



**UNIVERSITY OF GHANA
COLLEGE OF HEALTH SCIENCES
UNIVERSITY OF GHANA MEDICAL SCHOOL
DEPARTMENT OF PHYSIOLOGY**

**ELECTROCARDIOGRAPHIC PROFILES AND ASSOCIATED
FACTORS IN GHANAIS WITH TYPE 2 DIABETES**

BY

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DECLARATION

I, Sylvester Ameyaw-Gyan, certify that the work presented in this thesis is the result of my own research undertaken in the Department of Physiology, University of Ghana under the supervision of Professor Charles Hayfron-Benjamin and Dr. Winfred Baah and that all the references cited in this work have been properly acknowledged.

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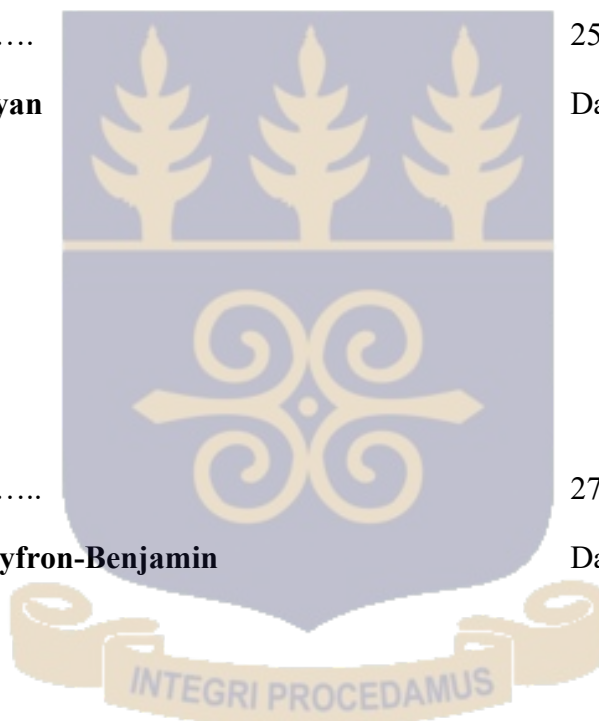
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DEDICATION

I dedicate this work wholeheartedly to my beloved family and cherished friends. Your love and support have been my foundation throughout this journey. Your encouragement and belief in me have guided and inspired me every step of the way. For this, I extend my deepest gratitude.



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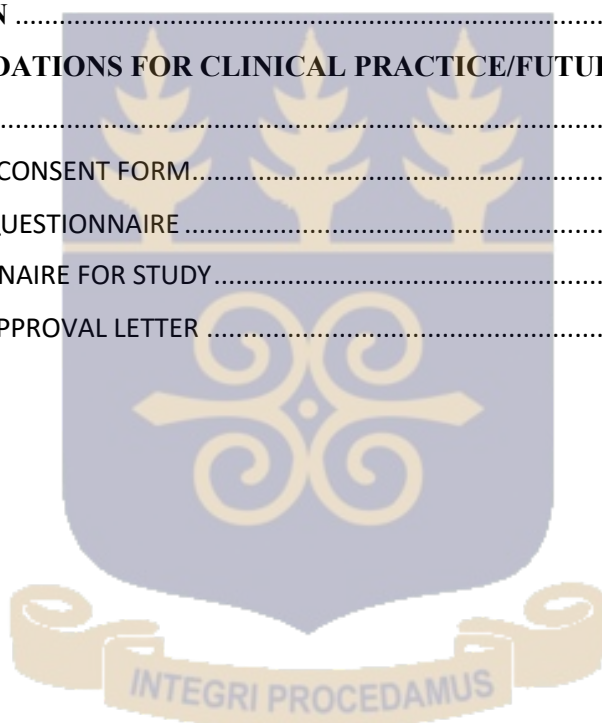
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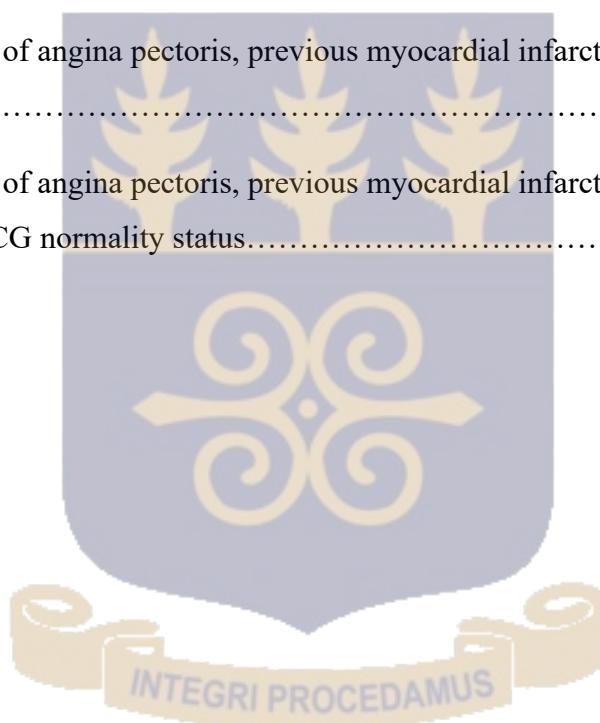
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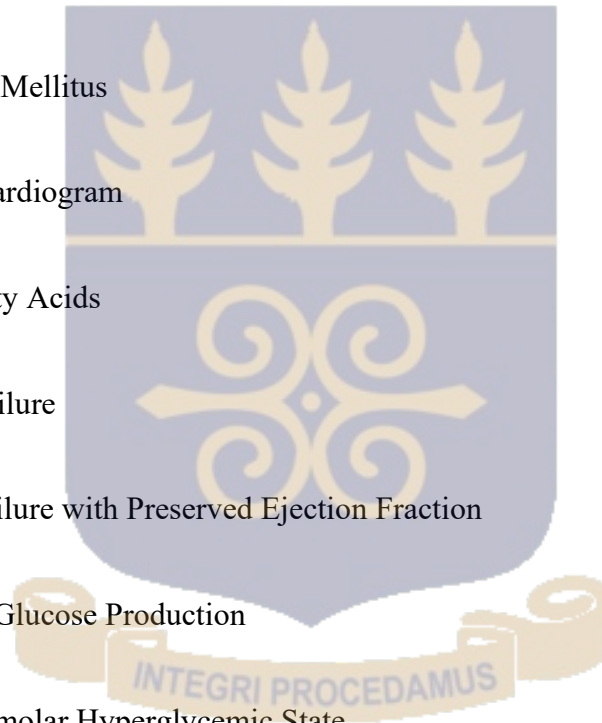
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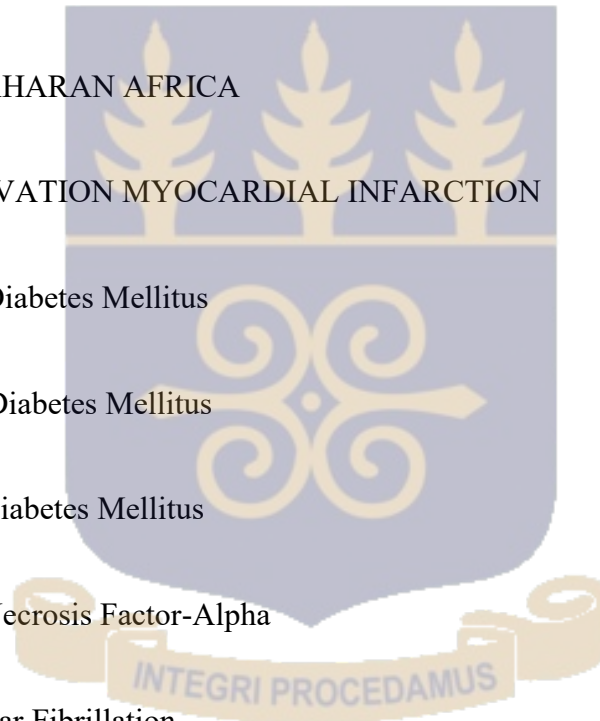


LIST OF ABBREVIATIONS

AGEs	Advanced Glycation End Products
CAD	Coronary Artery Disease
CDC	Centers for Disease Control and Prevention
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
ECG	Electrocardiogram
FFA	Free Fatty Acids
HF	Heart Failure
HfpEF	Heart Failure with Preserved Ejection Fraction
HGP	Hepatic Glucose Production
HHS	Hyperosmolar Hyperglycemic State
IGT	Impaired Glucose Tolerance
IL-1 α	Interleukin-1 Alpha
IL-6	Interleukin-6
KBTH	Korle-Bu Teaching Hospital
MACE	Major Adverse Cardiac Events



NDMRC	National Diabetes Management and Research Centre
NF-kB	Nuclear Factor-Kappa B
PAD	Peripheral Artery Disease
RAAS	Renin-Angiotensin-Aldosterone System
SCD	Sudden Cardiac Death
SCD	SUDDEN CARDIAC DEATH
SSA	SUB-SAHARAN AFRICA
STEMI	ST-ELEVATION MYOCARDIAL INFARCTION
T1DM	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TNF- α	Tumor Necrosis Factor-Alpha
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia



STRUCTURED ABSTRACT

Background: Globally, type 2 diabetes (T2D) remains highly prevalent among adults and is closely linked to cardiovascular diseases, including coronary artery disease (CAD). Individuals with T2D face a twofold increased risk of developing CAD compared to the general population. CAD significantly raises the likelihood of fatal complications, such as heart failure, myocardial infarction, and sudden cardiac death. Electrocardiography (ECG) serves as a valuable tool for identifying individuals with CAD. For individuals with type 2 diabetes, routine resting electrocardiograms are advised by the American Diabetes Association and the European Society of Cardiology/European Association for the Study of Diabetes. However, the benefits of these routine screenings have not been well established in many populations, including Ghanaians with T2D, due to a lack of data on the prevalence and patterns of ECG abnormalities in these groups.

General Aim: To determine the prevalence of resting ECG abnormalities and their associations with cardiovascular risk factors and current/prior adverse cardiac events in Ghanaian adults with T2D.

Methodology: In a cross-sectional design, resting standard 12-lead supine digital resting electrocardiography (ECG) testing was conducted on 430 Ghanaian adults with T2D managed at the National Diabetes Management and Research Centre at the Korle-Bu Teaching Hospital in Accra. A standard 12-lead supine digital resting electrocardiography (ECG) was recorded using the Vitalograph BT12 ECG™ and its Spirotrac® Software (Vitalograph, United Kingdom). The ECG tracings were processed with the device's inbuilt University of Glasgow 12-Lead ECG Analysis Algorithm¹. Two additional methods were used to evaluate each ECG: Minnesota coding and a trained physician's assessment. The ECG abnormalities were classified into seven main groups namely 1) QS pattern abnormalities, 2) QRS-axis deviation abnormalities; 3) R-waves abnormalities; 4) ST-segment abnormalities; 5) atrioventricular conduction defects; 6) ventricular conduction defects; and 7) arrhythmias including atrial flutter, atrial fibrillation and ventricular contractions or premature atrial. The identified ECG abnormalities were further categorized as either minor or major abnormalities. The prevalence of each abnormality was determined. Univariate logistic regression analyses were performed to assess the associations of potential predictor variables with the various pooled abnormality categories. Following this, a multivariate logistic regression model was built to assess predictors of each abnormal ECG category. The odds (OR) and 95% confidence interval (95% CI) were determined. A statistical test of significance was set at $p\text{-value} < 0.05$.

Results: In total, 61.6% of the study participants had abnormal ECG (23.9% had major abnormalities and 37.7% had minor abnormalities). Overall, 73.9% of the study participants were women. The mean ($\pm$ standard deviation) age, BMI, systolic BP, diastolic BP, duration of diabetes, HbA1c, and total cholesterol concentrations were 61.87 ($\pm$ 10.09) years, 29.46 ($\pm$ 5.81) kg/m², 135.33 ($\pm$ 18.50) mmHg, 75.56 ($\pm$ 11.20). 18.03 ($\pm$ 10.01) years, 8.74 ($\pm$ 2.25) % and 4.96 ($\pm$ 1.45) mmol/L. The proportion of smokers, individuals on statin therapy, and individuals who used insulin were 4.9%, 39.8%, and 36.3%, respectively. Compared to the normal ECG, individuals in the abnormal ECG group were significantly older (62.85 vs 60.30, $p=0.011$).

Aside age, the two groups did not differ in any of the baseline characteristics. In the study population, the mean heart rate was 73 beats per minute. The mean RR interval, PR interval, PQ interval, ST segment duration, QT interval, and corrected QT interval were respectively 839.24 ms, 167.13 ms, 166.11 ms, 114.99, 399.86 ms, and 422.36 ms respectively. The mean P wave and QRS complex widths were 114.83 ms and 94.97 ms respectively. The mean pooled p-axis, QRS-axis, and T-axis were 114.83° , 32.46° , and 32.60° , respectively. While the mean heart rate did not significantly differ between the two groups, the mean RR interval was 4% longer in the abnormal ECG group compared to the normal ECG group (853.94 ms vs. 818.54 ms, $p = 0.020$). Similarly, the mean PQ interval was 4.5% longer in individuals with abnormal ECG compared to those with normal ECG (169.21 ms vs. 161.83 ms, $p = 0.018$). The mean QT interval was 2% longer in participants with abnormal ECG compared to those with normal ECG (402.63 ms vs. 394.40 ms, $p = 0.015$). The mean QRS axis also differed significantly between the two groups (29.56° in the abnormal ECG group vs. 36.26° in the normal ECG group, $p = 0.037$). Additionally, the mean T-axis showed a significant difference between the groups (29.00° in the abnormal ECG group vs. 36.20° in the normal ECG group, $p = 0.045$). Among participants who reported symptoms of CAD, the majority (16.3%) reported angina symptoms; 3.0% of the study population reported symptoms of myocardial infarction. The proportion of individuals with CAD symptoms was higher in the abnormal ECG group compared with the normal ECG group (22.3% vs 9.7%, $p=0.001$). This was driven largely by differences in angina symptoms (20.8% vs 9.1%, $p=0.001$). In the multivariable regression model, hypertension was independently associated with QS pattern anomalies [odds ratio 1.65, 95% confidence interval 1.21 – 1.88, $p= 0.049$], very tall amplitude R-waves [1.31 (1.07 – 1.82), 0.041], ST-segment abnormalities [1.64 (1.31 – 1.93), 0.033], and ventricular conduction disorders [1.68 (1.32 – 1.99), 0.042]. HbA1c concentration $> 7\%$ was associated with abnormal Q-waves [1.27 (1.11 – 1.37), 0.032] while obesity was associated with atrioventricular conduction abnormalities [1.77 (1.36 – 2.17), 0.022]

Conclusion: This study shows a high burden of ECG abnormalities in Ghanaians with T2D. Which correlated with angina symptoms. Hypertension was the CVD risk factor most frequently independently associated with specific ECG abnormalities in our study population, including QS pattern anomalies, very tall amplitude R-waves, ST-segment abnormalities, and ventricular conduction disorders. Poor glycemic control and obesity were also independently associated with abnormal Q-waves and atrioventricular conduction abnormalities, respectively. These findings could inform the institution of frequent ECG testing in select groups of Ghanaians with T2D, to aid in the prevention of adverse CVD events.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Diabetes mellitus (DM) is a multisystem metabolic disease typified by aberrant glucose metabolism brought on by either a total or relative reduction in insulin secretion and/or peripheral insulin resistance². Worldwide, diabetes affects over 10% of adults². The incidence of diabetes is rising in the majority of the world's regions². Sub-Saharan Africa (SSA) is one area where the prevalence of diabetes is rising more quickly². For instance, it is anticipated that the estimated 24 million people in sub-Saharan Africa who currently have diabetes will have a 134% increase in diabetes prevalence by 2045, the greatest projected increase globally³.

Type 2 diabetes (T2D), which is the most common type of diabetes, is defined by a progressive loss of sufficient beta-cell insulin production, often with a history of insulin resistance^{2,4}. T2D is linked to modifiable risk factors like obesity, dyslipidemia, hypertension, and bad eating habits. It also appears to have a higher genetic relationship than type 1 diabetes (T1D)^{5,6}. As a major worldwide health concern, T2D diabetes is becoming more and more common everywhere, particularly in SSA⁷.

T2D may drive atherosclerotic macrovascular consequences such as cerebrovascular disease, coronary artery disease (CAD), and peripheral artery disease (PAD)⁸. Cardiovascular disease (CVD), especially the macrovascular complications, is twice as likely to occur in individuals with T2D as in the general population⁹. CAD is the primary cause of death for T2D individuals with CVD¹⁰. Angina pectoris, myocardial infarction, and heart failure are among the consequences or adverse events that can result from CAD and are linked to an increased risk

of death, including sudden death ⁸. T2D may also result in diabetes-specific microvascular disease including nephropathy, neuropathy, and retinopathy, as well as other microvascular complications including coronary microvascular disease ^{8,11}.

Electrocardiography is a quick, simple, and effective technique for evaluating the electrical activity of the heart and is valuable for identifying cardiac abnormalities including chamber enlargements, conducting defects, and electrolyte derangements ¹². Related or unrelated to established cardiovascular risk factors, resting electrocardiogram (ECG) abnormalities in the general population including bundle branch block and abnormal ST segment patterns such as elevation, depression, and T wave changes, are known to be associated with an increased risk of morbidity and mortality related to cardiovascular disease ¹³.

ECG abnormalities in individuals with T2D are thought to be prevalent. A recent well-conducted study that evaluated a core complete spectrum of CG abnormalities reported that a third of patients with T2D had ECG abnormalities ¹³. Of interest, the study reported that patients with diabetes without a CVD history also had a significantly high burden of ECG abnormalities ¹³. Specifically, 24% of these patients had ECG abnormalities ¹³

Drawing from this, the majority of professional associations, such as the American Diabetes Association and the recently published guidelines from the European Society of Cardiology and the European Association for the Study of Diabetes, recommend routinely doing a resting electrocardiogram (ECG) in individuals with T2D ^{14,15}. The usefulness of employing ECG for cardiac screening has long been questioned, despite its intuitive appeal and apparent clinical significance ¹³. An often-cited argument against routine ECG testing is the limited data of ECG testing in identifying individuals at risk of adverse cardiac and non-cardiac events in specific populations ¹³. The frequency of ECG anomalies in the context of T2D has been shown in numerous research conducted globally. These studies, however, have some limitations,

including as restricted sample sizes, limited data in certain racial or ethnic groups, such as sub-Saharan Africans, and those that concentrate on isolated ECG anomalies ¹³. Besides, ethnic-specific thresholds for what constitutes normal ECG in different populations including sub-Saharan Africans are unavailable. Like most physiological tests, the accuracy of ECG partly relies on background prevalence in healthy individuals. In apparently healthy individuals, C Cato Ter Haar and her colleagues have shown (using a multiethnic cohort) that there is a highly variable ethnicity-dependent prevalence of ECGs with ST-segment elevations exceeding STEMI thresholds ¹⁶. The findings of C Cato Ter Haar et al are relevant considering the potential consequences for ST-segment elevation myocardial infarction evaluations in individuals who are not of European ethnic origins, which are likely to underestimate or overestimate the diagnoses ST segment abnormalities. ST segment evaluation is important in individuals with diabetes given the likelihood of developing silent myocardial ischemic and/or infarctive events ¹⁷. Cardiovascular autonomic neuropathy, which may complicate T2D, increases the risk of silent myocardial events ^{18,19}. It has been demonstrated that in individuals with CAD, silent myocardial ischemia the existence of objective evidence of myocardial ischemia in the absence of chest discomfort or angina equivalent symptoms, such as dyspnea, nausea, or diaphoresis occurs considerably more frequently than angina episodes ²⁰. It is conceivable that aside from ST segment values which vary by ethnicity, other measures of ECG may also vary by ethnicity and could impact the utility of the existing thresholds in identifying individuals with ECG abnormalities in different populations.

Based on the currently used ECG threshold in defining what is considered normal, there is little information available on the prevalence of ECG abnormalities in many populations including sub-Saharan Africans with T2D. Studies done in other populations have been limited by small sample sizes and/or not reported on the complete range of ECG abnormalities based on cardiac electrophysiology ^{13,21–24}. For example, the study by Dawson et al focused on the epidemiology

of left ventricular hypertrophy only ²¹, the study by Hadaegh focused on ECG features related to CAD ²², the study by Singleton et al focused on QRS duration ²³ and the study by Cox et al looked at heart rate corrected QT interval ²⁴. Studies assessing a comprehensive range of ECG abnormalities in populations including sub-Saharan Africans with T2D are urgently needed. These significant gaps in the body of current material call for more research.

1.2 PROBLEM STATEMENT

The sub-Saharan African region is experiencing the fastest rate of increase in T2D prevalence anywhere in the world ³. In people under 60 years, Sub-Saharan Africa accounts for 77% of all diabetes-related deaths worldwide, according to the eighth edition of the Diabetes Atlas report³. T2D is also clinically relevant due to the additional risk for cardiovascular disease. For example, cardiovascular disease is twice as likely to occur in those with T2D as in the general population¹⁴. Diabetes alone or its associated cardiovascular disease is a key driver of the rising burden of recurrent hospitalization, healthcare-related expenses, reduced quality of life, and early mortality in afflicted individuals³. CVD, particularly CAD, is a major cause of morbidity and mortality in people with T2D ¹³. One of the biggest causes of early death in people with T2D is CAD³. Screening for CAD may aid in early detection and improve disease outcomes²⁵. Compared with the gold standard coronary angiography, ECG testing is a more widely available, cheaper, and non-invasive method for identifying people with CAD or at risk of CAD¹³. As a result, individuals with T2D are advised to undergo a resting electrocardiogram (ECG) frequently by the American Diabetes Association, the European Society of Cardiology, and the European Association for the Study of Diabetes¹³. Unfortunately, due to a lack of information regarding the prevalence of ECG abnormalities in many populations including Ghanaians with T2D, the benefits of such frequent assessments have not been proven. More recently, it has been shown that certain ECG characteristics, such as ST-segment alterations,

are extremely ethnically dependent, with a widely varying occurrence of ECGs with ST-segment elevations surpassing STEMI thresholds in people who appear to be in good condition¹⁶. Additionally, studies reporting a comprehensive range of ECG abnormalities in many populations with T2D including Ghanaians, as well as their associated factors, are lacking. All these limit the utility of ECG in screening and diagnosis of heart abnormalities in Ghanaians with T2D.

1.3 JUSTIFICATION OF THE STUDY

First, this study sought to quantify the burden of ECG abnormalities in Ghanaians with T2D, which will either justify or fail to justify the need for routine measurements of ECG in Ghanaians with T2D. Secondly, this study sought to report on the mean/estimated values of specific ECG components (including ST-segment) in Ghanaians with T2D with or without CVD risk factors or CAD symptoms. This is an important first step in assessing what thresholds or cut-off values are probably normal in individuals with T2D of ethnic Ghanaian origin. This will also shed light on possible unique cardiac electrophysiological features or functions in Ghanaians with T2D. This may be valuable in interpreting ECG in the study population. The study also sought to identify the factors associated with the various ECG abnormalities. This is important in guiding interventions targeting prevention and treatment.

1.4 GENERAL AIM

To determine the prevalence of resting ECG abnormalities and their associations with cardiovascular risk factors and current/prior adverse cardiac events in Ghanaian adults T2D

1.5 SPECIFIC OBJECTIVES

Among Ghanaian adults with T2D managed at the NDMRC, this study sought to:

1. Determine the prevalence of specific ECG abnormalities.
2. Identify factors associated with identified ECG abnormalities.
3. Assess the associations of ECG abnormalities with current/prior adverse cardiac events.



CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

The literature review is an essential component of any research effort, serving as a key component in every stage of the process. Its ability to create the theoretical foundation that would integrate the suggested study with the corpus of current knowledge makes it of utmost significance. This comprehensive review entails an exhaustive exploration, leveraging a diverse array of sources, including scholarly books, peer-reviewed journals, relevant articles, past research studies, and comprehensive internet databases. By engaging in a thorough examination of this expansive spectrum of literature, the review not only solidifies the theoretical foundation of the study but also establishes crucial connections with prior research, ensuring a robust and informed approach to the research inquiry.

2.2 DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by high blood glucose levels brought on by either insufficient or inefficient insulin use, or a combination of the two ^{26,27}. This disorder develops when the pancreas either cannot create enough insulin or the body is unable to use the insulin that is produced ²⁸. Hyperglycemia is the outcome, which is an accumulation of glucose in the bloodstream. Insulin production rises following a meal, allowing glucose from the blood to enter muscle, liver, and fat cells for usage as fuel or storage as fat or glycogen ²⁹. Insulin also prevents the breakdown of fat, protein, and glucose that have been accumulated. When blood glucose levels fall during a fast, the liver is stimulated to release

stored glucose by glucagon, which is released when basal insulin is constantly delivered to maintain glucose levels ³⁰. After an extended period of fasting, the liver first synthesizes glucose through the breakdown of glycogen (glycogenolysis), then switching to gluconeogenesis, where glucose is created from noncarbohydrate molecules ³⁰. This coordinated action of insulin and glucagon ensures a constant blood glucose level, essential for cellular energy metabolism³⁰. Deviations in this intricate regulatory system, such as insufficient insulin production or impaired cellular response to insulin, underlie the development of DM, leading to dysregulated blood glucose levels ³⁰.

Approximately 462 million people worldwide or 6.28% of the global population have T2D ³¹. With more than a million deaths associated with this illness in 2017 alone, it was the tenth most common cause of death ³¹. According to the International Diabetes Federation (IDF), the number of persons with T2D worldwide has increased, with 536.6 million (10.5%) expected to have the disease in 2021 and 783.2 million (12.2%) by 2045 ³. Eighty percent of those affected live in low- to middle-income countries (LMICs), where type 2 diabetes accounts for ninety to ninety-five percent of all instances of the disease in Africa ³². Remarkably, a considerable fraction, perhaps 49.7% worldwide and 69.2% in Africa, is still undiagnosed ³³. About 24 million individuals in Africa had diabetes in 2021; by 2045, that figure is predicted to increase to 55 million, representing a 129% increase. Despite this, just 1% of worldwide diabetes-related spending comes from the continent ³⁴. An estimated 15.5 million adults in sub-Saharan Africa had diabetes in 2017, representing a 6% regional prevalence and costing the area over USD 3.3 billion in medical expenses³⁵. Approximately 2.4 million people in Ghana suffer from diabetes, accounting for 7.5% of the adult population ³⁴.

Types of diabetes mellitus include T1D, T2D, gestational diabetes, and specific types of diabetes resulting from other causes, such as monogenic diabetes syndromes (like neonatal

diabetes and maturity-onset diabetes of the young), exocrine pancreas diseases (like pancreatitis and cystic fibrosis), and drug- or chemical-induced diabetes (like after organ transplantation, in the treatment of HIV/AIDS, or with the use of glucocorticoids). Each of these types of diabetes has unique causes, risk factors, and management strategies ³⁶. T1D is a long-term autoimmune disease that causes hyperglycemia due to inadequate insulin synthesis. It is brought on by the death of pancreatic beta cells and needs to be carefully managed to avoid serious side effects like stroke, kidney problems, heart disease, and eyesight loss. Exogenous insulin therapy is the principal treatment for T1D; yet, many people still struggle to achieve ideal blood glucose control ³⁶. Conversely, poor tissue response to insulin and insufficient insulin secretion cause T2D, a common metabolic illness. Management entails the use of metformin and insulin treatment ³⁶. Though the exact ratio varies by nation, 98% of all cases of diabetes globally are caused by T2D. 37.3 million persons worldwide have been diagnosed with diabetes in 2022, with 95% of those cases being T2D, according to data from the CDC ^{37(p2)}. Pregnancy-related diabetes is known as gestational diabetes, which is usually brought on by the body's incapacity to manufacture enough insulin to satisfy the increased demands brought on by hormonal changes ³⁶. Obesity, a family history of T2D, and a history of gestational diabetes in prior pregnancies are risk factors ³⁶. When discovered during the second or third trimester of pregnancy, it is treatable with insulin medication and dietary changes ³⁶.

A family history of diabetes (having parents or siblings with the disease), obesity (defined as being more than 20% overweight or having a body mass index (BMI) of more than 27 kg/m², and certain racial or ethnic backgrounds such as African Americans, Hispanic Americans, Native Americans, Asian Americans, and Pacific Islanders are risk factors for developing diabetes mellitus ³⁸. Other risk factors include being older than 45 years old, having impaired glucose tolerance or impaired fasting glucose previously detected, having hypertension (blood pressure $\geq 140/90$ mm Hg), having low HDL cholesterol (≤ 35 mg/dL or 0.90 mmol/L), having

elevated triglyceride levels (≥ 250 mg/dL or 2.8 mmol/L), and having a history of gestational diabetes or giving birth to babies weighing more than 9 pounds ³⁹.

2.3 PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

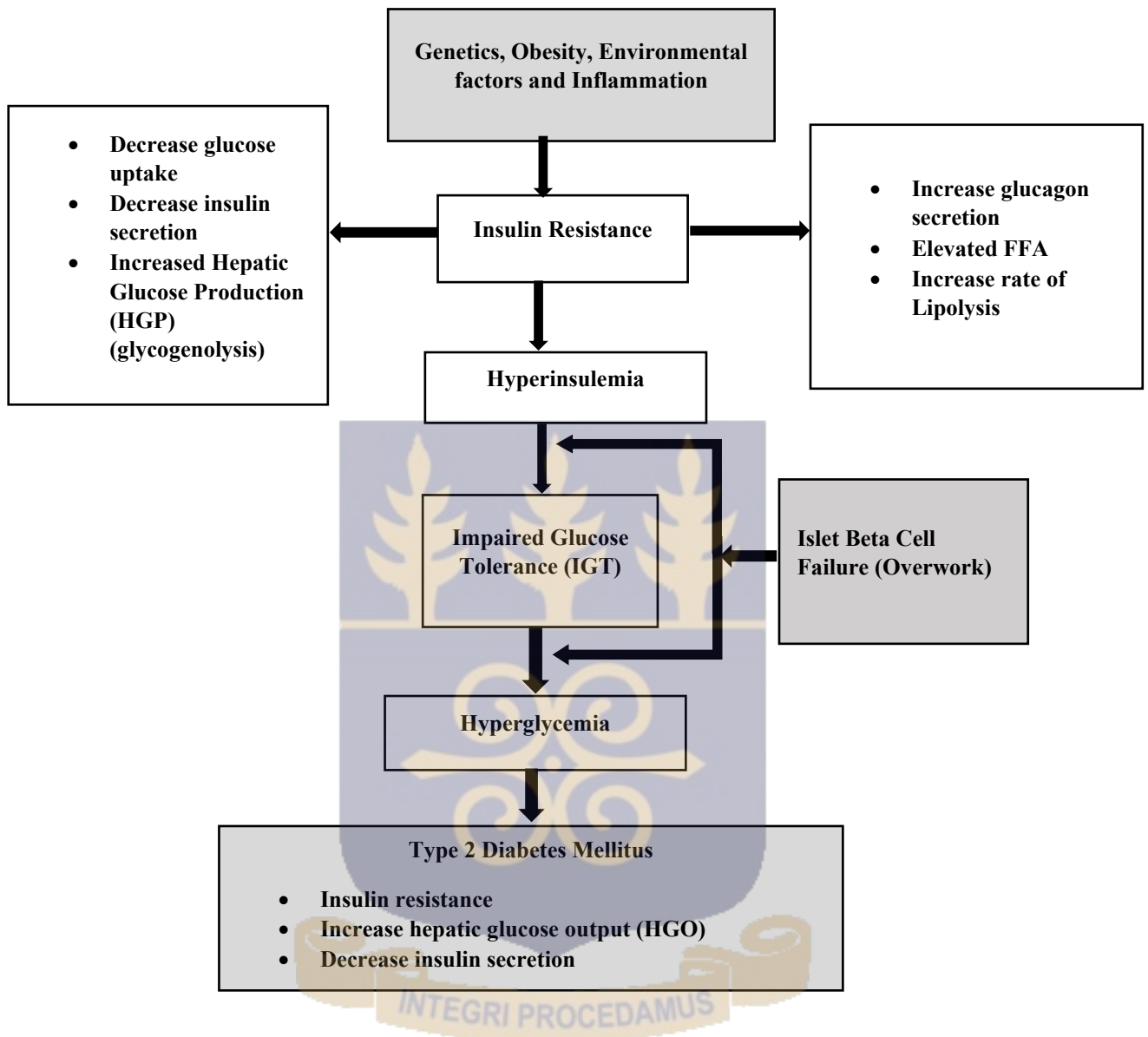
The pancreas has both endocrine and exocrine functions⁴⁰. Its endocrine functions are carried out by the islets of Langerhans, which contain alpha, beta, and delta cells⁴⁰. Alpha cells emit glucagon, which increases blood sugar by inducing the release of glucose from the liver, whereas beta cells secrete insulin, which lowers blood sugar by encouraging glucose uptake into cells ⁴⁰. Somatostatin, which controls glucagon and insulin, is produced by delta cells ⁴⁰. The pathophysiology of T2D is a complex interplay of genetic, environmental, and lifestyle factors ⁴¹. Insulin resistance and decreased insulin production are the two main insulin-related dysfunctions it includes ⁴². Insulin resistance causes organs to absorb glucose less efficiently, secrete less insulin, and increase hepatic glucose production (HGP) ^{29,42}. The pancreas first increases insulin output in response to insulin resistance, which causes hyperinsulinemia ^{29,42}. Despite this compensation, glucose intolerance develops due to the impaired ability of cells to take up glucose, leading to Impaired Glucose Tolerance (IGT) ^{29,36,42}. Over time, this persistent demand on the pancreatic beta cells leads to Islet Beta Cell Failure, which is characterized by the overworking and eventual exhaustion of beta cells, reducing insulin production ²⁹.

In addition, insulin resistance causes higher levels of free fatty acids (FFA), greater lipolysis rates, and increased glucagon output, all of which lead to hyperglycemia ^{29,42}. The defining feature of T2D, persistent hyperglycemia, is caused by the interaction of insulin resistance, decreased insulin production, and elevated HGP ^{29,42}. The result of these processes is full-blown T2D, which is marked by decreased insulin secretion, increased hepatic glucose output, insulin resistance, and chronic hyperglycemia ^{29,42,43}. This condition poses significant risks for various

complications if not properly managed ^{29,36}. Polyuria, polydipsia, unexplained weight loss, exhaustion, and blurred vision are typical warning signs and symptoms ⁴⁴. Heart disease, neuropathy, nephropathy, retinopathy, and issues involving the lower extremities, such as diabetic foot ulcers, are examples of long-term consequences ⁴⁴.



Figure 2.1: Pathophysiology of Type 2 Diabetes Mellitus



Source: Themes, (2017)

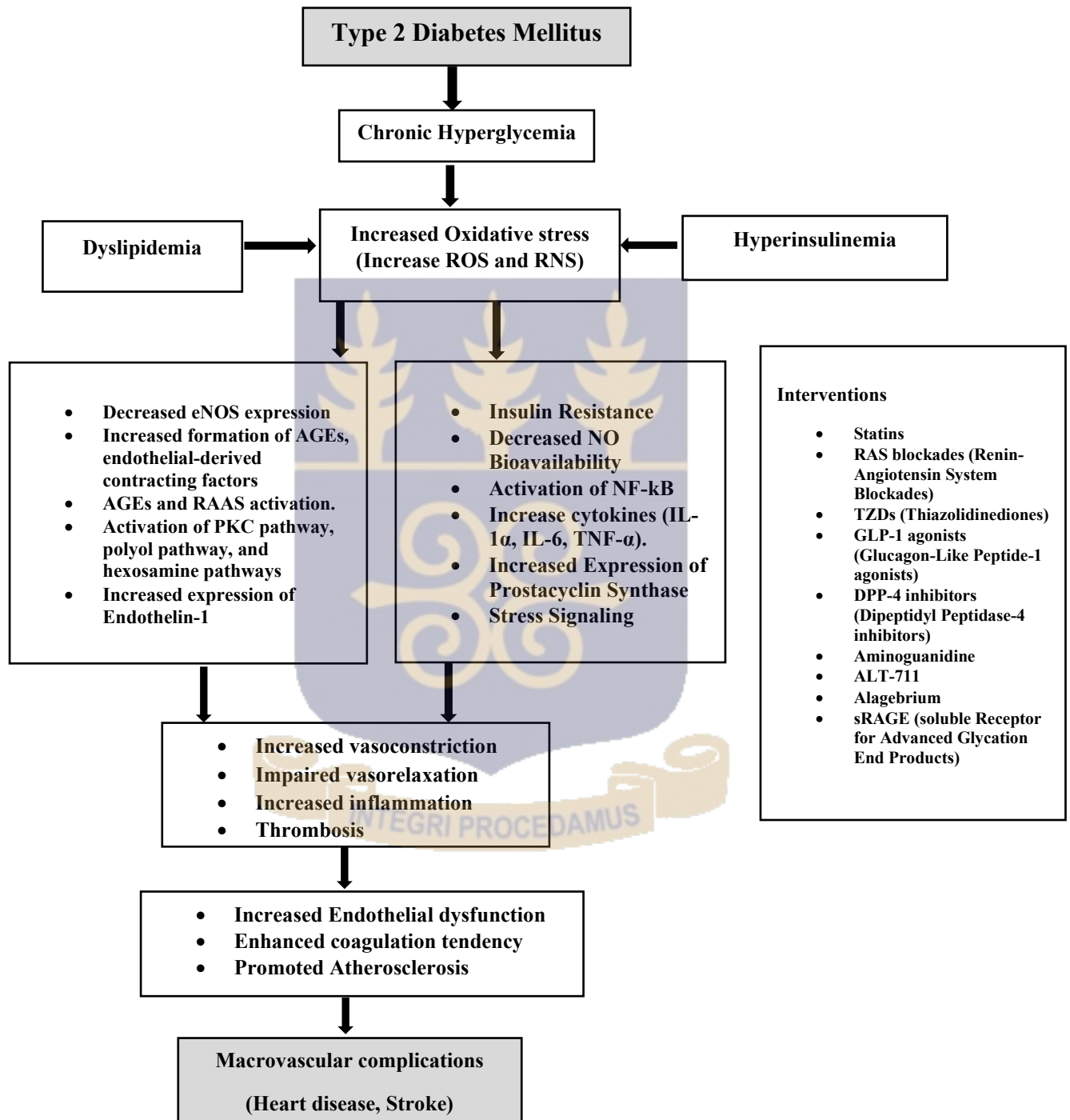
2.4 COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

There are two types of DM complications: acute problems and chronic problems. Hypoglycemia, diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and infections are among the acute consequences ⁴⁵. Dangerously low blood sugar levels, or hypoglycemia, can result in symptoms like confusion, dizziness, and even seizures ⁴⁵. High blood glucose and ketone accumulation are symptoms of diabetic ketoacidosis, which cause a severe metabolic acidosis ⁴⁶. Extreme hyperglycemia and dehydration, predominantly in T2D, are hallmarks of the hyperosmolar hyperglycemic condition, which also heightens vulnerability to infections ⁴⁶. Long-term complications of diabetes mellitus encompass both microvascular and macrovascular damage ^{8,47}. Diabetic retinopathy, which can result in blindness; nephropathy, which can cause chronic kidney disease; and diabetic neuropathy, which can cause nerve damage and raise the risk of diabetic foot ulcers, are examples of microvascular problems that impact small blood vessels ^{6,8}. DM is associated with a notable 15–40-fold increased incidence of lower limb amputation as compared to the general population ⁴⁸.

T2D causes persistent hyperglycemia, which sets off the renin-angiotensin-aldosterone system (RAAS) and the production of advanced glycation end products (AGEs) ^{49,50}. This activates NF- κ B, promoting oxidative stress via ROS, eNOS, and NADPH oxidase ^{50,51}. Simultaneously, inflammation increases through cytokines like IL-1 α , IL-6, and TNF- α ⁵⁰. These processes cause endothelial dysfunction, enhance coagulation, and promote atherosclerosis, ultimately leading to macrovascular complications such as heart disease and stroke ⁴⁹. Macrovascular complications are those that affect larger blood vessels and include peripheral artery disease, which affects circulation in the limbs and can cause pain and amputation, cerebrovascular disease, which causes strokes, and cardiovascular diseases like coronary artery disease, which

can cause heart attacks ⁵². These long-term issues can significantly lower quality of life and raise mortality risk ⁴⁸.

Figure 2.2 Pathophysiology of Macrovascular Complications in T2D



Source: Kaur, Kaur & Singh, (2018)

2.5 CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES MELLITUS

Cardiovascular diseases (CVDs) and T2D are closely intertwined, presenting a significant public health concern. The presence of CVD-related complications, such as myocardial infarction or stroke, significantly exacerbates the already elevated mortality risk associated with diabetes ⁵². CVD is a significant risk factor for disease and mortality in people with T2D ⁴⁸. This combination almost doubles the chance of dying, which is expected to shorten life expectancy by about 12 years ⁴⁸. The risk of cardiovascular problems, such as peripheral artery disease, coronary artery disease, and stroke, is much higher in people with T2D³². This risk is primarily due to shared pathophysiological mechanisms such as chronic hyperglycemia, insulin resistance, and dyslipidemia ⁵⁰. The development of advanced glycation end-products (AGEs) as a result of persistent hyperglycemia exacerbates oxidative stress and inflammation ⁵⁰. These processes activate nuclear factor-kappa B (NF- κ B), worsening endothelial dysfunction and promoting atherosclerosis ⁴⁹. Additionally, T2D often accompanies hypertension and obesity, exacerbating cardiovascular risk ^{49,50}.

Heart failure is a notable complication, as T2D can cause cardiac muscle dysfunction. The condition impairs cardiac contractility and diastolic function, leading to heart failure with preserved ejection fraction (HFpEF) ⁵³. T2D is closely linked to heart failure (HF) due to its association with multiple cardiovascular risk factors such as hypertension, obesity, and dyslipidemia ⁵³. T2D accelerates coronary and systemic atherosclerosis, vascular changes, and autonomic dysfunction, contributing to increased cardiovascular risk ⁵³. Advanced glycation end products (AGEs), high blood pressure, low-grade inflammation, and atherogenic lipid profiles are also linked to the condition, and these factors worsen cardiovascular damage and encourage heart failure ^{15,53}. People with DM are 2–4 times more likely to develop cardiovascular diseases and 2–5 times more likely to die from them than the general

population⁵⁴. T2D stands as a robust independent predictor of stroke and CVD, with patients having T2D facing a 150%-400% increased risk of stroke⁴⁸. Moreover, T2D impairs cardiac electrical conduction, raising the possibility of arrhythmias and SCD⁴⁴. The chronic inflammation associated with T2D, driven by cytokines like IL-1 α , IL-6, and TNF- α , further disrupts cardiac function by promoting endothelial dysfunction and increasing coagulation^{50,51}.

2.6 ELECTROCARDIOPHYSIOLOGY

2.6.1 History and Definition of Electrophysiology

The area of physiology known as electrophysiology examines the electrical characteristics of biological tissues and cells, especially as they relate to the heart⁵⁵. The origins of this field trace back to the late 19th century when physiologists began to understand the heart not just as a pump but as a complex electrochemical organ⁵⁶. The development of electrophysiology began with the discovery of the bioelectric potentials by Luigi Galvani in the 18th century, who observed that the muscles of dead frogs twitched when struck by a spark of electricity⁵⁶. This was a pivotal moment that laid the groundwork for the study of bioelectricity. In the 19th century, Carlo Matteucci demonstrated that injured muscle tissue could generate electricity, further solidifying the connection between bioelectric phenomena and muscle function⁵⁶.

However, the true birth of electrophysiology as a discipline is often credited to Willem Einthoven, a Dutch physiologist who invented the string galvanometer in 1903, allowing for the first accurate recordings of the heart's electrical activity⁵⁷. Because of Einthoven's research, the electrocardiogram, or EKG, was developed. This instrument is still essential for identifying and comprehending heart activity⁵⁷. Cardiac electrophysiology, encompasses the study of the

heart's electrical properties and how they manifest in the ECG ⁵⁶. At its core, this discipline seeks to unravel the mysteries of the heart's rhythm, conduction pathways, and the intricate interplay of ion channels that orchestrate cardiac function ¹³. Clinicians may diagnose and treat a wide range of cardiac problems, from benign arrhythmias to potentially fatal illnesses like ventricular fibrillation, by knowing the electrical foundations of the heart ⁵⁵. Central to electrocardiophysiology is the cardiac action potential, a sequence of electrical changes that occur in cardiac cells during each heartbeat. Ions move across cell membranes during this process, causing stages of depolarization and repolarization. These occurrences are recorded by the ECG, which offers an image of the electrical dynamics of the heart ¹³.

The heart relies on a complex network of ion channels, each playing a distinct role in regulating the flow of ions such as sodium, potassium, and calcium⁴⁰. Electrocardiophysiology scrutinizes the behavior of these channels, shedding light on abnormalities that can disrupt the delicate balance of ion flux, giving rise to arrhythmias ⁵⁸. Furthermore, the study of electrocardiophysiology explores the conduction system, which is a specialized cell network in charge of electrical signal transmission across the heart ⁴⁰. Disorders affecting this system, such as heart block, can be identified through ECG analysis, guiding clinicians in devising appropriate interventions ⁵⁸. In the realm of standards and recommended measures in electrocardiography, the discipline emphasizes the paramount importance of standardizing ECG acquisition for accurate interpretation. Proper lead placement and signal acquisition are highlighted to ensure a reliable representation of the heart's electrical activity ⁵⁵. Guidelines stipulate the placement of electrodes on specific anatomical locations to capture different aspects of cardiac conduction⁵⁷.

Electrocardiophysiology establishes normative values for ECG parameters, enabling clinicians to discern deviations indicative of pathology⁵⁸. Heart rate, PR interval, QRS duration, and QT

interval normal ranges are used as reference points to help identify irregularities linked to different cardiac diseases⁵⁵. The discipline provides comprehensive diagnostic criteria for various arrhythmias. Through meticulous analysis of ECG waveforms, clinicians can identify specific patterns associated with atrial fibrillation, atrial flutter, ventricular tachycardia, and other rhythm disturbances³². These criteria guide accurate diagnosis and subsequent treatment decisions³². Advances in imaging modalities like cardiac magnetic resonance imaging (MRI) and computed tomography (CT) combined with electrocardiophysiology hold potential for a deeper comprehension of both structural and functional cardiac problems¹³.

2.6.2 Cardiac Conduction System

The network of specialized cardiac muscle cells known as the cardiac conduction system is in charge of generating and transmitting the electrical impulses that regulate the contraction of the heart⁴⁶. This mechanism keeps the heart's beat regular and coordinated, which enables it to pump blood efficiently⁴⁰. The right atrium's sinoatrial (SA) node is where the conduction pathway begins. Due to its ability to produce the first electrical impulse, the SA node is frequently referred to as the heart's natural pacemaker⁴⁰. The atria then contract as a result of this impulse spreading across them, forcing blood into the ventricles⁴⁰. The impulse leaves the atria and proceeds to the atrioventricular (AV) node, which is situated where the ventricles and atria meet⁴⁰.

As a gatekeeper, the AV node slows down the impulse before it enters the ventricles^{40,59}. This delay is essential because it makes sure the ventricles contract before the atria have enough time to close to their maximum length⁵⁹. The impulse travels via the His-Purkinje system, a network of fibers that quickly conducts the electrical signal across the ventricles, after passing via the AV node⁴⁰. The impulse initially passes through the bundle of His, which splits into the bundle branches that run down the interventricular septum on the right and left⁴⁰. These

branches further divide into Purkinje fibers, which distribute the electrical signal to the ventricular myocardium, leading to a coordinated contraction of the ventricles and the subsequent ejection of blood into the pulmonary and systemic circulations ⁴⁰.

2.6.3 Ionic Basis of Cardiac Action Potential

An essential component of heart activity is the cardiac action potential, which is a series of ion movements across the cardiac cell membrane ⁴⁰. It consists of five phases: Phase 0 (Depolarization), where the rapid influx of sodium (Na^+) ions through voltage-gated channels causes a sharp rise in membrane potential; Phase 1 (Initial Repolarization), marked by the closure of Na^+ channels and a brief outward flow of potassium (K^+) ions; Phase 2 (Plateau Phase), where a balance between calcium (Ca^{2+}) influx and K^+ efflux maintains the action potential, enabling sustained muscle contraction; Phase 3 (Repolarization), during which Ca^{2+} channels close and K^+ channels open to return the membrane potential to its resting state; and Phase 4 (Resting Membrane Potential), where the Na^+/K^+ ATPase pump restores the ionic balance, preparing the cell for the next action potential ^{40,60}. This process underpins the rhythmic contraction of the heart, essential for effective blood circulation ^{40,60}.

2.6.4 Ionic Basis of SA Nodal Action Potential

The sinoatrial (SA) node, the heart's natural pacemaker, initiates electrical impulses that regulate the heartbeat. Unlike other cardiac cells, SA node cells lack a stable resting membrane potential and instead exhibit spontaneous depolarization, resulting in rhythmic action potentials ^{40,60}. This process begins in Phase 4 with the gradual depolarization of the membrane due to the slow influx of sodium (Na^+) through funny (I_f) channels and decreased potassium (K^+) efflux ⁴⁰. This gradual rise leads to Phase 0, where T-type calcium (Ca^{2+}) channels open, causing a rapid Ca^{2+} influx and a steep rise in membrane potential, marking the depolarization. In Phase 3, repolarization occurs as K^+ channels open, allowing K^+ to exit the cell while Ca^{2+}

channels close, returning the membrane to a more negative state ⁴⁰. The cycle then restarts with the gradual depolarization of Phase 4. The SA node's unique ionic behavior enables it to maintain the heart's rhythm by continuously generating action potentials ⁴⁰.

2.6.5 Ionic Basis of Cardiac Ventricular Muscle Function

Ventricular muscle cells, or cardiomyocytes, are crucial for the heart's forceful contractions that pump blood ⁴⁰. These cells have a longer action potential duration, ensuring a sustained contraction for effective blood ejection ⁴⁰. The process begins with Phase 0 as voltage-gated sodium (Na^+) channels open, leading to rapid depolarization. Phase 1 follows with initial repolarization due to the closure of Na^+ channels and brief potassium (K^+) efflux ⁴⁰. The Plateau Phase (Phase 2) is more pronounced in these cells, with a sustained influx of calcium (Ca^{2+}) through L-type channels and continued K^+ efflux, maintaining depolarization and prolonging contraction ⁴⁰. In Phase 3, repolarization occurs as Ca^{2+} channels close, and K^+ channels remain open, returning the membrane potential to its resting state ⁴⁰. The Na^+/K^+ ATPase pump sustains Phase 4, which primes the cell for the subsequent action potential ⁴⁰. This prolonged action potential ensures the heart contracts sufficiently to pump blood effectively, preventing premature contractions that could disrupt blood flow ⁴⁰.

2.6.6 Cardiac Dysrhythmias

Cardiac dysrhythmias, or arrhythmias, represent disturbances in the heart's normal rhythm due to disruptions in the generation or conduction of electrical impulses ^{40,61}. These can range from minor, benign conditions to severe, life-threatening scenarios. They can be broadly divided into two categories: tachyarrhythmias, or fast heart rates, and bradyarrhythmias, or slow heart rates ⁶¹. Bradyarrhythmias may arise from issues in the sinoatrial (SA) node, such as sick sinus syndrome, or from impaired conduction in the atrioventricular (AV) node, leading to a slow heart rate ^{40,61}. On the other hand, tachyarrhythmias, which include conditions like atrial

fibrillation and ventricular tachycardia, often stem from increased automaticity, triggered activity, or reentrant circuits, where abnormal ionic currents, such as enhanced Na^+ or Ca^{2+} inflow or reduced K^+ outflow, play a critical role ⁶¹.

Three primary mechanisms underlie the development of cardiac dysrhythmias: abnormal automaticity, triggered activity, and reentry ^{40,61}. Abnormal automaticity occurs when non-SA node cardiac cells spontaneously depolarize due to ionic changes, leading to arrhythmias like ectopic beats. Triggered activity arises from afterdepolarizations, either early (during the action potential plateau) or delayed (during resting potential), which can provoke premature action potentials, leading to arrhythmias like Torsades de Pointes ⁴⁰. Reentry involves the continuous circulation of an electrical impulse through a reentrant circuit in the heart, which can occur due to slow conduction or unidirectional block, resulting in conditions such as atrial flutter or ventricular tachycardia ⁴⁰. Examples of cardiac dysrhythmias illustrate the diverse ways in which ionic disturbances can impact heart rhythm. The most common persistent arrhythmia, atrial fibrillation (AF), is characterized by chaotic electrical activity in the atria, which results in irregular, frequently fast ventricular response and inefficient atrial contractions ⁴⁰. The ionic underpinnings of AF involve altered atrial action potentials with shortened refractory periods and increased automaticity, frequently exacerbated by structural changes like fibrosis that facilitate reentry circuits ^{40,61}.

Ventricular Tachycardia (VT), a potentially fatal arrhythmia originating from the ventricles, is characterized by a rapid heart rate that can severely impair cardiac output ⁴⁰. VT can arise from abnormal automaticity, triggered activity, or reentry, particularly in the context of heart disease such as myocardial infarction ^{40,60}. Ionic imbalances, including altered Na^+ , Ca^{2+} , or K^+ currents, contribute to its development, with reentry circuits often forming in scar tissue from previous infarctions ^{40,59}. An extended QT interval on the ECG, which indicates delayed

ventricular repolarization, and a higher incidence of torsades de pointes, a kind of polymorphic ventricular tachycardia, are symptoms of long QT syndrome (LQTS) ⁴⁰. LQTS is commonly linked to mutations in ion channels responsible for K⁺ currents, such as KCNQ1 or HERG, which lead to prolonged action potentials and an elevated risk for triggered activity ⁴⁰. Torsades de Pointes is a polymorphic VT condition that is linked to an extended QT interval. It is distinguished by twisted QRS complexes on the electrocardiogram (ECG) ⁴⁰. This arrhythmia often results from early afterdepolarizations during prolonged repolarization, with its ionic basis involving delayed rectifier K⁺ current abnormalities that extend the action potential duration ⁴⁰.

2.6.7 Electrocardiographic Abnormalities

Electrocardiographic abnormalities are pivotal indicators of various cardiac arrhythmias and disorders, offering crucial insights for accurate diagnosis and tailored treatment. An electrocardiogram (ECG) showing absent P-waves indicates atrial fibrillation (A-Fib), the most common chronic cardiac rhythm problem. A-Fib is characterized by disorganized episodes of fast, irregular atrial pounding ⁵⁸. The Hybrid Maze Procedure, an innovative intervention, showcases promise in addressing chronic A-Fib cases. Atrial Flutter (AFL) shares similarities with A-Fib but follows an organized pattern, presenting a distinctive sawtooth pattern in the P-waves on ECGs. Heart Block, marked by abnormally slow heartbeats, is discerned through prolonged PR intervals and atrioventricular dissociations on ECGs and may necessitate pacemaker implantation for severe cases. Prolonged QT intervals on electrocardiograms (ECGs) indicate Long QT Syndrome (LQTS), which increases the risk of sudden cardiac death and necessitates a multimodal therapy including medicine and device implantation ⁵⁸.

Sick Sinus Syndrome (SSS) arises from sinoatrial node dysfunction, leading to bradycardia or irregular heart rhythms, with symptoms ranging from fatigue to fainting^{13,62}. Supraventricular

Tachycardia (SVT) involves rapid heartbeats originating above the ventricles and manifests as sudden onset and offset of regular QRS complexes on ECGs^{58,63}. Ventricular Fibrillation (VF) is a life-threatening condition marked by rapid, disorganized ventricular contractions, requiring immediate defibrillation. Ventricular Tachycardia (VT), presenting as a very fast heart rate with wide QRS complexes on ECGs, demands prompt intervention, including medication, catheter ablation, or defibrillator implantation. Other ECG abnormalities encompass Premature Contractions, where the heart beats too early, and Bradycardia or Tachycardia, indicative of an excessively slow or fast heart rate. Understanding these electrocardiographic abnormalities is imperative for clinicians, with collaboration between electrophysiologists and other cardiac experts enhancing the comprehensive care provided to patients experiencing these conditions⁶³.

2.7 PREVALENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES AMONG INDIVIDUALS WITH T2D

Electrocardiographic (ECG) abnormalities are a significant concern in individuals with T2D, given their elevated risk for cardiovascular diseases (CVD)^{54,62}. Numerous studies have sought to uncover the prevalence, patterns, and factors associated with these abnormalities, contributing to our understanding of their clinical and epidemiological importance^{13,27}. This review integrates findings from various studies to explore the prevalence of ECG abnormalities in T2D patients, highlighting methodological approaches, key findings, and limitations while discussing their implications.

Harms et al. (2021) conducted a large-scale cross-sectional study on 8,068 participants in the Netherlands, analyzing ECG abnormalities within the Hoorn Diabetes Care System cohort. They reported a prevalence of 29.1% for ECG abnormalities in the total population, with 24% of those without a history of CVD exhibiting such abnormalities¹³. These findings align with

similar observations by Singh et al. (2022) in a prospective study in North India, where 29.1% of participants exhibited ECG abnormalities, with minor and major abnormalities found in 16% and 13.1%, respectively²⁷. Both studies emphasize a higher prevalence in older adults and those with hypertension, demonstrating robust associations between age, blood pressure, and cardiovascular risk factors^{26,27}. However, while Harms et al, (2021) utilized a larger sample size and the Minnesota Code classification for ECG abnormalities, Singh et al, (2022) reliance on a single tertiary hospital might limit the generalizability of their findings^{13,27}. These methodological differences highlight the importance of diverse population-based studies for a comprehensive understanding²⁷.

In contrast, Bedane et al. (2021) observed a markedly higher prevalence of 61% for ECG abnormalities among T2D patients in Southwest Ethiopia, indicating regional variations potentially influenced by demographic and clinical factors. This study found significant associations with body mass index (BMI), diabetes duration, and educational status, suggesting that socioeconomic factors and healthcare access might play critical roles in determining cardiovascular health³². Similarly, Sinamaw et al. (2022) reported a prevalence of 45% in Amhara, Ethiopia, with T-wave abnormalities being the most common⁶². Notably, their findings on diabetes duration and hypertension as key risk factors were consistent with Bedane et al.'s results, reinforcing the role of chronic disease management in mitigating cardiac risks. However, while both studies employed systematic sampling, their relatively smaller sample sizes and cross-sectional designs limit the ability to infer causality^{32,62}.

The pattern of abnormalities also varied across studies. Patel et al. (2023), in a case-control study, highlighted significant differences in QT interval prolongation, ST-segment changes, and T-wave abnormalities between T2D patients and healthy controls⁵⁵. The study's matched control design offered a clear comparison, confirming that these ECG alterations are predictive

of cardiovascular morbidity and mortality in diabetic populations. However, this study's small sample size (n=100) and lack of longitudinal follow-up constrain its capacity to predict long-term outcomes. Interestingly, these findings were corroborated by Ezeude et al. (2023) in Nigeria, where asymptomatic T2D patients also exhibited a high prevalence of T-wave and QT interval abnormalities⁶⁴. These parallels across geographically diverse populations underscore the universal cardiovascular risks posed by diabetes, though regional disparities in healthcare infrastructure might influence outcomes.

Khanal et al. (2023) introduced a novel perspective by linking ECG abnormalities with renal impairment in a Nepalese cohort⁶⁵. While the prevalence of ECG abnormalities (47.8%) was similar to other studies, this study uniquely highlighted the interplay between cardiovascular and renal complications, emphasizing hypertension and diabetes duration as shared risk factors. The integration of renal biomarkers adds depth to the analysis, although the lack of control groups and longitudinal data limits the study's ability to delineate causal pathways. Similarly, Asmare et al. (2023) focused on T-wave abnormalities, finding that poor glycemic control and hypertension were strongly associated with these changes⁶⁶. Their multicenter approach enhanced the generalizability of the findings, yet the absence of a control group remains a limitation.

While these studies consistently demonstrate a high prevalence of ECG abnormalities in T2D patients, discrepancies in reported rates ranging from 29.1% to 61% reflect differences in study populations, diagnostic criteria, and healthcare settings. For instance, the use of advanced ECG classification systems such as the Minnesota Code by Harms et al. might yield more precise diagnoses compared to simpler categorizations used in other studies¹³. Additionally, variations in access to healthcare, prevalence of comorbidities, and socioeconomic factors likely contribute to these differences. Limitations in cross-sectional designs, small sample sizes, and

lack of standardized protocols further complicate comparisons across studies. In conclusion, ECG abnormalities are highly prevalent in T2D populations globally, with age, hypertension, glycemic control, and disease duration consistently emerging as significant risk factors. These findings underscore the importance of routine ECG screening in diabetic care, particularly in resource-limited settings where undiagnosed cardiovascular complications may exacerbate morbidity and mortality. Future studies should prioritize longitudinal designs, larger sample sizes, and standardized diagnostic criteria to better elucidate the causal relationships and regional variations in ECG abnormalities among T2D patients.

2.8 PATTERNS OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN T2D INDIVIDUALS

Patterns of electrocardiographic (ECG) abnormalities in individuals with T2D reveal significant cardiovascular risks, underscoring the importance of early identification and management⁶². T2D is frequently accompanied by subclinical cardiac dysfunction, detectable through ECG, which serves as a non-invasive tool to identify risks such as arrhythmias, ischemia, and left ventricular hypertrophy (LVH)⁶⁴. These risks, often asymptomatic, contribute significantly to the morbidity and mortality associated with diabetes. Various studies have investigated ECG abnormalities in T2D populations, providing insights into their prevalence, characteristics, and clinical implications, while highlighting methodological nuances and regional differences^{13,27}.

Ndour et al. (2017) conducted a cross-sectional study in Dakar to assess ECG abnormalities among 100 individuals with T2D⁶³. The study found that 20% of participants exhibited rhythm abnormalities, while markers of hypertrophy and repolarization disturbances were also prominent. Specifically, left ventricular hypertrophy (25%) and right atrial hypertrophy (11%) were observed, along with notable anterior necrosis (15%) and a prolonged QT interval in 21%

of cases. This study emphasized the heterogeneity of ECG abnormalities, which ranged from conduction defects to myocardial necrosis⁶³. The findings align with Patel et al. (2023), whose research in India similarly identified significant QT prolongation and alterations in QRS complex duration among diabetic patients. Patel et al, (2023) study further delineated ECG variations, such as ST segment and T wave changes, as predictive markers for coronary events, especially in asymptomatic individuals⁵⁵. However, in Ndour et al's, (2017) study, smaller sample size and single-center design limit the generalizability of their findings compared to Patel et al's, (2023) inclusion of a control group and larger comparative analysis⁶³.

Pillay, Hift, and Aldous (2018) expanded on these observations by examining ECG abnormalities in 637 black South African T2D patients. Their findings highlighted a higher prevalence of LVH (36%) and silent myocardial infarctions (MIs), with 89.8% of MIs occurring in the inferior territory. The silent nature of most MIs is particularly alarming, as it indicates an often-overlooked cardiovascular burden in T2D⁶⁷. Compared to Ndour et al. (2017), this study offered a broader perspective on the systemic risk factors associated with ECG abnormalities, such as elevated triglyceride levels and suboptimal waist-to-height ratios^{63,67}. Both studies underscore the multifaceted nature of ECG abnormalities in T2D, yet Pillay et al's (2018) regional focus on South Africa may reflect demographic and genetic predispositions unique to their cohort. This contrasts with Patel et al's (2023) focus on an Indian population, where distinct lifestyle and healthcare access factors may have influenced the observed prevalence of abnormalities^{55,67}.

Harms et al. (2023) provided a longitudinal perspective by analyzing data from the Hoorn Diabetes Care System cohort, encompassing 11,993 individuals with T2D over a median follow-up of 6.6 years¹³. The study revealed that 45.4% of participants exhibited ECG abnormalities, with prolonged QRS duration and ST-segment/T-wave abnormalities as the

most prevalent. Unlike the cross-sectional designs of Ndour et al (2017) and Patel et al, (2023), Harms et al. utilized a prospective approach, enabling a direct assessment of the relationship between ECG changes and major adverse cardiac events (MACE)¹³. Their findings demonstrated strong associations between specific ECG patterns, such as decelerated conduction and hypertrophy, with the development of heart failure. Interestingly, while ischemic abnormalities were predictive of coronary heart disease, they were less influential in heart failure risk. This nuanced differentiation highlights the evolving role of ECG as a prognostic tool in diabetes management. The study's large sample size and longitudinal design provide robust evidence, though its reliance on self-reported cardiovascular events introduces potential bias.

A comparative analysis of these studies reveals both congruence and divergence in findings. While Ndour et al, (2017) and Pillay et al, (2018) emphasize the prevalence of hypertrophy and silent MIs, Harms et al (2021) broaden the scope to include long-term outcomes, such as MACE^{13,63,67}. Additionally, Patel et al, (2023) emphasis on QT interval prolongation and its predictive value for coronary events complements the prognostic insights offered by Harms et al, (2023) study^{13,55}. Methodological differences, such as sample size, population demographics, and study design, contribute to variations in reported prevalence and clinical significance. For instance, the relatively small sample size in Ndour et al, (2017) study limits statistical power, whereas Harms et al, (2021) longitudinal cohort offers stronger predictive value. Similarly, the regional focus of Pillay et al, (2023) study underscores the importance of contextual factors, such as genetic predisposition and healthcare access, in interpreting ECG abnormalities.

Despite these differences, a unifying theme across these studies is the critical role of routine ECG screening in T2D populations. Early detection of abnormalities, such as QT prolongation,

silent MIs, and hypertrophy, can inform targeted interventions to mitigate cardiovascular risks^{26,55,63}. However, gaps remain in understanding the interplay between diabetes duration, glycemic control, and specific ECG patterns. Future research should prioritize standardized methodologies and diverse population cohorts to enhance the generalizability of findings. Moreover, integrating advanced diagnostic tools, such as machine learning algorithms, with traditional ECG analysis may improve predictive accuracy and clinical outcomes. In conclusion, the patterns of ECG abnormalities in T2D individuals underscore a substantial cardiovascular burden, with significant implications for early detection and management. Collectively, these studies emphasize the necessity of routine ECG screening as an integral component of diabetes care, paving the way for improved cardiovascular outcomes in this high-risk population.

2.9 FACTORS ASSOCIATED WITH ELECTROCARDIOGRAPHIC ABNORMALITIES

Electrocardiographic (ECG) abnormalities in individuals with T2D are recognized as significant predictors of cardiovascular morbidity and mortality¹⁶. Several studies have investigated the factors contributing to these abnormalities, highlighting a complex interplay of demographic, clinical, and lifestyle factors^{13,27}. This review synthesizes findings from diverse studies, focusing on the determinants of ECG abnormalities, to provide a comprehensive understanding of their implications for clinical practice.

In the Hoorn Diabetes Care System cohort, Harms et al. (2021) reported a 29.1% prevalence of ECG abnormalities, with a substantial portion being major abnormalities. Older age, higher BMI, hypertension and male sex were significantly associated with these abnormalities ($p < 0.01$), findings consistent with other research¹³. For example, Singh et al, (2022) also demonstrated a strong correlation between ECG abnormalities and traditional cardiovascular

risk factors, particularly in older adults and men²⁷. Both studies used multivariable logistic regression to identify risk factors, but Singh et al, (2022) focused on a large prospective cohort in North India, enhancing the generalizability of their findings. However, while Harms et al (2021) included a comprehensive analysis of HDL cholesterol and eGFR as contributing factors, Singh et al, (2022) primarily emphasized hypertension and dyslipidemia, leaving gaps in the evaluation of renal impairment as a potential driver^{13,27}.

The interplay between glycemic control and ECG abnormalities was explored in depth by Sinamaw et al. (2022) in Ethiopia. Elevated fasting blood sugar levels (≥ 130 mg/dL) were associated with a fivefold increase in ECG abnormalities (AOR = 5.01, $p < 0.01$), paralleling findings by Patel et al. (2023), who noted significant changes in QT and QTC intervals in poorly controlled diabetic patients^{55,62}. While both studies underscored the impact of hyperglycemia, they differed in methodological approaches. Sinamaw et al, (2022) utilized a multicenter design, enhancing the external validity of their results, whereas Patel et al, (2023) conducted a case-control study, which, while insightful, could not establish temporal relationships. Additionally, Sinamaw et al, (2022) emphasized the duration of diabetes as a critical factor, with patients having diabetes for over a decade exhibiting significantly higher odds of ECG abnormalities (AOR = 4.5, $p < 0.05$). This contrasts with the narrower focus on glycemic parameters in Patel et al, (2023) study, which may underestimate the chronic impact of diabetes on cardiac electrophysiology^{55,62}.

Hypertension emerged as a pivotal factor in most studies, with significant associations reported by Harms et al, (2021), Sinamaw et al, (2022), and Khanal et al. (2023). Khanal et al, (2023) focusing on a Nepalese cohort, revealed that hypertensive patients were significantly more likely to exhibit both minor and major ECG abnormalities ($p = 0.01$)⁶⁵. Their findings align with Bedane et al. (2021) in Southwest Ethiopia, who reported a threefold increase in ECG

abnormalities among hypertensive individuals ($\text{AOR} = 3.36, p < 0.05$)³². These studies collectively emphasize the critical need for blood pressure control in mitigating cardiac risks in T2D populations. However, methodological differences warrant attention. Khanal et al, (2023) employed a multistage stratified sampling technique, ensuring a representative sample, while Bedane et al, (2021) relied on systematic random sampling, potentially introducing selection bias^{32,65}.

Sociodemographic factors, including education and income, were also implicated. Bedane et al, (2021) identified low educational status as a significant determinant of ECG abnormalities ($\text{AOR} = 3.07, p < 0.05$), suggesting that health literacy may influence outcomes³². Similarly, Asmare et al. (2023) found that higher income was associated with reduced odds of T-wave abnormalities ($\text{AOR} = 0.16, p < 0.01$), potentially reflecting better access to healthcare and adherence to treatment⁶⁶. These findings are supported by Ezeude et al. (2024), who reported that individuals with limited educational and financial resources exhibited higher rates of ECG abnormalities. While these studies highlight socioeconomic disparities, their reliance on cross-sectional designs limits the ability to infer causality, underscoring the need for longitudinal investigations.

Renal impairment, another critical factor, was addressed by Khanal et al, (2023) who found that participants with reduced eGFR exhibited significantly higher rates of ECG abnormalities⁶⁵. This finding complements Harms et al, (2021) observation of lower eGFR as an independent predictor, emphasizing the cardiorenal link in T2D. However, Khanal et al, (2023) also explored the intersection of renal impairment and hypertension, revealing a compounded risk in hypertensive individuals. This dual focus on cardiorenal and vascular health broadens the understanding of ECG abnormalities but requires further exploration in diverse populations to validate these associations.

In conclusion, the factors associated with ECG abnormalities in T2D encompass a broad spectrum of demographic, clinical, and lifestyle determinants. Older age, male sex, hypertension, poor glycemic control, and renal impairment consistently emerge as significant contributors across studies. While similarities in findings enhance the reliability of these conclusions, methodological heterogeneity ranging from sample size and design to variable selection, introduces variability. The integration of findings underscores the necessity for routine ECG screening and comprehensive management of cardiovascular risk factors in T2D patients.

2.10 ASSOCIATIONS OF ECG ABNORMALITIES WITH CURRENT/PRIOR ADVERSE CARDIAC EVENTS

Electrocardiogram (ECG) abnormalities have increasingly been associated with adverse cardiac events, particularly among individuals with T2D. Numerous studies have explored these associations, shedding light on the prevalence, patterns, and predictive value of specific ECG findings. These abnormalities, ranging from minor changes to significant conduction defects, are often linked to traditional cardiovascular risk factors and systemic complications inherent to T2D. This review integrates key findings from multiple studies to discuss the relationship between ECG abnormalities and adverse cardiac events, emphasizing their predictive and diagnostic significance.

The Hoorn Diabetes Care System cohort by Harms et al. (2021) identified a 29.1% prevalence of ECG abnormalities among individuals with T2D, categorizing them as minor (16.0%) or major (13.1%)¹³. The study further highlighted that patients with a higher cardiovascular risk score exhibited abnormalities more frequently, particularly ventricular conduction defects and arrhythmias, with a marked increase in older adults and men (p-trend < 0.01). Multivariable analysis revealed robust associations with age (OR: 1.06 per year; 95% CI: 1.06–1.07),

hypertension (OR: 1.38; 95% CI: 1.19–1.60), and low HDL cholesterol (OR: 0.58; 95% CI: 0.46–0.73). The findings align with those from Singh et al. (2022), who reported a similar prevalence in a tertiary care hospital setting and identified hypertension and dyslipidemia as significant contributors to ECG abnormalities²⁷. Both studies underscore the compounded impact of hypertension and metabolic disturbances in T2D on adverse cardiac electrical changes.

Adding to this, Sinamaw et al. (2022) observed that 45% of Ethiopian T2D patients displayed ECG abnormalities, with T-wave changes and left axis deviation being the most common. These abnormalities correlated strongly with longer diabetes duration (AOR: 4.5; 95% CI: 1.05–18.94) and poor glycemic control (AOR: 5.01; 95% CI: 2.13–12.20)⁶². Similar findings were echoed in Bedane et al. (2021), who reported a prevalence of 61% in Southwest Ethiopia, emphasizing the role of diabetes duration (>10 years: AOR = 3.36; 95% CI = 1.46–7.71) and BMI (AOR = 2.74; 95% CI = 1.67–4.50)³². These results align with Harms et al. (2021) strengthening the argument that long-standing diabetes exacerbates cardiovascular risks through chronic metabolic derangements. However, these Ethiopian studies also highlighted regional factors like access to healthcare and dietary habits, suggesting that socioeconomic conditions may modulate the prevalence and impact of ECG abnormalities.

The predictive significance of specific ECG changes, such as QT prolongation and T-wave abnormalities, was further emphasized by Patel et al. (2023). In their case-control study, diabetic patients demonstrated significantly prolonged QT intervals (mean 0.46 ± 0.06 seconds) and frequent ST-segment deviations compared to controls ($p < 0.001$)⁵⁵. These findings corroborate those from Asmare et al. (2023), where T-wave abnormalities were prevalent in 21.7% of participants and were strongly associated with hypertension (AOR = 5.55; 95% CI = 2.12–14.49) and elevated fasting blood sugar levels (AOR = 6.38; 95% CI = 1.94–20.94)⁶⁶.

The overlap between studies highlights the role of systemic hypertension and glycemic control in driving specific ECG alterations, which are early markers of silent ischemia and sudden cardiac death risk.

Renal impairment, often coexisting with T2D, has also been implicated in cardiac electrical disturbances. Khanal et al. (2023) found that both major (6.1%) and minor (45.8%) ECG abnormalities were prevalent in T2D patients with renal impairment. Older age (OR = 1.04; 95% CI = 1.01–1.07) and hypertension were key determinants, supporting the hypothesis that cardiorenal syndromes amplify cardiovascular vulnerability⁶⁵. These findings resonate with those of Harms et al, (2021) and Singh et al, (2022) who noted that lower eGFR and albuminuria were linked to ECG changes, further illustrating the systemic impact of T2D on both the renal and cardiac systems^{13,27}. Despite the consistency across studies in linking ECG abnormalities with adverse cardiac events, variations in methodology and sample characteristics present limitations. For example, while the large sample size in the Hoorn cohort enhances its generalizability, its cross-sectional design limits causal inference. In contrast, smaller studies like Sinamaw et al, (2022) and Patel et al, (2023) provide detailed insights into specific abnormalities but lack the statistical power for broader applicability^{55,62}. Additionally, the use of differing ECG classification systems and risk factor adjustments may influence outcome interpretations, necessitating standardized approaches in future research. In conclusion, ECG abnormalities are prevalent among individuals with T2D and are strongly associated with traditional cardiovascular risk factors, prolonged disease duration, and systemic complications such as hypertension and renal impairment.

2.11 INTEGRATIVE CONCEPTUAL LINK: T2D, RISK FACTORS, ECG CHANGES, AND CARDIAC OUTCOME

The relationship between T2D, associated risk factors, ECG changes, and cardiac outcomes can be conceptualized as a progressive continuum including the following:

Metabolic Dysregulation as the Initiating Driver^{8,68}

At the core of T2D is chronic hyperglycemia and insulin resistance. Persistent elevation of blood glucose promotes the formation of advanced glycation end products (AGEs), activation of protein kinase C pathways, oxidative stress, and systemic inflammation. These mechanisms impair endothelial function, reduce nitric oxide bioavailability, and promote vascular stiffness. Simultaneously, insulin resistance alters lipid metabolism, increasing circulating free fatty acids and promoting dyslipidemia. Over time, this metabolic milieu leads to accelerated atherosclerosis, microvascular dysfunction, myocardial lipid accumulation, and increased myocardial fibrosis. These early metabolic abnormalities may be clinically silent but initiate structural and functional changes within the cardiovascular system.

Interaction with Associated Risk Factors^{68,69}

T2D rarely exists in isolation. Hypertension, obesity, and dyslipidemia commonly coexist, creating a synergistic burden on the cardiovascular system. Each of these factors contributes distinct but overlapping pathological effects: 1) Hypertension increases left ventricular afterload, promoting hypertrophy and myocardial remodeling; 2) Dyslipidemia accelerates coronary plaque formation and instability; 3) Obesity contributes to systemic inflammation, altered cardiac geometry, and autonomic imbalance; 4) Poor glycemic control intensifies oxidative stress and myocardial fibrosis. The coexistence of these conditions amplifies

endothelial dysfunction and myocardial strain, accelerating the transition from subclinical pathology to detectable electrical abnormalities.

Structural and Electrical Remodeling of the Heart^{70,71}

As metabolic and vascular injury progresses, structural remodeling of the myocardium occurs. This includes left ventricular hypertrophy, interstitial fibrosis, impaired diastolic relaxation, and microvascular ischemia. Concurrently, diabetic autonomic neuropathy alters sympathetic–parasympathetic balance, impairing heart rate variability and repolarization stability. These structural and autonomic changes disrupt normal impulse generation and conduction, leading to measurable ECG abnormalities such as Prolonged QT interval, ST-segment and T-wave changes, conduction delays (e.g., bundle branch blocks), voltage criteria for left ventricular hypertrophy, and atrial enlargement and arrhythmias. At this stage, ECG becomes a critical intermediary marker—reflecting underlying myocardial and vascular pathology before the onset of overt cardiovascular events.

Transition to Clinical Cardiovascular Outcomes^{72–74}

ECG abnormalities represent a pivotal transition point in the continuum from metabolic disease to clinical cardiovascular disease. Abnormal findings may signify subclinical myocardial ischemia, ongoing myocardial remodeling, and/or electrical instability predisposing to arrhythmias. If unaddressed, these abnormalities may progress to overt clinical outcomes, including coronary artery disease and myocardial infarction, heart failure (particularly heart failure with preserved ejection fraction), atrial fibrillation, ventricular arrhythmias and sudden cardiac death, and increased cardiovascular and all-cause mortality. Importantly, diabetic neuropathy may mask classical ischemic symptoms, resulting in “silent ischemia.” In such cases, ECG findings may be the earliest detectable indicator of evolving coronary pathology.

The integrative relationship is not strictly linear; rather, it is cyclical and reinforcing. For example myocardial ischemia may worsen glycemic control through stress-mediated hormonal changes. Furthermore, heart failure can exacerbate insulin resistance and metabolic dysregulation. Also, recurrent ischemia and fibrosis further destabilize electrical conduction pathways. Thus, once cardiac involvement develops, it may perpetuate metabolic deterioration, creating a vicious cycle that increases morbidity and mortality.



CHAPTER THREE

METHODS

3.1 STUDY DESIGN

This study was part of a larger research project led by the principal supervisor of the MPhil candidate. The candidate obtained ethical clearance for this study and conducted ECG evaluations and other physiological assessments. Ethical approval was obtained from the University of Ghana College of Health Sciences Ethical and Protocol Review Committee (protocol identification number: CHS-Et/M.8-P4.2/2023-2024).

The study was designed as a cross-sectional investigation involving adults with an established diagnosis of T2D managed at the National Diabetes Management and Research Centre (NDMRC) in Accra, Ghana. The study examined various factors including sociodemographic aspects (such as age, sex, and education level), clinical factors (like the duration of diabetes, medication use, and history of cardiovascular disease), anthropometric measurements (BMI, waist circumference, hip circumference, and body fat percentage), biochemical markers (fasting plasma glucose, HbA1c, serum lipids, creatinine, urea, and electrolytes), electrocardiographic changes (both major and minor ECG abnormalities), and hemodynamic measures (blood pressure, heart rate, pulse pressure, and mean arterial pressure). Data collection was carried out using the questionnaire provided in Appendix III.

3.2 STUDY SITES

The study sites were the 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. The Korle-Bu Teaching Hospital is Ghana's largest and most renowned tertiary referral institution, drawing referral cases from all around the nation. In addition to doing research on diabetes and related topics, the NDMRC treats individuals with diabetes medically and offers advice. The NDMRC clinic sees between 50 and 100 diabetic patients on a weekday on average. The study project lab is equipped to conduct anthropometry, cardiac microvascular, macrovascular, and pulmonary function assessments, as well as interviews. It is located 20 meters from the NDMRC.

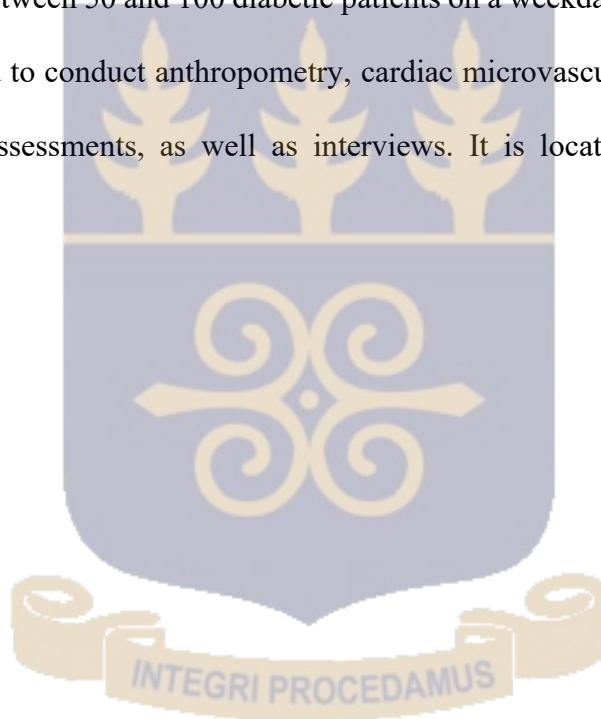
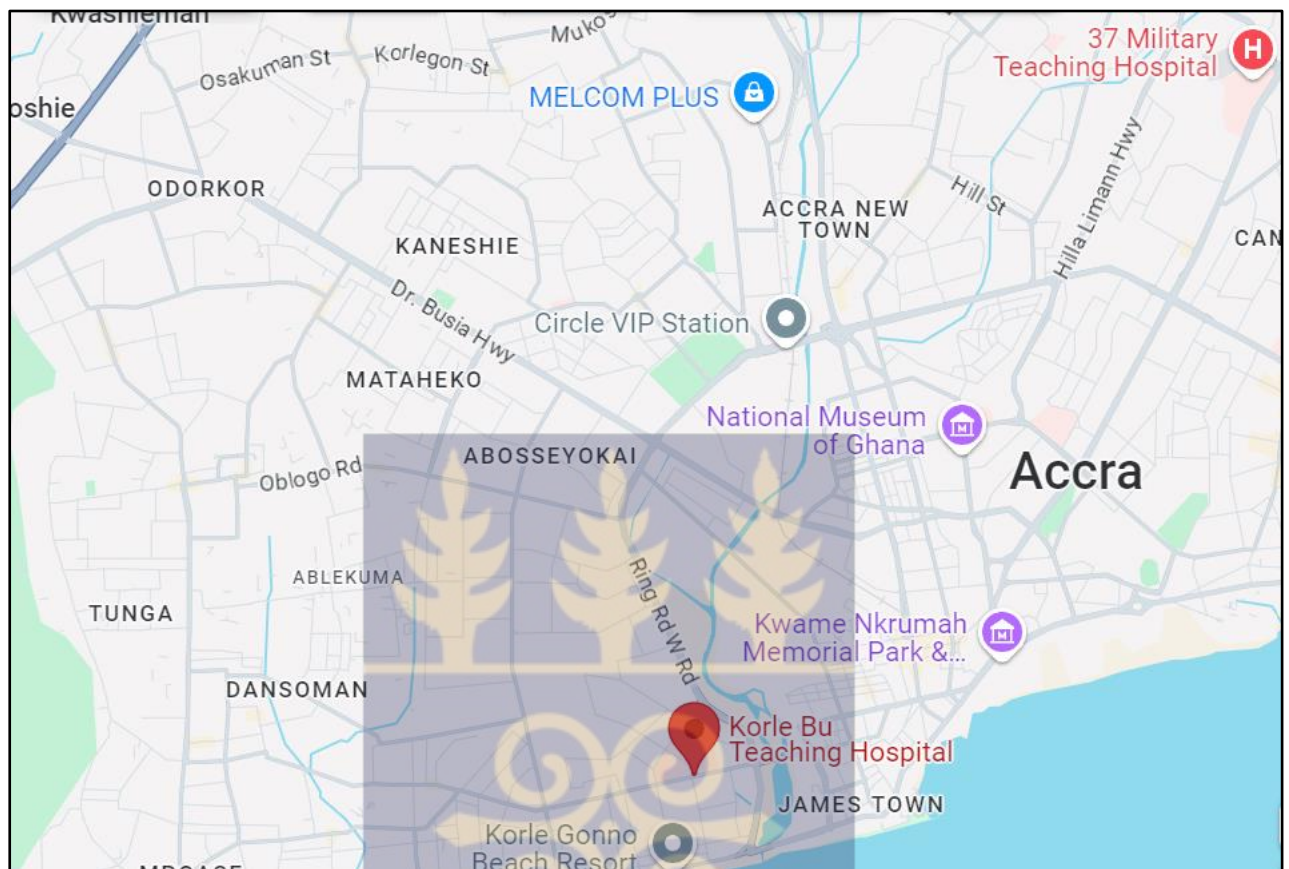


Figure 3.1: Map Showing a Section of Accra, Ghana, Featuring the Korle-Bu Teaching Hospital



3.3 STUDY POPULATION

Ghanaians who fulfilled the following study eligibility requirements made up the study population:

Inclusion criteria

1. Native Ghanaians.

Ghanaian nativity was determined by verifying the genealogy of the participants up to the second generation (grandparents). This was assessed via a nativity questionnaire (Appendix II).

2. Adults 18 years and above

3. 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).
4. Provision of informed consent.

Exclusion Criteria

1. Individuals with Pacemakers and Implantable Defibrillators

3.4 SAMPLE SIZE DETERMINATION

The minimum sample size N was determined using the formula below.

$$N = \frac{Z^2 p (1-p)}{e^2}$$

- Z is the statistic directly related to the desired confidence level
- e is the preferred level of precision
- p is the estimated proportion of an attribute that is present within the population.

Assumptions made in sample size determination.

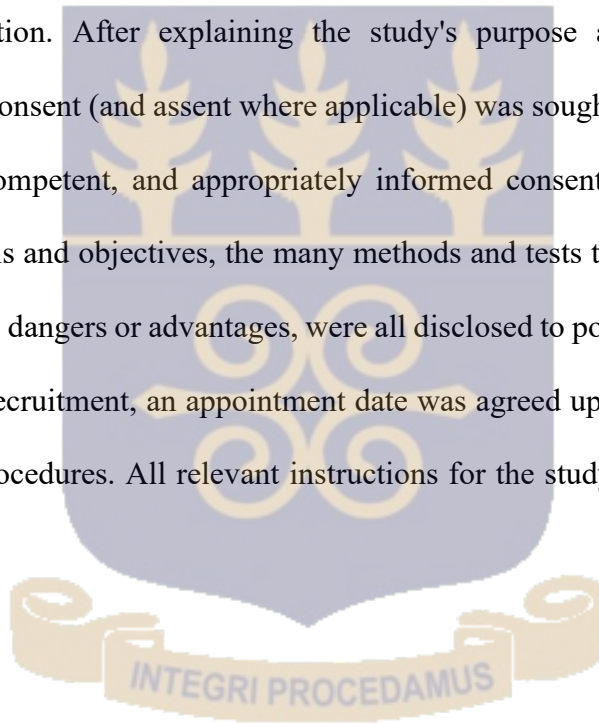
- Power of study: 80%
- $Z\alpha$ of 1.96 for 5% level of significance
- In a recent large study that included 8068 adults with T2D, the prevalence of minor and major ECG abnormalities was 29.1%¹³.

Solving gives $N = 317$

However, to enhance the reliability of the study and ensure strong statistical power, we increased the sample size to 430 participants. This adjustment accounted for potential challenges such as suboptimal ECG tracing and incomplete data needed for comprehensive statistical analyses.

3.5 RECRUITMENT OF STUDY PARTICIPANTS

Study participants were drawn from the NDMRC through a consecutive sampling technique. The sample frame consisted of every diabetes record book recorded at the NDMRC laboratory sample collecting station. After explaining the study's purpose and procedure to each participant, informed consent (and assent where applicable) was sought. Only individuals who provided voluntary, competent, and appropriately informed consent were recruited for the study. The study's goals and objectives, the many methods and tests that would be employed, as well as any potential dangers or advantages, were all disclosed to potential participants prior to recruitment. After recruitment, an appointment date was agreed upon for the participant to report for the study procedures. All relevant instructions for the study were discussed on the day of recruitment.



3.6 STUDY PROCEDURES

After recruitment, each participant had blood samples taken, followed by the use of a structured questionnaire (Appendix III) to capture baseline sociodemographic and clinical characteristics. A physical examination, anthropometry, and measurement of physiological variables, including ECG, were performed according to the standardized operational procedures of the laboratory. The structured questionnaire (Appendix III) was used to assess sociodemographic and clinical characteristics and to extract data on medication use, highest educational level,

smoking status, and current or previous cardiovascular disease events. There were four categories for the use of glucose-lowering drugs: no medicine, oral only, oral and insulin, and both oral and insulin.

Self-reported angina pectoris, myocardial infarction, cardiac arrest, heart failure, stroke or (ventricular) heart rhythm disturbance were considered to be indicators of a history of cardiovascular illness. Apart from the self-reported cases of CAD and the medical records of CAD diagnosed by a physician, the WHO Rose Angina Questionnaire was utilized to evaluate the symptoms of CAD. A positive answer to the question, "Have you ever had a severe pain across the front of your chest lasting for half an hour or more?" was considered to be indicative of a possible myocardial infarction. A yes answer to the question, "Have you ever had any pain or discomfort in your chest?" was considered angina, and "Do you experience this pain or discomfort when rushing or walking uphill?"

Table 3.1: WHO Rose Angina Questionnaire

	QUESTION	RESPONSE
1	Have you ever had any pain or discomfort in your chest?	• No • Yes
2	Where do you get this pain or discomfort?	• No • Yes
3	Do you get this pain when you're exerting yourself (for example, when you're climbing stairs, walking fast, or cycling)? [Do you get this pain or discomfort when you walk uphill or hurry]	• No • Yes
4	When you walk at an ordinary pace at the level, does this produce the pain?	• No • Yes
5	4. If "Yes" to Questions 2 or 3, where do you feel this pain or discomfort?	• Across the front of the chest • In the neck or jaw

		• Down the left arm • Other (Specify): _____
	When you get any pain or discomfort in your chest on walking, what do you do?	• Stop or slow down • Carry on as before
	Does the pain or discomfort in your chest go away if you stand still	• No • Yes
	How long does it take to go away?	
	Have you ever had a severe pain across the front of your chest lasting for half an hour or more?	• No • Yes

3.7 BLOOD SAMPLING AND BIOCHEMICAL MEASUREMENTS

The study participants were made to fast for 8-12 hours, after which 10 ml of venous blood was collected. The venipuncture was performed by a trained phlebotomist at the NDMRC of KBTH. The venous blood sampling was done in a sitting position, targeting any of the veins in the antecubital fossa (median cubital vein, cephalic vein, or basilic vein). In cases where sampling from the antecubital fossa veins was unsuccessful or not feasible, the basilic vein on the dorsum of the arm or dorsal hand veins were utilized. To ensure sample integrity, the skin at the venipuncture site was thoroughly cleaned with an alcohol swab. A tourniquet was applied firmly to block venous blood flow but not too tightly to block arterial flow. Once the vein was entered, the tourniquet was released, and blood was drawn into separate fluoride/oxalate, EDTA, and plain tubes. A cotton swab was then applied to the site of the blood draw as the needle was removed. Participants were instructed and shown how to maintain pressure on the cotton wool with the arm extended for two minutes. The obtained venous blood samples, specifically the fluoridated ones, were promptly placed on ice and subjected to centrifugation within 15 minutes of the blood draw. The fluoride tube with blood was gently inverted three times and placed immediately on ice in the cool boxes provided. The plain tube with blood was

allowed to stand at room temperature until the blood clotted, and the EDTA tube was rolled gently between the palms and then placed on ice in the cool box. The collected blood samples, including serum and plasma, were utilized for analyzing various parameters such as fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum fasting lipids, serum creatinine, urea, and electrolytes. Following centrifugation, both serum and plasma were separated and divided into cryotubes for storage under continuous refrigeration on ice. These cryotubes were subsequently transferred for permanent storage at -80°C .

Categorization of Biochemical Variables: Biochemical variables were categorized into normal and abnormal levels. The cut-off values for these categorizations were as follows:

- Fasting plasma glucose: $<7.0 \text{ mmol/l}$ (normal), $\geq 7.0 \text{ mmol/l}$ (abnormal)
- HbA1c: $<6.5\%$ (normal), $\geq 6.5\%$ (abnormal)
- Total cholesterol: $<5.2 \text{ mmol/l}$ (normal), $\geq 5.2 \text{ mmol/l}$ (abnormal)
- LDL-cholesterol: $<3.0 \text{ mmol/l}$ (normal), $\geq 3.0 \text{ mmol/l}$ (abnormal)
- HDL-cholesterol: $>1.0 \text{ mmol/l}$ (normal), $\leq 1.0 \text{ mmol/l}$ (abnormal)
- Triglycerides: $<1.7 \text{ mmol/l}$ (normal), $\geq 1.7 \text{ mmol/l}$ (abnormal)

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 (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol) were measured using commercial reagent kits with calibrators and controls (Randox, Crumlin UK) on the Daytona automated chemistry analyzer (Randox, Crumlin, UK). HbA1c was measured by affinity chromatography on the PDQ Plus analyzer (Primus Diagnostics, Trinity Biotech, Kansas, USA). The estimated glomerular

filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ⁷⁵.

3.8 RESTING ELECTROCARDIOGRAPHY

After at least 10 minutes of rest, a standard 12-lead supine digital resting electrocardiography (ECG) was recorded using the Vitalograph BT12 ECG™ combined with its Spirotrac® software (Vitalograph, United Kingdom). Transmission of the ECG trace was wireless with no leads to trip over, providing excellent signal quality, less artifact, and ensuring minimal patient discomfort. The ECG tracings were processed with the device's inbuilt University of Glasgow 12-Lead ECG Analysis Algorithm¹. Two additional methods were used to evaluate each ECG, namely Minnesota coding and assessment by a trained physician. The ECG abnormalities were classified into seven main groups¹³ namely

1. QS pattern abnormalities category comprised all abnormal Q-waves.
2. QRS-axis deviation category contained a leftward shift of the QRS-axis (-30° through -90°).
3. The R-waves category encompassed exceedingly tall amplitude R-waves (i.e., Sokolow-Lyon-criterion or any of the following criteria: >26 mm in V5 or V6; >20 mm in II, III or aVF; >15 mm in I; >12 mm in aVL;).
4. The ST-segment abnormalities category included all downward-sloping or depressed ST-segments, and/or T-waves that were flat, negative, or biphasic (negative-positive type only).
5. The atrioventricular conduction defects category encompassed prolonged PR (PQ) intervals in the limb leads (≥ 0.22 s).

6. The ventricular conduction defects category comprised incomplete right bundle branch block (BBB), intraventricular conduction delay, complete right BBB, and complete left BBB.
7. The arrhythmias category consisted of atrial fibrillation, atrial flutter, and premature atrial or ventricular contractions.

The identified ECG abnormalities were classified as minor or major abnormalities. Minor abnormalities category included minor ST-segment abnormalities, minor QS pattern abnormalities, premature atrial or ventricular contractions or complete right bundle branch block. The major abnormalities category included major ST-segment abnormalities, major QS pattern abnormalities, atrial fibrillation or flutter, complete left bundle branch block or intraventricular block. In cases where minor and major abnormalities occurred simultaneously, participants were classified into the major abnormalities category.

3.9 ANTHROPOMETRY AND HEMODYNAMIC MEASUREMENTS

A SECA-217 stadiometer was used to measure height without shoes, while SECA-877 scales were used to assess weight when wearing light clothing. Weight (kg) divided by height squared (m^2) yielded the body mass index (BMI). Underweight ($<18.5 \text{ kg/m}^2$), Normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), Overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), and Obesity ($\geq 30 \text{ kg/m}^2$) were the classifications assigned to it. The midpoint between the top of the iliac crest and the lower border of the lowest palpable rib was used to calculate waist circumference (WC). Using a tape measure parallel to the floor, the hip circumference (HC) was measured around the largest part of the buttocks, at the level of the greater trochanters. Using the Omron Body Composition BF-506 Monitor (Omron Healthcare, Inc., Vernon Hills, IL, USA), the arm-leg bio-impedance technique was used to evaluate the visceral body fat level and percentage of body fat. After at least five

minutes of rest while seated, blood pressure was measured three times with the Omron BP Monitor HEM-907XL device using appropriately sized cuffs. The studies made use of the mean of the previous two blood pressure readings. The clinical diagnosis of hypertension was based on documentation in the medical records, which included a verified systolic blood pressure (SBP) of at least 140 mmHg and/or diastolic blood pressure (DBP) of at least 90 mmHg, as well as being on antihypertensive drug treatment⁷⁶. According to the 2017 American College of Cardiology/American Heart Association guidelines and the European Society of Cardiology/European Society of Hypertension guidelines (for people with hypertension and diabetes), suboptimal blood pressure control was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg⁷⁷. These threshold levels are in line with the American Diabetes Association's advice for diabetics who have a higher risk of cardiovascular disease⁷⁸.

3.10 DATA MANAGEMENT

Data was entered in Castor EDC and exported to MS Excel and IBM SPSS version 26 after cleaning. To ensure data security, the following strategies were used

1. Names, dates of birth, contact details, and information about rare diseases that uniquely identify a patient were separated from the rest of the database. This information was encrypted and password-protected before being added to an MS Access database. The database and password were only accessible by the principal investigators.
2. The PI's office had a secured filing cabinet with hard copies of the codebook and personally identifiable information.
3. The remaining, anonymized data was entered into a different MS Access file, which was then exported to SPSS or Excel for analysis. Every data file, including SPSS, MS Excel,

and MS Access, was password- and encryption-protected. The only people with access to anonymized data were the statistician, supervisors, and PI.

4. The non-identifiable patient data (questionnaires, physical examination forms, and laboratory studies) were physically restricted to hard copies. Every physical copy was safely kept in a locked filing cabinet in the University of Ghana Medical School's Department of Physiology.
5. Our research PCs were equipped with antispyware and virus-detection software, and firewalls protected our networks.

To ensure the accuracy of data entry, data entered was crosschecked by another data entry staff for accuracy.

3.11 STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS version 26 for Windows. Summary statistics were produced for variables. The Shapiro-Wilk test was used to test for normality in data with continuous variables. Mean $\pm$ standard deviation was used to represent data with a normal distribution, and the median (interquartile range) was used to represent data that were not normally distributed. In the case of categorical data, frequency (%) was displayed. The t-test for continuous variables, the Mann-Whitney U-test for variables not normally distributed, or the chi-square test or Fisher's exact test for categorical variables were used to compare the differences in sociodemographic and clinical traits between people with normal and abnormal ECGs. Univariate logistic regression was performed to assess the associations of potential cardiovascular diseases or risk factors with various pooled abnormality categories. After that, a backward stepwise selection of covariates was used to construct a multivariate logistic regression model, which resulted in a subset of predictor variables included in the final model.

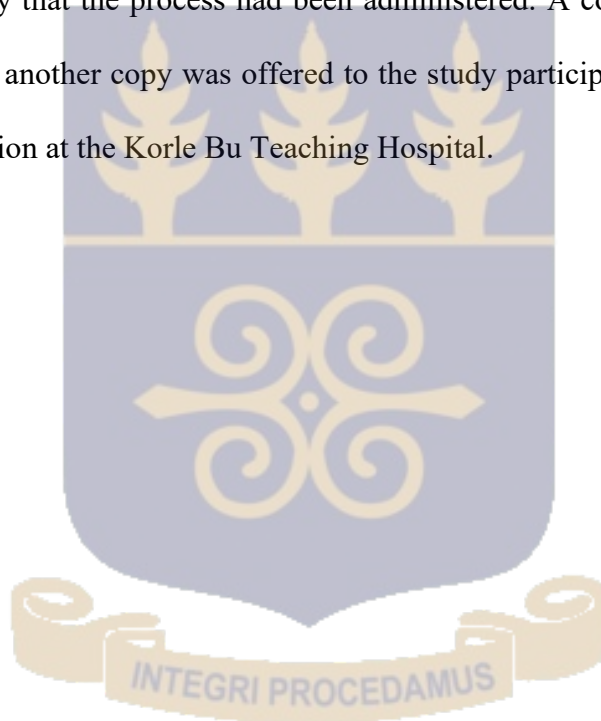
Up until all risk factors were significant ($p \leq 0.05$), non-significant modifiable cardiovascular disease and risk factors could be eliminated using the backward model selection strategy. A forward selection of predictor variables was used to cross-check the model selection procedure. Every p-value that was displayed had two tails, and a p-value < 0.05 was considered statistically significant.

3.12 ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Scientific and Technical Committee/Institutional Review Board of Korle-Bu Teaching Hospital and the University of Ghana, College of Health Sciences Ethical and Protocol Review Committee. The protocol identification number for this approval was CHS-Et/M.8 - P 4.2/2023-2024. According to the World Medical Association (2013), the research was carried out per the 1964 Helsinki Declaration on Human Experimentation, with any necessary amendments. For the study, only those who satisfied the qualifying requirements were enrolled. There was no elevated risk of involvement because the trial did not involve any novel experimental medications or treatments that were not authorized for use in patients with diabetes. The goal, design, methods, and possible dangers of the study were suitably disclosed to study participants, who were also given the freedom to decline participation or withdraw at any moment without consequence, as well as anonymity and confidentiality. Clinical management was unaffected in any manner by participation refusal. Written informed consent was acquired from every individual involved. Individuals exhibiting irregularities in their electrocardiogram were promptly informed of their findings and instructed on the subsequent measures for medical intervention. Furthermore, the test results were provided to the NDMRC so that they could be added to the patient's medical file and reviewed by doctors during the subsequent appointment. The attending physicians at the

NDMRC were alerted of any irregularities that required immediate medical attention, and an urgent visit was scheduled. Throughout the whole trial, the patients' well-being was given top priority.

Informed Consent: Written informed consent (Appendix I) was obtained from each adult participating in the study. Participants were provided with information about the purpose, benefits, risks, and voluntary nature of the research and were asked to sign a consent form. Once an individual consented to participate in the study, the interviewer signed and dated the consent form to signify that the process had been administered. A copy of the consent form was kept in a file, and another copy was offered to the study participant. All interviews took place in a private location at the Korle Bu Teaching Hospital.



CHAPTER FOUR

RESULTS

4.1 OVERVIEW

This chapter presents the study findings and results based on the data collected and analyzed regarding the prevalence of ECG abnormalities and their associations with cardiovascular risk factors and current/prior adverse cardiac events in Ghanaians with T2D managed at the NDMRC. The results are organized according to the specific objectives of the study, providing an overview of the factors associated with identified ECG abnormalities and the association between ECG abnormalities and cardiovascular risk factors in this population.

4.2 GENERAL CHARACTERISTICS OF THE STUDY POPULATION

4.2.1 Baseline Characteristics of the Study Population

Table 4.1 presents the baseline characteristics of the study participants. Of the 430 participants, 265 (61.6%) had an abnormal ECG. Compared to individuals with normal ECG, those with abnormal ECG were significantly older (62.85 vs 60.30, $p=0.011$). However, the two groups did not differ in terms of sex distribution (male-to-female ratio), diabetes duration, level of education, proportion of smokers, and alcohol consumption. Additionally, there were no significant differences between the groups regarding the proportion of participants using cholesterol lowering medications (statins) or insulin. Further, the mean BMI, mean systolic BP, mean diastolic BP, and the prevalence of hypertension did not vary significantly between the two groups.

Table 4.1: Baseline Characteristics of the Study Population

Baseline Characteristics	All Participants	Normal ECG	Abnormal ECG	p-value
N	430	165	265	
Age (years)	61.87 (± 10.09)	60.30 (± 9.90)	62.85 (± 10.105)	0.011
Sex (%)				0.820
Female	315 (73.3%)	122 (73.9%)	193 (72.8%)	
Male	115 (26.4%)	43 (26.1%)	72 (27.2%)	
Diabetes Duration (years)	18.03 (± 10.01)	17.10 (10.15)	18.60 (9.94)	0.358
Education (%)				0.103
Below Secondary	255 (59.3%)	68 (41.2%)	187 (70.6%)	
Secondary and Above	175 (40.7%)	97 (58.8%)	78 (29.4%)	
Smoking Status (%)				0.293
Non-smoker	404 (95.1%)	155 (96.3%)	249 (94.3%)	
Current or Ex-smoker	21 (4.9%)	6 (3.7%)	15 (5.7%)	
Alcohol Consumption (%)				0.301
No	279 (64.9%)	102 (61.8%)	177 (66.8%)	
Yes	151 (35.1%)	63 (38.2%)	88 (33.2%)	
Statin Use (%)				0.123
No	259 (60.2%)	107 (64.8%)	152 (57.4%)	

Yes	171 (39.8%)	58 (35.2%)	113 (42.6%)	
Insulin Use (%)				0.701
No	274 (63.7%)	107 (64.8%)	167 (63.0%)	
Yes	156 (36.3%)	58 (35.2%)	98 (37.0%)	
BMI (kg/m²)	29.46 (±5.81)	29.76 (±6.08)	29.21 (±5.63)	0.340
Obesity	171 (39.8%)	73 (44.2%)	98 (37.0%)	0.269
Hypertension (%)	326 (75.8%)	118 (71.5%)	208 (78.5%)	0.106
Mean Systolic BP (mmHg)	135.33 (±18.50)	134.65 (±19.11)	135.77 (±18.14)	0.558
Mean Diastolic BP (mmHg)	75.56 (±11.20)	76.82 (±11.11)	74.89 (±11.20)	0.094

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

4.2.2 Hematological and Biochemical Measures in Study Population

Table 4.2 presents the hematological and biochemical measures of the study population stratified by ECG normality status. While the fasting plasma glucose was 12% higher in the normal ECG group compared with the abnormal ECG group, the observed difference was not statistically significant at the 0.05 level (9.41 mmol/L vs 8.35 mmol/L, $p = 0.055$). The normal and abnormal ECG groups did not significantly differ in terms of mean glycated hemoglobin concentrations. Similarly, the measured lipid concentrations, including total cholesterol, triglycerides, and HDL-cholesterol were similar in the two groups. The calculated mean LDL-cholesterol concentrations were also similar in the two groups. Additionally, the mean blood urea and mean blood creatinine levels did not show significant differences between participants with normal and abnormal ECG.

4.2.3 Electrolyte Concentrations in Study Population

Table 4.3 compares the concentrations of key electrolytes in the serum of participants with and without abnormal ECG. The two groups showed no significant differences in mean sodium (Na^+) concentration, mean potassium (K^+) concentration, or mean total calcium (Ca^{2+}) concentration. Similarly, the mean ionized calcium (Ca^{2+}) concentration and mean chloride (Cl^-) concentration were also similar in the two groups.

Table 4.2: Hematological and Biochemical Measures in Study Population

Measure	All Participants (N=430)	Normal ECG (N=165)	Abnormal ECG (N=265)	p-value
FPG (mmol/L)	8.73 ± 4.48	9.41 ± 5.12	8.35 ± 4.04	0.055
HbA1c (%)	8.74 ± 2.25	8.77 ± 2.51	8.72 ± 2.10	0.833
Total cholesterol (mmol/L)	4.96 ± 1.45	4.99 ± 1.41	4.94 ± 1.48	0.747
Triglyceride (mmol/L)	1.15 ± 3.09	1.42 ± 5.03	0.99 ± 0.59	0.211
HDL-cholesterol (mmol/L)	1.41 ± 0.50	1.42 ± 0.47	1.40 ± 0.52	0.731
LDL-cholesterol (mmol/L)	6.12 ± 19.58	5.85 ± 19.85	6.26 ± 19.48	0.871
Blood Urea (mmol/L)	4.36 ± 2.30	4.09 ± 1.86	4.51 ± 2.51	0.106
Blood Creatinine (μmol/L)	96.41 ± 39.78	94.21 ± 38.86	97.69 ± 40.34	0.428

Values for continuous variables as mean (± SD)

List of abbreviations: *FPG = Fasting Plasma Glucose; HDL = High-Density Lipoprotein, HbA1c = Glycosylated Hemoglobin, LDL = Low-Density Lipoprotein*

Table 4.3: Electrolyte Concentrations in Study Population

Measure	All Participants (N=430)	Normal ECG (N=165)	Abnormal ECG (N=265)	p-value
Na ⁺ (mmol/L)	140.04 ± 3.95	142.28 ± 3.84	142.56 ± 3.98	0.518
K ⁺ (mmol/L)	4.47 ± 0.67	4.20 ± 0.45	4.10 ± 0.42	0.181
Total Ca ²⁺ (mmol/L)	2.39 ± 0.39	2.26 ± 0.11	2.28 ± 0.10	0.675
Ionized Ca ²⁺ (mmol/L)	1.22 ± 0.22	1.22 ± 0.05	1.24 ± 0.04	0.396
Cl ⁻ (mmol/L)	106.14 ± 3.51	103.5 ± 4.2	103.3 ± 4.1	0.666

4.2.4 Electrocardiographic Measures of the Study Population

The electrocardiographic measures of the study population are summarized in Table 4.4. In the study population, the mean heart rate was 73 beats per minute. The mean RR interval, PR interval, PQ interval, ST segment duration, QT interval, and corrected QT interval were respectively 839.24 ms, 167.13 ms, 166.11 ms, 114.99, 399.86 ms, and 422.36 ms. The mean P wave and QRS complex widths were 114.83 ms and 94.97 ms respectively. The mean pooled p-axis, QRS-axis, and T-axis were 114.83 degrees, 32.46 degrees, and 32.60 degrees, respectively.

While the mean heart rate did not significantly differ between the two groups, the mean RR interval was 4% longer in the abnormal ECG group compared to the normal ECG group (853.94 ms vs. 818.54 ms, $p = 0.020$). Similarly, the mean PQ interval was 4.5% longer in

individuals with abnormal ECG compared to those with normal ECG (169.21 ms vs. 161.83 ms, $p = 0.018$). The mean QT interval was 2% longer in participants with abnormal ECG compared to those with normal ECG (402.63 ms vs. 394.40 ms, $p = 0.015$). The mean QRS axis also differed significantly between the two groups (29.56° in the abnormal ECG group vs. 36.26° in the normal ECG group, $p = 0.037$). Additionally, the mean T axis showed a significant difference between the groups (29.00° in the abnormal ECG group vs. 36.20° in the normal ECG group, $p = 0.045$).

Table 4.4: Electrocardiographic Measures of Study Population

Measurement	All Participants (Mean $\pm$ SD)	Normal ECG (Mean $\pm$ SD)	Abnormal ECG (Mean $\pm$ SD)	p-value
N	430	165	265	
HR (/min)	72.60 $\pm$ 12.26	73.95 $\pm$ 12.37	71.65 $\pm$ 12.16	0.060
RR (ms)	839.24 $\pm$ 153.20	818.54 $\pm$ 141.61	853.94 $\pm$ 159.89	0.020
PR (ms)	167.13 $\pm$ 38.83	163.65 $\pm$ 41.64	169.59 $\pm$ 36.02	0.118
PQ (ms)	166.11 $\pm$ 31.10	161.83 $\pm$ 19.29	169.21 $\pm$ 36.91	0.018
P (ms)	114.83 $\pm$ 13.51	115.82 $\pm$ 10.21	114.25 $\pm$ 16.20	0.266
P-axis (degrees)	114.83 $\pm$ 13.51	115.82 $\pm$ 10.21	114.25 $\pm$ 16.20	0.266
ST (ms)	114.99 $\pm$ 49.21	112.75 $\pm$ 42.46	116.64 $\pm$ 54.52	0.436

QRS-axis (degrees)	32.46 ± 31.16	36.26 ± 26.58	29.56 ± 35.20	0.037
QRS (ms)	94.97 ± 41.31	94.38 ± 66.82	95.31 ± 15.81	0.828
T-axis (degrees)	32.60 ± 30.95	36.20 ± 26.55	29.00 ± 35.35	0.045
QT (ms)	399.86 ± 33.34	394.40 ± 30.51	402.63 ± 36.17	0.015
QTc (ms)	422.36 ± 23.43	421.22 ± 20.58	423.49 ± 26.29	0.347

Values for continuous variables as mean (± SD)

Definition of Abbreviations

HR = Heart Rate

P = Duration of the P wave

P-axis = Axis of the P wave

PQ=Duration of the PQ interval

PR = Duration of the PR interval

QRS = Duration of the QRS complex

QRS axis = Axis of the QRS complex

QT = Q-T interval

QTc = T interval, corrected by HR with options Fridericia, Framingham, Bazett and Hodges

RR = R-R interval

ST = Duration of the ST segment

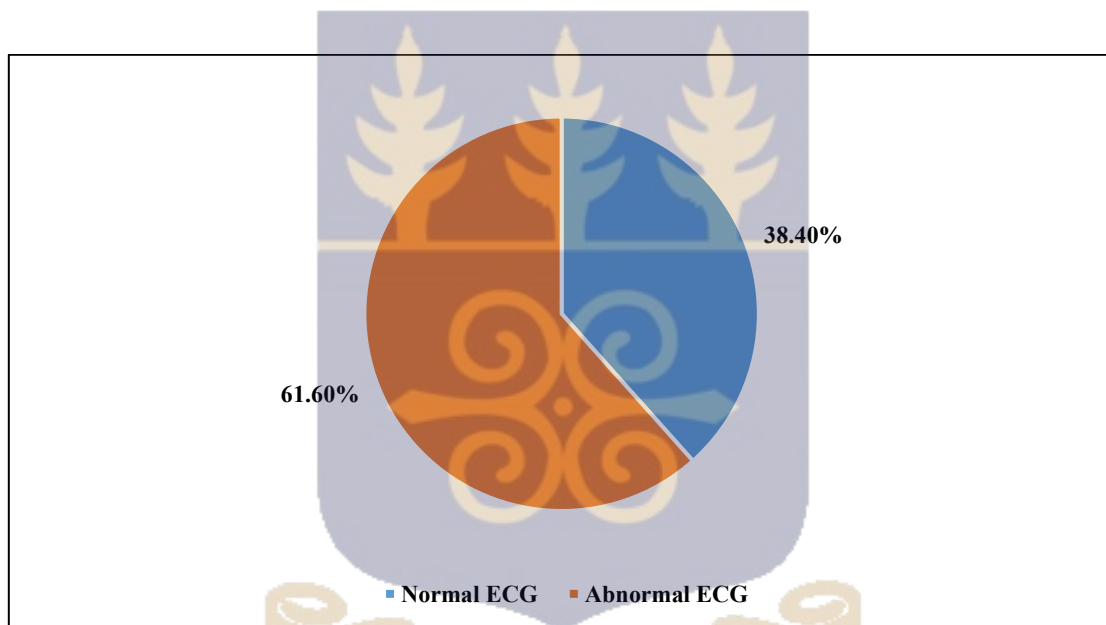
T-axis = Axis of the T wave

4.3 PREVALENCE OF ECG ABNORMALITIES IN T2D

4.3.1 Prevalence of ECG Abnormalities in the Study Population

Figure 4.1 presents the pooled prevalence of ECG abnormalities in the study population. Based on the pie chart 265 study participants representing 61.6% had at least one abnormal ECG pattern; the remaining 165 study participants (38.40%) had a normal ECG.

Figure 4.1: Prevalence of ECG Abnormalities in the Study Population

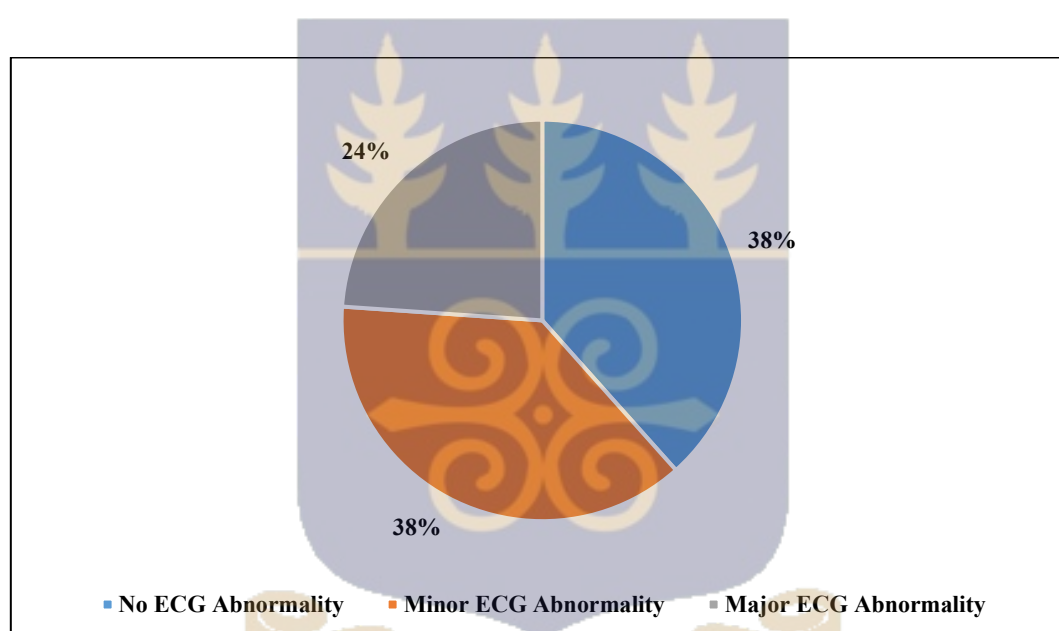


Abnormal ECG patterns included the following: 1) QS pattern abnormalities, 2) QRS-axis deviation abnormalities; 3) R-waves abnormalities; 4) ST-segment abnormalities; 5) atrioventricular conduction defects; 6) ventricular conduction defects; and 7) arrhythmias including atrial fibrillation, atrial flutter, and premature atrial or ventricular contraction

4.3.2 Distribution of Major and Minor Abnormalities based on ECG

Figure 4.2 below illustrates the distribution of ECG abnormalities with stratification of abnormal ECG results into major and minor ECG abnormalities. Overall, 23.9% of the study population had major ECG abnormalities while 37.7% of the study participants had minor ECG abnormalities. The remainder of the study participants had normal ECG results.

Figure 4.2: Distribution of Major and Minor Abnormalities based on ECG



Minor abnormalities category include minor ST-segment abnormalities, minor QS pattern abnormalities, ventricular contractions or premature atrial or complete right bundle branch block.

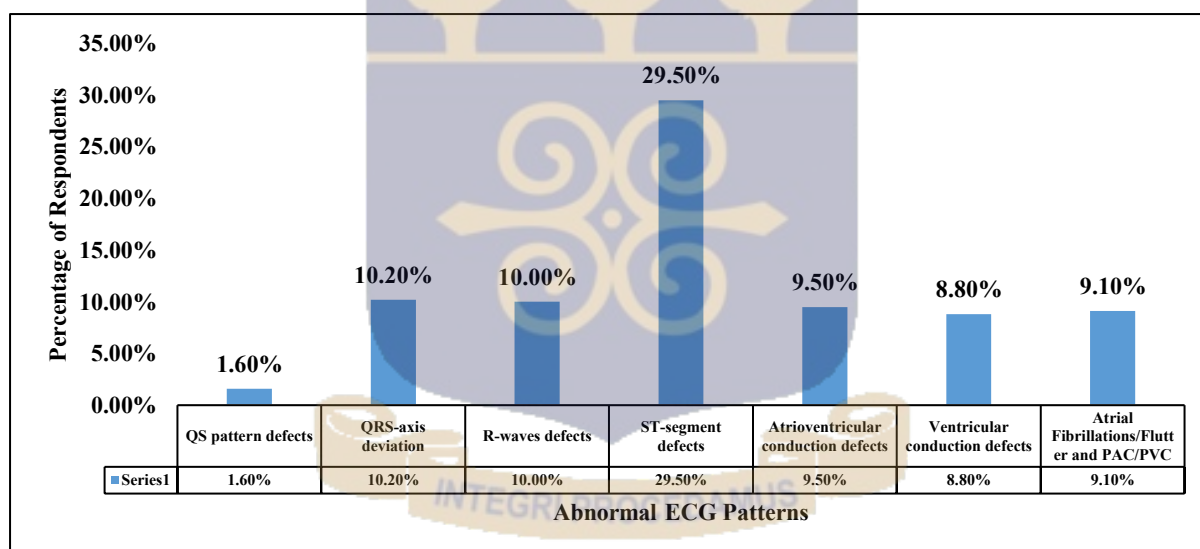
Major abnormalities category include major ST-segment abnormalities, major QS pattern abnormalities, atrial fibrillation or flutter, complete left bundle branch block or intraventricular block.

4.4 PATTERNS OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN T2D

4.4.1 Distribution of Abnormal ECG Patterns

Figure 4.2 presents the distribution of abnormal ECG patterns observed in the study population. ST-segment defects were the most common abnormality, present in 29.5% of cases. This was followed by QRS-axis deviation (10.2%) and R-wave defects (10.00%). Other abnormalities include atrioventricular conduction defects (9.5%), atrial fibrillations/flutter and PAC/PVC (9.10%), ventricular conduction defects (8.80%), and QS pattern defects (1.60%).

Figure 4.2: Distribution of Abnormal ECG Patterns

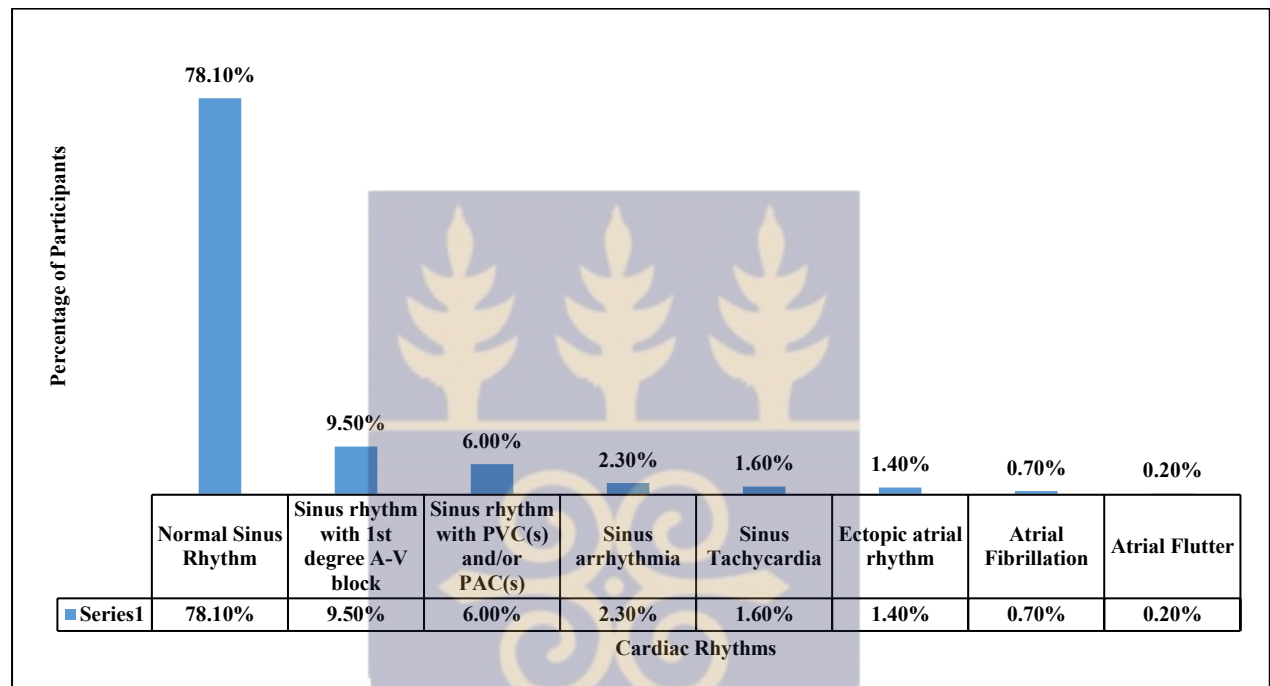


4.4.2 Distribution of Cardiac Rhythms

Figure 4.3 illustrates the distribution of cardiac rhythms within the study population. Normal sinus rhythm was the most common, observed in 78.1% of individuals. The next most frequent rhythm was sinus rhythm with 1st degree A-V block, comprising 9.5% of cases. Sinus rhythm with PVC(s) and/or PAC(s) followed at 6.0%. The less frequent rhythms included sinus

arrhythmia (2.3%), sinus tachycardia (1.6%), ectopic atrial rhythm (1.40%), atrial fibrillation (0.70%), and atrial flutter (0.20%).

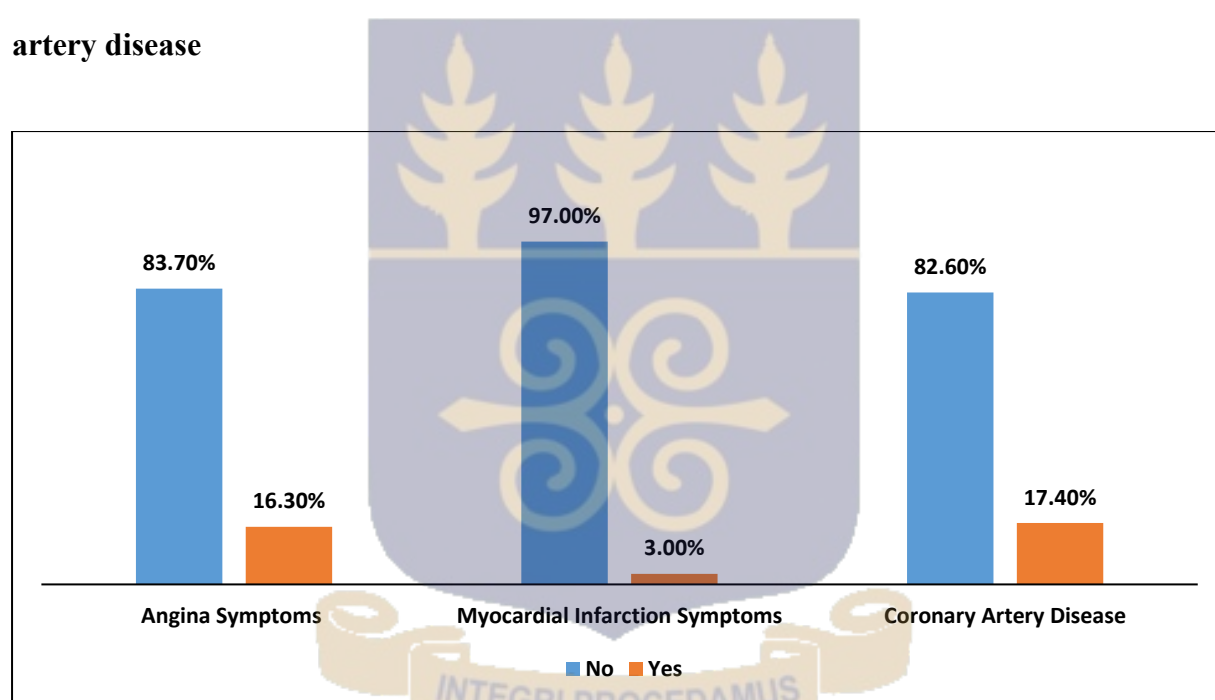
Figure 4.3: Distribution of Cardiac Rhythms



4.5 SYMPTOMS OF CAD

Figure 4.4 shows the symptoms of CAD assessed by the ROSE Angina questionnaire. Overall, 17.4% of the study population reported symptoms of either myocardial infarction or angina pectoris. Among those who reported symptoms of CAD, the majority (16.3%) reported angina symptoms; 3.0% of the study population reported symptoms of myocardial infarction.

Figure 4.4: Prevalence of angina pectoris, previous myocardial infarction and coronary artery disease



Symptoms of CAD were assessed using the WHO Rose Angina Questionnaire ⁷⁹.

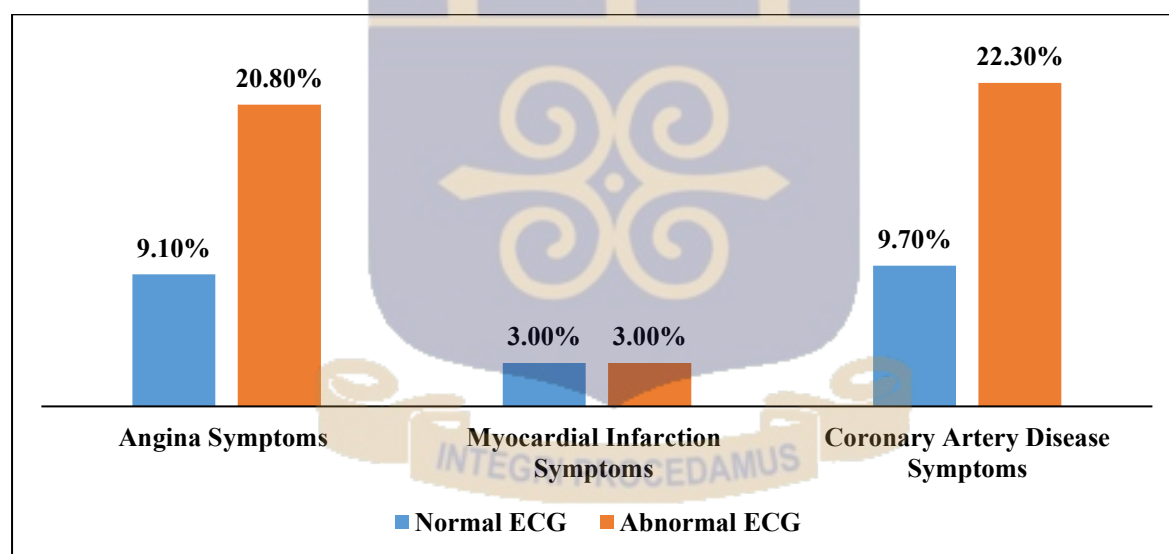
Possible myocardial infarction was defined as a positive reply to the question 'Have you ever had a severe pain across the front of your chest lasting for half an hour or more?'

Angina was defined as a positive reply to the questions 'Have you ever had any pain or discomfort in your chest?' and 'Do you get this pain or discomfort when you walk uphill or hurry?'

4.6 SYMPTOMS OF CAD STRATIFIED BY ECG PATTERN (NORMAL OR ABNORMAL)

Figure 4.5 compares the CAD symptoms in individuals with normal and abnormal ECG patterns. The proportion of individuals with CAD symptoms was over twice as high in the abnormal ECG group compared with those in the normal ECG group (22.3% vs 9.7%, $p=0.001$). This was driven largely by differences in angina symptoms (20.8% vs 9.1%, $p=0.001$); there was no significant difference in the two ECG groups concerning the proportion of individuals with myocardial infarction symptoms.

Figure 4.5: Prevalence of angina pectoris, previous myocardial infarction and coronary artery disease stratified by ECG normality status



Symptoms of CAD were assessed using the WHO Rose Angina Questionnaire ⁷⁹.

Possible myocardial infarction was defined as a positive reply to the question 'Have you ever had a severe pain across the front of your chest lasting for half an hour or more?'

Angina was defined as a positive reply to the questions 'Have you ever had any pain or discomfort in your chest?' and 'Do you get this pain or discomfort when you walk uphill or hurry?'

4.7 ASSOCIATION BETWEEN ECG ABNORMALITIES AND CARDIOVASCULAR RISK IN T2D

Table 4.5 summarizes the results of the multivariable regression models that sought to identify CVD risk factors (if any) associated with the individual / specific ECG abnormalities. In the models built, we identified no CVD risk factor associated with a leftward shift of the QRS-axis as well as premature atrial or ventricular contractions, atrial fibrillations, and atrial flutter. Previous or newly diagnosed hypertension was independently associated with QS pattern anomalies, very tall amplitude R-waves, ST-segment abnormalities, and ventricular conduction disorders. Specifically, a diagnosis of hypertension was associated with 65% higher odds of QS Pattern anomalies [odds ratio 1.65, 95% confidence interval 1.21 – 1.88, $p=0.049$], 31% higher odds of very tall amplitude R-waves [1.31 (1.07 – 1.82), 0.041], 64% higher odds of ST-segment abnormalities [1.64 (1.31 – 1.93), 0.033], and 68% higher odds of ventricular conduction disorders [1.68 (1.32 – 1.99), 0.042]. HbA1c concentration exceeding 7% was associated with 27% higher odds of abnormal Q-waves [1.27 (1.11 – 1.37), 0.032]. Obesity was associated with 77% higher odds of atrioventricular conduction abnormalities [1.77 (1.36 – 2.17), 0.022]

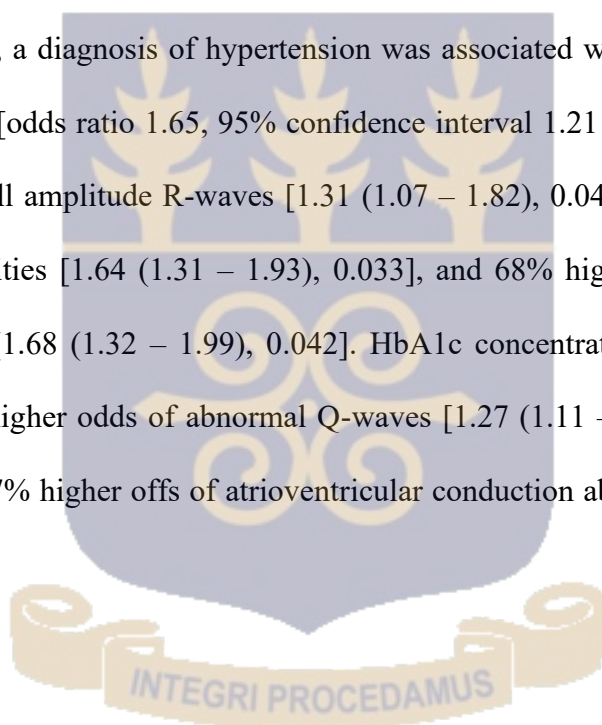
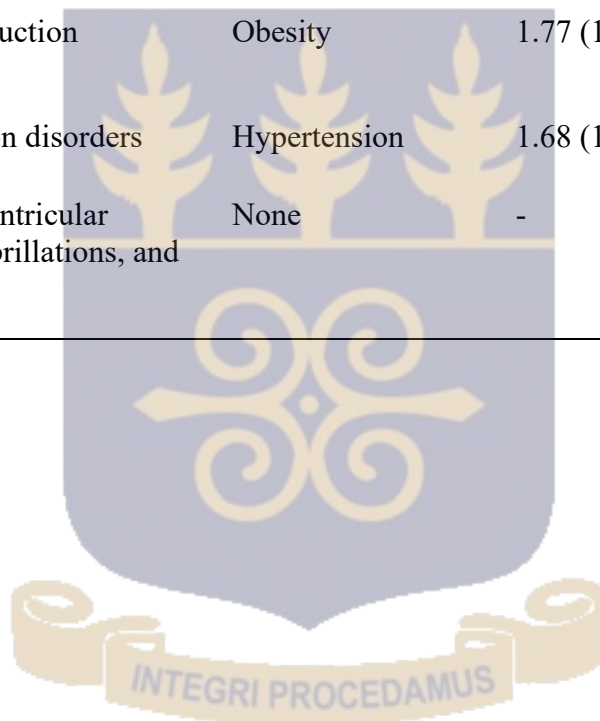


Table 4.5: Most predictive factors associated with various specific ECG abnormalities

Pattern (ECG abnormalities)	Predictive Factor	OR (95% CI), p-value
All abnormal Q-waves	Elevated HbA1c	1.27 (1.11 – 1.37), 0.032
QS Pattern anomalies	Hypertension	1.65 (1.21 – 1.88), 0.049
Leftward shift of the QRS-axis	None	-
Very tall amplitude R-waves	Hypertension	1.31 (1.07 – 1.82), 0.041
ST-segment abnormalities	Hypertension	1.64 (1.31 – 1.93), 0.033
Atrioventricular conduction abnormalities	Obesity	1.77 (1.36 – 2.17), 0.022
Ventricular conduction disorders	Hypertension	1.68 (1.32 – 1.99), 0.042
Premature atrial or ventricular contractions, atrial fibrillations, and atrial flutters	None	-



CHAPTER FIVE

DISCUSSIONS

5.1 SUMMARY OF KEY FINDINGS

This study shows that 61.6% of Ghanaians with T2D had abnormal ECGs, with 23.9% exhibiting major abnormalities and 37.7% having minor abnormalities. Overall, 17.4% of the study population reported symptoms of either myocardial infarction or angina pectoris. Among those who reported symptoms of CAD, the majority (16.3%) reported angina symptoms and the minority (3.0%) reported symptoms of myocardial infarction. The proportion of individuals with CAD symptoms was higher in the abnormal ECG group compared with the normal ECG group. This was driven largely by differences in angina symptoms. In the multivariable regression model, hypertension was independently associated with QS pattern anomalies, very tall amplitude R-waves, ST-segment abnormalities, and ventricular conduction disorders. Poor glycemic control was associated with abnormal Q-waves while obesity was associated with atrioventricular conduction abnormalities.

5.2 GENERAL CHARACTERISTICS OF THE STUDY POPULATION

The study showed that individuals with abnormal ECG had a higher mean age than those with normal ECG. Other modified and non-modifiable risk factors including sex, BMI, hypertension, and lipid concentrations did not differ between the two groups. The observation that individuals in the abnormal ECG group being older highlights the influence of aging on cardiac electrical activity¹⁷. This aligns with findings from Harms et al. (2021), where age was a key determinant of ECG abnormalities in individuals with T2D ($p < 0.01$)¹³. Both studies emphasize the physiological impact of aging on cardiovascular structures, such as increased

arterial stiffness and left ventricular hypertrophy, which predispose older adults to electrical conduction abnormalities. Age-related changes, including myocardial fibrosis and reduced autonomic regulation, may also explain this association ⁸⁰.

In this study, there was no significant difference in the female-male ratio in the normal and abnormal ECG groups. This contrasts with Harms et al., where male sex was associated with increased ECG abnormalities¹³. This discrepancy could stem from the higher proportion of females in our sample, potentially masking sex-specific differences.

The observed lack of significant differences in systolic and diastolic blood pressures in our two study groups aligns with findings from Bedane et al. (2021), who observed that hypertension, while common, did not directly correlate with ECG abnormalities in certain populations³². This could reflect the complex interplay of factors such as antihypertensive medication use and diabetes duration. Physiologically, sustained hypertension may cause structural heart changes that manifest as ECG abnormalities only over prolonged periods⁸¹. Conversely, well-managed blood pressure might limit the progression of these changes, explaining the minimal difference in our findings ⁸¹. Regular ECG screening remains crucial for the early detection of subclinical cardiovascular dysfunction in T2D.

The observed fasting plasma glucose levels were slightly higher in participants with normal ECG compared to those with abnormal ECG, though the difference was not statistically significant (9.41 vs 8.35, $p=0.055$). Similar trends in glucose levels among diabetic populations have been noted by Harms et al. (2021) in their study on the Hoorn cohort. They reported that higher glucose levels are associated with subclinical cardiovascular risk rather than overt ECG abnormalities($p=0.74$)¹³. Physiologically, chronic hyperglycemia can induce vascular endothelial dysfunction and contribute to atherosclerosis, but compensatory mechanisms in some individuals may delay detectable ECG changes despite elevated glucose levels⁵¹.

Lipid profile measures, including total cholesterol, HDL, LDL, and triglycerides, were similar between groups, aligning with findings from Sinamaw et al. (2022), who observed no significant association between lipid levels and ECG abnormalities in diabetic populations⁶². The lack of variation may reflect effective lipid-lowering therapies among participants or a similar baseline cardiovascular risk profile in both groups. Mechanistically, while dyslipidemia accelerates atherogenesis, its immediate impact on ECG changes depends on factors like plaque stability and arterial stiffness⁸². This may be explained physiologically by the fact that while dyslipidemia contributes to macrovascular complications, the progression of microvascular damage and electrophysiological changes might be more influenced by long-standing hyperglycemia and oxidative stress⁸². The chronic exposure of cardiac tissue to high glucose levels promotes advanced glycation end-products (AGEs), impairing ion channel function and myocardial conductivity independent of lipid status⁴².

Finally, the electrolyte concentrations, including sodium, potassium, and calcium, were similar across the study groups, consistent with Bedane et al. (2021), who also found no significant correlation between electrolyte imbalance and ECG changes in diabetic patients³². The absence of differences might suggest effective renal regulation of electrolytes in this population, despite diabetes being a known risk factor for electrolyte disturbances. It may be that the majority of our study population had normal electrolyte concentrations. Therefore, the impact of abnormal electrolyte concentrations on measures of cardiac dysfunction including abnormal amplitude of T waves and the presence of u waves was not seen¹². Potassium plays a crucial role in cardiac conduction, and abnormalities in potassium levels can lead to significant ECG changes, yet normokalemia here reflects stable cardiac electrophysiological function³².

5.3 PREVALENCE AND PATTERNS OF ECG ABNORMALITIES IN T2D

The study found a high prevalence of ECG abnormalities, with 61.6% of participants presenting with at least one abnormality, categorized into major (23.9%) and minor (37.7%) abnormalities. This findings is inconsistent with findings from well-conducted sufficiently powered studies that assessed a broad range of ECG abnormalities including that by Harms et al. (2021), where the prevalence of ECG abnormalities in individuals with T2D was 29.1%, with 16% classified as minor and 13.1% as major¹³. The relatively high burden of ECG abnormalities in the current study may reflect overall poor glycemic and metabolic control observed in the current study compared with that by Harms et al. (2021). Aside the poor glycemic and general cardiometabolic control, the observed high burden of abnormal ECG may be attributed to the impact of ethnicity on cardiovascular outcomes. Using data from two large community-based cohorts, Rajalakshmi Santhanakrishnan and his colleagues have previously reported ethnic differences in ECG characteristics⁸³. It also remains uncertain whether the absence of sub-Saharan African ethnic-specific ECG normative values played a role in possibly overestimating the prevalence of abnormal ECGs. Like most physiological tests, the accuracy of diagnosing ECG abnormalities relies on background prevalence in healthy individuals. In apparently healthy individuals, C Cato Ter Haar and her colleagues have demonstrated that there is a highly variable ethnicity-dependent prevalence of ECGs with ST-segment elevations exceeding STEMI thresholds¹⁶. This may be the case given the wide discrepancy between the prevalence of ECG abnormalities and the prevalence of CAD symptoms (61.6% having abnormal ECG findings and yet only 17.4% having CAD symptoms). However, one may argue that in individuals with diabetes, mapping symptoms to abnormal ECG findings may be excessively problematic given the impact of impaired autonomic function on the ability of patients with diabetes to detect symptoms often resulting from cardiac dysfunction. It has been established that cardiovascular autonomic neuropathy in T2D increases the risk of silent

myocardial events^{18,19}. Therefore affected patients may not experience symptoms like chest pain, which forms the basis of CAD evaluation using the WHO Rose Angina Questionnaire⁷⁹.

Regardless, findings from this study and those of other researchers emphasize that the presence of ECG abnormalities, particularly major which could result in adverse events such as sudden cardiac death. The relatively high burden of minor ECG abnormalities like premature ventricular or atrial contractions and ST-segment abnormalities is clinically relevant because they may be indicative of underlying cardiovascular issues. These findings suggest that minor ECG abnormalities might act as early markers for more serious cardiac events, which is consistent with the understanding that T2D increases the risk for both subtle and severe heart conditions. The physiological mechanisms underlying these abnormalities often involve increased autonomic dysfunction, impaired myocardial oxygenation, and fibrosis, which are common in diabetic patients, leading to arrhythmias and conduction disturbances⁸⁴.

In the current study, ST-segment abnormalities were the most common, observed in 29.5% of cases, followed by QRS-axis deviation (10.2%) and R-wave defects (10.0%). These findings align with Sinamaw et al. (2022), where ST-segment changes were also among the most frequent ECG abnormalities in T2D patients. ST-segment abnormalities, often associated with ischemia, can indicate myocardial injury or increased sympathetic tone, which is prevalent in diabetic individuals due to their increased risk of coronary artery disease (CAD)⁶². The QRS-axis deviation observed here is particularly notable, as it can signal conduction disturbances such as left or right bundle branch blocks or left ventricular hypertrophy, often linked to long-standing hypertension and diabetes. In T2D, the interplay between hyperglycemia, endothelial dysfunction, and increased stiffness of the vascular walls contributes to these abnormalities by disrupting normal conduction pathways and myocardial function⁴⁰.

Notably, the study also found that individuals with abnormal ECGs were more likely to report symptoms of CAD, particularly angina, compared to those with normal ECGs (22.3% vs. 9.7%, $p=0.001$). This finding supports the notion that abnormal ECGs, especially those with major abnormalities like ST segment abnormalities, atrial fibrillation and bundle branch blocks, reflect significant underlying cardiovascular pathology. The link between ECG abnormalities and CAD symptoms is well-documented, as seen in Harms et al. (2021), which reported that individuals with hypertension and diabetes had a higher prevalence of arrhythmias and conduction defects¹³. These ECG changes, particularly atrial fibrillation and flutter, could result from diabetic-induced fibrosis and inflammation in the heart's electrical system. Physiologically, the altered electrical activity in the heart due to fibrosis and poor vascular perfusion in T2D can lead to arrhythmias, exacerbating CAD symptoms like angina⁴⁰. Thus, ECG monitoring in T2D patients is critical for early detection of such disturbances, potentially guiding timely interventions to prevent further cardiovascular events.

Lastly, the present study revealed that nearly 10% of the study population exhibited AV nodal conduction blocks. This prevalence is notably higher than the <5% reported in previous studies examining similar populations. For instance, studies by Movahed et al, (2005) and Ezeude et al, (2024) found a lower prevalence of AV nodal blocks in the general population, typically under 5%. The reasons for the higher occurrence in our cohort are not immediately clear, but there are several factors that could explain this discrepancy^{64,85}.

5.4 MEASURES OF ECG INDICES IN T2D

A noteworthy finding from this study is the significant difference in the RR interval between individuals with normal and abnormal ECGs, with those in the abnormal ECG group having a longer RR interval (853.94 ms vs. 818.54 ms, $p=0.020$). Sinamaw et al. (2022) found that prolonged RR intervals were common in T2D patients, particularly those with comorbid

hypertension⁶². Prolongation of the RR interval is often due to impaired autonomic regulation of the heart, a characteristic of T2D⁴⁰. In T2D, insulin resistance and hyperglycemia contribute to autonomic dysfunction, which in turn affects heart rate variability and prolongs the RR interval^{40,42}. Although hypertension did not significantly differ between the two groups in the current study, the link between diabetes and autonomic dysfunction may still explain the observed difference in RR intervals.

The QT interval was significantly longer in the abnormal ECG group (402.63 ms vs. 394.40 ms, $p=0.015$). This finding is in agreement with Patel et al. (2023), who found prolonged QT intervals in T2D patients. Prolonged QT intervals in diabetes can be attributed to electrolyte imbalances, particularly changes in potassium and calcium levels, which affect myocardial repolarization⁶⁵. Additionally, metabolic abnormalities such as hyperglycemia and insulin resistance can lead to structural changes in the heart, further prolonging the QT interval⁶⁵. The current study's finding of a longer QT interval in the abnormal ECG group highlights the increased risk of arrhythmias and sudden cardiac death in T2D patients, reinforcing the need for regular ECG monitoring as part of cardiovascular risk assessment.



5.5 ASSOCIATIONS OF ECG ABNORMALITIES WITH CURRENT/PRIOR ADVERSE CARDIAC EVENTS

The findings of the current study, which identified hypertension as a major contributor to various ECG abnormalities in individuals with T2D [1.65 (1.21 – 1.88), $p=0.049$], align with results from multiple studies on the cardiovascular risks in T2D patients. Similar to the study by Harms et al. (2021), which demonstrated a strong association [1.99 (1.68–2.36)] between hypertension and the prevalence of ECG abnormalities such as ventricular conduction defects and arrhythmias, the present study confirms hypertension's significant impact on specific ECG

patterns¹³. Hypertension, through mechanisms like increased left ventricular afterload and myocardial remodeling, contributes to the observed alterations in the electrical activity of the heart⁴⁰. These changes are critical as they may predispose T2D individuals to higher risks of cardiovascular events such as arrhythmias and heart failure, reinforcing the need for close cardiovascular monitoring in T2D patients with hypertension.

The relationship between elevated HbA1c and abnormal Q-wave findings, as observed in this study [1.27 (1.11 – 1.37), $p=0.032$], supports findings from Patel et al. (2023), who reported that poor glycemic control is associated with increased cardiovascular risk in T2D patients, evidenced by changes in ECG parameters like prolonged QT intervals and ST-segment abnormalities⁵⁵. In the current study, a 27% higher likelihood of abnormal Q-waves with HbA1c levels exceeding 7% suggests that chronic hyperglycemia may exacerbate myocardial ischemia or fibrosis, leading to specific ECG changes. The pathophysiological mechanism likely involves hyperglycemia-induced oxidative stress and inflammation, which contribute to myocardial remodeling and disturbances in conduction pathways, aligning with previous research on the deleterious effects of elevated blood glucose on cardiac health²⁹.

Lastly, obesity was identified as a significant factor for atrioventricular conduction abnormalities in this study [1.77 (1.36 – 2.17), $p=0.022$], which mirrors findings from Sinamaw et al. (2022), where overweight individuals with T2D exhibited a higher prevalence of ECG abnormalities⁶². Obesity-induced inflammation and adipokine dysregulation may contribute to conduction disturbances by promoting fibrosis and altering the electrical properties of the heart⁴⁵. The study's emphasis on the impact of obesity on cardiac function highlights the importance of weight management in mitigating cardiovascular risks among T2D patients. This association underscores the need for integrated management strategies that address both metabolic and cardiovascular health in individuals with T2D. The mechanical impact of obesity

on altering thoracic and abdominal anatomy and adversely impacting ECG tracing cannot be excluded ⁸⁶.

5.6 STRENGTHS/NOVELTY AND LIMITATIONS OF THE STUDY

Strengths

1. Electrocardiography was done according to the American Heart Association guidelines and the reporting of the ECG was very robust including the device's inbuilt University of Glasgow 12-Lead ECG Analysis Algorithm¹, the Minnesota coding, and assessment by a trained physician.
2. Well-standardized study protocols were used in this study. Further, a wide range of conventional CVD risk factors were assessed

Novelty

To the best of my knowledge, this current study is the first to report a comprehensive spectrum of ECG abnormalities in sub-Saharan Africans with T2D. The study also links the abnormal ECGs to CAD symptoms based on a structured instrument such as the WHO ROSE Angina questionnaire.

6.2 LIMITATIONS

1. The cross-sectional design limits assessment of causality with respect to the study objectives that assessed the associations of abnormal ECGs with CVD risk factors. Based

on biological plausibility, it is the conventional CVD risk factors that puts a strain on cardiac function and result in abnormal ECG patterns.

2. In the assessment of CAD based on the WHO Rose angina questions, recall bias could have negatively impacted the participant's responses.
3. In assessing CAD, the gold standard i.e. coronary angiography was not performed due to feasibility⁸⁷.
4. We did not perform stress ECG in the study. Stress ECG may be valuable in identifying cardiac arrhythmias, myocardial ischemia, or recent acute coronary syndromes in some patients who otherwise will have a normal resting ECG.
5. We did not assess cardiac biomarkers, such as troponins, which limited our ability to correlate ECG abnormalities with acute myocardial injury or ischemia. Also, we did not examine inflammatory markers, which are important in understanding cardiovascular risk.
6. Lack of ethnic-specific reference values for ECG in our study population could have led to over diagnoses or underdiagnoses of the specific ECG abnormalities.
7. A key limitation of this study is the non-inclusion of cardiac enzymes (e.g., troponins or CK-MB), which limits the ability to correlate ECG abnormalities with biochemical evidence of myocardial injury. Without cardiac biomarker data, it was not possible to distinguish between ischemic changes associated with acute myocardial injury and ECG abnormalities related to other clinical conditions. This may have led to misclassification and limits the strength of conclusions regarding the clinical significance of the observed ECG findings.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSION

Results from this cross-sectional study that assessed the prevalence of resting ECG abnormalities and their associations with cardiovascular risk factors and current/prior adverse cardiac events in Ghanaian adults with T2D reports a high prevalence of abnormal ECG findings in the study population. Approximately six out of ten study participants had abnormal ECG. This is clinically relevant given the impact of abnormal ECG on cardiovascular health of affected patients. This study further reports that the observed ECG abnormalities correlated with angina symptoms, which gives credence to the clinical significance of the abnormal ECG findings. Hypertension was the CVD risk factor most frequently independently associated with specific ECG abnormalities in our study population, including QS pattern anomalies, very tall amplitude R-waves, ST-segment abnormalities, and ventricular conduction disorders. Poor glycemic control and obesity were also independently associated with abnormal Q-waves and atrioventricular conduction abnormalities, respectively. These results provide opportunities for institution of preventive and treatment strategies targeting abnormal ECG in the study population. Overall, the study findings could inform the institution of frequent ECG testing in select groups of Ghanaians with T2D, to aid in the prevention of adverse CVD events.

6.2 RECOMMENDATIONS FOR CLINICAL PRACTICE/FUTURE RESEARCH

1. To better characterize the causal relationships between CVD risk factors and associated ECG abnormalities, as well as the associations of abnormal ECG abnormalities and adverse cardiovascular events / symptoms, a longitudinal study is recommended. This proposed study should
 - a. be a multicenter study to enhance external validity
 - b. include study participants with newly diagnosed diabetes to better assess the impact of diabetes on ECG pattern
 - c. include a comparative group without diabetes
 - d. include children with diabetes. The impact of diabetes on heart health in Ghanaian children is not reported
 - e. include a larger proportion of males and/or stratify analyses based on sex considering the sex differences in cardiovascular disease and its impact on ECG.
 - f. assess other objective measures of CAD including coronary angiography (at least in a sub-set of study participants)
 - g. assess biomarkers of ischemic cardiac events (at least in a sub-set of study participants)
2. Based on the study findings, Ghanaians with T2D should undergo routine ECG testing to identify at risk individuals.
 - a. Individuals with hypertension, obesity and/or poor glycemic control may benefit from more frequent ECG testing.
 - b. This will facilitate early detection and management of cardiovascular abnormalities and prevent adverse cardiac events.

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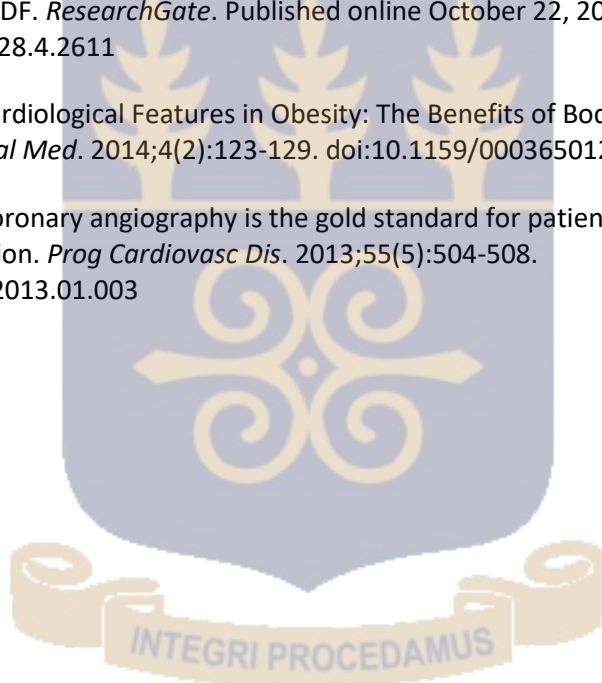
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APPENDIX I: INFORMED CONSENT FORM

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.

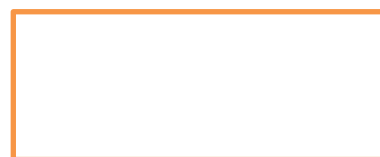
I voluntarily agree to be part of this research.

(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.

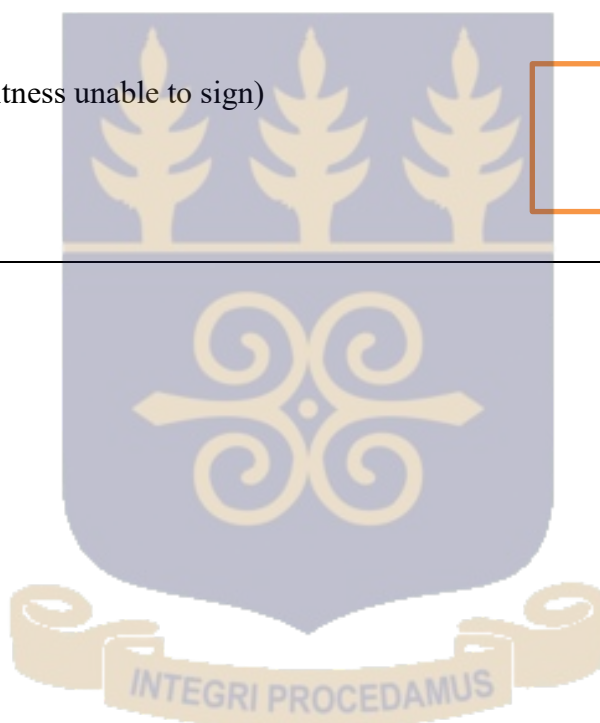
.....

(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 II: NATIVITY QUESTIONNAIRE

The following questions are aimed at confirming your Ghanaian nativity Please answer the questions as accurately as you can.

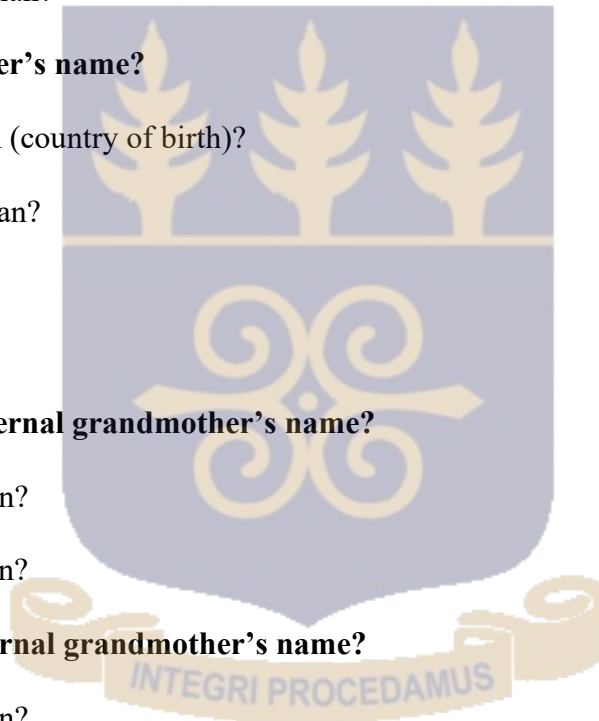
A

- 1. What is your mother's name?**
2. Where was she born (country of birth)?
3. Is/was she a Ghanaian?
- 4. What is your father's name?**
5. Where was he born (country of birth)?
6. Is/was he a Ghanaian?

B

- 7. What is your maternal grandmother's name?**
8. Where was she born?
9. Was she a Ghanaian?
- 10. What is your paternal grandmother's name?**
11. Where was she born?
12. Was she a Ghanaian?
- 13. What is your maternal grandfather's name?**
14. Where was he born?
15. Was he a Ghanaian?

- 16. What is your paternal grandfather's name?**



17. Where was he born?

18. Was he a Ghanaian?



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	Tribes (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? <u>[If Never Smoked, skip to 27]</u>	1. Never Smoked	2. Currently smokes
		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
		<i>If yes, please specify</i>
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			

WHO ROSE ANGINA QUESTIONNAIRE

	QUESTION	RESPONSE
1	Have you ever had any pain or discomfort in your chest?	• No • Yes
2	Where do you get this pain or discomfort?	• No • Yes
3	Do you get this pain when you're exerting yourself (for example, when you're climbing stairs, walking fast, or cycling)? [Do you get this pain or discomfort when you walk uphill or hurry]	• No • Yes
4	When you walk at an ordinary pace at the level, does this produce the pain?	• No • Yes
5	If "Yes" to Questions 3 or 4, where do you feel this pain or discomfort?	• Across the front of the chest • In the neck or jaw • Down the left arm • Other (Specify): _____
	When you get any pain or discomfort in your chest on walking, what do you do?	• Stop or slow down • Carry on as before
	Does the pain or discomfort in your chest go away if you stand still	• No • Yes
	How long does it take to go away?	
	Have you ever had a severe pain across the front of your chest lasting for half an hour or more?	• No • Yes

APPENDIX IV: ETHICAL APPROVAL LETTER



UNIVERSITY OF GHANA COLLEGE OF HEALTHSCIENCES

ETHICAL AND PROTOCOL REVIEW COMMITTEE

EPRC/MAR/2024

August 9, 2024.

Mr. Sylvester Ameyaw-Gyan
Department of Physiology
University of Ghana Medical School
Korle Bu - Accra

Dear Mr. Ameyaw-Gyan,

ETHICAL CLEARANCE

Protocol Identification Number: **CHS-Et/M.8 – P 4.2 /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: “Electrocardiographic Profiles and Associated Factors in Ghanaians with Type 2 Diabetes”

Principal Investigator: Mr. Sylvester Ameyaw-Gyan

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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