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UNIVERSITY OF GHANA MEDICAL SCHOOL
DEPARTMENT OF PHYSIOLOGY**

**RELATIONSHIP BETWEEN OBESITY AND DIAPHRAGM MUSCLE
STRENGTH IN DIABETES MELLITUS**

BY

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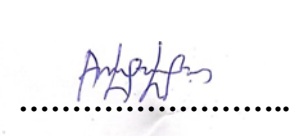
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DECLARATION

I, **Mageed Mohammed**, affirm that the study "Relationship between obesity and diaphragm muscle strength in diabetes" thesis is my original work. This thesis has never been submitted in whole or in part for a degree at this university or any other. Additionally, I certify that I have properly credited the writers whose work I have used.



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Date

DEDICATION

I dedicate this body of work to my mother, Mrs. Nasata Amadu. She has been an unwavering pillar and as I conclude this journey I want to thank her profusely for my unflinching support.

Additionally, this study is dedicated to my unwavering supervisors, Drs. Charles Hayfron-Benjamin and Joachim Amoako. This masterwork is the result of your leadership and gentle guidance, contributing to the expanding scientific body of knowledge.



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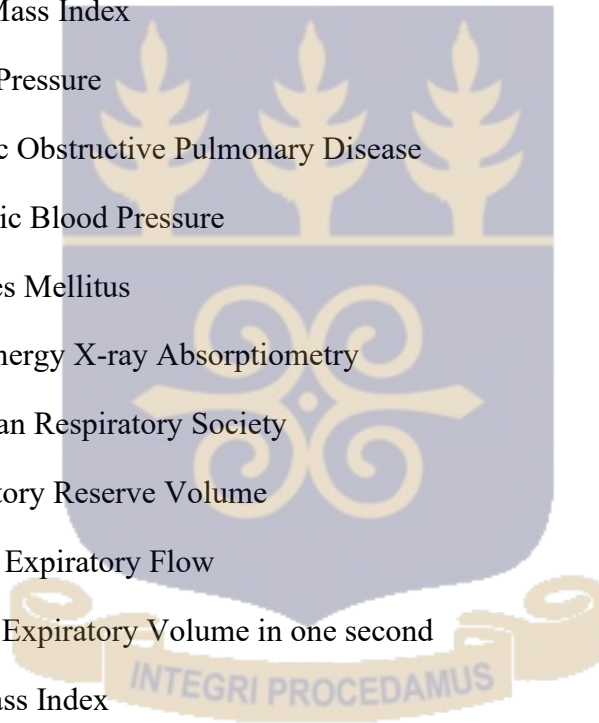
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LIST OF ABBREVIATIONS

ATS	America Thoracic Society
BAE	Body Adiposity Estimator
BF%	Body Fat Percentage
BIA	Bioelectric Impedance Analyses
BMI	Body Mass Index
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DXA	Dual-energy X-ray Absorptiometry
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
FEF	Forced Expiratory Flow
FEV	Forced Expiratory Volume in one second
FMI	Fat-Mass Index
FPG	Fasting Plasma Glucose
FVC	Forced Vital Capacity
GDM	Gestational Diabetes Mellitus
HbA1C	Glycated Hemoglobin
HDL	High-Density Lipoprotein
JNK	Janus N-Terminal Kinase
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal



LMS	Low Muscle Strength
MODY	Maturity Onset Diabetes of the Young
MRI	Magnetic Resonance Imaging
NDMRC	National Diabetes Management and Research Centre
NGS	Normalised Grip Strength
PEK	Peak Expiratory Flow
PERK	Protein Kinase R-Like Endoplasmic Reticulum Kinase
PHI	Principal Health Information
RHR	Resting Heart Rate
SBP	Systolic Blood Pressure
SM%	Skeletal Muscle Percentage
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TLC	Total Lung Capacity
USD	United States Dollars
WC	Waist Circumference
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-To-Hip Ratio



STRUCTURED ABSTRACT

Background: Worldwide, diabetes remains prevalent, affecting one in ten adults. As a metabolic disease, diabetes affects nearly all organs and organ systems due to its adverse effects on the macrovascular and microvascular circulation. Diabetes also affects the pulmonary system and is associated with specific pulmonary defects such as airway obstruction, pulmonary restriction, and impaired pulmonary gas exchange. Very recently, the diaphragm has been recognized as a potential target organ for diabetes, with nearly one in five adults with diabetes having impaired diaphragm muscle strength. The biological basis of diaphragm muscle weakness remains uncertain. The effect of fat on diaphragm muscle is one possible influencing factor. Obesity, especially central obesity could restrict the vertical movement of the hemidiaphragms as well as result in metabolic inflammation that could adversely impact the functions of the diaphragm. To date, studies on the relationships of different measures of obesity with diaphragm muscle strength in individuals with diabetes remain unreported.

General Aim To investigate the relationships of measures of obesity with diaphragm muscle weakness in adults with diabetes.

Methods: This cross-sectional study included 500 participants with an established diagnosis of diabetes, who were managed at the Ghana National Diabetes Management and Research Center, Accra. Spirometry was sequentially done in the sitting and supine positions in compliance with the standards of the American Thoracic Society and European Respiratory Society (ERS). Measured spirometric indices included forced expiratory volume in one second (FEV₁), and forced vital capacity (FVC). Diaphragm muscle weakness was defined as a decline in FVC by 10% or more from sitting/upright to supine position (Δ FVC $\geq$ 10%). Isolated or disproportionate bilateral diaphragm weakness is defined Δ FVC $\geq$ 30%. Measures of obesity included waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI). General obesity was defined as BMI $\geq$ 30 kg/m² for both sexes. Central obesity was defined as WHR $>$ 0.85 in females and $>$ 0.9 in males and/or WC $\geq$ 80 cm in females and $\geq$ 94 cm in males. Multivariate logistic regression analyses were used to examine the associations between measures of obesity (independent variable) and diaphragm muscle weakness (dependent variable), with adjustment for potential covariates including age, sex, smoking, HbA1c concentration, diabetes duration, and LDL cholesterol concentration, and peripheral neuropathy.

RESULTS: Women were the majority of study participants (73.4%). BMI, systolic blood pressure, diastolic blood pressure, duration of diabetes, and mean ($\pm$ standard deviation) age were 29.16 ($\pm$ 5.75) kg/m², 1315.66 ($\pm$ 17.9) mmHg, 76.27 ($\pm$ 10.82) mmHg, 61.02 ($\pm$ 10.19) years, and 11.56 ($\pm$ 8.03) years, respectively. The mean HbA1c, fasting plasma glucose, total cholesterol, triglycerides, HDL, and LDL cholesterol concentrations were 8.12 ($\pm$ 1.56) %, 8.93 ($\pm$ 3.14) mmol/L, 4.92 ($\pm$ 1.12) mmol/L, 1.92 ($\pm$ 0.98) mmol/L, 1.24 ($\pm$ 0.34) mmol/L and 3.12 ($\pm$ 0.91) mmol/L respectively. The mean ($\pm$) FEV₁ pp, FVC pp, and FEV₁/FVC ratio were 82.6 ($\pm$ 17.4)%, 85.3 ($\pm$ 18.1)%, and 0.82 ($\pm$ 0.07) respectively. Respectively 17.6% and 0.4% of the study participants had diaphragm muscle weakness and isolated or disproportionate bilateral diaphragm weakness. In a multivariable regression model, peripheral neuropathy (OR 4.72, 95% CI [1.30 - 17.06], p = 0.018) but not general obesity (1.09 [0.41 - 2.86], p =0.868) or central obesity (0.91 [0.17 - 4.71], p =0.907) was significantly associated with diaphragm muscle weakness. In the fully adjusted multivariate regression models, No substantial independent relations between general obesity and (1.38 [0.25 - 7.55], p =0.709) or central obesity (1.55 [0.55 - 4.36], 0.410) with diaphragm muscle weakness.

CONCLUSIONS: The study shows a relatively high proportion of diaphragm muscle dysfunction in adults with T2D with nearly one in five study participants affected. This is clinically relevant considering the adverse impact of diaphragm muscle weakness on respiratory function including alveolar minute ventilation and pulmonary gas exchange. Based on this study, the positive associations of general obesity and central obesity with diaphragm muscle weakness were not statistically significant. However, the strength of association could be clinically significant considering the magnitude of the observed odds ratio. Future studies could characterize the clinical consequences of impaired diaphragm muscle strength in the setting of T2D.

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Diabetes mellitus (also called diabetes) is a disease of inadequate control of blood levels of glucose and may be grouped into type 1, type 2, gestational diabetes, neonatal diabetes, maturity-onset diabetes of the young (MODY), and steroid-induced diabetes¹. Diabetes is a global health pandemic that has reached alarming levels in current trends, affecting one out of every 10 adults in the world in 2021². Worldwide, 44% of adults (240 million) who live with diabetes are undiagnosed.³ The prevalence of diabetes is on the rise. For example, diabetes is predicted to rise to one in every nine adults by 2030 and one in every eight adults by 2045².

Diabetes is of important clinical and public health concern given its adverse impact on the lives of affected individuals as well as the economies of nations. Diabetes increases the risk of repeated hospitalizations including emergency hospitalization, increases healthcare-related costs, decreases the quality of life of affected persons, and increases the risk of macrovascular (e.g. coronary artery disease, peripheral artery disease, and cerebrovascular disease) as well as microvascular (e.g. diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy) complications^{3,4}. Diabetes affects the economies of nations due to different reasons including reduced productivity, early mortality of active workforce members, and hospital-related costs. In 2021, Diabetes was responsible for an estimated 966 billion United States Dollars (USD) in current global health expenditures². This amount represents a 316% increase in health expenditure on Diabetes over the last 15 years.

Recently, the pulmonary system has been identified as a target organ for diabetes^{5,6}. Large epidemiological studies including the Framingham study⁷ and the Fremantle study⁸ have shown

important reductions in the pulmonary mechanical functions in individuals with diabetes, including both restrictive pulmonary defects and obstructive airway disorders. For example, Framingham's study demonstrated that diabetes is strongly associated with a lower mean adjusted residual forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)⁷. In addition to impaired spirometry, other studies have shown that diabetes is associated with impairment of other pulmonary functional measures including impaired pulmonary gas exchange, impaired pulmonary microvascular function, and a reduction in lung volumes^{9–13}. Pulmonary dysfunction in the setting of diabetes is clinically relevant given the evidence from the Fremantle study that decreased FEV₁ percentage predicted (pp) is an independent predictor of all-cause mortality in individuals with diabetes¹⁴.

Recently, work done at the University of Ghana Medical School (PI: Hayfron-Benjamin C, Graduate Student: Awuttey E; yet to be published) showed that diaphragm muscle weakness is common in adults with diabetes. Specifically, 18% of the study population had diaphragm muscle weakness, and 1.3% had isolated or isolated disproportionate bilateral diaphragm muscle weakness. While the clinical significance of this high burden of diaphragm muscle weakness in individuals with diabetes remains unknown, its biological basis is also unknown. It could well be the case that the splinting effect of abdominal obesity could contribute to diaphragm muscle weakness in the setting of diabetes¹⁵. Obesity, especially central obesity has a significant impact on metabolic inflammation¹⁶, which could adversely affect diaphragm muscle function directly, or through its impact on phrenic nerves¹⁷. Studies to assess the impact of obesity on diaphragm muscle strength are required.

1.2 PROBLEM STATEMENT

Over half a billion people (537 million) globally struggle with diabetes, making it a public health concern. It is estimated that by 2045, 784 million will be affected by diabetes¹⁸. The rate of increase in the rampancy of diabetes is highest in sub-Saharan Africa, including Ghana³. The impact of diabetes on the pulmonary systems has been explored, with diabetes known to affect multiple aspects of pulmonary physiology including lung mechanical function and pulmonary gas exchange, and increasing the risk of early death¹⁹. Regardless, there is a dearth in the literature on an important aspect of pulmonary function i.e. diaphragm muscle strength. Very recently, a team at the University of Ghana Medical School demonstrated that nearly one in five adults with diabetes have diaphragm muscle weakness. Diaphragm muscle weakness may be clinically relevant given its likelihood to complicate a reduction in alveolar minute ventilation and hypoxemia, impaired cough, sputum retention, and chest infections²⁰. However, the underlying mechanisms remain uncertain. A limited understanding of the biological basis of diaphragm muscle weakness could hinder interventions targeting the prevention and treatment of diaphragm muscle weakness in individuals with diabetes.

1.3 JUSTIFICATION

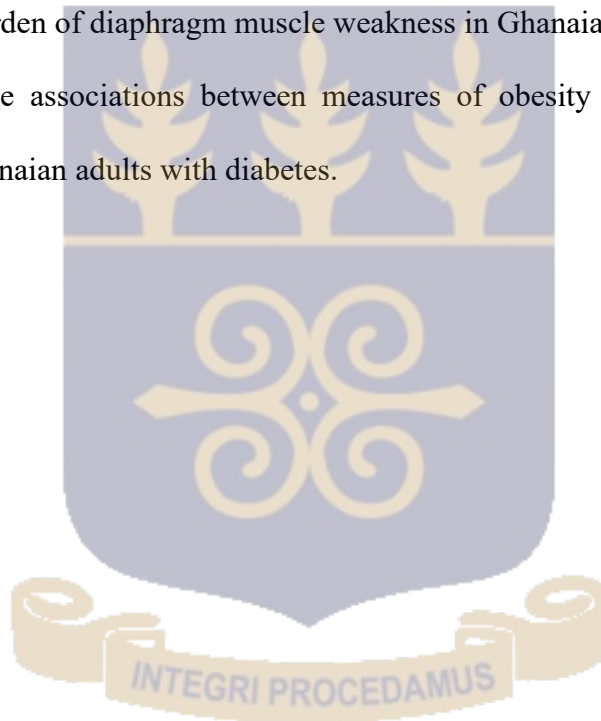
This proposed study explores the potential role of measures of obesity on diaphragm muscle function in individuals with diabetes. This study has benefits in terms of contributing to the biological basis of diaphragm muscle weakness in diabetes. Findings from the study may give others the opportunities for future research aimed at further exploring the underlying mechanisms for diaphragm muscle weakness in diabetes. Findings from the study may also inform preventive and treatment strategies for diaphragm muscle weakness in diabetes.

1.4 GENERAL AIM

To investigate the relationships of measures of obesity with diaphragm muscle weakness in adults with diabetes

1.5 SPECIFIC OBJECTIVES

1. To assess measures of general and central obesity in Ghanaian adults with diabetes.
2. To assess the burden of diaphragm muscle weakness in Ghanaian adults with diabetes
3. To determine the associations between measures of obesity and diaphragm muscle weakness in Ghanaian adults with diabetes.



CHAPTER 2

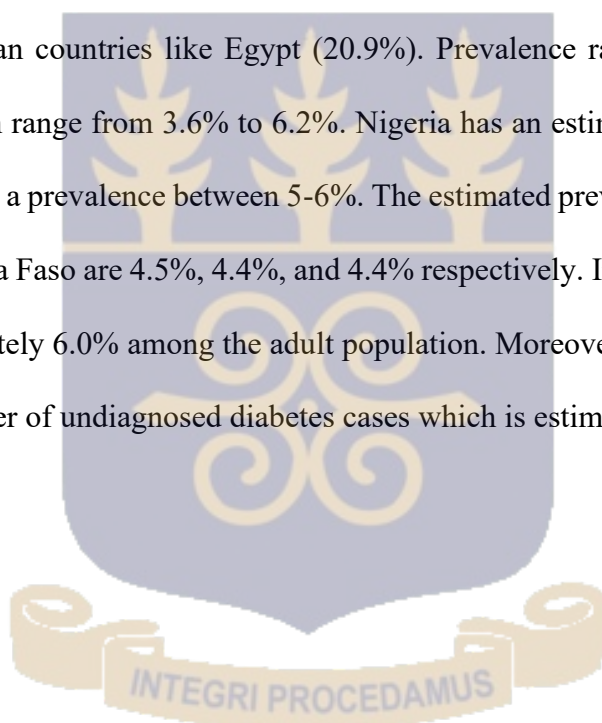
LITERATURE REVIEW

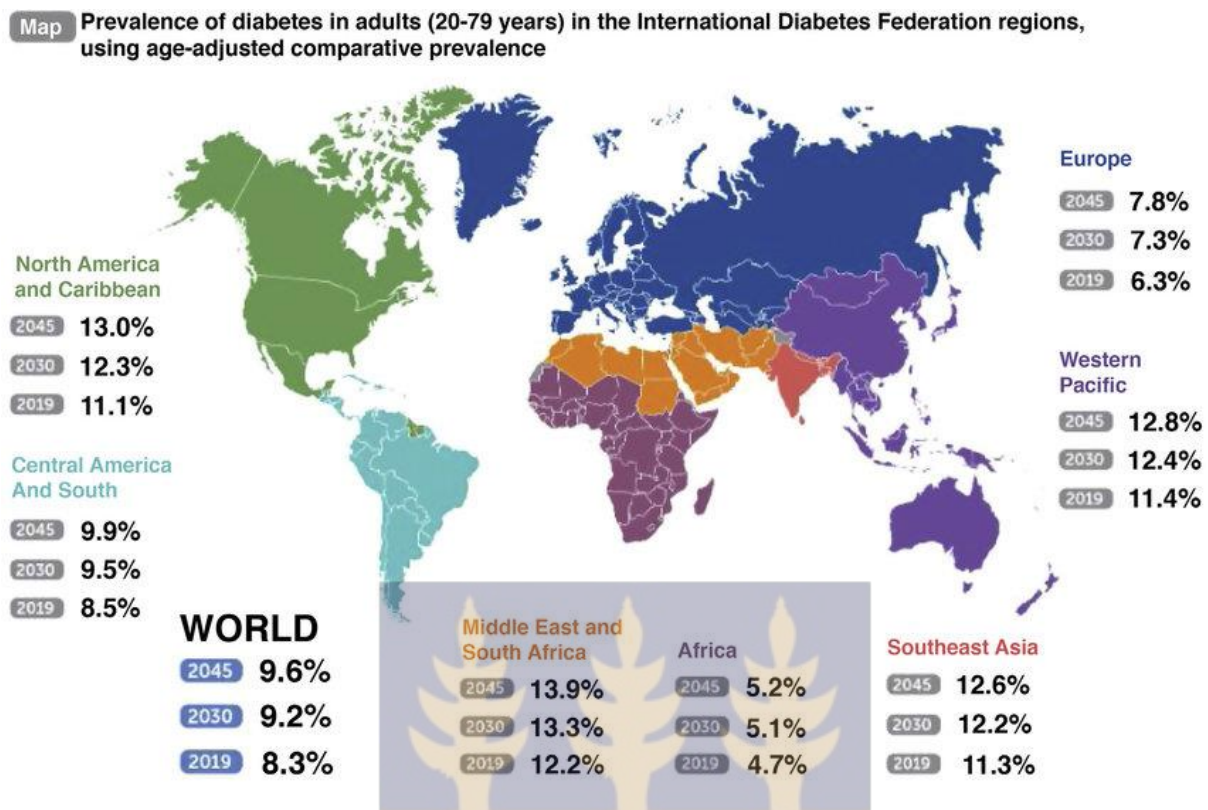
2.1 DIABETES MELLITUS, DEFINITION, AND PREVALENCE

Diabetes, technically known as diabetes mellitus, is a chronic metabolic disease marked by a continuous rise in blood glucose levels. This happens when the body tissues become unable to uptake glucose into the cells due to either ineffective use of insulin or little to no production of insulin from the pancreas². The attributes of this insulin inefficiency ultimately lead to insulin resistance (IR). These affect the metabolism of carbohydrates, fat, and proteins. Both decreased and inadequate insulin production occur simultaneously and/or separately in persons with diabetes. A blood glucose level of >126 mg/dL after 8 hours of fasting or >200 mg/dL² after 2 hours of meals is the precise criterion for diabetes^{2,8}. Hyperglycaemia is a common feature of uncontrolled diabetes which consequently renders severe damage to many bodily systems including nerves, kidneys, and blood vessels. General symptoms include, incessantly feeling very thirsty, urgent need to urinate, blurred vision, feeling tired, and unintentional weight loss. Blood vessel nerve damage could to impaired blood flow to the feet leading to foot ulcers and amputation⁴.

Globally, currently available data shows that over 529 million have diabetes mellitus. This number has been projected to progress aggressively, affecting 700 million people by 2045 and 1.31 billion by 2050. Though data shows that one in every two people living with diabetes is undiagnosed, prevalence rates in urban regions are higher compared to rural centers. Similarly, prevalence rates in high-income regions are higher than in low-income or poor regions^{1,2}. In the 2019 Global Burden of Disease Collaborative Network report, Diabetes directly caused 1.5 million fatalities, while 48% of deaths from diabetes were among people below 70 years. In the

same report, diabetes accounted for 46000 kidney disease deaths and 20% of cardiovascular deaths. In Europe, about 10% of the adult population representing 64 million are known to be living with diabetes with countries such as Spain, Italy, and Germany leading the pack with prevalence rates of 14.8%, 12%, and 10% respectively. Moreover, total prevalence rates in the USA stand at 11.3% accounting for 37 million of the adult population^{1,2}. Current prevalence rates in other regions of the world include 8% in Central and South America, 12.3% in Oceania, and the Middle East with countries such as Kuwait, Qatar, and Iraq with approximately 15%. Africa, particularly, has the lowest estimated prevalence rate (4.5%) though higher rates are reported in North African countries like Egypt (20.9%). Prevalence rates reported across the West African sub-region range from 3.6% to 6.2%. Nigeria has an estimated 3.6 million adults living with diabetes with a prevalence between 5-6%. The estimated prevalence rates reported in Mali, Benin, and Burkina Faso are 4.5%, 4.4%, and 4.4% respectively. In Ghana, the prevalence rate stands at approximately 6.0% among the adult population. Moreover, the African continent shows the highest number of undiagnosed diabetes cases which is estimated at 53.6%²





Source: International Diabetes Federation, 2019. <http://www.diabetesatlas.org>.

Figure 2.1: The International Diabetes Federation adults (20-79 years) diabetes prevalence

2.2 TYPES OF DIABETES

Diabetes results in the condition of either inefficient use of the hormone insulin or inadequate production of the hormone by the pancreas and or increased plasma glucose levels. Mature-onset diabetes of the young (MODY), type 1 and type 2 diabetes, gestational diabetes, neonatal diabetes, and secondary causes from endocrinopathies, steroid use, etc¹. Type 1 diabetes, Type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM) are the three predominant forms of the condition²¹.

2.2.1 Type 1 Diabetes

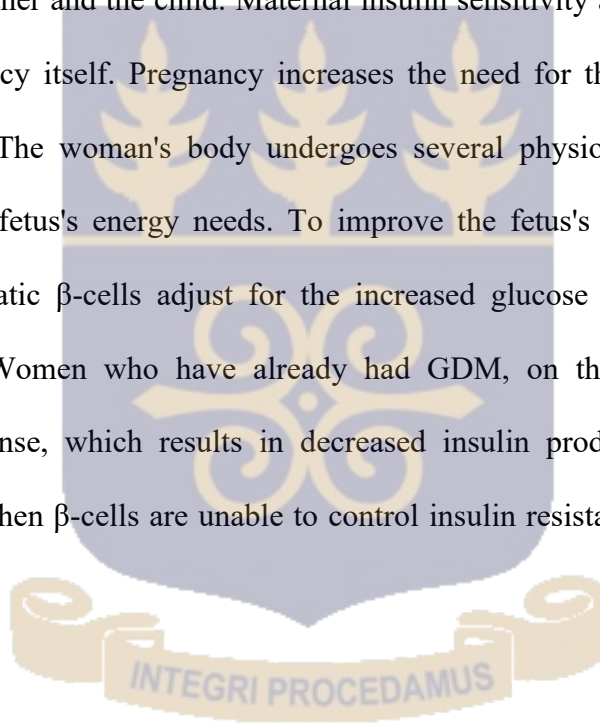
Type 1 diabetes mellitus (T1DM) also referred to as insulin-dependent or juvenile type of diabetes entails little to no insulin production which is very significant in controlling blood glucose levels. It is an autoimmune condition whereby the body's immune system sees the pancreatic beta cells as a foreign body and develops antibodies against it, so the antibodies destroy the beta cells. Though it could develop at any age, it often manifests in childhood or adolescence. There is no known cause-and-effect association nor preventive mechanism for type 1 diabetes. Individuals living with type 1 diabetes undergo life-long insulin therapy to keep blood glucose levels low to prevent complications. This type of diabetes accounts for just 5-10% of all diabetes cases²⁰. The global incidence rate stands at 15 per 100,000 people. There are 8.4 million individuals estimated to be living with Type 1 diabetes, projected to increase to 13.5-17.4 million by 2040¹⁸.

2.2.2 Type 2 Diabetes Mellitus (T2dm)

This occurs primarily as a result of insulin resistance, where the body is unable to effectively use insulin. This implies that, unlike in T1DM, insulin may be produced in sufficient quantities but the body's cells do not effectively respond to it^{1,14}. The beta cells of the pancreas initially increase the production of the insulin in response to the body's demands but over time, they are not able to keep up. This type of diabetes is oftentimes, lifestyle associated with a sedentary lifestyle and poor dieting chief culprits. It typically develops in adults. Though progression varies among individuals, factors such as family history, age, and ethnicity could influence its occurrence¹⁸. Insulin resistance, hyperglycemia, and a relative decrease in insulin production are indicative of type 2 diabetes mellitus. Although its pathophysiology is poorly understood, it is diverse, and environmental factors like obesity as well as genetic factors alter insulin release²²

2.2.3 Gestational Diabetes

The third key kind, gestational diabetes, occurs in elevated blood glucose levels in pregnant women who have never been diagnosed with diabetes²³. Globally, GDM affects 15% of pregnancies, which translates to over 18 million babies per year. Women having gestational diabetes mellitus are susceptible to pre-eclampsia, gestational hypertension, and Caesarean section pregnancy termination²⁴. GDM raises the risk of problems such as obesity, cardiovascular disease, and impaired glucose metabolism, which can cause type 2 diabetes (T2DM) in both the mother and the child. Maternal insulin sensitivity and glucose metabolism are induced by pregnancy itself. Pregnancy increases the need for the mother's pancreas to produce more insulin. The woman's body undergoes several physiological changes during pregnancy to meet the fetus's energy needs. To improve the fetus's glucose supply, insulin resistance rises. Pancreatic β -cells adjust for the increased glucose demand, resulting in a normoglycemic state. Women who have already had GDM, on the other hand, have an inadequate β -cell response, which results in decreased insulin production and, ultimately, hyperglycemia. Thus, when β -cells are unable to control insulin resistance, glucose sensitivity may develop²¹.



2.2.4 Maturity-Onset Diabetes of the Young

MODY is a diverse condition characterized by non-insulin-dependent diabetes that is diagnosed early (usually before the age of 25). It is transmitted by autosomal dominant and does not involve autoantibodies, unlike type 1 diabetes. Several genes are implicated in MODY, including mutations in glucokinase (GCK) and hepatocyte nuclear factor-1-alpha (HNF1A) genes, which occur in 52 to 65 and 15 to 32 percent of cases, respectively¹.

2.3 OBESITY AND T2D, DEFINITION OF OBESITY, RISK FACTORS

Obesity is the body's build-up of extra fat. The World Health Organization diagnoses obesity using the body mass index (BMI). Individuals who present values 30 or higher are considered obese while values less than 30 but greater than 25 are considered overweight. From the global nutrition report in 2017, 2 billion people were either overweight or obese and 41 million children were overweight². Progressively, currently, over a billion people globally are classified as obese, constituting about 12.5% of all adults worldwide. The estimated prevalence in children and adolescents stands at 8%. In the United States, the commonest of obesity is 22.4% with approximately 42% of the adult population being obese. Across Europe, the prevalence stands at approximately 20% with high prevalence in Russia (15.9%) and Turkey (17.5%). The prevalence of obesity in Africa has seen an upward trend in recent years from 3.85% in 1980 to 10.9% as of 2019 with higher in-country prevalence in South Africa (23%). In Ghana, as of 2022, the widespread presence of obesity was about 13% of the adult population between 20-49 years with a higher prevalence among women (20.6%). Moreover, two studies have reported overweight and obesity rates exceeding 50% in the Greater Accra region^{25,26}.

The predisposing factors underlining the cause of obesity can be classified into genetic and environmental causes which result in imbalances between calories consumed and calories expended by the body. A family history of obesity and certain genetic variations increases one's risk of obesity^{26,22}. The report of the Genome-wide Association Studies shows that over 250 genes are associated with obesity. Among these genes, the one linked to fat mass and obesity (FTO) was found to play a significant effect on the development of type 2 diabetes and obesity. Further studies done among adults demonstrate a favorable relationship between these genes and high BMI, fat-mass Index (FMI), and the concentration levels of leptin^{25,28,32}. Several studies have identified a favorable association between the onset and progression of obesity and certain

socio-demographic factors. Older age, low socioeconomic status, urban residence, low education level, and pregnancy^{1,3,18,32}. Additionally, certain behavioral factors and patterns have been implicated in the development of type 2 diabetes. Consumption of foods high in energy, such as alcohol, sugar, soft drinks, candy, and fats, has been reported to show a high correlation with obesity and chronic diseases^{27, 28}.

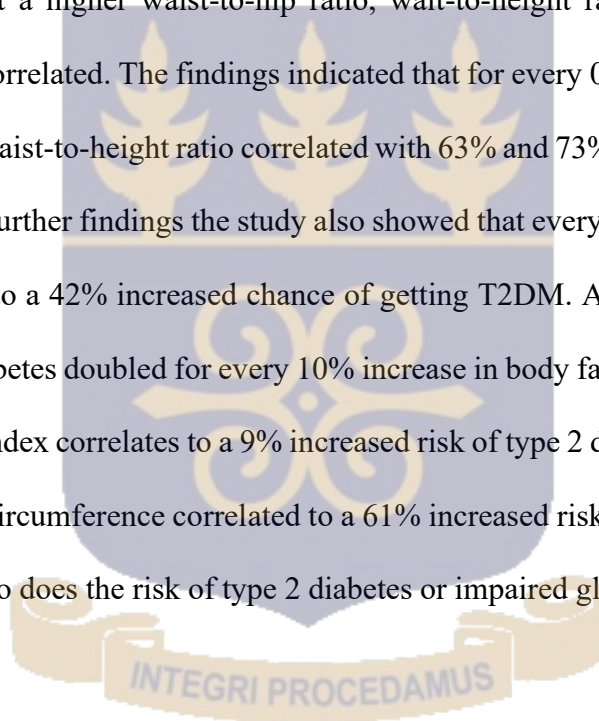
Lack of regular exercise and physical inactivity have also been reported to enhance the onset or exacerbate the symptoms of diabetes. In addition, short sleep cycles, night-shift work, stress, and smoking have equally been associated with diabetes mellitus^{29, 30, 31}.

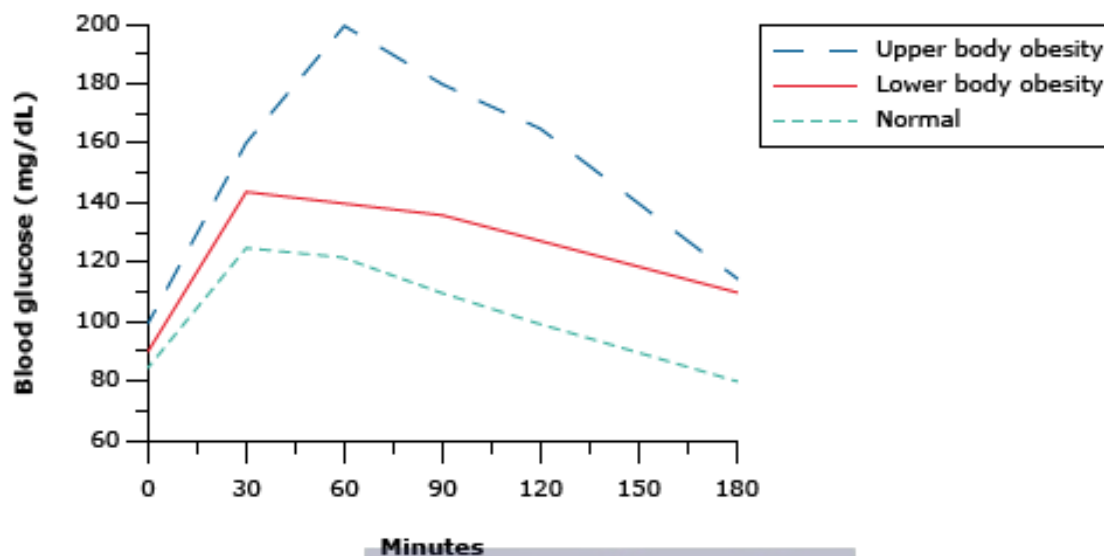
2.4 RELATIONSHIP BETWEEN OBESITY AND DIABETES

There is a strong relationship between diabetes mellitus and obesity stemming from the common underlying factor being defects in insulin action. This relationship is chiefly attributed to insulin resistance and deficiency^{27, 30}. The report from the National Diabetes Statistics showed that over 80% of adults living with diabetes were either overweight or obese^{1,2}. There is a generally accepted belief that consistent overeating could be a driver of obesity which consequently serves as a key factor for T2DM development and progression. Excess nutrients are primarily stored as glycogen and fat for use as energy with the majority of the stored energy, in the form of triglycerides (fat). These excess triglycerides accumulate in adipose tissues around the organs and beneath the skin leading to obesity^{32,33}. Moreover, excess glucose is also metabolized by insulin action into fatty acids and glycerol-3-phosphates in the adipose tissues which combine to form triglycerides. The transport of fatty acids by the transmembrane protein (CD36/SR-B2) into the cytoplasm of fat cells is identified to be facilitated by insulin³⁰. This implies that the intracellular manufacture of fat requires glucose, fatty acids, and insulin to establish and maintain obesity. As the fat stores and the fat cells increase, the adipocytes tend to be less insulin-

responsive for glucose transport³³. Because of this, individuals who store excessive amounts of fat have been found to have insulin resistance, which is thought to be the origin of type 2 diabetes, and higher insulin levels proportionate to the fat that has been deposited. Effective insulin action is required to store body fat, hence, people living with type 1 diabetes mellitus are noted to experience weight and fat loss due to insufficient insulin availability^{27,34,35}.

Other studies have shown that there are both elevated levels of insulin and glucagon in the fasting state, among people living with obesity and T2DM^{29,36–38}. Additionally, results from large cohort studies have shown that a higher waist-to-hip ratio, waist-to-height ratio, and risk of type 2 diabetes are positively correlated. The findings indicated that for every 0.1 unit increase in either of waist-to-hip ratio or waist-to-height ratio correlated with 63% and 73% respectively, increased risk of type 2 diabetes. Further findings the study also showed that every unit increase in visceral adiposity corresponded to a 42% increased chance of getting T2DM. Additionally, the chances of developing type 2 diabetes doubled for every 10% increase in body fat, while every 0.005 unit increase in body shape index correlates to a 9% increased risk of type 2 diabetes. Moreover, each 10cm increase in waist circumference correlated to a 61% increased risk of type 2 diabetes³². As body weight increases, so does the risk of type 2 diabetes or impaired glucose tolerance (IGT).²²





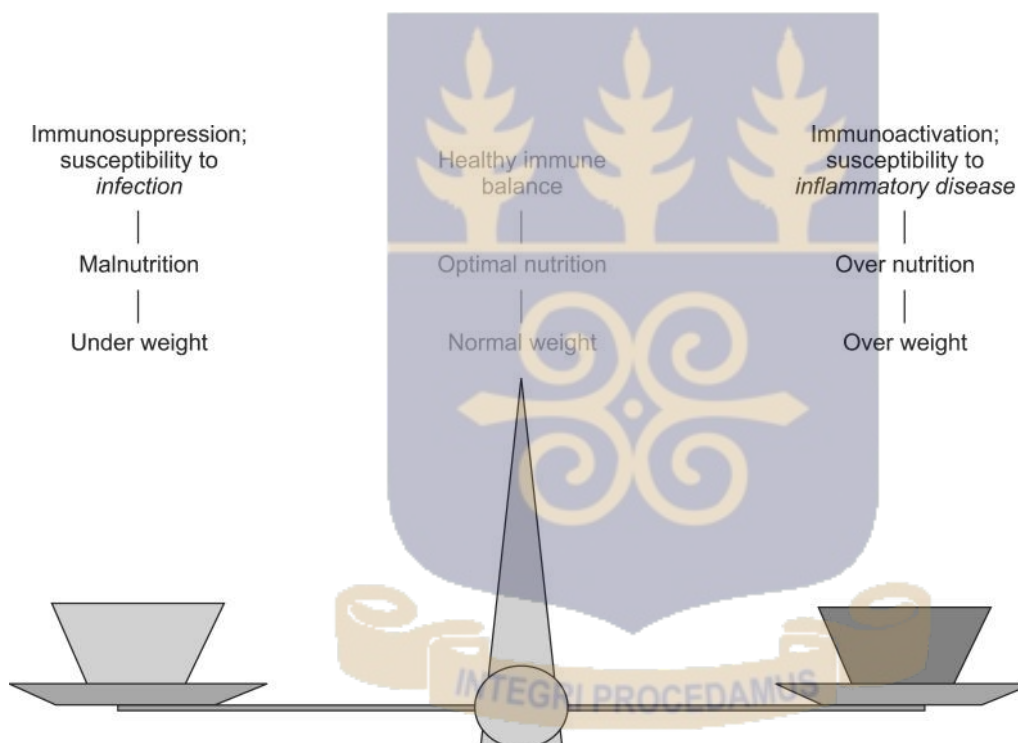
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Fig 2.2: Obesity and fat distribution impair glucose tolerance.

In conducting a test for oral glucose tolerance, nine patients who were obese in the upper body, sixteen patients with lower body obesity, and nine control participants don't have obesity showed sequential variations in blood glucose concentrations. Although glucose tolerance was compromised in the obese groups, the anomaly was more noticeable in the upper-body obese group. Since the group with upper body obesity also had significantly higher peak blood insulin concentrations as opposed to 115 and 65 microU/mL in the other two groups (225 microU/mL), the degree of glucose intolerance overestimated the degree of insulin resistance. Serum insulin is converted to pmol/L by multiplying by 6 and blood glucose is converted to mmol/L by dividing by 18²². One of the main ways that obesity contributes to type 2 diabetes is by causing resistance to insulin-mediated peripheral glucose absorption, which probably reveals the portion of the population with low insulin secretion. Obesity reversal lowers the case of type 2 diabetes and can result in remission in those who already have the condition by improving glycemic control

2.5 ROLE OF DIET, OBESITY AND INFLAMMATION

Numerous theories have been put forth. According to one theory, adipocytes' nutritional excess causes intracellular stress, which triggers inflammatory cascades¹⁴. One significant regulating aspect of the immune response is diet. There is strong evidence that immunosuppression brought on by a vulnerability to infection results from starvation. Conversely, immune activation results from overnutrition since it increases the risk of developing an inflammatory disease. Thus, a good immunological balance necessitates optimum nutrition²⁴



Source: Lee *et al*, (2013)³⁹

Fig 2.3: Malnutrition and overnutrition in a healthy immunological balance.

The commonest of impaired glucose tolerance has significantly risen among the people of the United States in the past 20 years. Increased weight gain and physical inactivity increase the chance of T2DM in these groups. Compared to lower-body obesity, central obesity is more associated with insulin resistance and decreased glucose tolerance. Obesity reduces beta cell

sensitivity to glucose and results in peripheral resistance to insulin-mediated glucose absorption. Because losing weight dramatically corrects these defects and results in blood glucose levels returning to normal when diabetes is remitted, the causative nature of these impairments is evident.

Adipose tissue, the primary component of obesity, was once thought to be an inert tissue primarily used for energy storage, but it is now understood to play an active role in the regulation of both pathological and physiological processes, such as inflammation and immunology. Interleukin [IL]-4, tumor necrosis factor [TNF]- α , interferon [IFN]- γ , IL-6, and other adipokines and cytokines (pro- or anti-inflammatory cytokines) such as leptin, adiponectin, resistin, and visfatin are all synthesized and secreted by adipose tissue. The production of pro-inflammatory chemicals by adipose tissue has been linked to the onset of metabolic diseases such as type 2 diabetes²⁴. As the primary cellular component of adipose tissue, macrophages are essential for controlling chronic inflammation and influencing the release and differentiation of different pro- and anti-inflammatory cytokines. Several signaling pathways are also involved in inflammation, and they could be the target of novel treatments and interventions⁴⁰. Insulin resistance is associated with inflammatory activity stimulated by adipokines, substances secreted from adipose tissue. Intensive lifestyle changes have been demonstrated to reduce inflammatory markers⁴¹.

2.5.1 Factors Released From Adipose Tissue

Leptin: Leptin is produced and released by the adipocytes in proportion to their mass. The hypothalamus is informed of the amount of fat that has been accumulated. Leptin resistance and deficiency have been associated with insulin resistance and obesity in both human and animal studies⁴¹.

Retinol-binding protein 4: The level of insulin resistance in individuals with type 2 diabetes, obesity, or impaired glucose tolerance, as well as in healthy individuals with or without a significant family history of the disease is correlated with the amount of retinal-binding protein 4 (RBP4), also a type of protein produced by the adipocytes⁴¹.

Resistin: Resistin is a signaling protein secreted by adipocytes in mice with hereditary or diet-induced obesity. Resistin administration reduces insulin-mediated glucose uptake by adipocytes, but resistin neutralization increases it. Moreover, resistin administered hypothalamically increases the generation of glucose, regardless of the changes in glucoregulatory hormones. Thus, resistin might be a hormone that links obesity and diabetes⁴¹.

Obestatin: This hormone, which was first isolated from the stomach of rats, is the gene that encodes ghrelin and mitigates the appetite-regulating effects of ghrelin. When compared to people with normal glucose tolerance, those with diabetes and impaired glucose tolerance had lower levels of circulating obestatin. Furthermore, the obestatin receptor expression in adipose tissue is downregulated in type 2 diabetes associated with obesity but not in normal blood glucose obese people, indicating that obestatin might contribute to glucose control and type 2 diabetes development independently of obesity⁴¹.

Adiponectin: This cytokine, which is synthesized and secreted from adipocytes, lowers blood-free fatty acid levels and has been linked with improved glucose regulation, less inflammation, and improved lipid profiles in diabetic patients. In groups without diabetes, adiponectin has also been inversely linked to the likelihood of developing the disease⁴¹.

2.6 RESPIRATORY CHANGES IN DM

Respiratory defects and changes among diabetics have gained increasing traction as several studies have reported the dire effect hyperglycemia and insulin resistance have on respiratory muscle innervation and vessels. Diabetic microangiopathy and the inflammatory response triggered by hyperglycemia and insulin resistance are known to confer structural modifications of pulmonary tissue and pulmonary-capillary network^{4,6,31}. These studies have identified the lungs as a target organ for damage caused by diabetes, leading to reduced lung volumes and airflow limitation (Diaz-Guzman & Mannimo, 2014; Bianchi *et al.*, 2016; Glaser *et al.*, 2015). The study of De Santi *et al.* (2017) in assessing the respiratory symptoms between diabetics and the general population found 3-4 fold increased second-degree dyspnoea among diabetics than in the general population. Moreover, in the study of Al-Khlaiwi *et al.* (2021) in their assessment of pulmonary function and respiratory muscle strength among type 2 diabetes patients, there was significantly decreased Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV₁) and Forced Expiratory Flow (FEF₂₅₋₇₅) among the patients compared their non-diabetic counterparts, signifying lung function impairment. In a large cohort study by Zaigham *et al.* (2016), significantly low mean FVC, FEV₁%, and resultant FVC/FEV₁ ratio were considered poor lung function parameters linked with the risk of diabetes mellitus. Other large prospective cohort studies have equally reported a reduction in FVC and FEV₁ as associated with an increased risk of diabetes Yeh *et al.*, 2011; Kim *et al.*, 2015; Yamane *et al.*, 2013; Kwon *et al.*, 2012). Obstructive and restrictive ventilation dysfunction (FVC/FEV₁ < 0.7 and FVC < 0.8, respectively) have also been associated with the progression of diabetes mellitus. Restrictive ventilation dysfunction defined by the FVC/FEV₁ is significantly had a link with a very high risk of T2DM in many large retrospective and prospective cohort studies^{42,43,28}. Moreover, the study of Sonoda and colleagues showed that people living with diabetes had a 1.6-fold increased risk of restrictive pulmonary function impairment than non-diabetics, though no positive association

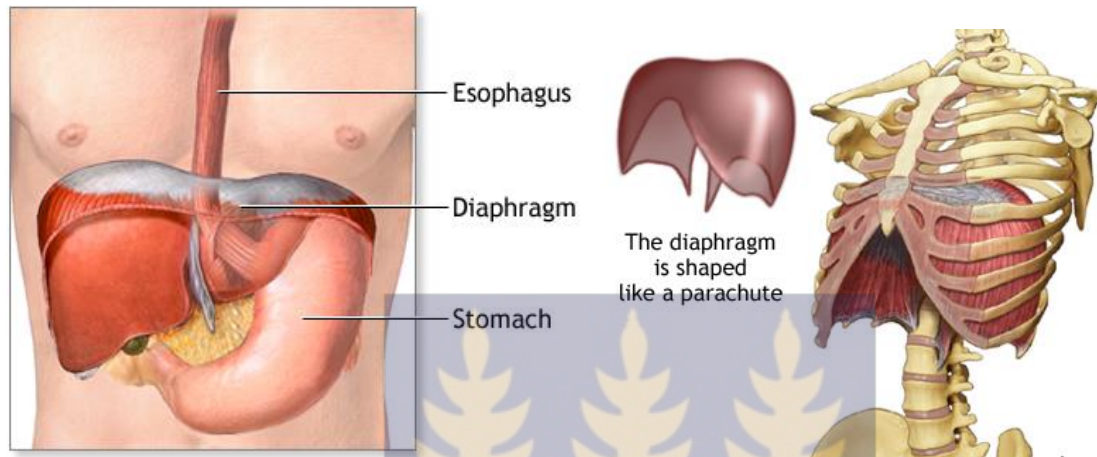
was found with obstructive pulmonary dysfunction⁴⁴. In the study of Mandal and colleagues, comparing the lung function in patients with type 2 diabetes mellitus and non-diabetics, statistically positively remarkable associations were observed between diabetes disease and reduced FVC, FEV1, and peak expiratory flow (PEF) rates, indicative of restrictive lung function⁴⁵.

2.7 THE DIAPHRAGM, TYPE OF DIAPHRAGM MUSCLES AND THE PHYSIOLOGY.

The diaphragm is a dome-shaped skeletal muscle that surrounds a central tendon or aponeurosis. It separates the contents of the abdominal cavity from that of the thoracic cavity ^{46,47}. The diaphragm functions in a two-way fashion. This involves its contraction to expand the thoracic cavity during breathing-in and secondly, to enhance the close-up of the gastroesophageal junction during breathing-out to prevent reflux from the stomach into the esophagus^{46,48}. Anatomically, three different muscle groups make up the peripheral muscular parts of the diaphragm. The xiphoid process serves as the precursor of the sternal group, the costal group begins from the inner surface of the lower six ribs, while the two right and left crura and arcuate ligaments attached to the lumbar vertebra serve originator of the third group. Centrally, the strong aponeurotic tendinous ligaments lack any bone attachment. Its C-shaped anatomical structure has both right and left lateral and middle leaflets⁴⁸.

The diaphragm is the main muscle primarily for respiratory function in normal humans^{49,47}. In the event of a normal quiet breathing-in, there is a slight alteration in the dome shape of the diaphragm as a result of the muscular contraction of the muscles in the apposition zone (the contact area between the diaphragm and the floor of the lower rib cage). Moreover, there is a subsequent expansion of the rib cage causing it to open up. This results in an increase in abdominal pressure and lowered pressure in the thoracic cavity causing the diaphragm to assume

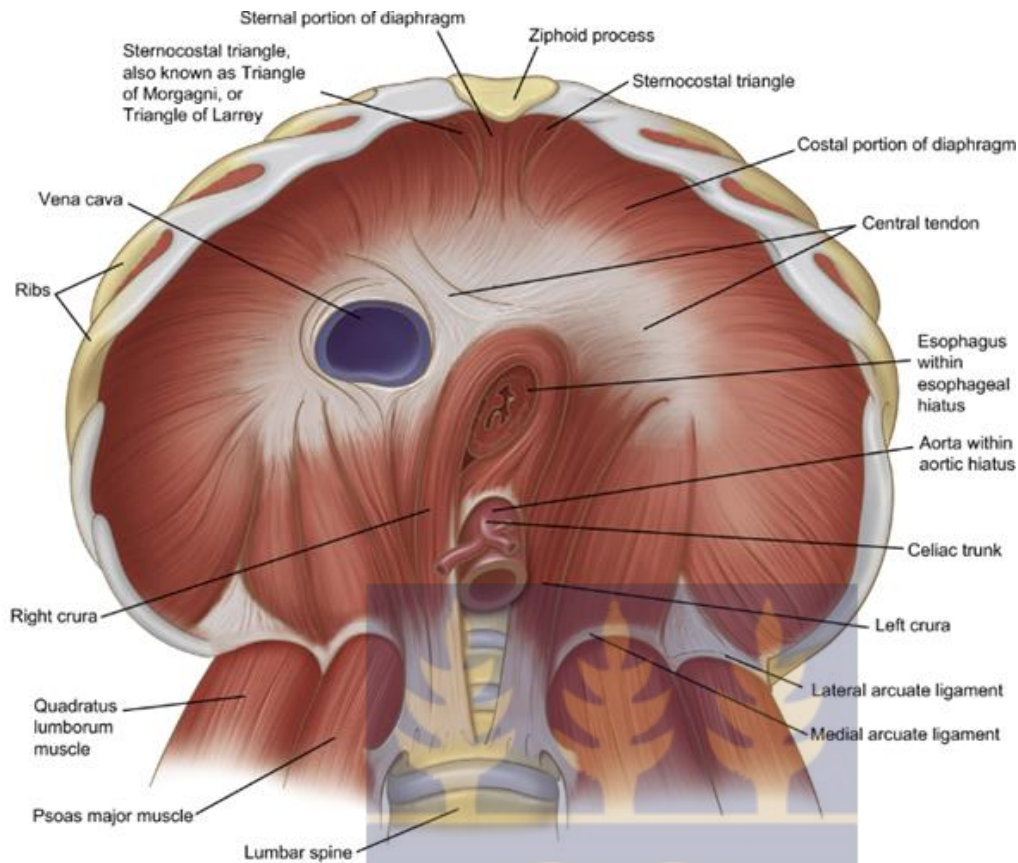
a caudal piston-like shape. The lowered pleural pressure in turn lowers the alveoli pressure causing them to inflate to accommodate inhaled air⁴⁷.



Source: Downey R.,(2011)⁴⁷

Figure 2.4: Abdominal view showing the diaphragm.





Source: Downey R.,(2011)⁴⁷

Figure: 5 Abdominal view showing the muscular diaphragm's lumbar, costal, and sternal portions.

2.8 FACTORS AFFECTING DIAPHRAGM MUSCLE STRENGTH/WEAKNESS

The diaphragm serves as the boundary between the thoracic cavity and the abdominal cavity. It is the main respiratory muscle and it is supplied with phrenic nerves that originate from the 3rd, 4th, and 5th cervical vertebra nerve roots. Given this, any disease or condition that interferes with the nerve supply or directly obstructs the contractile muscle fibers or mechanical action in the thorax can affect diaphragm function through weakness or paralysis⁴⁹⁻⁵¹

Respiratory symptoms of diaphragmatic dysfunction include; dyspnoea, exercise intolerance, sleep disturbances, and hypersomnia⁴⁶. Significant respiratory failure usually results from weakness of both halves but paresis of one hemidiaphragm may be asymptomatic due to the compensatory function of the other half and the support from external intercostal muscles in respiratory mechanics. Moreover, atrophy and muscle weakness or damage to the nerve supply to the diaphragm could lead to diaphragmatic palsy or paresis. Weakness of one half of the diaphragm is commonly observed compared to the spontaneous weakness of the two halves. The weakness may be transient or permanent, depending on the underlying cause.^{31,32,50,52,53}. There are several categories under which diaphragmatic weakness can be attributed: (1) Trauma: The most common cause of weakness in the diaphragm is of traumatic origin. This usually causes damage to the phrenic nerve supply. Surgery traumas from cardiac bypass are identified to be the commonest according to about 20% increased risk of diaphragmatic weakness. The phrenic nerve sustains phrenic frostbite during cold cardioplegia for bypass, which results in a brief loss of diaphragmatic functions. This usually happens in the left hemidiaphragm due to its longer course compared to the right half. Any mediastinal procedures, oesophageal surgeries, or lung transplantation equally confer a risk of diaphragmatic weakness. Penetrating injuries to the thorax can also result in damage to the phrenic nerve^{36,43}. (2) Compression: Any physical compression of the phrenic nerve supplying the diaphragm could lead to paralysis and weakness of the diaphragmatic muscles. Lesions in the thoracic cavity and cancers of the lungs in proximity to the phrenic nerve as well as tumors of the mediastinum could cause compressional defects in the function of the diaphragm. Five percent of lung cancers involve the phrenic nerve. Cervical spondylosis, substernal goiter, and an aortic aneurysm are other causes of compressive injury.. (3) Neuropathic origin: Muscle sclerosis, diabetic neuropathy, dermatomyositis, inclusion body myositis, chronic demyelinating disease, and anterior horn cell disease are neurological defects that are known to impact phrenic nerve damage and innervation of the diaphragm⁴⁷. (4)

Inflammatory: Several systemic diseases that can cause inflammations in the muscles of the diaphragm and the phrenic nerve could render the respiratory muscles paralyzed and ultimately lead to loss of function and weakness of the diaphragm. Infections of viral origin such as HIV and weakness of the diaphragm have been linked to bacterial infections like Lyme disease, non-infectious causes such as sarcoidosis and amyloidosis, and West Nile virus poliomyelitis virus.

(5) Idiopathic: This accounts for nearly 20% of all cases of diaphragm weakness. After thorough medical investigations, if no obvious cause is detected, it is classified as idiopathic⁴⁸.

2.9 BURDEN OF DIAPHRAGM MUSCLE WEAKNESS IN OBESITY AND DIABETES

Several studies have reported muscle weakness in both obese and diabetic conditions. The attributable factors include insulin resistance muscle fat infiltration and hyperglycemia are common features in obese and diabetic individuals. These lead to gradual and significant loss of skeletal muscle strength, sarcopenia, and disability^{46,48}. An imbalance in the synthesis and breakdown of contractile proteins, which can be brought on by several illnesses, including Type 2 Diabetes Mellitus (T2DM), is the cause of muscle atrophy. Patients with type 2 diabetes who have reduced muscle quality experience negative effects on their quality of life, ability to carry out everyday tasks, and muscular function. Ultimately, this may raise their chance of dying young. Muscle atrophy is caused by the proteasome-ubiquitin, autophagy-lysosome, and caspase-3-mediated proteolytic processes, which break down proteins in the muscle⁵⁴.

When the diaphragm contracts, the thoracic cavity expands, pushing the contents of the abdomen forward and downward during a typical quiet inspiration. In addition to this, there is spontaneous contraction of the external intercostal muscles which pulls the ribs upward and forward^{49,51}. However, in obese people, this mechanism is duly defected as a result of the accumulation of excess fat lining the thoracic cavity and the abdominopelvic regions which consequently impedes

the free contraction and relaxation of the respiratory muscles. These structural alterations in the thoracic and abdominal cavities restrict free movement of the diaphragm muscles and respiratory compliance of the ribs as well^{46,55}. In effect, either through mechanical obstruction or systemic inflammation, obesity hurts the respiratory system^{56,57}. In addition to creating respiratory sleep problems and ultimately hypercapnic respiratory failure, it heightens the work or workload of breathing, which in turn raises neural respiratory drive. Respiratory complications in obese individuals range from simple dyspnea on exertion to life-threatening obesity referred to as hypoventilation syndrome (OHS)²⁷. OHS is characterized by partial pressure of CO₂ of 45mmHg in people with BMI greater than 30 kg/m² with no known alternative cause of hypercapnia and worsened risks of heart failure and early mortality²⁷. The pathophysiology of OS may not be fully understood but, excess visceral adipose tissues lining the thorax which prevents free expansion of the respiratory muscles is identified to be a major contributor to the condition²⁷. The postmortem samples of OHS patients reveal noticeable intra-diaphragmatic adipocyte inclusions, despite clinical research showing that respiratory muscle weakness is similar to this physical constraint. This evidence implies that anatomic remodeling of the diaphragm itself may contribute to obesity-induced respiratory impairment²⁰. Even though research has tried to establish a causal link between pulmonary disease and obesity, not much has been revealed as to whether it occurs in other populations. Large systematic review studies have attempted to establish a relationship between obesity and chronic obstructive pulmonary disease (COPD)²⁰. In one epidemiological study, the commonest of obesity was much higher in patients with COPD than in individuals with no medical history of COPD (24.6% and 17.1 %) ²⁰. This may be partly explained by the presence of pro-inflammatory mediators, which are seen in both obesity and COPD conditions ²⁰. Reductions in important functional respiratory parameters such as functional residual capacity (FRC), total lung capacity (TLC), and expiratory reserve volume are easily detected with a transient increase in weight. These reductions come about as a result

of the imbalance between inflationary and deflationary pressures on the lungs due to the heavy deposition of adipose tissues in the thoracoabdominal cavity and on the respiratory muscles in obese individuals²⁰. Additionally, in the study of Jones and Nzekwu, they reported a reduction in ERV, FRC, and TLC as a result of mechanical defects showing exponential association with increased BMI. The mechanical impairments in the respiratory muscles were directly correlated to the accumulation of adipocytes in the thoracic and abdominal cavities. These findings conclude that obesity reduces respiratory muscle compliance and in effect produces mechanical restrictions on the muscles for breathing²⁰. Respiratory muscle malfunction contributes to obesity-related ventilatory issues and is epidemiologically linked to metabolic syndrome and diabetes. The mechanism underlying the clinically substantial weakening of respiratory muscles linked to obesity is still unknown²⁰. The results of the study suggest that ectopic lipid accumulation causes decreased diaphragmatic function in obese people. Jun N-terminal kinase (JNK) or Protein kinase R (PKR)-like endoplasmic reticulum kinase signaling are activated in the pathophysiology of lipotoxicity-induced diaphragm weakness in obese hypoventilation syndrome²⁰. Initially, large epidemiological research showed that body weight and/or obesity impacted muscle quality (strength or power normalized to muscle size)⁵¹. Previous research has demonstrated a connection between ectopic adipose tissue deposition, defined by lipid infiltration into skeletal muscle, and decreased rate of torque formation, slower thigh muscle contraction velocity, and impaired strength and power²⁰.

2.10 CONCEPTUAL FRAMEWORK

This study is grounded in the emerging recognition of the pulmonary system as a target organ in diabetes mellitus. Diabetes, particularly Type 2 diabetes mellitus, is characterized by chronic hyperglycemia and metabolic dysregulation, which contribute to widespread microvascular and macrovascular complications. Beyond its well-established cardiovascular, renal, and

neurological sequelae, diabetes has been associated with impaired pulmonary mechanical function, reduced lung volumes, and decreased forced expiratory indices. Recent local evidence from the University of Ghana Medical School further suggests a high burden of diaphragm muscle weakness among adults with diabetes, highlighting a critical but understudied dimension of pulmonary dysfunction in this population.

The conceptual framework for this study proposes that obesity—especially central obesity—may play a significant role in diaphragm muscle weakness in individuals with diabetes. Obesity is highly prevalent among persons with T2DM and is associated with metabolic inflammation, increased adipokine release, insulin resistance, and mechanical loading effects on the thoracoabdominal cavity. These obesity-related factors may influence diaphragm muscle strength through multiple interconnected pathways.

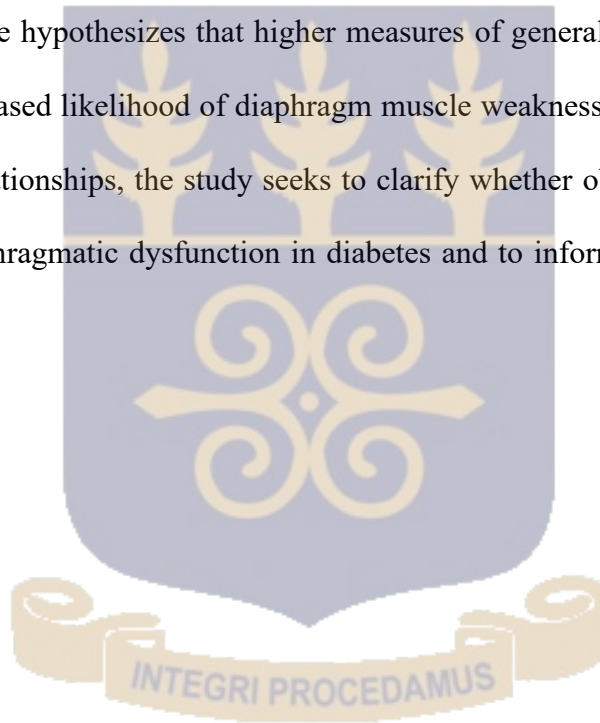
First, the mechanical pathway posits that central obesity increases intra-abdominal pressure, leading to upward displacement and splinting of the diaphragm. This mechanical restriction may impair diaphragmatic excursion and reduce muscle efficiency over time, potentially contributing to weakness.

Second, the metabolic-inflammatory pathway suggests that obesity-related adipokine dysregulation and chronic low-grade systemic inflammation may directly impair skeletal muscle structure and function, including the diaphragm. Inflammatory mediators and metabolic stress may promote muscle atrophy, reduced contractility, and impaired regeneration.

Third, the neuropathic pathway recognizes that diabetes-related peripheral neuropathy, potentially exacerbated by obesity-induced metabolic stress, may involve the phrenic nerves. Phrenic nerve dysfunction could compromise neural input to the diaphragm, thereby contributing to muscle weakness.

Within this framework, measures of general obesity (e.g., body mass index) and central obesity (e.g., waist circumference, waist-hip ratio) serve as the primary independent variables. Diaphragm muscle weakness represents the primary dependent variable. Diabetes provides the underlying pathological context within which these interactions occur. Potential confounders such as age, sex, glycemic control, and duration of diabetes may influence the observed relationships.

The framework therefore hypothesizes that higher measures of general and central obesity are associated with an increased likelihood of diaphragm muscle weakness in adults with diabetes. By examining these relationships, the study seeks to clarify whether obesity contributes to the biological basis of diaphragmatic dysfunction in diabetes and to inform future preventive and therapeutic strategies.



CHAPTER 3

METHODOLOGY

3.1 STUDY DESIGN

The study design was cross-sectional. This study utilizes cross-sectional data and forms part of a larger longitudinal study approved by the University of Ghana College of Health Sciences Ethics and Protocol Review Committee [Protocol Identification Number: CHS-Et/M.3-P4.3/2023-2024].

3.2 STUDY SITES

The study sites were the National Diabetes Management and Research Centre (NDMRC) and the laboratory of the principal supervisor of the MPhil Student (i.e. the Hayfron-Benjamin Laboratory). The Hayfron-Benjamin laboratory is situated at the University of Ghana Medical School and is about 20 meters from the NDMRC. It has the equipment and set-up for interviewing study participants, anthropometric measurements, and measurement of pulmonary function evaluation including spirometry, lung diffusion capacity testing, diaphragm muscle strength assessment, and bronchoprovocation testing; these are set up by the guidelines of the American Thoracic Society(ATS) and the European Respiratory Society(ERS). The research office is also set up for vascular function testing including macrovascular and microvascular function testing as well as cardiac function evaluation. The NDMRC is situated at the Korle Bu Teaching Hospital in Accra being the biggest and the leading tertiary referral center in Ghana, the hospital attracts referral cases from all parts of the country. The NDRMC provides medical care and consultation for patients with diabetes. Further, it hosts several research projects

focusing on diabetes. A multidisciplinary team including physicians, nurses, dieticians, and clinicians specializing in eye care is managing the NDMRC. The NDMRC runs a diabetes clinic that sees about 50-100 patients daily.

3.3 STUDY POPULATION

The study population is made up of adults with diabetes managed at the NDMRC meeting the eligibility criteria as follows:

3.3.1. Inclusion criteria:

1. Aged ≥ 18 years at their last birthday.
2. Established diagnosis of diabetes (2-hour plasma glucose $\geq 11.1\text{mmol/l}$ or fasting plasma glucose (FPG) greater than or equal to 7.0mmol/l).

3.3.2. Exclusion Criteria

1. Contraindications to spirometry testing include the following: (Miller *et al.*, 2005):
 - a. Diagnoses of primary heart disease, heart failure from any cause, ischemic heart disease within a month, chest pain of any cause; thoracic, abdominal, or, cerebral aneurysm
 - b. a. Any cause of abdominal pain
 - c. c. Recent surgery in the nasopharynx, thorax, abdomen, or mouth
 - d. d. Hearing and cognitive impairments can have a big impact on verbal communication, thereby limiting the ability to follow instructions required to perform technically acceptable spirometry.
 - e. Any acute illness that can limit the participant from performing technically acceptable pulmonary function tests.

2. Primary diaphragm muscle dysfunction or primary phrenic nerve dysfunction (self-reported or review of medical records)

3.4 DETERMINATION OF SAMPLE SIZE

This formula was used to determine the minimal sample size.

$$N = Z^2 p(1-p) / d^2$$

where p is the predicted prevalence, d is accuracy, Z is the statistic that represents the degree of confidence, and n is the sample size.

The following assumptions were made:

- Power of 90% ($Z_\beta = 0.84$)
- The alpha risk or level of statistical significance of 0.05 ($Z_\alpha = 1.96$)
- Prevalence of diaphragm muscle weakness in individuals with diabetes = 18% (based on work done by Awutley E and Hayfron-Benjamin C)

Solving gives

$$N = Z^2 p(1-p) / d^2 = 1.96^2 \times 0.18 (1-0.18) / 0.05^2 = 227 \text{ participants}$$

To account for some participant's inability to perform spirometry in the supine position, we planned to include an additional 20% of study participants. Therefore, 275 participants were taken in this study.

3.5 STUDY RECRUITMENT

A screening log is completed by the principal investigator at the study site to provide thorough documentation of all study participants who are reviewed as eligible for the study and approached during the clinic to participate in the study. The screening log had these specifications:

1. The study identification number of participant
2. Participant's name, age, gender, and ethnicity
3. Participant's contacts including email and telephone number.
4. The date of approach
5. The date of consent to partake in the study
6. Participants; eligibility status for the study
7. Reasons that make an individual ineligible for the study.

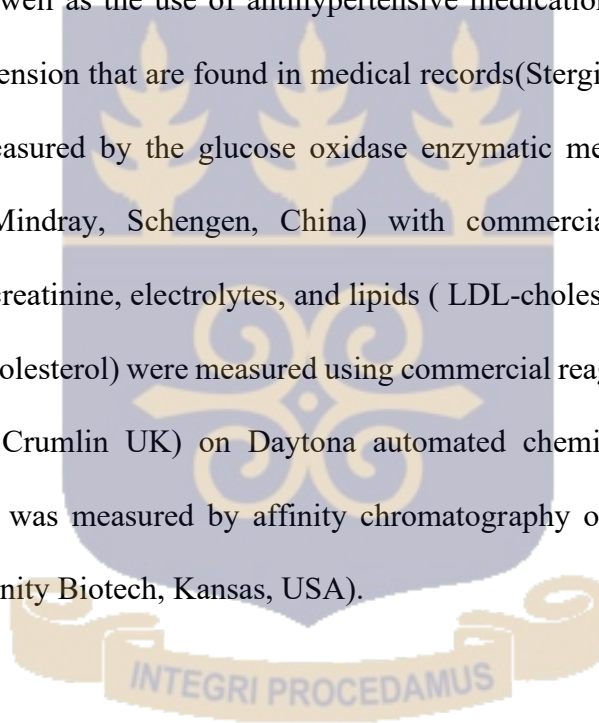
The screening log was updated every week by the principal investigator at the study site until the 275th participant was reached. The screening log is kept secure and confidential at the study site only to act as the master list for linking participants to protected health information (PHI).

3.6 RECRUITMENT OF STUDY PARTICIPANTS

A consecutive sampling method was used to recruit study participants from the NDMRC. The sample frame consists of all the records of individuals with diabetes registered at the laboratory test sample collection of the NDMRC. After an explanation of the study's specifics to each participant, informed consent was sought and obtained. Before data collection from a participant, the aims and objectives of the research as well as the various processes and tests including possible risks and benefits were explained.

3.7 BASELINE MEASUREMENTS

A structured questionnaire (Appendix I) was used to capture sociodemographic and clinical characteristics and to extract data on medication use, highest educational level, smoking status, and current or previous alcohol consumption. Following at least five minutes of rest while seated, blood pressure was taken three times using the Omron BP Monitor HEM-907XL device and appropriately sized cuffs. For the analysis, the average of the previous two blood pressure readings was utilized. Systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, as well as the use of antihypertensive medication, are clinical diagnosis codes or proof of hypertension that are found in medical records (Stergiou *et al.*, 2021). Fasting plasma glucose was measured by the glucose oxidase enzymatic method using the BS-400 Chemistry Analyzer (Mindray, Schengen, China) with commercial controls for quality assurance. Serum urea, creatinine, electrolytes, and lipids (LDL-cholesterol, triglycerides, total cholesterol, and HDL-cholesterol) were measured using commercial reagent kits with calibrators and controls (Randox, Crumlin UK) on Daytona automated chemistry analyzer (Randox, Crumlin, UK). HbA1c was measured by affinity chromatography on a PDQ Plus analyzer (Primus Diagnostics, Trinity Biotech, Kansas, USA).

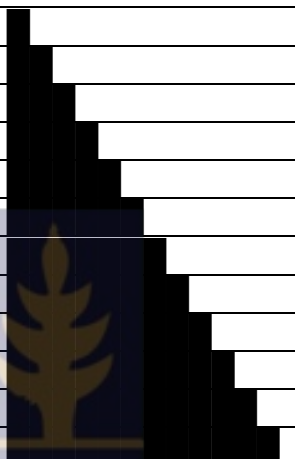


3.8 ASSESSMENT OF OBESITY AND BODY COMPOSITION

Measurements of obesity include waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI). To compute BMI, weight and height were measured. Using SECA-877 scales, weight was recorded without shoes while wearing light clothing. Without shoes, height was measured with a SECA-217 stadiometer. BMI was calculated by dividing weight (kg) by height squared (m²). Based on the World Health Organization (WHO) definitions, overweight is

defined as a BMI ≥ 25 kg/m² and obesity as a BMI ≥ 30 kg/m², regardless of sex ('Obesity: preventing and managing the global epidemic. Report of a WHO consultation', 2000).

Table 3.1: Interpreting BMI Results

BMI	BMI Designation (by WHO)	BMI Classification Bar	BMI Rating
Less than 18.5	Underweight		7.0 - 10.7
			10.8 - 14.5
			14.6 - 18.4
18.5 or more and less than 25	Normal		18.5 - 20.5
			20.6 - 22.7
			22.8 - 24.9
25 or more and less than 30	Overweight		25.0 - 26.5
			26.6 - 28.2
			28.3 - 29.9
30 or more	Obese		30.0 - 34.9
			35.0 - 39.9
			40.0 - 90.0

Source: Values for obesity judgment proposed by WHO, the World Health Organization.

The measurement of waist circumference (WC) was taken halfway between the top of the iliac crest and the bottom edge of the lowest palpable rib. Using a tape parallel to the floor, the hip circumference (HC) was measured around the broadest part of the buttocks, at the level of the greater trochanters. Central obesity is defined as a waist circumference of >94 cm in men and >80 cm in women (C, Gt, and S, 2010). Waist-to-hip ratio (WHR) is determined as the ratio of WC to HC and was used to define central obesity. Males with WHR >0.9 and females with WHR >0.85 were considered to have central obesity. The same assessor took two measures of each anthropometric measure, and the analysis was based on the average of the two measurements.

Table 3.2: Interpreting the Body Fat Percentage Result

Gender	Age	Low(0)	Normal(-)	High(+)	Very High(++)
Female	20-39	< 21.0	21.0 - 32.9	33.0 - 38.9	≥ 39.0
	40-59	< 23.0	23.0 - 33.9	34.0 - 39.9	≥ 40.0
	60-79	< 24.0	24.0 - 35.9	36.0 - 41.9	≥ 42.0
Male	20-39	< 8.0	8.0 - 19.9	20.0 - 24.9	≥ 25.0
	40-59	< 11.0	11.0 - 21.9	22.0 - 27.9	≥ 28.0
	60-79	< 13.0	13.0 - 24.9	25.0 - 29.9	≥ 30.0

Source: NIH/WHO Guidelines for BMI

Using the Omron Body Composition BF-506 Monitor (Omron Healthcare, Inc., Vernon Hills, IL, USA), the arm-leg bio-impedance approach was used to determine the visceral body fat level and body fat percentage. Body fat is the total mass of fat, assuming that the body consists of two compartments: fat mass and fat-free mass. Body fat percentage was calculated by applying the formula by Kyle et al. (Ug *et al.*, 2001, p. 2) on the generated Bodystat output. The percentage of body muscle was estimated using the same methods. Abdominal obesity was measured using the waist-to-hip ratio, which is a measure of body fat distribution.

3.9 PULMONARY FUNCTION TESTING

The pulmonary function testing was conducted in the research office by trained physicians, respiratory therapists, and technicians trained in pulmonary function testing. Pre-bronchodilator spirometry (sitting and lying positions) and post-bronchodilator spirometry (for participants with obstructive spirometric patterns) were performed using the Vitalograph Pneumotrac Portable Screening Pneumotachograph (Vitalograph Ltd, Maids Moreton, Buckingham England)

according to the American Thoracic Society/European Respiratory Society(ATS/ERS) guidelines(Graham *et al.*, 2019). The spirometer was calibrated every day. The spirometry procedure is first demonstrated to each participant, after which the participant is made to perform spirometry. A full and quick breath is taken by the study participant once they have positioned themselves correctly and attached the nose clip. The mouthpiece is then placed in their mouth, with their lips sealed around it and their tongue not covering the mouthpiece. The forced vital capacity (FVC) maneuver is then started with minimal hesitation(within 1–2 seconds after inspiring to the total lung capacity). While keeping their posture straight, the participant is instructed to "blast" the air out of their lungs and then to exhale absolutely until no more air can be expelled. Using suitable body language and phrases like "keep blowing" or "keep going," each participant receives enthusiastic instruction throughout the FVC motion. Until at least three maneuvers (and no more than eight) produced outcomes that were both acceptable and repeatable results were obtained. Spirometric indicators such as FEV₁, FVC, and FEV₁/FVC ratio were measured and computed. The predicted values of the FEV₁, FVC, and FEV₁/FVC were determined for each participant using the Global Lung Function Initiative 2012 equations(Quanjer *et al.*, 2012). Based on the recent ATS recommendation, race-neutral average reference equations were used(Bhakta *et al.*, 2023). Spirometric index abnormalities were identified by comparing the results to their lower limits of normal (LLN) (Quanjer *et al.*, 2012). According to ATS/ERS standards, patterns of pulmonary function were classified as normal, restrictive, obstructive, and or mixed obstructive based on the values of FEV₁/FVC and FVC(Stanojevic *et al.*, 2022).

3.10 ASSESSMENT OF DIAPHRAGM MUSCLE WEAKNESS

Diaphragm muscle weakness is defined as $\Delta\text{FVC}/\text{Sitting FVC} \times 100\%$, $\Delta\text{FVC} = \text{Sitting} - \text{Supine FVC}$. supine FVC $\geq 10\%$ lower than a sitting or upright FVC (Allen, Hunt, and Green, 1985). Isolated or disproportionate bilateral diaphragm weakness is defined as a supine FVC $\geq 30\%$ lower than a sitting or upright FVC (Laroche *et al.*, 1988; Mier-Jedrzejowicz *et al.*, 1988).

3.11 DATA MANAGEMENT

All collated data is used only for research purposes. Participant data is managed with strict confidentiality. Patients' bio (full name, accurate date of birth, contact information, and rare diseases) is decoupled from the remainder of the database. The document on the participant's identification is kept separately in Dr Charles Hayfron-Benjamin, the principal investigator's office. The hard copy results of all physiological and biochemical tests are kept secure and confidential. Data collection and coding were done accurately and appropriately. Evaluations on completeness, correctness, and consistency of data were done weekly. All computer networks used for data management are secured with firewalls as well as running antispyware and virus-detection programs.

3.12 STATISTICAL ANALYSES

Data was analyzed using IBM SPSS version 26 for Windows. The Shapiro-Wilk test is used to assess whether continuous variables were normally distributed or not. Data with normal distribution and skewed distribution is presented as mean $\pm$ standard deviation and median (interquartile range) respectively. Categorical data is presented as frequency and expressed as a

percentage. After controlling for potential variables, multivariate logistic regression analyses were utilized to investigate the relationships between assessments of diaphragm muscle weakness (a dependent variable) and obesity (an independent variable). The data was analyzed using three models. Model 1 was left unaltered, but Model 2 and Model 3 were modified to account for smoking, systolic blood pressure, peripheral neuropathy, HbA1c, and LDL cholesterol levels, and age and sex.

3.13 ETHICAL CONSIDERATIONS

Ethical consent for the research was sought from the Ethics and Protocol Review Committees of the UG CHS. Additionally, the research was conducted in line with the Ethical tenets outlined in the Helsinki Declaration on Human Experimentation, 1964 with subsequent revisions (World Medical Association, 2013). Only individuals meeting the eligibility criteria were allowed to participate in the study. The research does not include new procedures or investigational drugs that haven't been approved for patients with diabetes. Hence, there was no increased risk for individuals who participated in the study. Participants in the study were fully informed regarding the study's purpose, nature, procedure, and possible adverse effects. Anonymity, confidentiality, and the ability to withdraw from the study at any moment without encountering punishment are all crucial points to emphasize. Clinical management of the patient is unaffected in any way by refusal to participate in the study.

CHAPTER 4

RESULTS

4.0 GENERAL CHARACTERISTICS OF THE STUDY POPULATION

Tables 1 and 2, summarize the study populations' baseline characteristics, which were categorized by central and general obesity, respectively. In the study population, approximately two-thirds (73.4%) were females. The mean ($\pm$ standard deviation) age, duration of diabetes, BMI, systolic blood pressure, and diastolic blood pressure were 61.02 ($\pm$ 10.19) years, 11.56 ($\pm$ 8.03) years, 29.16 ($\pm$ 5.75) kg/m², 135.66 ($\pm$ 17.9) mmHg and 76.27 ($\pm$ 10.82) mmHg respectively.

In an analysis stratified by general obesity, individuals who were in the obese group had a greater percentage of females compared with the non-obese group. Additionally, duration of diabetes, mean BMI, and mean WC, were higher in the obese group as compared with the non-obese group. While the mean systolic and mean diastolic blood pressures were similar between the two groups, the proportion of participants with hypertension was higher in the obesity group as compared with the non-obesity group. The two groups were comparable in terms of the proportion of people who use insulin and statin as well as the proportion of individuals who use cigarettes and drink alcohol.

In the analysis stratified by central obesity, similar observations were made concerning the proportion of females, mean BMI, mean WC, and proportion of hypertensive. However, participants with central obesity had a greater proportion of never smokers and those who do not consume alcohol.

Table 4.1: Baseline Characteristics of the study population (participants stratified based on general obesity)

Characteristics	All Participants	No General Obesity	General Obesity	p-value
N	500	309	191	-
Sex (%)				<0.001
Female	367 (73.4%)	194 (62.8%)	173 (90.6%)	
Male	133 (26.6%)	115 (37.2%)	18 (9.4%)	
Age (years)	61.02 (± 10.19)	61.57 (± 10.44)	60.14 (± 9.73)	0.128
Diabetes duration (years)	11.56 (± 8.03)	10.92 (± 7.88)	12.65 (± 8.18)	0.045
Higher education (%)	153 (45.0%)	110 (50.9%)	43 (34.7%)	0.005
Never smokers (%)	334 (95.2%)	200 (94.3%)	134 (96.4%)	0.453
Consume alcohol (%)	126 (25.3%)	81 (26.3%)	45 (23.7%)	0.527
Statin use (%)	53 (10.6%)	39 (12.6%)	14 (7.3%)	0.071
Insulin use (%)	172 (34.4%)	103 (33.3%)	69 (36.1%)	0.561
BMI (kg/m ²)	29.16 (± 5.75)	25.52 (± 3.05)	35.04 (± 3.91)	<0.001
WC (cm)	99.12 (± 18.63)	91.66 (± 15.04)	111.18 (± 17.56)	<0.001
Hypertension (%)	323 (64.6%)	189 (61.2%)	134 (70.2%)	0.044
Mean systolic BP (mmHg)	135.66 (± 17.93)	135.69 (± 18.44)	135.63 (± 17.13)	0.974
Mean diastolic BP (mmHg)	76.27 (± 10.82)	76.22 (± 11.25)	76.36 (± 10.11)	0.884
Pulse Rate (bpm)	78.45 (± 11.87)	77.49 (± 11.67)	79.99 (± 12.05)	0.022

List of abbreviation

BMI = body mass index

WC = waist circumference

Smoking status was self-reported and stratified into current/previous smokers and never-smokers

Higher education is based on secondary education and above

General obesity based on $BMI \geq 30 \text{ kg/m}^2$



Table 4.2: Baseline characteristics of the study population (participants stratified based on central obesity)

Characteristics	All Participants	No Central Obesity	Central Obesity	p-value
N	500	80	420	-
Sex (%)				<0.001
Female	367 (73.4%)	25 (31.3%)	342 (81.4%)	
Male	133 (26.6%)	55 (68.8%)	78 (18.6%)	
Age (years)	61.02 (± 10.19)	60.58 (± 11.45)	61.11 (± 9.91)	0.723
Diabetes duration (years)	11.56 (± 8.03)	10.77 (± 7.91)	11.73 (± 8.06)	0.310
Higher education (%)	153 (45.0%)	53 (66.3%)	100 (38.8%)	<0.001
Never smokers (%)	334 (95.2%)	71 (88.8%)	263 (96.8%)	0.003
Consume alcohol (%)	126 (25.3%)	33 (41.3%)	93 (22.1%)	<0.001
Statin use (%)	53 (10.6%)	16 (20.0%)	37 (8.8%)	0.001
Insulin use (%)				0.752
No	328 (65.6%)	53 (66.3%)	275 (65.5%)	
Yes	172 (34.4%)	27 (33.8%)	145 (34.5%)	
BMI (kg/m ²)	29.16 (± 5.75)	26.62 (± 5.31)	29.69 (± 5.65)	<0.001
WC (cm)	99.12 (± 18.63)	84.51 (± 7.51)	102.38 (± 17.89)	<0.001
Hypertension (%)	323 (64.6%)	41 (51.3%)	282 (67.1%)	0.010
Mean systolic BP (mmHg)	135.66 (± 17.93)	132.21 (± 18.73)	136.34 (± 17.68)	0.081

Mean diastolic BP (mmHg)	76.27 (± 10.82)	75.54 (± 10.01)	76.43 (± 10.99)	0.570
Pulse Rate (bpm)	78.45 (± 11.87)	77.41 (± 12.65)	78.67 (± 11.70)	0.451

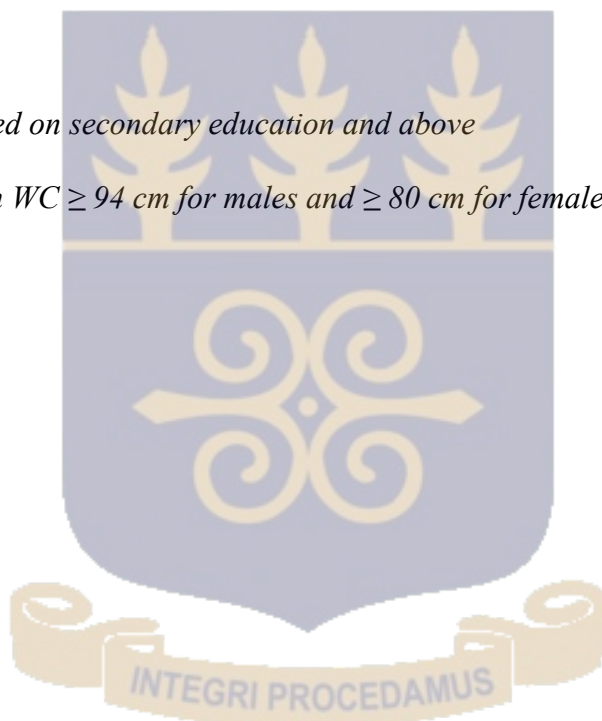
Values for categorical variables are given as numbers (percentage); values for continuous variables as mean ($\pm$ SD)

List of abbreviations: *BMI* = *body mass index*, *WC* = *waist circumference*

Smoking status was self-reported and stratified into current/previous smokers and never-smokers

Higher education is based on secondary education and above

Central obesity based on $WC \geq 94$ cm for males and ≥ 80 cm for females



4.1 METABOLIC PROFILE OF STUDY PARTICIPANTS

Tables 3 and 4 compared the glycemic measures and the cholesterol concentrations in two study groups. The mean HbA1c and fasting plasma glucose concentrations in the overall study population were 8.12 (± 1.56) % and 8.93 (± 3.14) mmol/L respectively. The mean total cholesterol, triglycerides, HDL, and LDL cholesterol concentrations were 4.92 (± 1.12) mmol/L, 1.92 (± 0.98) mmol/L, 1.24 (± 0.34) mmol/L and 3.12 (± 0.91) mmol/L respectively.

Individuals with general obesity had significantly higher mean HbA1c concentration, mean fasting plasma glucose concentrations, mean total cholesterol concentration, triglyceride concentration, and mean LDL cholesterol concentrations. Also, individuals in the general obesity group had lower concentrations of HDL compared with those in the general obesity group

With the exception that the measures of glycemic control did not differ between the two groups, Similar findings were seen in the central obesity-stratified analysis.

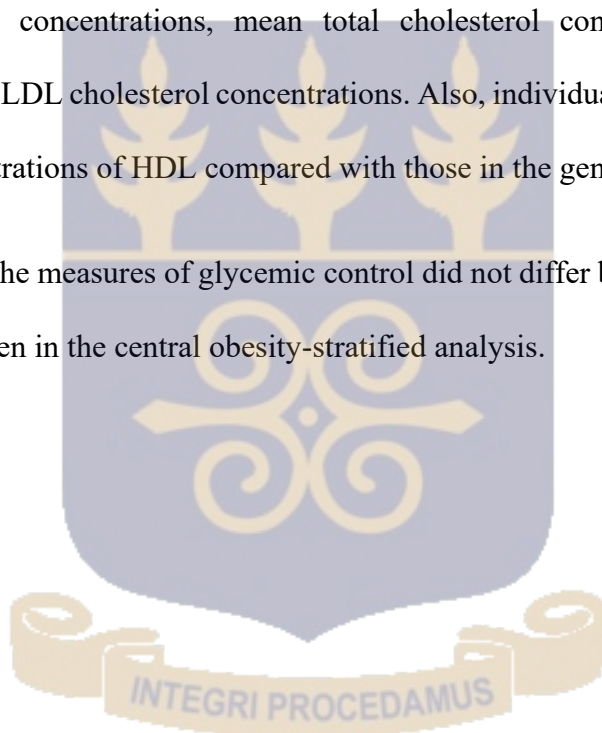


Table 3: Laboratory measures in study participants (participants stratified based on general obesity)

Measure	All Participants	No General Obesity	General Obesity	p-value
N	500	309	191	-
HbA1c (%)	8.12 (± 1.56)	7.98 (± 1.50)	8.36 (± 1.62)	0.012
FPG (mmol/L)	8.93 (± 3.14)	8.72 (± 3.05)	9.25 (± 3.27)	0.045
Total cholesterol (mmol/L)	4.92 (± 1.12)	4.78 (± 1.08)	5.16 (± 1.16)	<0.001
Triglycerides (mmol/L)	1.92 (± 0.98)	1.76 (± 0.91)	2.21 (± 1.02)	<0.001
HDL-cholesterol (mmol/L)	1.24 (± 0.34)	1.34 (± 0.37)	1.07 (± 0.26)	<0.001
LDL-cholesterol (mmol/L)	3.12 (± 0.91)	3.04 (± 0.87)	3.24 (± 0.97)	0.028

Values for continuous variables as mean ($\pm$ SD)

List of abbreviations: *HDL* = High-Density Lipoprotein, *HbA1c* = Glycosylated Hemoglobin,

LDL = Low-Density Lipoprotein

General obesity based on $BMI \geq 30 \text{ kg/m}^2$

Table 4: Laboratory measures in study participants (participants stratified based on central obesity)

Measure	All Participants	No Central Obesity	Central Obesity	p-value
N	500	80	420	-
HbA1c (%)	8.12 (± 1.56)	7.85 (± 1.48)	8.18 (± 1.58)	0.078
FPG (mmol/L)	8.93 (± 3.14)	8.58 (± 3.07)	9.00 (± 3.16)	0.274
Total cholesterol (mmol/L)	4.92 (± 1.12)	4.71 (± 1.07)	4.96 (± 1.13)	0.029
Triglycerides (mmol/L)	1.92 (± 0.98)	1.66 (± 0.88)	1.97 (± 0.99)	0.002
HDL-cholesterol (mmol/L)	1.24 (± 0.34)	1.43 (± 0.37)	1.20 (± 0.32)	<0.001
LDL-cholesterol (mmol/L)	3.12 (± 0.91)	2.99 (± 0.86)	3.14 (± 0.93)	0.089

Values for continuous variables as mean ($\pm$ SD)

List of abbreviations: *HDL* = High-Density Lipoprotein, *HbA1c* = Glycosylated Hemoglobin, *LDL* = Low-Density Lipoprotein

Central obesity based on *WC* ≥ 94 cm for males and ≥ 80 cm for females

4.3 BASELINE PULMONARY FUNCTION IN THE STUDY POPULATION

Mean ($\pm$) FEV₁ pp, FVC pp, and FEV₁/FVC ratio were 82.6 ($\pm$ 17.4)%, 85.3 ($\pm$ 18.1)%, and 0.82 ($\pm$ 0.07) respectively. Individuals with general obesity had significantly lower FEV₁ pp, and FVC pp compared with those in the general obesity group. However, the two groups were similar in terms of the mean FEV₁/FVC ratio. When Z score measures were compared, individuals in the general obesity group had significantly lower FEV₁ Z score, FVC Z score, and FEV₁/FVC Z score. Similar observations were made on analysis stratified by central obesity

Table 4.3: Pulmonary functional measures in study participants (participants stratified based on general obesity)

Measure	All Participants	No General Obesity	General Obesity	p-value
N	500	309	191	-
FEV ₁ pp	82.6 ($\pm$ 17.4)	87.2 ($\pm$ 16.3)	74.1 ($\pm$ 17.2)	<0.001
FVC pp	85.3 ($\pm$ 18.1)	89.7 ($\pm$ 16.8)	77.2 ($\pm$ 18.5)	<0.001
FEV ₁ /FVC ratio	0.82 ($\pm$ 0.07)	0.83 ($\pm$ 0.07)	0.81 ($\pm$ 0.07)	0.056
FEV ₁ z-score	-0.85 ($\pm$ 1.20)	-0.65 ($\pm$ 1.13)	-1.22 ($\pm$ 1.23)	<0.001
FVC z-score	-0.67 ($\pm$ 1.25)	-0.42 ($\pm$ 1.20)	-1.08 ($\pm$ 1.29)	<0.001
FEV ₁ /FVC ratio z-score	0.15 ($\pm$ 0.98)	0.28 ($\pm$ 0.95)	-0.06 ($\pm$ 1.00)	0.009

Values for continuous variables as mean ($\pm$ SD)

List of abbreviations: *FEV₁* = forced expiratory volume in one second; *FVC* = forced vital capacity; *pp* = percentage predicted

The calculation of percent predicted and z-score spirometric indices were all based on the Global Lung Function Initiative equations using race-neutral average reference equations.

General obesity based on $BMI \geq 30 \text{ kg/m}^2$

Table 4.4: Pulmonary functional measures in study participants (participants stratified based on central obesity)

Measure	All Participants	No Central Obesity	Central Obesity	p-value
N	500	80	420	-
FEV1 pp	82.6 (± 17.4)	88.9 (± 16.8)	81.3 (± 17.2)	<0.001
FVC pp	85.3 (± 18.1)	91.7 (± 17.4)	84.0 (± 18.3)	<0.001
FEV1/FVC ratio	0.82 (± 0.07)	0.84 (± 0.07)	0.82 (± 0.07)	0.047
FEV1 z-score	-0.85 (± 1.20)	-0.54 (± 1.10)	-0.92 (± 1.22)	0.008
FVC z-score	-0.67 (± 1.25)	-0.28 (± 1.18)	-0.76 (± 1.26)	0.003
FEV1/FVC ratio z-score	0.15 (± 0.98)	0.31 (± 0.96)	0.12 (± 0.98)	0.042

Values for continuous variables as mean ($\pm$ SD)

List of abbreviations: *FEV₁* = forced expiratory volume in one second; *FVC* = forced vital capacity; *pp* = percentage predicted

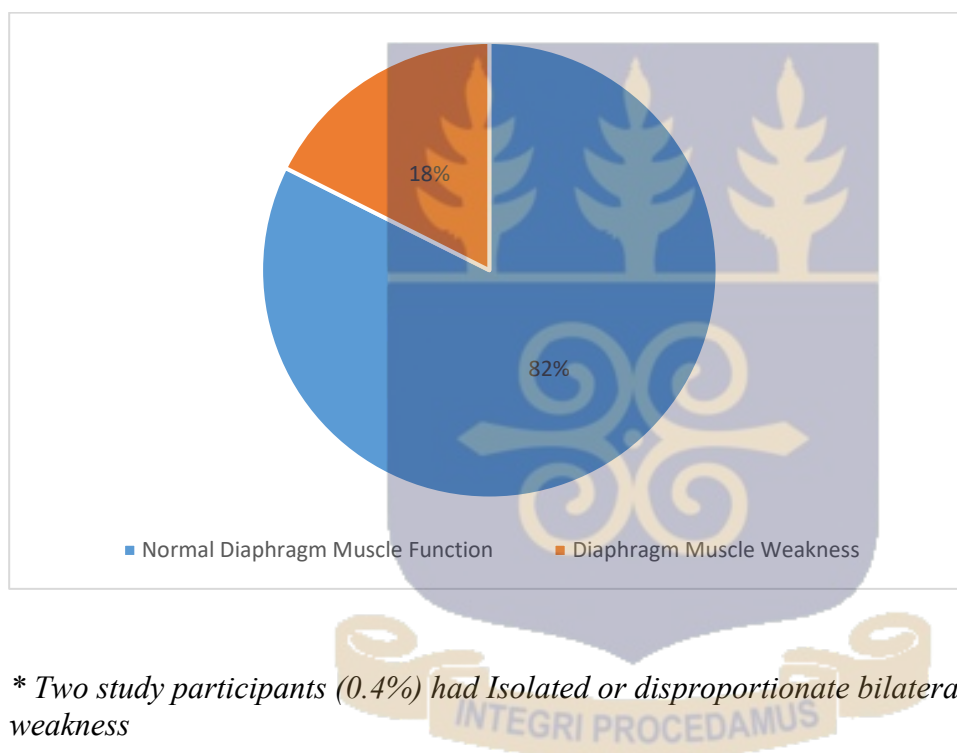
The calculation of percent predicted and z-score spirometric indices were all based on the Global Lung Function Initiative equations using race-neutral average reference equations.

Central obesity based on *WC* ≥ 94 cm for males and ≥ 80 cm for females

PREVALENCE OF DIAPHRAGM MUSCLE WEAKNESS.

Figure 4.1 shows the prevalence of impaired diaphragm muscle weakness in the study population. Overall, 88 out of the 500 study participants (representing 17.6%) had diaphragm muscle weakness. Out of these 88 participants, two (representing 0.4% of the entire study population) had isolated or disproportionate bilateral diaphragm weakness

Figure 4.1: Prevalence of Impaired Diaphragm



* Two study participants (0.4%) had Isolated or disproportionate bilateral diaphragm weakness

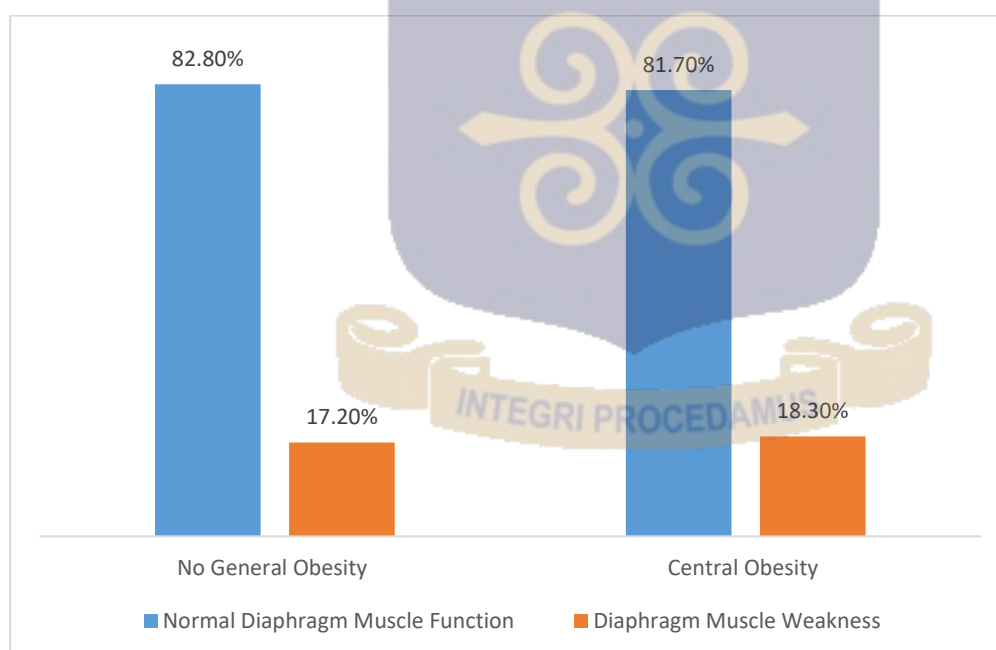
Diaphragm muscle weakness is defined as $\Delta FVC / \text{Sitting FVC} \times 100\%$, $\Delta FVC = \text{Sitting} - \text{Supine FVC}$. supine FVC $\geq 10\%$ lower than a sitting or upright FVC⁶⁴.

Isolated or disproportionate bilateral diaphragm weakness is defined as a supine FVC $\geq 30\%$ lower than a sitting or upright FVC^{65,66}.

In analyses stratified by general obesity, (Figure 4.2), there was no significant difference in the proportion of individuals with diaphragm muscle weakness in the obesity and no obesity groups. When the analyses were stratified by central obesity, the proportion of individuals with diaphragm muscle weakness was 66.4% higher in the central obesity group compared with the group without central obesity, although the strength of association was not statistically significant (18.8% vs 11.3%, $p = 0.104$).

Figures 4.4 and 4.5 compare the distribution of BMI and WC in the groups with and without diaphragm muscle weakness. The median BMI and WC were identical across categories of diaphragm muscle weakness.

Figure 4.2: Diaphragm muscle weakness stratified by general obesity

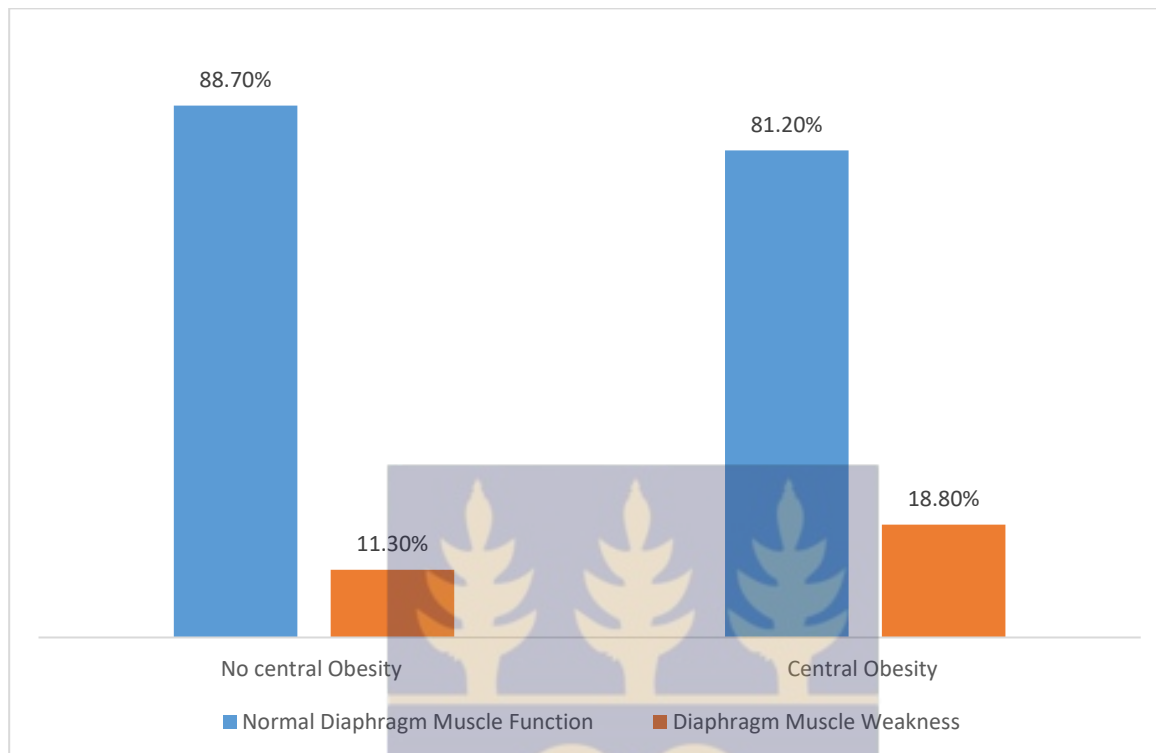


P-value = 0.738

Diaphragm muscle weakness is defined as $\Delta FVC / \text{Sitting FVC} \times 100\%$, $\Delta FVC = \text{Sitting} - \text{Supine FVC}$. supine FVC $\geq 10\%$ lower than a sitting or upright FVC⁶⁴.

General obesity based on BMI $\geq 30 \text{ kg/m}^2$

Figure 4.3: Diaphragm muscle weakness stratified by central obesity

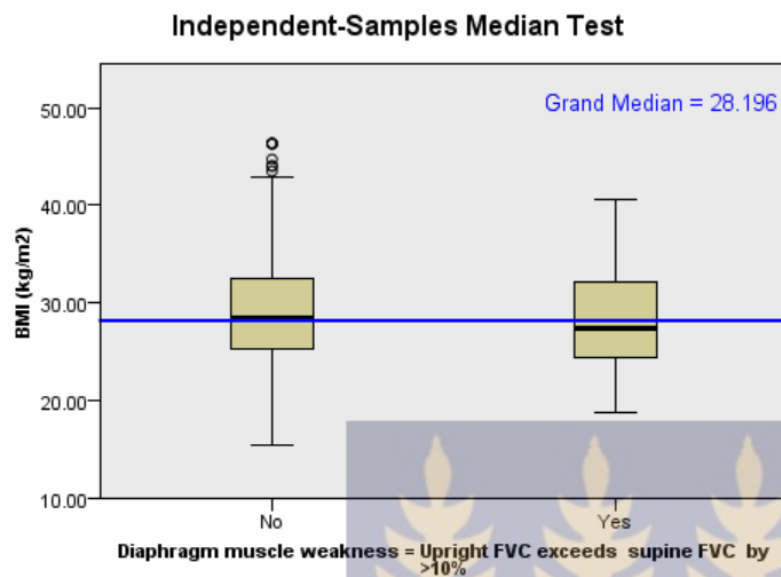


P-value = 0.104

Diaphragm muscle weakness is defined as $\Delta FVC / \text{Sitting FVC} \times 100\%$, $\Delta FVC = \text{Sitting} - \text{Supine FVC}$. supine FVC $\geq 10\%$ lower than a sitting or upright FVC⁶⁴.

Central obesity based on WC ≥ 94 cm for males and ≥ 80 cm for females

Figure 4.4: Distribution of BMI in individuals with and without diaphragm muscle weakness



P=0.557

Figure 4.5: Distribution of WC in individuals with and without diaphragm muscle weakness

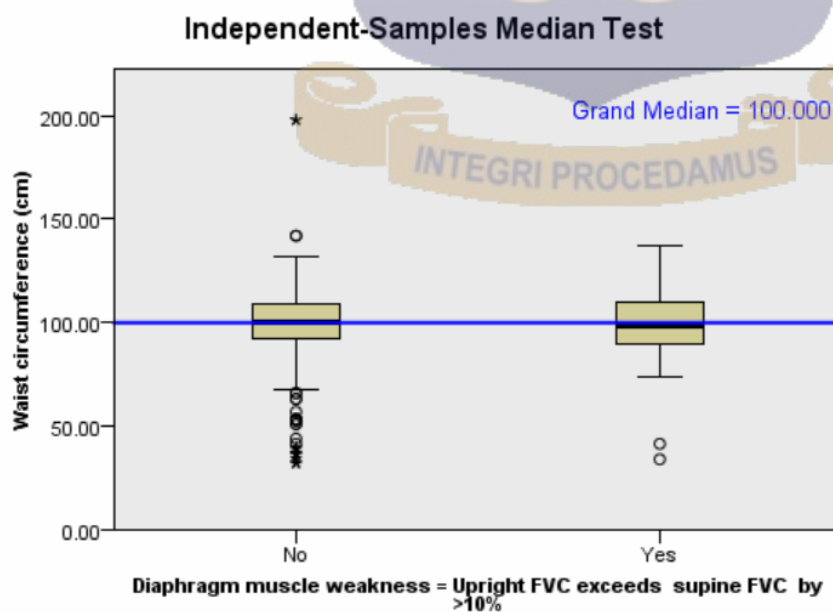
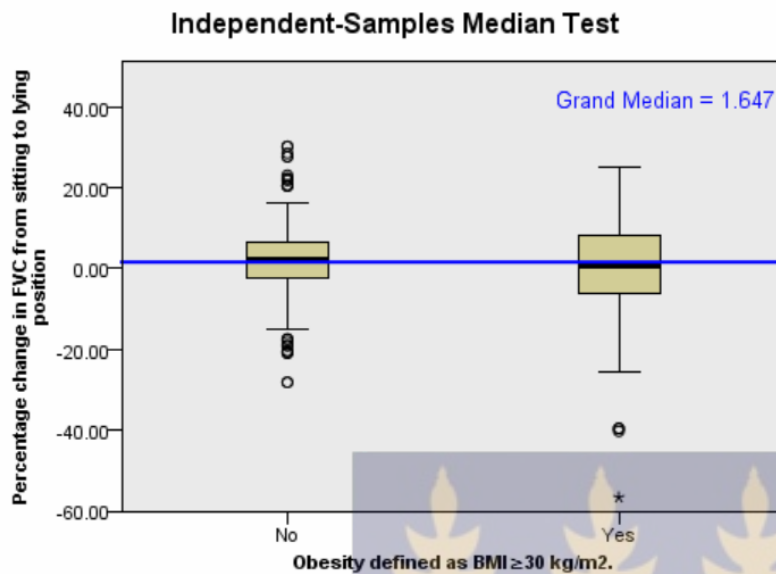


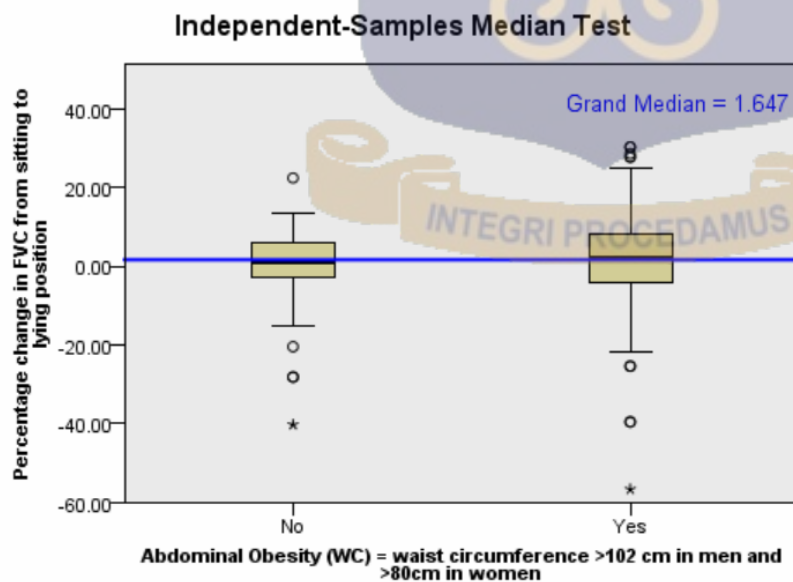
Figure 4.6: Distribution of Δ FVC in the study population stratified by general obesity



p-value = 0.54

List of abbreviations: BMI = Body Mass Index; FVC = forced vital capacity

Figure 4.7: Distribution of Δ FVC in the study population stratified by general obesity



p-value = 0.542

List of abbreviations: FVC = forced vital capacity; VC = waist circumference

ASSOCIATIONS OF Δ FVC IN OBESITY GROUPS AND MEASURES

Figures 4.6 and 4.7 show the distribution of Δ FVC in study participants with and without general and central obesity, respectively. The medians of the percentage change in FVC from sitting to lying positions were similar across the different categories of general and central obesity.

Figures 4.8 and 4.9 show the linear relationships of Δ FVC with BMI and WC. There were inverse associations of Δ FVC with BMI and WC although the associations were more marked with BMI. Overall, 3.3% of the variance in Δ FVC was explained by its linear relationship with BMI while its linear relationship with WC explained 0.4% of the variance in Δ FVC.

ASSOCIATIONS OF MEASURES OF OBESITY WITH DIAPHRAGM MUSCLE WEAKNESS

In a multivariable regression model, peripheral neuropathy was associated with a nearly 5-fold increased risk of diaphragm muscle weakness (OR 4.72, 95% CI [1.30 - 17.06], $p = 0.018$) (Table 6). General Obesity (1.09 [0.41 - 2.86], $p=0.868$) and central obesity (0.91 [0.17 - 4.71], $p=0.907$) were not associated with diaphragm muscle weakness. Similarly, Duration of diabetes (0.99 [0.94 - 1.04], $p=0.664$), increasing HbA1c concentration (0.90 [0.67 - 1.22], $p=0.492$), and smoking (6.78 [0.32 - 144.35], $p=0.220$).

In the multivariate regression models, there were no significant associations between general obesity and diaphragm muscle weakness in the unadjusted (OR 1.83, 95% CI [0.88 - 3.81], $p = 0.108$), age and sex-adjusted model (1.30 [0.59 - 2.89], $p=0.512$), and fully adjusted model (1.38 [0.25 - 7.55], $p=0.709$). There were also no significant associations between central obesity and diaphragm muscle weakness in the unadjusted (1.08 [0.68 - 1.74], $p=0.738$), age and sex-adjusted model (1.12 [0.68 - 1.81], $p=0.652$), and fully adjusted model (1.55 [0.55 - 4.36], 0.410).

Figure 4.8: Relationships between BMI and Δ FVC

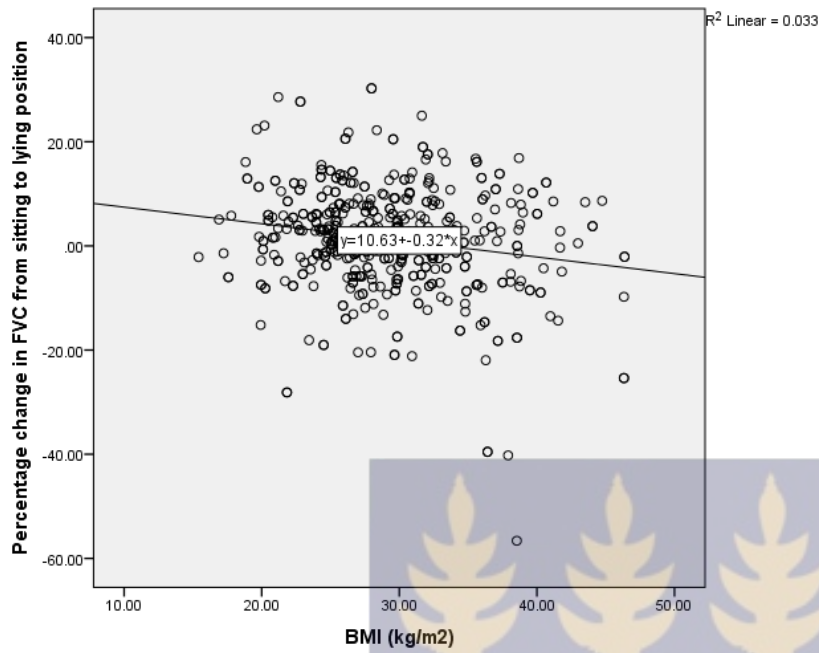


Figure 4.9: Relationships between WC and Δ FVC

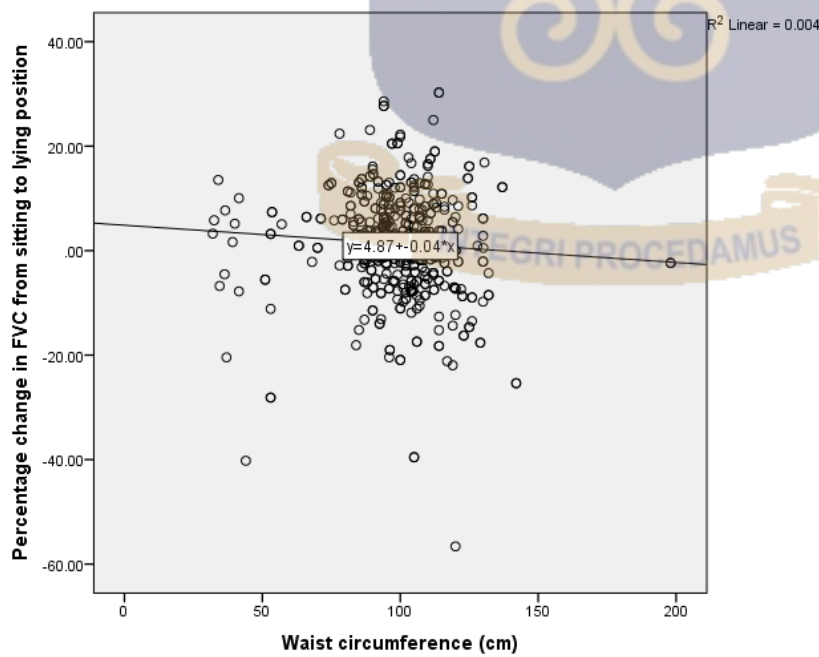


Table 4.5: Multivariable logistic regression models for diaphragm muscle weakness among Ghanaians with T2D

	Odds ratio	95% confidence interval	p-value
General Obesity	1.09	0.41 - 2.86	0.868
Neuropathy	4.72	1.30 - 17.06	0.018
Duration of diabetes	0.99	0.94 - 1.04	0.664
HbA1c	0.90	0.67 - 1.22	0.492
Previous or current smoking	6.78	0.32 - 144.35	0.220

	Odds ratio	95% confidence interval	p-value
Central Obesity	0.91	0.17 - 4.71	0.907
Neuropathy	4.71	1.30 - 17.05	0.018
Duration of diabetes	0.99	0.94 - 1.04	0.675
HbA1c	0.90	0.67 - 1.21	0.491
Previous or current smoking	6.71	0.32 - 142.41	0.222

* There was collinearity between WC and BMI. Therefore, central and general obesity were included in separate models

** Age and sex were not significant predictors and were excluded from the final model

Diaphragm muscle weakness is defined as $\Delta FVC / \text{Sitting FVC} \times 100\%$, $\Delta FVC = \text{Sitting} - \text{Supine FVC}$. supine FVC $\geq 10\%$ lower than a sitting or upright FVC⁶⁴.



Table 4.6: Multivariate logistic regression models for association between obesity and diaphragm muscle weakness

	Diaphragm Muscle Weakness		
	Odds ratio	95% confidence interval	p-value
A. General Obesity			
Unadjusted model	1.83	0.88 - 3.81	0.108
Age and sex-adjusted model	1.30	0.59 - 2.89	0.512
Fully adjusted model	1.38	0.25 - 7.55	0.709
B. Central Obesity			
Unadjusted model	1.08	0.68 - 1.74	0.738
Age and sex-adjusted model	1.12	0.68 - 1.81	0.652
Fully adjusted model	1.55	0.55 - 4.36	0.410

The fully adjusted model was adjusted for age, sex, smoking, HbA1c concentration, diabetes duration, and LDL cholesterol concentration., and peripheral neuropathy

CHAPTER 5

DISCUSSION

SUMMARY OF KEY FINDINGS

This study shows a relatively high prevalence of diaphragm muscle weakness in individuals with T2D, with nearly one of every five study participants affected. Less than 1% of the study participants had isolated or disproportionate bilateral diaphragm weakness. Unlike neuropathy, general obesity or central obesity was not independently associated with diaphragm muscle weakness. The positive correlations between diaphragm muscle weakness and central and general obesity were not statistically significant in a fully adjusted model.

DISCUSSION OF KEY FINDINGS

Nearly one in five study participants (17.6%) had impaired diaphragm muscle strength. A previous study in the same laboratory that hosted this study (Awuthey et al; yet to be published) has reported a slightly higher prevalence of impaired diaphragm muscle strength (18%) using a much smaller sample size. Aside from this study, studies in the existing literature reporting on the burden of diaphragm muscle weakness in diabetes are very limited. Studies on the commonest of diaphragm muscle weakness reported already in other populations including individuals with Chronic Obstructive Pulmonary Disease (COPD) (47.6%)⁶⁷, individuals hospitalized and managed in the intensive care units (63%)⁶⁸, and patients with acute cerebrovascular accidents (51.7%).⁶⁹

Identifying a high proportion of individuals with diabetes who have diaphragm muscle weakness has important clinical implications. Diaphragm dysfunction may contribute to reduced alveolar ventilation, impaired cough efficiency, sputum retention, and increased susceptibility to lower respiratory tract infections. In individuals already at heightened risk of morbidity due to metabolic and vascular complications, compromised respiratory muscle function may further worsen functional status, exercise tolerance, and overall quality of life. Additionally, undetected diaphragmatic weakness could complicate the clinical course during acute illnesses, surgery, or hospitalization, potentially increasing the risk of respiratory failure or prolonged recovery. Early identification of diaphragm muscle weakness in patients with diabetes may therefore support more comprehensive risk stratification and prompt targeted interventions such as optimized glycemic control, respiratory muscle training, weight management, and closer monitoring during acute care. Integrating respiratory muscle assessment into routine diabetes care may ultimately improve long-term outcomes and reduce respiratory-related complications in this vulnerable population.

Respiratory muscle function has been previously investigated in individuals with diabetes. The respiratory muscle function was explored by Fuso et al (2012) in forty healthy nonsmoking control subjects who were matched by age and sex and was compared to 75 nonsmoking patients with type 2 DM who did not smoke and had no pulmonary or cardiac conditions. maximal inspiratory and expiratory pressures (MIP, MEP) and Maximum Voluntary Ventilation (MVV) which indicate the strength and endurance of the respiratory muscles, respectively, were evaluated, and a thorough evaluation of respiratory function was recorded⁷⁰. The patients' total lung capacity and diffusing lung capacity for carbon monoxide were, on average, normal, and their metabolic circumstances were steady. However, when compared to control participants, MIP and MVV were much lower. Lung volumes and carbon monoxide diffusion capacity were substantially connected with both MIP/MEP and MVV. The study found that whereas respiratory

muscle endurance was compromised in individuals with microvascular problems, respiratory muscle strength was decreased in type 2 DM and was substantially correlated with lung volumes and metabolic control quality⁷⁰.

Data on the impact of diaphragm muscle dysfunction in the setting of diabetes is limited. In a case report by Aslam et al (2010), treponema (ie difficulty breathing in only one lateral decubitus position) was observed in a 55-year-old individual with diabetes with unilateral diaphragmatic paralysis secondary to isolated diabetic phrenic neuropathy⁷¹. Their observation suggests that impaired diaphragm muscle strength may result in clinically relevant pulmonary symptoms including different levels of dyspnea severity. Further studies are required to better characterize the clinical impact of diaphragm muscle dysfunction in the setting of diabetes.

Similar to unilateral diaphragm muscle impairment in diabetes, bilateral impairments, and their clinical impact have also been reported⁷². Costa et al (2018) presented a case report of a 64-year-old male with type 2 diabetes who had bilateral phrenic nerve palsy resulting in bilateral diaphragm muscle impairment. This impairment resulted in respiratory failure requiring intensive care unit admission⁷².

Improved diaphragm muscle function may be beneficial in patients with diabetes. Albarrati, Taher, and Nazer (2021) conducted a randomized controlled trial that assessed the impact of inspiratory muscle training on exercise capacity and strength in individuals with type 2 diabetes. The authors reported that Incremental inspiratory muscle training resulted in improved diaphragm muscle strength and enhanced exercise capacity based on the six-minute walk test⁷³. This may be clinically relevant in individuals with diabetes who are encouraged to be on an exercise plan to improve glycemic control, macrovascular health, and microvascular health²⁰.

Sklar and his colleagues reported the association between low baseline diaphragm mass with increased mechanical ventilation and increased risk of in-hospital mortality in a prospective

cohort study (2020). In 193 adult patients in severe conditions receiving invasive mechanical breathing, their study sought to ascertain whether a lower baseline diaphragm thickness (Tdi) was associated with delayed-release from mechanical ventilation acute respiratory failure complications. The results indicated that a baseline Tdi of 2.3 mm or less was linked to delayed release from mechanical ventilation. Moreover, though, this study failed to measure diaphragm muscle strength, their findings showed that lower baseline Tdi was linked to a greater risk of in-hospital mortality, extended weaning, and complications from acute respiratory failure⁷⁴.

Diaphragmatic dysfunction is proven to be significantly associated with moderate to severe dyspnoea. In the study of Bernardinello et al. (2023), the rampancy of diaphragmatic dysfunction was assessed among patients with interstitial lung disease. In their cross-sectional hospital-based study which comprised 41 adult male patients with connective tissue disease (CTD) and 41 adult patients with idiopathic pulmonary fibrosis (IPF), the results showed a higher prevalence of diaphragmatic dysfunction in IPF as compared to CTD. Moreover, TF positively correlated to patients' functional parameters in the CTD-ILD group while not in the IPF group. Though this study was limited by its small sample size and its incapability to regulate the breathing workload due to the setting of the measurement, it showed that in interstitial lung disease (ILD) patients, thickening function (TF) is related to patients' lung function and, if a $TF < 30\%$ is a predictor of dyspnea⁷⁵.

This study was conducted by Goswami et al. (2002) on the effect of carbimazole on diaphragm muscle weakness and dyspnea in individuals with Grave's disease. This weakness is mostly observed during a maximal respiratory maneuver, indicating a diminished diaphragmatic reserve which could be the cause of dyspnoea seen in exertion among patients with thyrotoxicosis. In a hospital-based cross-sectional study among 27 patients, the report of Goswami et al. (2002) showed that reevaluation of thoracic diaphragmatic muscle weakness after carbimazole therapy,

a notable decrease in visual analog dyspnea during maximal respiratory maneuver. Moreover, significant improvement was observed in the vital capacity, forced expiratory volume in the first second, total lung capacity, and diaphragmatic movement during deep respiration⁷⁶.

Among COVID-19 survivors, diaphragm muscle atrophy is understood to contribute to low physical capacity. This is highlighted in a hospital-based cross-sectional retrospective study by Ocean et al. (2024) on whether possible diaphragm dysfunction is a factor in the deterioration of physical functioning in post-COVID-19 patients. Their report shows a high percentage of patients with diaphragm muscle function disorders (75%). However, there was no correlation between the pace of atrophy and the severity of the disease, age, gender, BMI, or use of oxygen therapy during the COVID-19 infection. Additionally, patients with fever, cough, and no loss of smell during the COVID-19 period had diaphragm inspiratory thickness values that were noticeably higher. Conversely, the percentage of diaphragm atrophy was considerably lower in patients who coughed and did not have any smell problems. Additionally, their analysis demonstrated a substantial correlation between diaphragm functional characteristics and certain exercise tolerance variables, including a six-minute walk test distance, oxygen saturation levels, weariness, and effort on the Borg scale⁷⁷.

In this study, a positive association was observed between measures of obesity and diaphragm muscle weakness. However, the strength of association was not statistically significant. Given the magnitude of the odds ratio (for example the odds of diaphragm muscle weakness were 55% higher in individuals with central obesity compared with those without central obesity, after adjustment for covariates), the association could be clinically significant.

This observed association occurred in a model that adjusted for metabolic determinants of respiratory function including HbA1c. While hyperglycemia may induce muscle weakness, the mechanisms are unclear. High concentrations of reactive oxygen species could be an underlying

mechanism. In basic science research, Callahan and Supinski (2014) tested the hypothesis that hyperglycemia-induced impaired diaphragm muscle function is mediated by excessive superoxide generation. In their experiment, they observed that hyperglycemia-induced impaired diaphragm muscle function occurred principally at the level of the contractile proteins and was associated with depletion of troponin T and increased indices of oxidative stress. As proof of concept, the authors administered a specific superoxide scavenger (f PEG-SOD) and observed that this ablated the derangements caused by excessive superoxide generation Oxidate Stress ⁷⁸

In the multivariable regression model that included potential factors that could negatively impact diaphragm muscle function, only neuropathy was identified as a significant predictor of diaphragm muscle weakness in T2D. while the statistical tools used were different, this observation partly agrees with the findings by Awuttey et al that reported a positive association between neuropathy and diaphragm muscle weakness in adults with diabetes. Based on the results of this study only, peripheral nerve dysfunction assessed by measurement of peripheral nerve function correlates with diaphragm muscle weakness. Given that neuropathy in the peripheral nervous system may also indicate phrenic nerve neuropathy, the association could reflect impaired phrenic nerve function adversely impacting diaphragm muscle function.

The impact of clinically diagnosed neuropathy (cdNP) on respiratory muscle strength in individuals with type 2 diabetes mellitus (T2DM) was examined in this cross-sectional study. Depending on whether cdNP was present, 110 T2DM patients and 35 healthy, non-diabetic controls (≥ 60 years) were divided into three groups: T2DM without cdNP (D-; $n = 28$), T2DM with cdNP (D+; $n = 82$), and controls without cdNP (C; $n = 35$). The Diabetic Neuropathy Symptom score and the Vibration Perception Threshold comprised the clinical neurological diagnostic evaluation. Peak Expiratory Flow (PEF) was used to measure respiratory function, while peak inspiratory and expiratory pressures (P_Imax and P_Emax) were used to measure

respiratory muscle strength. An Isometric Handgrip and Brief Physical Performance Battery were used to assess Peripheral skeletal muscle strength and physical performance. Age, degree of physical activity, and body mass index were utilized as factors in the univariate analysis of covariance. In comparison to D⁻ and D⁺, C had greater P_Imax, P_Emax, and PEF values. Further investigation revealed that D⁺ had substantially lower P_Imax, P_Emax, and PEF than C. Additionally, P_Emax and PEF were substantially lower in D compared to C. Physical performance and measures of peripheral muscle strength were less associated with T2DM and cdNP⁷⁹. When compared to healthy controls, T2DM patients' respiratory muscle strength is impacted by the existence of cdNP. Although diabetes and cdNP each had a unique influence on respiratory muscle strength and function, this study was unable to determine if these effects added up. The inclusion of P_Imax, P_Emax, and PEF measurements in the assessment of respiratory muscle weakness may be beneficial in the (early) screening for neuropathy in patients with type 2 diabetes at the time, as commonly used measures of peripheral muscle strength and physical performance appeared to be less affected.⁷⁹.

The observed positive association between measures of obesity and diaphragm muscle weakness carries important clinical implications. If increased general or central adiposity contributes to diaphragmatic dysfunction, this suggests that obesity may not only worsen metabolic control in diabetes but also compromise respiratory muscle performance. Clinically, individuals with obesity and diabetes may therefore represent a subgroup at heightened risk of reduced ventilatory efficiency, impaired cough, and increased susceptibility to respiratory complications. This finding underscores the importance of routine assessment of obesity indices in diabetes care and supports more aggressive weight management strategies as part of comprehensive treatment. Interventions such as lifestyle modification, structured exercise programs—including respiratory muscle training—and optimized metabolic control may help preserve diaphragmatic function. Furthermore, recognizing obesity as a potentially modifiable contributor to diaphragm weakness

highlights an opportunity for preventive strategies aimed at reducing respiratory morbidity in individuals with diabetes.

This study by Lin and Lin included twenty obese women between the ages of 20 and 35 who were sedentary, nonsmokers, and free of lung disease. Their BMI ranged from 35 to 49.99 kg/m². The non-obese group consisted of 20 women aged 20–35 who were sedentary, nonsmokers, free of lung disease, and had a body mass index between 18.5 and 24.99 kg/m². Every participant took a spirometry test. There was no significant difference between the obese and non-obesity groups in terms of age, vital capacity, tidal volume, forced vital capacity, or forced expiratory volume in one second. Nonetheless, the fat group had a larger inspiratory reserve volume. Obesity-induced damage to the chest mechanics is indicated by the alterations observed in the vital capacity components (inspiratory reserve volume and expiratory reserve volume). These conditions most likely led to a decrease in the maximal voluntary ventilation⁸⁰.

STRENGTHS /NOVELTY

Novelty

1. In the existing public literature, we found no study assessing the associations of measures of obesity with diaphragm muscle weakness. This study thus provides novel data on the potential impact of measures of obesity on diaphragm muscle weakness.

Strengths

2. In assessing obesity, multiple measures ie general and central obesity were used.
3. In this study, well-standardized study protocols including standardized spirometry testing and objective measures of diaphragm muscle function were performed. A large range of covariates were also assessed in this study.

4. A wide range of covariates were adjusted for in the multivariate regression models.

LIMITATIONS

1. The cross-sectional design limits claiming causality. However, it is biologically plausible that the mechanical effect of obesity can splint the diaphragm, resulting in limited diaphragm muscle strength, and not vice versa ⁸¹.
2. The absence of a non-diabetic control group limits this study. Without a comparator population, it was not possible to determine whether the observed diaphragm muscle weakness is specific to individuals with diabetes or reflects the independent effects of obesity. The inclusion of non-diabetic controls would have strengthened causal interpretation and enhanced the ability to distinguish diabetes-related effects from obesity-related influences. Future studies incorporating appropriate control groups are therefore recommended.
3. The gold standard of assessing body composition, ie dual-energy X-ray absorptiometry (DXA) was not employed due to feasibility. Based on the existing data, DXA measurements provide a more comprehensive evaluation of body compartments, regardless of alterations in conventional anthropometry including WC and BMI, identifying a significant redistribution of lean and fat mass and providing clues to explain changes in cardiovascular risk profile ⁸².
4. The study included a small proportion of males. Based on the sample strategy, this was expected due to the male-to-female ratio observed at the NDMRC clinic visits.
5. Transdiaphragmatic pressure measurement, diaphragm electromyography (EMG), and phrenic nerve conduction studies (PNCS) were not performed in the assessment of diaphragm muscle function due to feasibility. These tests are mainly invasive and not routinely performed in clinical practice. Transdiaphragmatic pressure is performed using

transnasal placement of two thin-walled balloon-tipped catheters, which is invasive. The recommended diaphragmatic EMG using esophageal electrodes is invasive; non-invasive measures using surface electrodes are less sensitive and have not been validated in many populations. The recommended diaphragmatic PNCS is performed using invasive stimulation techniques, often intraoperatively; the use of percutaneous noninvasive stimulation (typically preoperatively) is less accurate and hasn't been validated in many populations.

6. Measurements of maximal inspiratory pressure (P_Imax) were not done. A decreased FVC from sitting to a supine position is less specific for respiratory muscle weakness compared with the P_Imax^{83,84}. However, a fall in FVC > 30% when lying down as opposed to standing up (indicative of isolated or disproportionate bilateral diaphragm weakness) was assessed and may be more reliable than the maximal inspiratory pressure (P_Imax) in this regard^{65,66}.

CONCLUSION

The study shows a relatively high proportion of diaphragm muscle dysfunction in adults with T2D with nearly one in five study participants affected. This is clinically relevant considering the adverse impact of diaphragm muscle weakness on respiratory function including alveolar minute ventilation and pulmonary gas exchange. Future studies could characterize the clinical consequences of impaired diaphragm muscle strength in the setting of T2D. Based on this study, the positive associations of general obesity and central obesity with diaphragm muscle weakness were not statistically significant. Given the magnitude of the observed odds ratio for the associations of obesity with diaphragm muscle weakness, the strength of the association could be clinically significant. Future studies could assess the clinical significance of this association. Also, the study showed that general obesity or central obesity did not independently predict

diaphragm muscle weakness. Diaphragm muscle weakness in T2D may thus result from other processes including neuropathy instead of obesity

RECOMMENDATIONS FOR CLINICAL PRACTICE / FUTURE RESEARCH

1. Longitudinal studies are required to better characterize the relationship of different measures of obesity with diaphragm muscle dysfunction. These future studies should
 - a. include multiple measures of body composition including DEXA measurement
 - b. be multisite to improve external validity^{85,86}.
 - c. include children with diabetes to enhance the wider application of the findings
 - d. include a larger proportion of males and/or stratify analyses based on sex considering the sex differences in respiratory disease⁸⁷.
2. While the strength of associations was not statistically significant, the positive associations of obesity measures with diaphragm muscle weakness suggest that obesity control could improve diaphragm muscle function in adults with T2D.
3. Future studies are required to assess the clinical consequences of impaired diaphragm muscle strength in individuals with T2D

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TIMELINES

ACTIVITY					
	December 2023- March 2024	March 2024-July 2024	August 2024- September 2024	September 2024 – December 2024	December 2024 – February 2025
Development of study proposal					
Application For Ethical Clearance					
Data acquisition and analysis					
Preparation, and submission of thesis.					
Preparation of Manuscripts					

BUDGET & LOGISTICS

BUDGET ITEM	TOTAL COST (GH¢)
Equipment	Freely available in the lab
Spirometry mouthpieces	2500.00
Biochemical analyses	4500.00 (subsidized)
Office Stationery	100.00
Communication (internet and telephone)	100.00
Contingency	300.00
Total	7500.00

APPENDIX I

INFORMED CONSENT FORM

CONSENT FORM FOR LARGER STUDY

(This candidate's work was part of a larger study that had his supervisor as a principal supervisor. The consent form was that of the larger study)

Principal Investigator

Professor Charles Hayfron-Benjamin, Department of Anesthesia, Korle Bu Teaching Hospital/Department of Physiology, University of Ghana Medical School, Korle Bu

Study Title

Pulmonary and vascular dysfunction in sub-Saharan Africans with diabetes: unraveling causal pathways.

What the study is about:

Diabetes mellitus is a condition that is associated with high blood glucose (sugar). The high blood glucose if not controlled over time, may lead to complications that can result in poor eyesight or blindness, kidney damage, amputation (loss of toe, foot, or leg), or abnormal function of the lungs. In a previous study we conducted from 2019 to 2021, we observed that many Ghanaians with diabetes managed at the National Diabetes Management and Research Centre develop these complications. We do not fully understand why some people develop these complications and the risk factors for developing these complications that occur in people with diabetes. To answer these questions, we are carrying out this study that will assess changes in the functions of the lungs and blood vessels that supply important organs in the body over time, and what are the risk factors for developing abnormal functions of the lungs and blood vessels.

Procedures for the study

If you agree to participate in this study, you will be asked to come for a study visit at the National Diabetes Management and Research Centre once a year for the next five years. We will aim to schedule these visits, so they coincide with your usual clinic visits.

- You will be made to fast overnight (for 8 to 12 hours) before the reporting date for the study.
- You will be asked to provide certain information about your socioeconomic status, lifestyle, quality of life, physical fitness, lung function, eye function, kidney function, and nerve function. This will take about 30 minutes on the first visit interview, and then less than 15 minutes for subsequent visits. You are not obliged to answer all the questions.
- A general examination will be done after which blood samples tests for investigations will be collected. The general examination will assess the whole body as is normally done when you visit the hospital.
- We will take blood samples (about 10 ml) from your veins for blood tests.

This amount of blood we will take is not very different from what you will normally be asked to provide when you visit the laboratory for a blood test.

Only sterile techniques and disposable, single-use equipment will be always used.

Rarely, you might experience minor bruising at the site of taking of blood sample as with any blood test. All study participants will receive appropriate treatment as necessary.

The blood we take will help in performing special tests such as fasting blood sugar, fasting lipids, HbA1c, full blood count, liver function tests, and others that will help with diagnosis and assist in the monitoring of complications associated with diabetes. Some of the blood samples may be stored for analysis later.

Any future analyses of the blood samples will be done with prior approval from the Ethics Committees of the Korle Bu Teaching Hospital and the College of Health Sciences, University of Ghana.

- You will also be given a bottle for the collection of early morning urine samples at home on the morning of the reporting date.
- We will conduct tests to assess your lungs, heart, eyes, and nerves. All these tests are very safe. For lung function, you will be made to blow air into a device. To assess your eyes, a camera (fundus camera) will be used to look at the back of your eyes. A device (called the neurothesiometer) that delivers a clinically safe amount of vibration will be used to assess your nerves. We will assess your kidney function using blood and urine tests. You will also be made to walk at your own pace for six minutes on a leveled ground to help us assess some portions of your cardiac function. Finally, electrocardiography and echocardiography will be used to assess your heart function. Electrocardiography and echocardiography are the usual tests we use to assess heart function in the hospital. For some study participants, we will attach some devices on their bodies and use it to measure their blood pressure and heart function over 24 hours. They will send these devices home and return them the next day. The cost of transportation for these people will be borne by the study.
- All the tests we conduct will be at no cost to you.
- We will provide you copies of the results of tests done on you at no cost to you.

PATIENT BURDEN

This research presents minimal risk to you. The main risks include psychological distress from discussing potentially upsetting issues such as any medical conditions you have, as well as

information you may consider as private. However, you are not required to answer all questions we ask. A trained health worker will take a total of 10 ml of blood for medical tests. These tests are required for patients with diabetes. The risks of having blood drawn include pain from the needle and a small risk of bruising and/or infection at the site. There will be no compensation for participating in the research.

CONFIDENTIALITY

- All information collected from this research will be kept confidential.
- If this study is reported, you will not be identified by name.

To emphasize, your name will not be captured into the database and no private record of yours will be available to the public. Information that will be published (available to the public) is based on a combination of the results of all individuals who participated in the study. If we need to use your blood sample for any other analysis aside from the one stated in this study, we will seek permission from the university and hospital authorities regulating research (called the institutional review board or ethics committee) before doing so.

MY RIGHT

- Taking part in the research is entirely voluntary.
- You may refuse to take part or withdraw from the study at any time without anyone objecting and without penalty. Refusing to take part in the study or withdrawing from the study will not affect your care in the hospital.
- You also have the freedom of choice of what questions to answer. Deciding not to answer some questions will not affect your care in the hospital.

WHO TO CONTACT (RESEARCH PARTICIPANTS)

The following people will be available to answer any questions you may later have about this study:

- Prof. Charles Hayfron-Benjamin, Department of Anesthesia, Korle-Bu Teaching Hospital (Tel: 057 608 4885)
- Professor Albert Amoah, Department of Medicine and Therapeutics, Korle Bu Teaching Hospital (Telephone:020 201 2224)

WHO TO CONTACT (ABOUT THE RIGHTS OF RESEARCH PARTICIPANTS)

For issues related to your right as a research participant, as well as questions related to the ethical conduct of the research, please contact the institutional review board of the Korle Bu Teaching Hospital or the ethics and protocol review committee of the University of Ghana, College of Health Sciences as follows:

Ethics and Protocol Review Committee of the University Of Ghana College Of Health Sciences

- Physical Address: Research Office, First Floor GEMP Building, Room 6 & 7, Korle-Bu Teaching Hospital, Korle-Bu
- Postal Address: College of Health Sciences, University of Ghana, P.O.Box KB 52, Korle-Bu, Accra
- Digital Address: GA-270-0053, Harley St, Accra, Ghana
- Email: eprc@ug.edu.gh
- Telephone: +233 [030] 294 0528, +233 [030] 2665103

Institutional Review Board of Korle-Bu Teaching Hospital

- Physical Address: 2nd Floor, Central Administration Block, Korle Bu Teaching Hospital
- Email: rdo@kbth.gov.gh
- Telephone: 0302739510 ext. Research Office/Medical Directorate

STATEMENT BY STUDY PARTICIPANT

I acknowledge that I have read or have had the purpose and contents of the informed consent document read and satisfactorily explained to me in a language I understand. I fully understand the contents and any potential implications as well as my right to change my mind (thus, withdraw from the study) even after I have signed/thumb-printed this form. I understand that if I choose to withdraw from this study, my care in the hospital will not be affected.

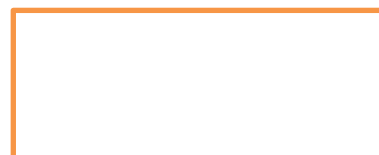
I voluntarily agree to be part of this research.

(Signature)

Full Name of Study Participant

Date

Thumbprint (for the participant unable to sign)



STATEMENT OF WITNESS

I was present when the purpose and contents of the study were read and explained satisfactorily to the participant in (Ga / Twi / Ewe / Hausa/..... [Specify other languages]). I confirmed that he/she was given the opportunity to ask questions/seek clarifications and the same were duly answered to her satisfaction before voluntarily agreeing to be part of the research.

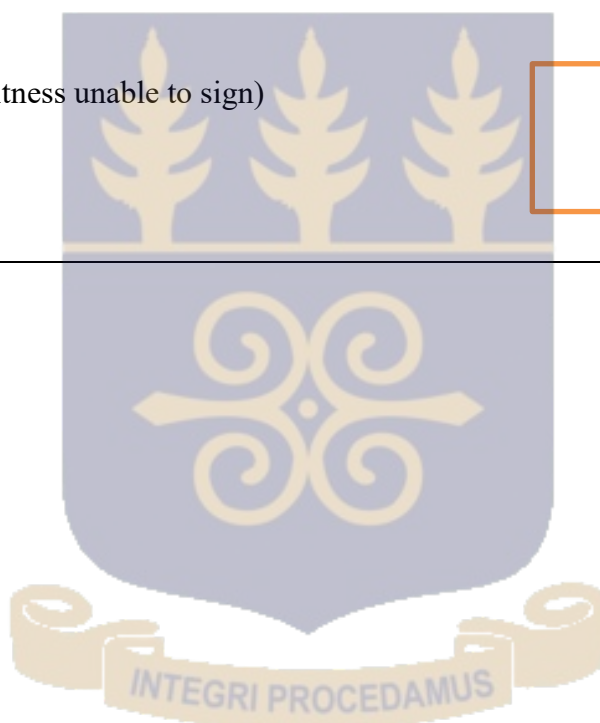
.....

(Signature)

Full Name of Witness to

Date

Thumbprint (for the witness unable to sign)



STUDY TEAM MEMBER ADMINISTERING THE CONSENT

I have fully explained to the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered and will answer all questions to the best of my ability.

.....

(Signature)

Full Name of Staff Member

Date



APPENDIX III:**QUESTIONNAIRE FOR STUDY****QUESTIONNAIRE FOR CURRENT STUDY**

(This student's work was part of a larger study that had his supervisor as a principal supervisor. The questionnaire below includes only segments important for the student's thesis)

PART A: DATE, TIME, AND INTERVIEWER'S ID		
1.	Date of completion of the instrument	___ - ___ - ___ DD MM Y Y Y Y
2.	Time of interview (24-hour clock)	___ - ___ HH MM
3.	Interviewer's ID (Name)	

PART B: CONSENT, INTERVIEW LANGUAGE NAME, AND CONTACTS				
4.	Interview Language (<i>Insert Language</i>)	1. English	2. Akan	3. Ga
		4 Ewe	5 Hausa	6. Other
5.	Consent has been read and obtained	1. Yes	2. No	If NO, END
6.	Contact phone number of participant (1)			
7.	Contact phone number of participant (2)			
8.	Contact e-mail of participant			
9.	Family Name			
10	First Name			
11	Hospital Folder Number			
12	Urine samples collected	1. Yes	2. No	Ensure they are taken
13	Blood samples taken	1. Yes	2. No	Ensure they are taken
14	Glucose drink administered (<u>for controls</u>)	1. Yes	2. No	Ensure administered

PART C: SOCIODEMOGRAPHIC INFORMATION OF PARTICIPANT

15	Participants ID number			
16	Gender	1. Male	2. Female	
17	Age (in years)			
	<i>[Check against the DOB; if there is a discrepancy, confirm of both DOB and AGE and correct accordingly]</i>			
18	Tribe (please tick)	1. Akan	2. Ewe	3. Ga/Dangbe
		4. Mole/Dagomba	5. Mamprusi	6. Gruma
		7. Guan	8. Other (please specify)	
19	Marital status (please tick)	1. Never Married	2. Married	3. Separated
		4. Divorced	5. Widowed	6. Cohabiting
20	Highest level of education you have completed (please tick)	1. No formal schooling		
		2. Basic (Primary to JHS)		
		3. Secondary school		
		4. Tertiary		
		5. Postgraduate degree		
		6. Refused		
21	Work Status (please tick) (Which of the ff best describes your main work status over the past 12 months?)	1. Government employee	2. Non-government employee	
		3. Self-employed	4. Student	
		5. Homemaker/Housewife	6. Retired	
		7. Unemployed (able to work)	8. Unemployed (unable to work)	
		9. Other (please specify)		
22	What is your occupation?			
23	Taking the past year, can you tell me what the average earnings of the household have been?	1. Per week (in cedis):		
		2. OR Per month (in cedis):		
		3. OR Per year (in cedis):		
		4. Refused		

PART D: BEHAVIORAL MEASUREMENTS

24.	Do you smoke tobacco products?	1. Never Smoked	2. Currently smokes
	<u>[If Never Smoked, skip to 27]</u>	3. Previous smoked	
25.	If you currently smoke, how long (in years) have you been smoking?		

26.	On average, how many sticks do you smoke each day?		
27.	If you previously smoked, how long did you smoke for?		
28.	On average, how many sticks did you smoke each day?		
29.	Do you use other recreational drugs	1. Yes 2. No	
		If yes, please specify	
30.	Have you ever consumed any alcohol such as beer, wine, or spirits?	1. Yes 2. No	
31.	Have you consumed any alcohol within the past 12 months?	1. Yes 2. No	
32.	During the past 12 months, how frequently have you consumed an alcoholic drink?	1) Daily	2) 5-6 days per week
		3) 3-4 days per week	4) 1-2 days per week
		5) 1-3 days per month	6) less than once a month

PART E: MEDICAL HISTORY

Do you have/have you had any of the following medical conditions?

Please indicate which of the following illnesses and disorders you have now or that you have had in the past 12 months, and whether or not this was diagnosed by a doctor.

	Medical condition	1. No	2. Yes not diagnosed by a doctor	3. Yes diagnosed by a doctor
34.	Hypertension			
35.	Kidney Disease?			
36.	Coronary artery disease			
37.	Stroke / TIA (transient ischemic attack)			
38.	Chest pain from heart disease (Angina)			
39.	Heart attack (myocardial infarction)			
40.	Heart failure			
41.	OTHERS			

PART F: DRUGS

42. Kindly state all medications you are currently taking, with their doses (may retrieve from a folder or hospital records)? Also how frequent do you take the medications

Medication	All The Time / Most of the Time	Some of the time	Once in a while
Herbal medication			
Aspirin			
Anti-cholesterol			
Insulin			

DIABETIC NEUROPATHY SYMPTOM (DNS) SCORE

4	1	Are you suffering from unsteadiness in walking? [need for visual control, increase in the dark, walking like a drunk man, lack of contact with floor] 0 No 1 Yes
4	2	Do you have a burning, aching pain or tenderness in your legs or feet? [occurring at rest or night, not related to exercise, exclude claudication intermittens] 0 No 1 Yes
4	3	Do you have prickling sensations in your legs and feet? [occurring at rest or night, distal>proximal, stocking-glove distribution] 0 No 1 Yes
4	4	Do you have places of numbness on your legs or feet? [Distal>proximal, stocking-glove distribution] 0 No 1 Yes

APPENDIX III

ETHICAL APPROVAL



UNIVERSITY OF GHANA COLLEGE OF HEALTHSCIENCES

ETHICAL AND PROTOCOL REVIEW COMMITTEE

EPRC/MAR/2024

August 9, 2024.

Mr. Mageed Mohammed
Department of Physiology
University of Ghana Medical School
Korle Bu - Accra

Dear Mr. Mohammed,

ETHICAL CLEARANCE

Protocol Identification Number: *CHS-Et/M.8 – P 4.3 /2023-2024*

FWA: 000185779

IORG: 0005170

IRB: 00006220

The College of Health Sciences Ethical and Protocol Review Committee (EPRC) on August 7, 2024, reviewed and approved your re-submitted protocol.

Title of Protocol: "Relationship between obesity and diaphragm muscle strength in Diabetes Mellitus"

Principal Investigator: Mr. Mageed Mohammed

This approval requires that you submit six-monthly review report(s) of the study to the Committee and a final full review report to the EPRC at the completion of the study. The Committee may observe, or cause to be observed, procedures and records of the study before, during and after implementation.

Please note that any significant modification(s) to this project/study must be submitted to the Committee for review and approval before its implementation.

You are required to report all serious adverse events related to this study to the EPRC within seven (7) days verbally and fourteen (14) days in writing.

As part of the review process, it is the Committee's duty to review the ethical aspects of any manuscript that may be produced from this study. You will therefore be required to furnish the Committee with any manuscript for publication.

This ethical clearance is valid till August 8, 2025.

Please always quote the protocol identification number in all future correspondence in relation to this protocol.

Signed:

Professor Andrew Anthony Adjei
Chair, Ethical and Protocol Review Committee

cc: Provost, CHS
Dean, UGMS
Head, Department of Physiology, UGMS

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