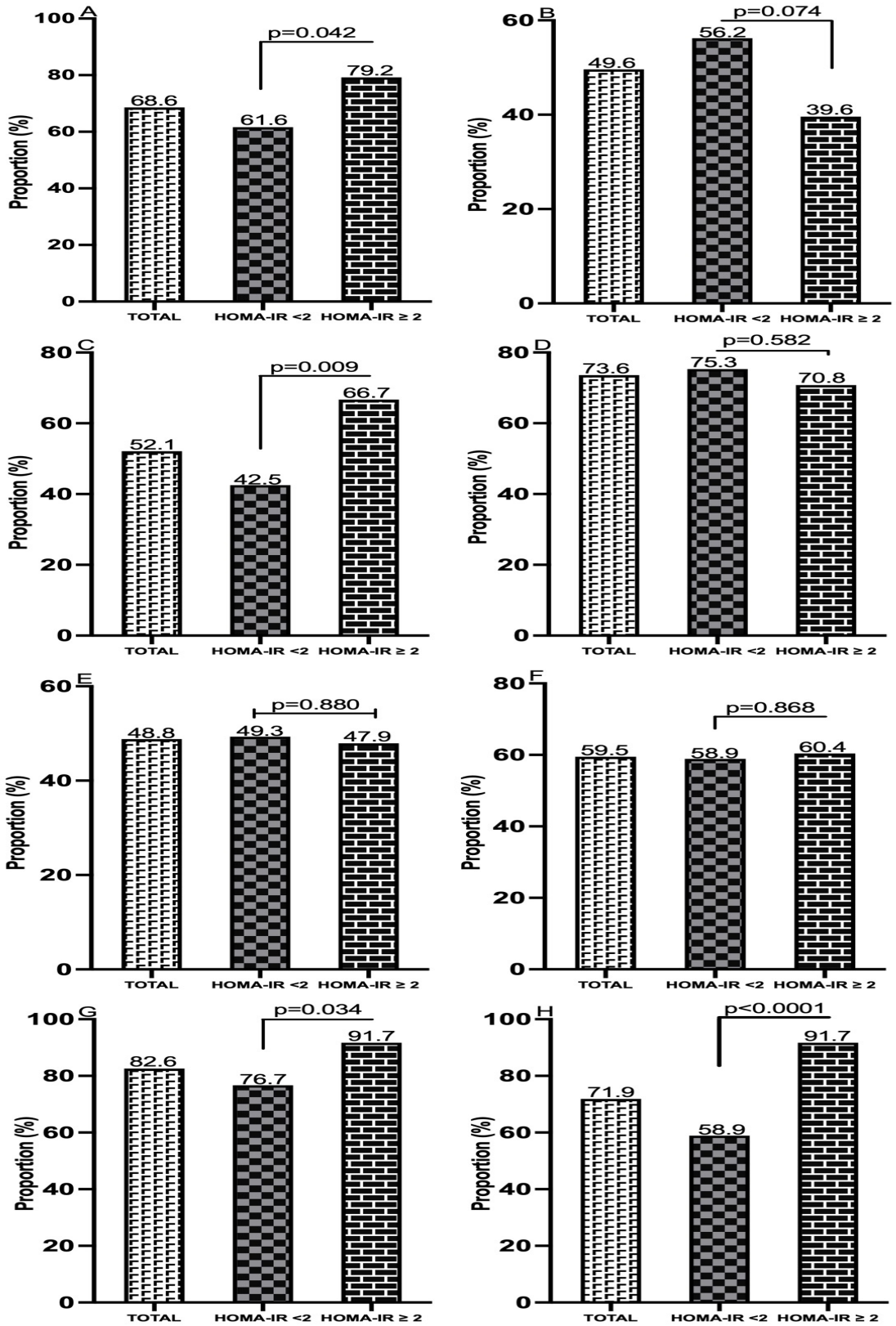

Figure 4.6: Distribution of SD (A), impotence (B), premature ejaculation (C), non-sensuality (D), avoidance (E), dissatisfaction (F), non-communication (G) and infrequency (H) in the study population stratified by HOMA-IR.

4.5.2 Sexual Dysfunction, SD domains and Sex hormones as Determinants of Insulin Resistance

The impact of SD, its domains and sex hormones on the occurrence of insulin resistance are shown in Table 4.16. Sexual dysfunction (OR=2.4, p=0.045), premature ejaculation (OR=2.7, p=0.010), non-communication (OR=3.3, p=0.041) and infrequency (OR=7.67, p<0.0001) were found to significantly affect the occurrence of insulin resistance (HOMA-IR ≥2). After adjusting for confounding variables, non-communication (aOR=3.9, p=0.041) and infrequency (aOR=7.51, p=0.001) were found to independently affect the occurrence of insulin resistance as shown in Table 4.16.

Table 4.16: Effects of SD, its domains and testosterone on insulin resistance

Variable	OR (95%CI)	P-value	aOR (95%CI)	P-value
Sexual Dysfunction				
No	1.0	-	1.0	-
Yes	2.4(1.02-5.48)	0.045	0.99(0.35-2.77)	0.981
Impotence				
No	1.0	-	1.0	-
Yes	0.5(0.24-1.07)	0.076	0.4(0.14-1.01)	0.053
Premature Ejaculation	1.0	-	1.0	-
No				
Yes	2.7(1.27-5.79)	0.010	2.2(0.94-5.34)	0.068
Non-Sensuality				
No	1.0	-	1.0	-
Yes	0.8(0.35-1.8)	0.583	0.6(0.24-1.68)	0.356
Avoidance				
No	1.0	-	1.0	-
Yes	0.95(0.46-1.96)	0.880	1.3(0.51-3.37)	0.571
Dissatisfaction				
No	1.0	-	1.0	-
Yes	1.1(0.51-2.24)	0.868	0.6(0.21-1.73)	0.341
Non-Communication				
No	1.0	-	1.0	-
Yes	3.3(1.05-10.64)	0.041	3.9(1.06-14.48)	0.041
Infrequency				
No	1.0	-	1.0	-
Yes	7.7(2.49-23.63)	<0.0001	7.5(2.27-24.79)	0.001
Testosterone (ng/dL)	1.0(1.00-1.01)	0.561	1.0(1.00-1.01)	0.454
Free Testosterone (ng/dL)	1.0(0.99-1.02)	0.732	0.99(0.98-1.01)	0.416
Bioavailable Testosterone (ng/dL)	1.0(1.00-1.01)	0.582	1.0(1.00-1.01)	0.438
Sex Hormone Binding Globulin (nmol/l)	1.03(0.95-1.12)	0.513	1.01(0.92-1.1)	0.908

4.5.3 Correlation of Insulin, Indices of Insulin Resistance against Sexual Dysfunction (SD), SD Domains and Sex Hormones

Pearson's correlation was done to assess the association between insulin, indices of insulin resistance (HOMA-IR and QUICKI), index of pancreatic beta function (HOMA-B) and Sex hormones, raw and stanine scores of SD and its domains as shown in Table 4.17. Insulin, HOMA-IR and HOMA-B showed significant positive correlations with both raw and stanine scores of SD, premature ejaculation, non-communication and infrequency. Whiles QUICKI showed significant inverse relations with raw and stanine scores of SD, premature ejaculation, non-communication and infrequency as shown in Table 4.17.

Table 4.17: Partial correlation of insulin resistance indices against SD, SD domains and testosterone

Parameter	Insulin r	HOMA-IR r	QUICKI r	HOMA-B r
Raw Score				
Sexual Dysfunction	0.22*	0.20*	-0.24**	0.23*
Impotence	-0.11	-0.13	0.15	-0.10
Premature Ejaculation	0.28**	0.27**	-0.24**	0.28**
Non-Sensuality	-0.16	-0.14	0.00	-0.19
Avoidance	0.07	0.07	-0.03	0.05
Dissatisfaction	0.19*	0.17	-0.11	0.22*
Non-Communication	0.30**	0.26**	-0.35***	0.30**
Infrequency	0.37***	0.31**	-0.32***	0.41***
Stanine Score				
Sexual Dysfunction	0.21*	0.18*	-0.21*	0.23*
Impotence	-0.08	-0.09	0.13	-0.07
Premature Ejaculation	0.29**	0.28**	-0.24**	0.29**
Non-Sensuality	-0.18	-0.16	-0.03	-0.20
Avoidance	0.09	0.08	-0.04	0.08
Dissatisfaction	0.20*	0.18	-0.13	0.24**
Non-Communication	0.30**	0.26**	-0.32***	0.30**
Infrequency	0.39***	0.32***	-0.31**	0.46***
Sex Hormones				
Testosterone (ng/dL)	-0.01	0.00	0.00	-0.03
Free Testosterone (ng/dL)	-0.03	-0.01	0.01	-0.05
Bioavailable Testosterone (ng/dL)	-0.02	0.00	0.00	-0.04
Sex Hormone Binding Globulin (nmol/l)	0.02	-0.01	0.04	0.11

Significant correlation at the 0.05 level, ** Significant correlation at the 0.01 level, ***Significant correlation at the 0.001 level.

4.5.4 Receiver Operator Characteristics (ROC) for Sexual Dysfunction, SD domains and Sex hormones

The ROC curves and the Area Under Curves (AUC) showing the comparable abilities of sexual dysfunction and its domains (Figure 4.7) as well as testosterone and its derivatives (Figure 4.8) to classify Insulin resistance and their respective cut-off points for classification of insulin resistance are shown in Table 4.18. Premature ejaculation (AUC=0.645, p=0.003), non-communication (AUC=0.684, p=0.001), and infrequency (AUC=0.696, p=0.001) as well as testosterone (AUC=0.648, p=0.004), free testosterone (AUC=0.650, p=0.004) and bioavailable testosterone, significantly classified subjects as insulin resistance.

Infrequency showed superior ability in classifying insulin resistance, at a cut-off of > 3, with a Youden index of 0.33 (Sensitivity=91.7 and Specificity=41.1) (Table 4.18).

Table 4.18: Cut-offs, sensitivity, specificity of SD and its domains and testosterone

Parameter	Youden Index	Cut-off	Sensitivity	Specificity
Sexual Dysfunction	0.19	>4	91.7	27.4
Impotence	0.21	≤5	77.1	43.8
Premature Ejaculation	0.24	>4	66.7	57.5
Non-Sensuality	0.07	≤8	95.8	11.0
Avoidance	0.19	>6	43.8	75.3
Dissatisfaction	0.09	>5	35.4	74.0
Non-Communication	0.32	>5	56.3	75.3
Infrequency	0.33	>3	91.7	41.1
Testosterone (ng/dL)	0.35	>20	81.3	53.4
Free Testosterone (ng/dL)	0.40	>0.90	81.3	58.9
Bioavailable Testosterone (ng/dL)	0.40	>19.7	81.3	58.9
Sex Hormone Binding Globulin (nmol/l)	0.16	≤0.5	35.4	80.8

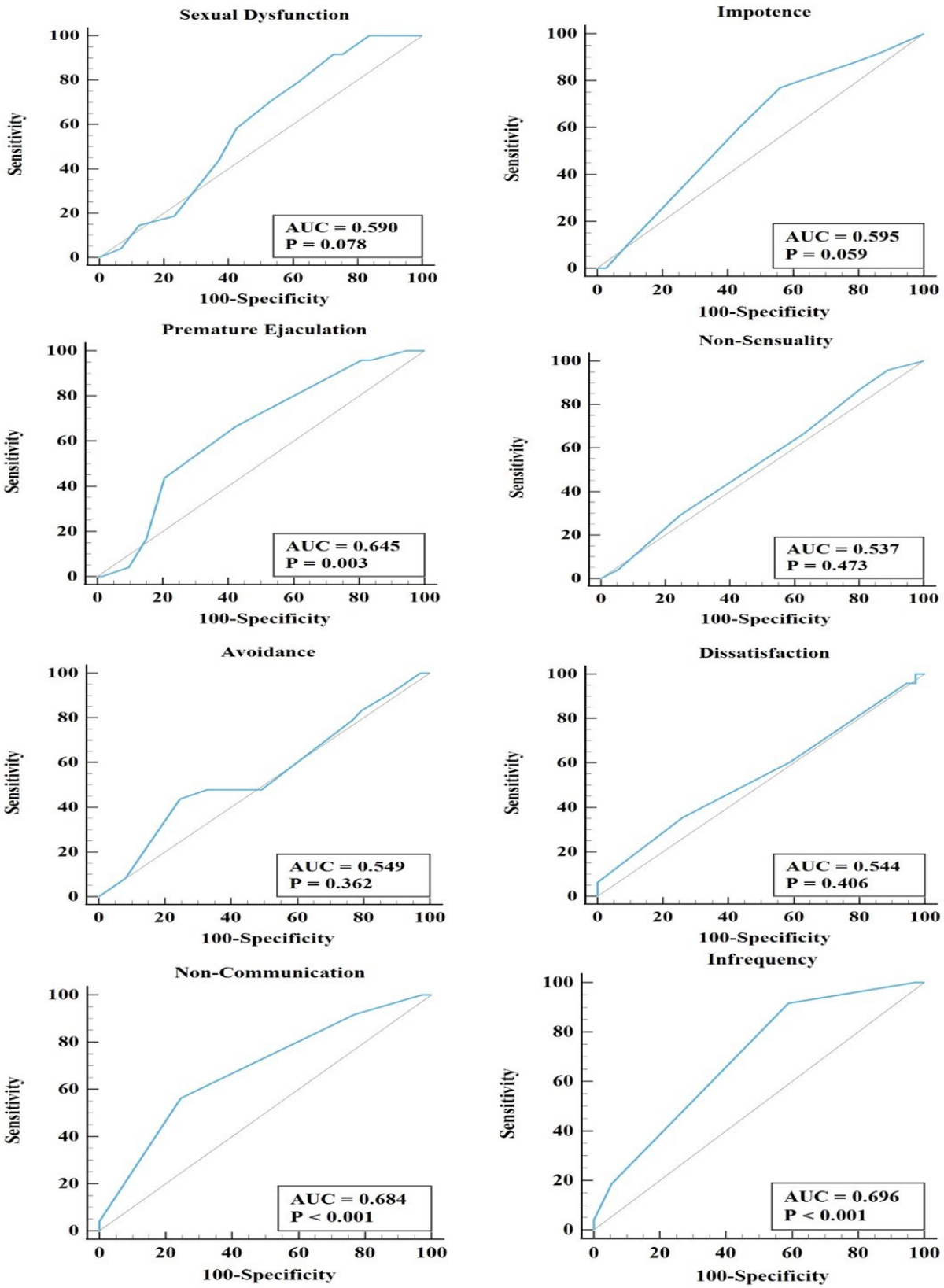

Figure 4.7:ROC curves for sexual dysfunction and its domains in classifying insulin resistance

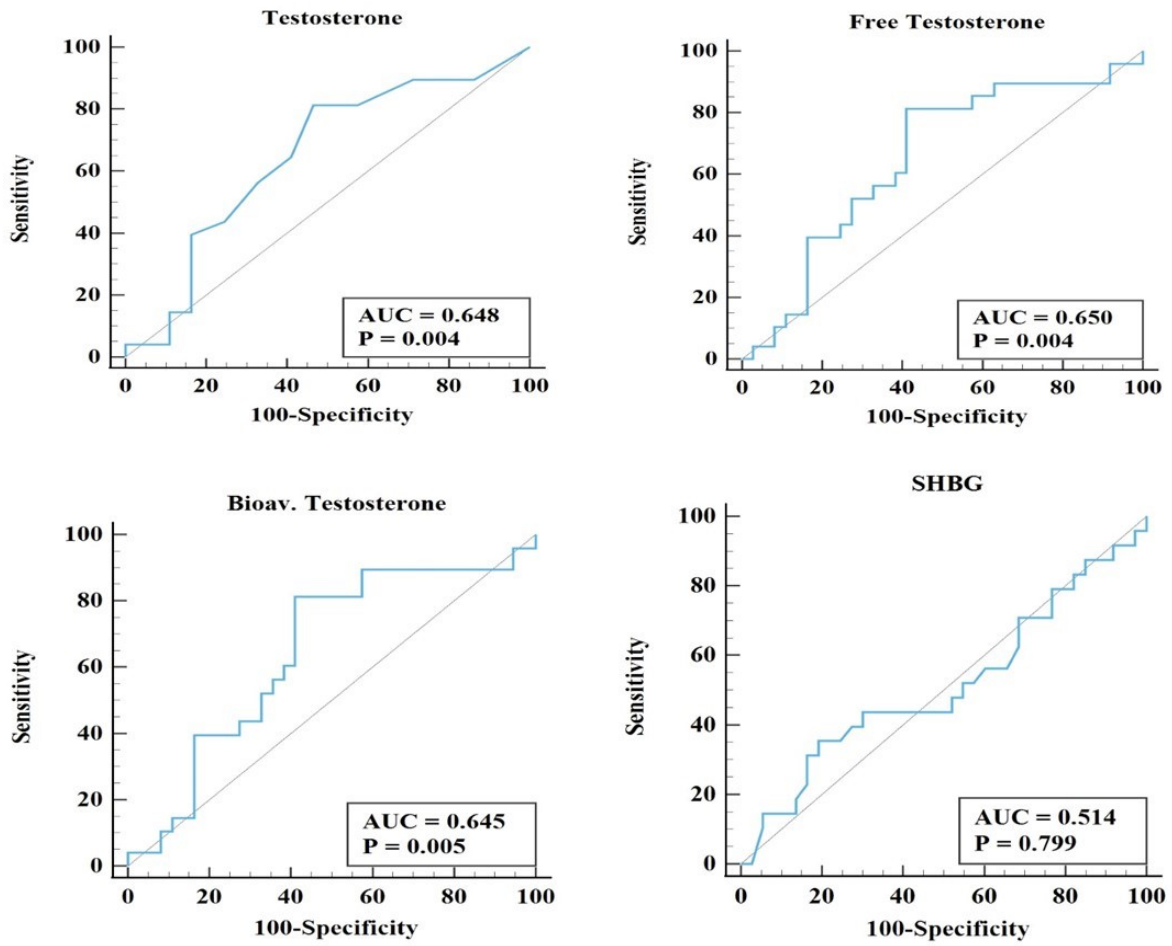

Figure 4.8: ROC curves for testosterone, its derivatives and SHBG in classifying insulin resistance

4.6 Synergistic Effect of Obesity and Insulin Resistance on Adipokines, Hypertension, Dyslipidaemia, NAFLD and Sexual Function

Effects of Obesity and Insulin on Adipokines, Blood Pressure and Dyslipidaemia

The combined effect of obesity and insulin resistance (+OB/+IR), obesity alone (+OB/-IR) and insulin resistance alone (-OB/+IR), on adipokines, blood pressure and lipid parameters were assessed, in comparison to a non-obese, non-insulin resistant subjects (-OB/-IR), as shown in Table 4.19. Adiponectin levels were higher among the +OB/-IR group (222.42±82.5 ng/mL, $p<0.0001$), lower in the -OB/+IR group (30.33±11.9 ng/mL) and rose marginally in the +OB/+IR group (81.13±89.9 ng/mL). However, the adiponectin levels in -OB/+IR and +OB/+IR were significantly lower than that in the -OB/-IR group.

Insulin levels were higher in the +OB/+IR group (295.2±169.7 pg/mL) followed by the -OB/+IR group (252.05±181.4 pg/mL), whiles total cholesterol (4.87±1.3 mmol/L) and LDL-cholesterol (3.18±1.0 mmol/L) levels were higher in the +OB/+IR group ($p=0.013$) compared to the other three categories. TG/HDL was higher in the +OB/-IR group (2.12±1.2, $p=0.008$) whiles diastolic blood pressure was higher in the -OB/+IR group (115.86±15.6 mmHg) group as shown in Table 4.19

Table 4.19: Adipokine, blood pressure and lipid parameters stratified by different combinations of presence or absence of insulin resistance and obesity.

Parameter	-OB/-IR n=42	+OB/-IR n=31	-OB/+IR n=14	+OB/+IR n=34	P-values
Age	60.19±11.9	67.13±9.7‡	56±7.9	65.62±9.1	0.001
Adiponectin (ng/mL)	194.57±100.9	222.42±82.5	30.33±11.9***	81.13±89.9†††	<0.0001
Leptin (ng/mL)	2.34±2.2	2.97±2.7	1.81±1.6	2.88±2.6	0.373
Leptin/Adiponectin	0.03±0.1	0.02±0.02	0.07±0.06	0.07±0.06††	<0.0001
Insulin (pg/mL)	4.11±9.9	2.06±0.4	252.05±181.4***	295.21±169.7†††	<0.0001
Systolic Blood Pressure	151.62±28.7	158.65±19.7	172.43±27.3	159.56±24.6	0.067
Diastolic Blood Pressure	98.48±12.6	100.16±11.7	115.86±15.6***	98.5±11.8	<0.0001
Pulse	84±12.2	87.97±14.9	86.71±9.8	81.79±16.6	0.321
Total Cholesterol (mmol/L)	4.44±1.0	3.96±1.1	4.71±0.8	4.87±1.3	0.013
Triglyceride (mmol/L)	0.78±0.4	0.96±0.5	0.99±0.5	0.97±0.4	0.186
HDL-Cholesterol (mmol/L)	1.36±0.5	1.18±0.5	1.28±0.3	1.25±0.3	0.348
LDL-Cholesterol (mmol/L)	2.72±0.7	2.34±0.8	2.98±0.6	3.18±1.05†	0.001
Atherogenic Index of Plasma	0.12±0.2	0.25±0.3‡	0.2±0.3	0.23±0.2	0.044
TC/HDL	3.54±0.9	3.64±1.0	3.74±0.5	4.01±0.9	0.160
TG/HDL	1.43±0.6	2.12±1.2‡‡	1.84±0.9	1.82±0.7	0.008

Data expressed as mean SD and were compared using the one-way ANOVA. * Comparing -OB/+IR group with -OB/-IR group, † Comparing +OB/+IR group with -OB/-IR group, ‡ Comparing +OB/-IR group with -OB/-IR group. *Comparison is significant at the 0.05 level, **Comparison is significant at the 0.01 level, ***Comparison is significant at the 0.001 level.

4.6.1 Effects of Obesity and Insulin Resistance on Prevalence of Hypertension and Dsylipidaemia

The proportions of various lipid and blood pressure abnormalities among the four groups (-OB/-IR, +OB/-IR, -OB/+IR, +OB/+IR) are shown in Table 4.20. The proportion of subjects with elevated blood pressure was higher in the -OB/+IR group (85.7%), whiles the proportion with high LDL-cholesterol was higher in the +OB/+IR group (20.6%) as shown in Table 4.20

Table 4.20: Distribution of abnormal blood pressure and lipid parameters stratified by different combinations of presence or absence of insulin resistance and obesity.

Parameter	-OB/-IR n=42	+OB/-IR n=31	-OB/+IR n=14	+OB/+IR n=34	P-values
Systolic Blood Pressure					
Normal	16(38.1%)	6(19.4%)	2(14.3%)	6(17.6%)	0.101
Elevated	26(61.9%)	25(80.6%)	12(85.7%)	28(82.4%)	
Diastolic Blood Pressure					
Normal	10(23.8%)	4(12.9%)	0(0%)	6(17.6%)	0.194
Elevated	32(76.2%)	27(87.1%)	14(100%)	28(82.4%)	
Blood Pressure					
Normal	18(42.9%)	6(19.4%)	2(14.3%)	6(17.6%)	0.029
Elevated	24(57.1%)	25(80.6%)	12(85.7%)	28(82.4%)	
Total Cholesterol					
Normal	30(71.4%)	25(80.6%)	8(57.1%)	23(67.6%)	0.407
High	12(28.6%)	6(19.4%)	6(42.9%)	11(32.4%)	
Triglyceride					
Normal	40(95.2%)	27(87.1%)	12(85.7%)	31(91.2%)	0.581
High	2(4.8%)	4(12.9%)	2(14.3%)	3(8.8%)	
HDL-Cholesterol					
Normal	30(71.4%)	18(58.1%)	12(85.7%)	22(64.7%)	0.283
Low	12(28.6%)	13(41.9%)	2(14.3%)	12(35.3%)	
LDL-Cholesterol					
Normal	40(95.2%)	31(100%)	14(100%)	27(79.4%)	0.006
High	2(4.8%)	0(0%)	0(0%)	7(20.6%)	
Dyslipidemia					
No	18(42.9%)	10(32.3%)	4(28.6%)	13(38.2%)	0.715
Yes	24(57.1%)	21(67.7%)	10(71.4%)	21(61.8%)	
Atherogenic Index					
Normal	28(66.7%)	12(38.7%)	8(57.1%)	14(41.2%)	0.057
Abnormal	14(33.3%)	19(61.3%)	6(42.9%)	20(58.8%)	

Data as proportions and were compared using unpaired using the Chi-square test.

4.6.2 Effects of Obesity and IR on Liver Function and Fatty Liver Index

Table 4.21 represents the levels of liver function parameters and the fatty liver index, across the four groups (-OB/-IR, +OB/-IR, -OB/+IR, +OB/+IR). AST concentration was higher in the -OB/+IR followed by the +OB/+IR group, whiles FLI was higher in the +OB/+IR group followed by the +OB/-IR group as shown in Table 4.21.

Table 4.21: Liver function parameters and fatty liver index stratified by different combinations of presence or absence of insulin resistance and obesity.

Parameter	-OB/-IR n=42	+OB/-IR n=31	-OB/+IR n=14	+OB/+IR n=34	P-values
Total Protein (g/dl)	7.77±0.9	7.74±0.9	7.60±0.6	7.72±0.7	0.925
Albumin (g/dl)	4.09±0.5	4.13±0.5	3.94±0.1	4.18±0.4	0.413
Globulin (g/dl)	3.68±0.8	3.61±0.7	3.66±0.6	3.54±0.5	0.851
Alkaline Phosphatase (IU/L)	80.05±30.2	90.16±31.5	77.43±20.2	86.09±43.8	0.528
Alkaline Transaminase (IU/L)	12.9±10.3	12.61±11.9	12.57±3.9	13.82±6.7	0.951
Aspartate Transaminase (IU/L)	22.57±11.4	20.71±13.5	47±14.1***	37.47±16.2†††	<0.0001
γ-Glutamyl Transferase (IU/L)	21.76±17.1	22.71±20.5	24.29±20.7	24.91±15.1	0.884
Total Bilirubin (µmol/L)	1.33±0.5	1.36±0.5	1.47±0.6	1.29±0.9	0.860
Direct Bilirubin (µmol/L)	0.48±0.2	0.46±0.2	0.51±0.2	0.46±0.3	0.878
Indirect Bilirubin (µmol/L)	0.85±0.3	0.90±0.3	0.96±0.4	0.84±0.6	0.796
AST/ALT	3.49±3.3	3.45±4.3	3.91±1.2	3.51±2.2	0.972
Fatty Liver Index	28.94±18.1	48.73±18.9‡‡‡	38.15±23.5	76.48±24.8†††	<0.0001

Parametric data were expressed as mean SD and were compared using unpaired One-way ANOVA test. Non-parametric data were summarised as medians (Interquartile Range) and compared using the Kruskal-Wallis test. * Comparing -OB/+IR group with -OB/-IR group, † Comparing +OB/+IR group with -OB/-IR group, ‡ Comparing +OB/-IR group with -OB/-IR group. *Comparison is significant at the 0.05 level, **Comparison is significant at the 0.01 level, ***Comparison is significant at the 0.001 level.

4.6.3 Effects of Obesity and Insulin on Prevalence of NAFLD

Figure 4.9 represents the proportions of NALFD among the four groups compared. As shown in the figure, the proportions of NAFLD rose steadily from -OB/-IR (9.5%) to +OB/-IR (25.8%) to -OB/+IR (28.6%), with steep rise in the +OB/+IR group (76.5%).

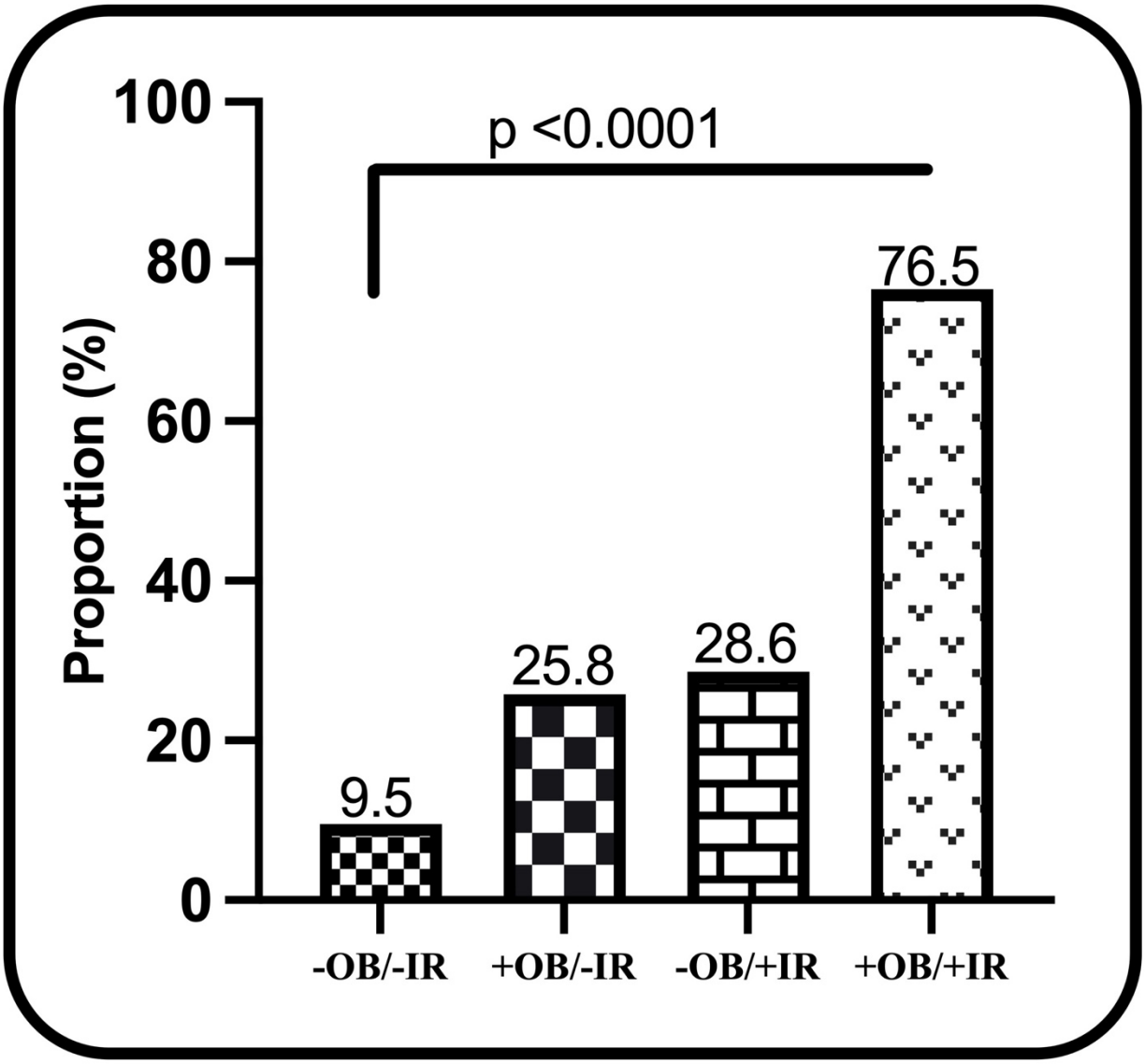

Figure 4.9: Distribution of high risk of NAFLD stratified by different combinations of presence or absence of insulin resistance and obesity.

4.6.4 Effect of Obesity and Insulin Resistance on SD, SD Domains and Sex Hormones

Table 4.22 shows the raw and stanine scores for sexual dysfunction and its domains as well as hormone levels within the four groups compared (-OB/-IR, +OB/-IR, -OB/+IR, +OB/+IR). The mean raw and stanine scores for dissatisfaction, non-communication and infrequency were higher in the -OB/+IR group followed by the +OB/+IR group. Levels of total testosterone, free testosterone and bioavailable testosterone increased from the -OB/-IR group to the +OB/-IR group to the -OB/+IR group reaching the highest level in the +OB/+IR group. However, the concentrations of SHBG were similar across of four groups (Table 4.22).

Table 4.22: Raw and stanine scores of SD, SD domains and testosterone levels stratified by different combinations of presence or absence of insulin resistance and obesity.

Parameter	-OB/-IR n=42	+OB/-IR n=31	-OB/+IR n=14	+OB/+IR n=34	P-values
Raw Score					
Sexual Dysfunction	77.76±3.8	76.55±4.3	79.14±2.2	78.56±2.5	0.055
Impotence	12.57±1.7	11.74±1.5	11.43±0.8	11.82±1.6	0.030
Premature Ejaculation	8.48±1.6	8.55±2.3	9.14±1.9	9.26±1.0	0.167
Non-Sensuality	11.48±1.5	11.23±1.1	11.57±1.2	11±1.1	0.330
Avoidance	10.52±2.1	10.65±2.2	10.14±2.5	11.38±2.0	0.213
Dissatisfaction	11±0.9	10.45±0.9	11.43±0.8	10.74±1.2	0.015
Non-Communication	4.95±0.9	5.03±0.5	5.71±0.7**	5.44±0.7†	0.001
Infrequency	5.67±0.7	5.55±0.6	6.57±1.5**	6.09±0.6†	<0.0001
Stanine Score					
Sexual Dysfunction	5.07±2.1	4.52±2.1	5.84±1.2	5.51±1.4	0.078
Impotence	5.83±2.2	4.72±1.9	4.3±1.0	4.83±2.1	0.030
Premature Ejaculation	4.77±1.7	4.77±2.2	5.48±2.1	5.6±1.1	0.114
Non-Sensuality	5.26±2.3	4.87±1.6	5.4±1.9	4.52±1.7	0.330
Avoidance	4.88±1.9	4.99±2.0	4.53±2.2	5.66±1.9	0.213
Dissatisfaction	5.21±1.8	4.16±1.8	6.03±1.5	4.79±2.1	0.012
Non-Communication	4.57±2.2	4.7±1.2	6.33±1.7**	5.74±1.8†	0.002
Infrequency	4.51±1.7	4.21±1.6	5.88±1.3**	5.58±1.4††	<0.0001
Sex Hormones					
Testosterone (ng/dL)	20.0 (9.3-39.0)	20.0 (6.0-166.0)	48.0 (12.0-119.0)	54.0 (24-119.0)††	0.025
Free Testosterone (ng/dL)	0.7(0.3-1.7)	0.8 (0.2-7.5)	1.1 (0.6-4.7)	2.0 (1.1-5.7)††	0.018
Bioavailable Testosterone (ng/dL)	15.8 (8.3-36.1)	18.9 (4.8-152.0)	24.5 (11.8-102.0)	43.4 (23.7-118.0)††	0.020
Sex Hormone Binding Globulin (nmol/l)	2.4 (0.6-6.3)	2.7 (0.8-5.8)	5.6 (0.4-11.0)	3.8 (0.2-5.8)	0.549

Parametric data were expressed as mean SD and were compared using unpaired One-way ANOVA test. Non-parametric data were summarised as medians (Interquartile Range) and compared using the Kruskal-Wallis test. . * Comparing -OB/+IR group with -OB/-IR group, † Comparing +OB/+IR group with -OB/-IR group, ‡ Comparing +OB/-IR group with -OB/-IR group. *Comparison is significant at the 0.05 level, **Comparison is significant at the 0.01 level, ***Comparison is significant at the 0.001 level.

4.7 Effects of Obesity and Insulin on Prevalence of SD and Its Domains

As shown in Table 4.23, the prevalence of SD did not differ across all four groups. However, the prevalence of subjects with non-communication was higher in the -OB/+IR group (100%), followed by the +OB/-IR (90.3%) whiles the proportions +OB/-IR (100%) with infrequency was higher among the four groups, followed by the proportions of infrequency in the +OB/+IR group (88.2%).

Table 4.23: Distributions of SD and SD domains stratified by different combinations of presence or absence of insulin resistance and obesity.

Parameter	-OB/-IR n=42	+OB/-IR n=31	-OB/+IR n=14	+OB/+IR n=34	P-values
Sexual Dysfunction					
No	14(33.3%)	14(45.2%)	2(14.3%)	8(23.5%)	0.128
Yes	28(66.7%)	17(54.8%)	12(85.7%)	26(76.5%)	
Impotence					
No	16(38.1%)	16(51.6%)	10(71.4%)	19(55.9%)	0.142
Yes	26(61.9%)	15(48.4%)	4(28.6%)	15(44.1%)	
Premature Ejaculation					
No	24(57.1%)	18(58.1%)	6(42.9%)	10(29.4%)	0.057
Yes	18(42.9%)	13(41.9%)	8(57.1%)	24(70.6%)	
Non-Sensuality					
No	12(28.6%)	6(19.4%)	2(14.3%)	12(35.3%)	0.343
Yes	30(71.4%)	25(80.6%)	12(85.7%)	22(64.7%)	
Avoidance					
No	22(52.4%)	15(48.4%)	10(71.4%)	15(44.1%)	0.377
Yes	20(47.6%)	16(51.6%)	4(28.6%)	19(55.9%)	
Dissatisfaction					
No	14(33.3%)	16(51.6%)	2(14.3%)	17(50%)	0.051
Yes	28(66.7%)	15(48.4%)	12(85.7%)	17(50%)	
Non-Communication					
No	14(33.3%)	3(9.7%)	0(0%)	4(11.8%)	0.006
Yes	28(66.7%)	28(90.3%)	14(100%)	30(88.2%)	
Infrequency					
No	14(33.3%)	16(51.6%)	0(0%)	4(11.8%)	<0.0001
Yes	28(66.7%)	15(48.4%)	14(100%)	30(88.2%)	

Data expressed as proportions and compared using Chi-square test.

Chapter 5

DISCUSSION

5.1 Introduction

Type 2 diabetes mellitus (formerly known as non-insulin dependent or adult onset), which affects 90% of patients with diabetes worldwide, is associated with insulin resistance, notably in the liver, and β-cell dysfunction (Ferrannini and Mari, 2014; World Health Organization, 2015). Several metabolic disorders, such as dyslipidaemia, obesity, non-alcoholic fatty liver disease, hypertension, cardiovascular disease, sleep apnea, and sexual and erectile dysfunction, have been linked to hyperinsulinaemia and underlying insulin resistance (Kelly, 2000; Tsai *et al.*, 2004; Krentz, 2008; Chen *et al.*, 2013; Li *et al.*, 2015; Ormazabal *et al.*, 2018).

Pathophysiologically, insulin resistance alone and insulin deficiency alone can alter plasma glucose levels and lead to adverse outcomes (Thow *et al.*, 1988; Taylor *et al.*, 1994). However, it is not clear whether type 2 diabetics with marked insulin resistance or those with relative insulin deficiency are more prone to adverse cardiometabolic outcomes. Therefore, an assessment of insulin resistance and its associated metabolic outcomes among diabetic men, is necessary in the evaluation, risk stratification and monitoring of treatment of type 2 diabetes. This study therefore sought to assess the association between insulin resistance (IR) on one hand, and obesity, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD) and sexual dysfunction (SD) as well as the synergistic effect of insulin resistance and obesity on adverse cardiometabolic outcomes among men with type two diabetes mellitus.

5.2 Insulin Resistance, Obesity and Adipokines

Obesity is a known modifiable risk factor for type 2 diabetes and from this study, the prevalence of obesity ranged from 54% to 59% using BMI, WC and WHR. In a study on obesity among the general population in Ghana, Amegah *et al.* (2011) reported an obesity prevalence of 4.7% among men. Obirikorang *et al.* (2015) also reported prevalence of obesity of 14.4% and 28.9%, using BMI and WC respectively as criteria for classification. A higher prevalence of obesity in this study compared to the general male population is expected because type 2 diabetes mellitus is most strongly and clearly related with obesity and hence, type 2 diabetes mellitus patients are more likely to be obese compared to the general population (Abdullah *et al.*, 2010). The figures from this study were however higher than the 13% reported by Mogre *et al.* (2016), 13.5% - 15% by Obirikorang *et al.* (2016) and the 38.2% by Bawady *et al.* (2022) but lower than the 69.9% by Damian *et al.* (2017), 83.3% by Marjani (2011) and the 72.2% by Vasanthakumar and Kambar

(2020) in diabetic men. The disparity between the findings could be as a result of the differences in criteria for classification of obesity, sample size, and differences in levels of urbanisation and modernisation which have been found to influence the incidence and prevalence of obesity. In this study, a cut-off of 94 cm and 0.9 for WC and WHR respectively were used for the classification of obesity. However, in the study by Obirikorang *et al.* (2016), a higher cut-off for WC (≥102) and WHR (≥1.0) was used for the classification of obesity in men, which classified fewer people as being obese.

Several studies have demonstrated higher prevalence of obesity among different populations with insulin resistance and associations between obesity and insulin resistance among non-diabetics have been reported (Bellou *et al.*, 2018). In this study which compared diabetic male subjects with insulin resistance (HOMA-IR ≥2) to those without insulin resistance (or relative insulin deficiency), the prevalence of all forms of obesity (general obesity, abdominal obesity and central obesity) considered in this study were significantly higher among the insulin resistant male diabetics compared to those without insulin resistance. Similarly, on the average, BMI, WC and WHR were higher among the insulin resistant group. Also, significant positive correlations were seen between anthropometric indices of obesity and HOMA-IR. A higher prevalence of obesity in the insulin resistant group and hence an association between obesity and insulin resistance has been reported in many studies (Carey *et al.*, 1997; Bellou *et al.*, 2018). However, McLaughlin *et al.* (2011) indicated obesity, particularly general or subcutaneous adipose deposition rather reduced the odds of insulin resistance, explaining that, abdominal obesity, rather than general obesity has more adverse outcomes and a negative impact on insulin sensitivity.

The role of obesity in insulin resistance is multifaceted and is thought to be mediated through, increased production of proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1); reduced production of protective adipokines and increased release of non esterified fatty acids (NEFA) (Wellen and Hotamisligil, 2005; Scherer, 2006; Shoelson *et al.*, 2006). A rise in intracellular fatty acid metabolites such as fatty acyl-coenzyme A (fatty acyl-CoA) and diacylglycerol is caused by either an increase in NEFA supply or a decrease in intracellular fatty acid metabolism (DAG). These cause insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) to become phosphorylated subsequent to the activation of a serine/threonine kinase cascade, reducing their ability to activate PI3K (Shulman, 2000). Subsequently, insulin-receptor signaling is reduced and hence insulin resistance in obesity.

The finding from this study that abdominal obesity (WHR > 0.90), and not general obesity, is independently associated with insulin resistance, is in sync with many studies which have reported that visceral deposition of fat as found in abdominal obesity, rather than subcutaneous fat as measured by BMI is more likely to lead to insulin resistance (Shah *et al.*, 2014; Borel *et al.*, 2015). Intra-abdominal fat is more lipolytic than subcutaneous fat and is also less sensitive to the anti-lipolytic effect of insulin (Montague and O'Rahilly, 2000). Due to this disparity in adipocyte properties and the liver's close proximity to the intra-abdominal fat depot, the liver is highly exposed to NEFAs more than peripheral organs are. As a result of this disparity in exposure and the presence of a portal-peripheral NEFA gradient, the liver may be insulin resistant at a time when the peripheral tissues are not (Kim *et al.*, 2003).

In this study, the levels of adiponectin were compared between the two strata of type two diabetic males. Adiponectin levels were significantly lower in the insulin resistant group and showed inverse correlation with HOMA-IR. An inverse relation between adiponectin and insulin resistance has been reported in a number of studies (Arita *et al.*, 1999; Hotta *et al.*, 2000; Yadav *et al.*, 2013). Adiponectin has been shown to be a protective hormone against several metabolic abnormalities including insulin resistance. It acts as an insulin sensitizer, It stimulates fatty acid oxidation in an AMP-activated protein kinase (AMPK) and peroxisome proliferator activated receptor-α (PPAR-α) dependent manner and also acts as an insulin sensitizer (Kadowaki *et al.*, 2006; Scherer, 2006). Lower levels could therefore influence the occurrence of insulin resistance.

Reduced plasma levels of adiponectin have been shown to be influenced by obesity (Arita *et al.*, 1999; Hotta *et al.*, 2000) and studies have demonstrated that adipocytes in the intra-abdominal area which have excess fatty acids, have the ability to suppress transcription of the adiponectin gene by secreting inflammatory and angiogenic molecules subsequently lowering its plasma levels (Bruun *et al.*, 2003). It may therefore be implied that, association between low adiponectin levels and insulin resistance in this study may have been influenced by the higher prevalence of obesity among the insulin resistant group. However, upon adjusting for obesity as a confounding factor following multivariate analysis, adiponectin concentration was found to be independently associated with insulin resistance which implies that, even among the non-obese, lower levels of adiponectin may induce insulin resistance.

The comparative abilities of individual indices of obesity and the adipokines to classify subjects as insulin resistant were assessed. Among the anthropometric indices of obesity, BMI better classified subjects as being insulin resistant at a cut-off of >28.8 kg/m^2. A similar finding was reported by Okura *et al.* (2018) where a BMI of ≥ 23 kg/m^2 properly classified insulin resistance.

Kotlyarevska *et al.* (2011), indicated no clear superior indicator of insulin resistance between BMI and WC. Lee *et al.* (2006) on the other hand, reported a superior ability of WC in classifying insulin resistance. The conflicting results may be due to differences in the populations studied and the methods of assessing insulin resistance.

5.3 Insulin Resistance, Hypertension and Dyslipidaemia

The study assessed the association between insulin resistance, hypertension and dyslipidaemia, and observed a 73.6% prevalence of elevated blood pressure among the study population. This figure is slightly lower than the self reported figure of 78.5% by the study participants. The prevalence of hypertension in this study is similar to the 73.7% among type 2 diabetic men reported by Hu *et al.* (2007). It is however higher than the 66.8% reported by Vasanthakumar and Kambar (2020), 62.1% reported by Mogre *et al.* (2016) and 65% by Akalu and Belsti (2020). The contrasting figures between this study and those of the other studies could be attributed to the differences in cut-offs used, levels of urbanisation and socioeconomic status which are known to significantly affect the prevalence of hypertension among different populations.

The prevalence of hypertension was significantly higher among the insulin resistant group and systolic blood pressure showed significant inverse correlation with insulin sensitivity. Studies on the association between hypertension and insulin resistance has seen conflicting findings from different studies. In this study, even though the frequency of elevated blood pressure was significantly higher among the insulin resistance group, it was not independently associated with insulin resistance after adjusting for obesity and other confounding variables. Ferrannini *et al.* (1987), demonstrated a link between insulin resistance and essential hypertension in a general population. It is unclear how insulin resistance is connected to high blood pressure and hypertension. It is believed that compensatory hyperinsulinemia brought on by insulin resistance could result in hypertension. Hypertension may be caused by insulin's stimulation of the sympathetic nervous system, increase in salt retention in the kidneys, modulation of cation transport, and induction of vascular smooth muscle hypertrophy. In consonance with the findings in this study, however, Saad *et al.* (2004), found no relation between insulin resistance and hyperinsulinemia and hypertension among diabetics, after adjusting for age, obesity and sex. They explained that, acute insulin infusion has a vasodilator hypotensive effect and that insulin could lower blood pressure in diabetics (Creager *et al.*, 1985; Laakso *et al.*, 1989). They however add that, the possibility of resistance to the vasodilator effect of insulin in an insulin resistant state, could lead to a rise in blood pressure. Consequently, the association between insulin

resistance and hypertension may not be causal but rather the two are linked indirectly through other metabolic abnormalities such as obesity, as observed in this study.

Lipid profile analysis of the male diabetic subjects showed 62.8% subjects with at least one lipid abnormality. Diabetes has been shown to be an independent risk factor for the development of dyslipidaemia and the phenomenom is well recognised (Wang *et al.*, 2018; Peng *et al.*, 2021). The prevalence in this study compares to the 61.3% among diabetic men in a study by Haile and Timerga (2020) but higher than the 43.3% reported by Li *et al.* (2018) and lower than the 94% and 72.6% reported by Omodanisi *et al.* (2020) and Ahmmed *et al.* (2021) respectively.

Relations between different lipid parameters and insulin resistance have been studied in the past (Moro *et al.*, 2003; Bansal *et al.*, 2005; Al-Mahmood *et al.*, 2006) and it is quite clear that there is an association between dyslipidaemia and Insulin resistance. The levels of total cholesterol (TC), LDL-cholesterol and total cholesterol to HDL-cholesterol ratio (TC/HDL) were significantly higher in the insulin resistance group. Similarly, TC, LDL-cholesterol and TC/HDL showed significant direct correlations with insulin resistance. Also, the prevalence of subjects with high LDL-cholesterol was significantly higher among the insulin resistance group. Based on in vitro studies, some researchers have hypothesized that excessive levels of triglyceride-rich VLDL particles could impair insulin action by preventing insulin from attaching to its receptor, i.e., insulin resistance might be a secondary symptom of primary dyslipidaemia (Steiner and Vranic, 1982; Berliner *et al.*, 1984). Other researchers have however failed to show this causal effect (Rinninger *et al.*, 1986). Garg *et al.* (1989), showed that, marked reduction in hypertriglyceridaemia did not lead to an improvement in the insulin sensitivity of patients with hypertriglyceridaemia, thus indicating that, insulin resistance is probably the underlying mechanism of dyslipidaemia. Upon adjusting for obesity as a confounding factor, none of the lipid parameters was independently associated with insulin resistance in this study, hence the association between increased LDL-c and insulin resistance may be mediated by obesity, which is known to cause dyslipidaemia independent of insulin resistance (Mc Auley, 2020).

The comparative ability of various lipid markers as screening tools for insulin resistance was also explored in this study. LDL-cholesterol concentration showed superiority in the classification of insulin resistance and at a cut-off of > 2.3 mmol/L. LDL-c may prove useful in the classification of insulin resistance among diabetic men. Insulin resistance is characterised by increased LDL-c concentration but the role and importance of LDL-c in the classification of IR is not fully investigated and is unclear from this current study.

5.4 Insulin Resistance, Liver Function and Non-Alcoholic Fatty Liver Disease

This study was limited to men with type two diabetes and estimated prevalence of high risk of NAFLD was found to be 34.7%. This figure is in consonance with the pooled African prevalence of 30.4% reported by Younossi *et al.* (2019b). It is however lower than the global prevalence of 55.5% (Younossi *et al.*, 2019b), the 75% reported by Andrade *et al.* (2016), but higher than the 5% reported by Portillo-Sanchez *et al.* (2015) and the 16.7% reported by Olusanya *et al.* (2016) in a similar population of diabetics. The observed variations in prevalence are largely attributable to the differences in methods of diagnosis and classification of NAFLD. This study was limited to the use of fatty liver index for classification of high risk of NALFD while other studies employed the use of more superior methods like the ultrasound scan and the proton magnetic resonance spectroscopy (H-MRS).

The prevalence of NAFLD was significantly higher among the insulin resistant group. The average fatty liver index was also higher in the insulin resistant group and showed significant positive correlation with insulin resistance. Subjects with high risk of NAFLD were about 10 times more likely to have insulin resistance. An association between NAFLD and insulin resistance has been reported in many studies around the globe (Bajaj *et al.*, 2004; Utzschneider and Kahn, 2006; Sharma *et al.*, 2009; Bae *et al.*, 2010). It is unclear from this study whether insulin resistance is a cause or effect of NAFLD, however, the association is thought to be bidirectional, with some studies reporting that, NAFLD is a common cause of insulin resistance (Kahn and Flier, 2000; Shulman, 2000; Samuel *et al.*, 2004) whiles others have shown that, NAFLD may be an effect of insulin resistance (Wolfrum *et al.*, 2004; Bugianesi *et al.*, 2005). Proponents of NAFLD being the cause of insulin resistance have explained that, fat accumulation in the liver inhibits insulin signalling in hepatocytes, specifically, impairment of insulin-stimulated insulin receptor substrate (IRS)-1 and IRS-2 tyrosine phosphorylation resulting in reduced insulin sensitivity and increased gluconeogenesis (Kahn and Flier, 2000; Shulman, 2000; Samuel *et al.*, 2004).

Contrarily, insulin resistance may exacerbate the formation of fatty liver by reducing insulin's capacity to inhibit lipolysis, which results in an increase in the distribution of FFAs to the liver. (Luyckx *et al.*, 2000; Marchesini *et al.*, 2001; Day and Saksena, 2002). Subjects with NAFLD have greater FFA levels (Marchesini *et al.*, 2001; Chalasani *et al.*, 2003; Bugianesi *et al.*, 2005) and impaired insulin suppression of lipolysis (Marchesini *et al.*, 2001; Seppälä-Lindroos *et al.*, 2002; Bugianesi *et al.*, 2005). By deactivating the forkhead transcription factor (Foxa2), the ensuing hyperinsulinemia may also lead to triacylglycerol buildup in the liver (Wolfrum *et al.*,

2004). In the liver, Foxa2 stimulates the oxidation of fatty acids, although IRS1 or IRS2 signaling pathways can phosphorylate Foxa2 to render it inactive. Foxa2 remains responsive to insulin's effects in the liver as such hyperinsulinemia can completely suppress Foxa2, which reduces fatty acid oxidation and promotes fat storage, which in turn causes NAFLD (Wolfrum *et al.*, 2004).

A high prevalence of NAFLD has been reported among obese populations (Bellentani *et al.*, 2000), with other studies reporting NAFLD in almost all morbidly obese individuals (Dixon *et al.*, 2001). Consequently, obesity is thought to be the link between NAFLD and insulin resistance. Visceral fat disturbs metabolism by exposing the liver to high concentrations of FFA through the portal vein leading to either insulin resistance or NAFLD or both (Frayn, 2000). In this study, however, NAFLD was independently associated with insulin resistance, after adjusting for abdominal obesity and similar findings have been reported by Seppälä-Lindroos *et al.* (2002). It is possible that the flux of FFA to the liver could originate from other sources such as hydrolysis of dietary chylomicrons and increased de novo lipogenesis (Fong *et al.*, 2000) which may be responsible for the development of NAFLD and insulin resistance, independent of obesity.

Liver enzymes have been shown to be elevated in insulin resistance, and is thought to be associated with NAFLD. AST and GGT levels were significantly higher in the insulin resistant group and similar reports linking insulin resistance with elevated liver enzymes have been published in the past (Cruz *et al.*, 2015; Li *et al.*, 2015; Sheng *et al.*, 2018). Other studies reported associations between serum ALT and insulin resistance but not AST or GGT (Gray *et al.*, 2013; Simental-Mendía *et al.*, 2017). Increased liver enzyme levels are a result of hepatocyte injury and inflammation brought on by increased triglyceride accumulation, increased delivery of free fatty acids to the liver, occurrence of oxidative stress, lipid peroxidation, mitochondrial dysfunction, and cytokine release, all of which are linked to insulin resistance (Ghamar-Chehreh *et al.*, 2012; Alam *et al.*, 2016; Wainwright and Byrne, 2016).

In assessing the comparative abilities of different liver parameters and fatty liver index as possible screening tools for insulin resistance, AST concentration showed superior ability in classifying insulin resistance compared to other parameters which may prove clinically important, since AST concentration is easier to assay than the calculation of fatty liver index which requires several parameters.

5.5 Insulin Resistance, Sexual Dysfunction, SD domains and Testosterone.

This study explored the relation between insulin resistance and sexual function in male type 2 diabetics. The prevalence of SD from this population was 68.6%. This prevalence was largely influenced by non-satisfaction, non-communication and infrequency. The prevalence of SD as reported in this study is comparable to the 69.5% reported by Getie Mekonnen *et al.* (2021) in a general male population, and the 70% reported by Amidu *et al.* (2010) among diabetic men. The prevalence in this study is however lower than the 86.2% among type 2 diabetic men reported by Getie Mekonnen *et al.* (2021) but slightly higher than the 65.1% reported by Likata *et al.* (2012) and the 63.6% reported by Siu *et al.* (2001). Differences in prevalence of SD among different studies is not surprising and have been attributed to variations in differences in tools for assessing SD, type of diabetic population, as well as geographic and ethnic variations which are known to affect the occurrence of SD.

The median total testosterone, free testosterone and the bioavailable testosterone concentrations estimated from this study were below what is considered to be their respective normal values in men. Serum concentrations of testosterone and its derivatives have been reported to be reduced in diabetic subjects (Yeap *et al.*, 2012; Kundu *et al.*, 2018) and is associated with higher prevalence of SD among diabetic subjects compared to apparently healthy men. Through visceral obesity, decreased sex hormone binding globulin (SHBG), inhibition of gonadotrope secretion or production of testosterone by Leydig cells, cytokine-mediated inhibition (e.g., TNF-, IL-1, IL-6) of steroid production, and increased aromatase activity leading to oestrogen excess, the hyperglycemia associated with diabetes mellitus may be a risk factor for hypogonadism. Others have implicated the use of antidiabetic drugs such as metformin (Cai *et al.*, 2021), as a cause of the reduced testosterone levels in diabetic males with good glycaemic control, through its negative impact on cell proliferation and the change in secretory ability of testicular Sertoli cells (Faure *et al.*, 2016) which regulate synthesis and secretion of testosterone in Leydig cells (Zhang *et al.*, 2012).

The prevalence of SD, premature ejaculation, non-communication and infrequency were higher in the insulin resistant diabetic men compared to their counterparts with lower HOMA-IR. Sexual function is known to be inversely associated with insulin resistance as reported earlier (Knoblovits *et al.*, 2010; Chen *et al.*, 2013). They attribute their findings to the endothelial dysfunction associated with insulin resistance (Knoblovits *et al.*, 2010) and that insulin resistance alters the balance between NO and endothelin-1, leading to reduced vasodilation, penile vascular insufficiency (Pitteloud *et al.*, 2005; Muniyappa *et al.*, 2008).

Upon adjusting for confounding variables such as obesity, sexual dysfunction was not independently associated with insulin resistance. Consequently, the higher prevalence of SD in the insulin resistant group may be as a result of a higher prevalence of obesity and not the insulin resistance per se. Infrequency and non-communication were however independently associated with insulin resistance in this study with infrequency better classifying subjects as insulin resistant. The reason for this finding is not clear from the current study but may be attributed to anxiety and depression. Anxietry and depression is associated with sexual disorders (Asefa *et al.*, 2019) and is also known to be associated with presence and severity of chronic conditions such as obesity, NAFLD, hypertension and dyslipidaemia (Peltzer and Pengpid, 2016), some of which have been shown to be associated with insulin resistance in this study.

Paradoxically, even though the prevalence of sexual dysfunction was higher among the insulin resistant group, levels of total testosterone, free testosterone and bioavailable testosterone were significantly higher in the same group. Higher testosterone among insulin resistant subjects and the resulting hyperinsulinaemia, has also been reported by Pasquali *et al.* (1995) and Pasquali *et al.* (1997). In their study, Pasquali *et al.* (1997) explains that, insulin can stimulate gonadal testosterone production and release, and is implicated in the pathogenesis of polycystic ovary syndrome (PCOS) associated with insulin resistance in women. They further explained that, testosterone synthesis can be stimulated by insulin like growth factor-I receptors (Lin *et al.*, 1986) and that since insulin and insulin like growth factor-I receptors have similar biochemical and functional structures, it is possible that in insulin resistant states, the resulting hyperinsulinaemia can stimulate the production of testosterone through the IGF-I receptors (Pasquali *et al.*, 1997).

Grossmann (2011) and Ottarsdottir *et al.* (2018) conversely found lower testosterone levels to be associated with insulin resistance. They pointed out that the relationship between insulin resistance and testosterone levels is bidirectional, and whiles low levels of testosterone may be a risk factor for insulin resistance, insulin resistance may be a cause of hypogonadism in men. Testosterone is thought to modulate the expression of GLUT4 and the insulin receptors in muscle and adipose tissues, a reduction of which could lead to insulin resistance (Sato *et al.*, 2008; Muthusamy *et al.*, 2009). Insulin resistance on the other hand could affect testosterone levels through functional defects at different levels of the hypothalamus-pituitary-gonadal axis (Pitteloud *et al.*, 2005). However, Tsai *et al.* (2004), in their study on the association between insulin resistance and testosterone, showed that the inverse relation between insulin resistance and testosterone levels was influenced by the levels of sex hormone binding globulin (SHBG) and that no relation was observed after adjusting for SHBG. In this present study, the levels of

SHBG were similar in both strata and hence did not affect the levels of testosterone. This may have accounted for the differences in findings between this study, that of Pasquali *et al.* (1997) and those of Muthusamy *et al.* (2009) and Sato *et al.* (2008).

5.6 Synergistic Effect of Obesity and Insulin Resistance on Adipokines, Hypertension, Dyslipidaemia, NAFLD and Sexual Function

Obesity and insulin resistance have been shown to affect different metabolic pathways, independent of each other. The link between obesity and the development of insulin resistance has been well documented and both increased abdominal subcutaneous adipose tissue and visceral adipose tissue are strongly correlated with insulin resistance (Tulloch-Reid *et al.*, 2004). In fact, some researchers believe that insulin resistance (IR) is the main culprit in the association between visceral obesity and other metabolic as well as non-metabolic diseases (Gallagher *et al.*, 2010). In this study therefore, the combined effect of obesity and insulin resistance on other metabolic abnormalities were assessed.

The study population was stratified into four groups comprising subjects with obesity and insulin resistance (+OB/+IR), obesity alone (+OB/-IR), insulin resistance alone (-OB/+IR) and non-obese, non-insulin resistant (-OB/-IR) subjects to enable comparison of biochemical analytes and metabolic abnormalities. The concentration of insulin was higher in the +OB/+IR group when compared to other groups, which is expected since obesity is independently linked with insulin resistance and the resulting hyperinsulinemia which consequently results in higher circulating insulin levels.

Comorbidity of obesity and insulin resistance resulted in elevated total cholesterol and LDL-cholesterol, with a higher prevalence of increased LDL. Obesity and insulin resistance are known to affect lipid metabolism independently of each other and studies have shown that weight gain is associated with higher rates of cholesterol synthesis (Stahlberg *et al.*, 1997), as a result of increased levels of hepatic HMG Co-A reductase (HMGCR) and consequently increased cholesterol synthesis in obese individuals (Angelin *et al.*, 1982; Stahlberg *et al.*, 1997). Similarly, hyperinsulinaemia consequent to insulin resistance is known to decrease cholesterol absorption secondary to increase cholesterol synthesis through an upregulation of lipogenesis by the liver X receptors (Horton *et al.*, 2002; Tobin *et al.*, 2002; Pihlajamäki *et al.*, 2004), resulting in the hypercholesterolaemia seen in insulin resistance. The combined effect of the two conditions, consequently leads to a elevated cholesterol.

The role of insulin resistance in the development of NAFLD is thought to be secondary to obesity (Frayn, 2000), but some studies including the current study have indicated an independent association between insulin resistance and NAFLD (Fong *et al.*, 2000). The prevalence of NAFLD among individuals with insulin resistance and obesity comorbidity was high (76.5%) when compared to those with individual abnormalities (+OB/-IR =25.8%; -OB/+IR=28.6%). Fatty liver index was higher in the +OB/+IR group which was expected and supports the reported increased risk for NAFLD associated with obesity and insulin resistance. Higher fatty liver index in the +OB/-IR compared to the -OB/+IR group may indicate a higher contribution of obesity alone than insulin resistance alone, in the synergistic effect of the two in the development and progression of NAFLD. On the contrary, a study by Yang *et al.* (2016) indicated an association between NAFLD and the metabolic syndrome was independent of insulin resistance and obesity and that, non-esterified fatty acid concentrations are associated with NAFLD severity independent of insulin resistance and obesity (Holt *et al.*, 2006). The conflicting findings could be due to differences diagnostic criteria for NAFLD. Whiles this study used the fatty liver index to assess NAFLD risk among diabetic males, Yang *et al.* (2016) used the ultrasonography assessment method among a general population.

The association between obesity and hypogonadism has been well studied (Wu *et al.*, 2008; Allan and McLachlan, 2010; Tajar *et al.*, 2010; Cao *et al.*, 2012). Increased visceral fat in obesity releases increased amounts of pro-inflammatory cytokines, which may inhibit the activity of the hypothalamus-pituitary-testis axis at different levels leading to reduced testosterone production especially in type 2 diabetics (Grossmann *et al.*, 2010). Similarly, insulin resistance is said to cause hypogonadism, as a result of reduced sensitivity to insulin mediated testosterone production (Ahn *et al.*, 2013) and the impact of inflammation associated with insulin resistance on the hypothatalamus-pituitary-gonadal axis (Pitteloud *et al.*, 2005). In this study, the median testosterone in subjects with comorbidity was higher than those of other comparable groups, even though testosterone for all groups were lower than the normal testosterone values for males. The finding of higher testosterone in the +OB/+IR group was unexpected especially with the presence of obesity. However, considering that the testosterone levels in the -OB/+IR group was higher than that in the +OB/-IR, it is possible that the synergistic effect of the two on testosterone levels was largely determined by the insulin resistance and the resulting hyperinsulinaemia. Hyperinsulinaemia in insulin resistance has been shown to stimulate testosterone synthesis through the insulin like growth factor receptors, even in the presence of classical insulin resistance (Pasquali *et al.*, 1995), hence the finding in this study.

Chapter 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

- Insulin resistance among type 2 diabetic males is associated with all forms of obesity. Abdominal obesity measured by waist to hip ratio is indepently associated with insulin resistance and at a cut-off of > 28.8 kg/m^2, BMI better classifies diabetic men as insulin resistant compared to other anthropometric markers of obesity. Similarly, reduced levels of adiponectin are associated with insulin resistance in type 2 diabetic men, independent of abdominal obesity.

- Hypertention and dyslipidaemia are associated with insulin resistance among type 2 diabetic men. This may however be mediated by obesity associated with insulin resistance. An LDL-c cut-off of > 2.3 mmol/L better classifies type 2 diabetic men as insulin resistant than other lipid markers.

- Higher fatty liver index and subsequently, high risk of non-alcoholic fatty liver disease is independently associated with insulin resistance in type 2 diabetic men. Higher AST levels are also associated with insulin resistance in type 2 diabetic men and with a cut-off of > 24 IU/L, AST may be able to classify patients as insulin resistant.

- Sexual dysfunction and its domains; premature ejaculation, non-communication and infrequency are associated with insulin resistance in type 2 diabetic men, however only non-communication and infrequency were independently associated with increased risk of insulin resistance. Generally, hypogonadism is associated with type 2 diabetes, however higher levels are associated with insulin resistance and at a cut-off > 20 ng/dL, total testosterone is able to classify type 2 diabetics as insulin resistant.

- A comorbidity of insulin resistance and obesity is seen to be associated with adverse metabolic outcomes such as dyslipidaemia, non-alcoholic fatty liver disease and sexual dysfunction, compared to isolated cases of obesity or insulin resistance. Obesity may however, play a major role in the pathogenesis of these conditions compared to insulin resistance, when the two co-exist. Conversely, higher testosterone levels are associated with an obesity-insulin resistance comorbidity, with insulin resistance playing a major role in this synergy.

6.2 Limitations

- The dependence on a single approach for the evaluation of insulin resistance is a significant study restriction. Therefore, it was impossible to assess how different methodologies affected the results.

- The effect of hepatic clearance on insulin concentrations and hence insulin resistance could not be assessed.

- Given the very small sample size, it may be difficult to generalize the current findings.

- The direction of risk variables and health outcomes cannot be assessed using a cross-sectional design. It is unclear from this design if obesity, non-alcoholic fatty liver disease, dyslipidaemia, or sexual dysfunction happen before or after insulin resistance.

6.3 Recommendations

- There is the need for proper sensitization of health personnel on the need to adopt proper diagnostic techniques to enhance proper stratification of type 2 diabetic men, to enhance treatment options.

- Future studies should consider the potential effect of hepatic clearance on insulin and the use of c-peptide concentrations instead of insulin concentration for the assessment of insulin resistance.

- Rather than an analysis of cross-sectional associations, it would be optimal to assess the role of the insulin resistance in a longitudinal study that will focus on disease development.

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