PREVALENCE AND CORRELATES OF CARDIAC ABNORMALITIES AMONGST NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

BY

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTERS OF MEDICINE IN INTERNAL MEDICINE, MOI UNIVERSITY.

DECLARATION

Candidate's declaration

This research thesis is my original work and to the best of my knowledge has not been presented for an award of a university degree or any academic credit in any other University. No part of this proposal may be reproduced without prior permission of the author and/or Moi University.

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DEDICATION

This thesis is dedicated to my dad and my siblings for their support and encouragement and to my late mum who inspired my interest in medicine.

ABSTRACT

Background: **Background**: Type 2 Diabetes Mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD), the leading cause of mortality globally. Its prevalence is increasing globally and in Kenya; it is currently estimated at 3.3%, with the projection of reaching 4.5% by the year 2025. It has a long asymptomatic latent period (prediabetes) that is associated with increased risk of CVD. Incidence of CVD is 2-3 times higher in T2DM than in those without. Identifying underlying cardiac abnormalities at the time of diagnosis of T2DM by echocardiogram and electrocardiogram can guide timely interventions that prevent, reverse, or delay cardiovascular complications. Data on preexisting cardiac abnormalities amongst newly diagnosed T2DM patients in our setting is limited.

Objective: To determine the prevalence and correlates of cardiac abnormalities amongst newly diagnosed T2DM patients seen at Moi Teaching and Referral Hospital (MTRH).

Methods: This cross-sectional study was conducted between November 2021 and July 2022 at the MTRH diabetic clinic and medical wards.160 newly diagnosed (≤6months) T2DM patients were recruited using consecutive sampling. Sample size was calculated by Fishers Exact and Peduzzi formulae. Participants' socio-demographic and clinical characteristics were captured on interviewer-administered structured questionnaires. The dependent variable was a composite of functional and structural cardiac abnormalities assessed for by echocardiogram and electrocardiogram. The independent variables were age, sex, smoking, HbA1C, body mass index, albuminuria, dyslipidemia, creatinine clearance, hypertension and calculated 10-year atherosclerotic CVD (ASCVD) risk. Continuous variables (Age, HbA1C, DM duration) were summarized as mean (SD) or median (IQR). Categorical variables such as ASCVD risk categories and smoking history were summarized as frequencies and proportions. Bivariate and multivariate logistic regression analysis was done to test for associations. Statistically significant variables (P value <0.05) on bivariate analysis were entered into a multivariable model and strength of association calculated as adjusted odds ratio with 95% confidence intervals.

Results: Of the 160 participants recruited, the mean age was 56(SD±11) years, females were 85(53.1%), the median diabetes duration was 4 months and the mean HbA1c was 8.99%(SD±4).The prevalence of composite cardiac abnormalities was 54.7% (95%CI 47-63).Isolated functional and structural cardiac abnormalities were present in 83.8%(95%CI77.9-89) and 62.9%(95%CI 50-70) respectively. Prevalence of specific structural abnormalities was: Left ventricular hypertrophy (17.5%), ST segment abnormalities (6.9%), T wave abnormalities (51%) and wall motion abnormalities (13.2%). Functional abnormalities were present in: left ventricular systolic dysfunction (15%) left ventricular diastolic dysfunction [(LVDD) 66.87%], arrhythmias (37.1%) and conduction abnormalities (37.1%). In multivariate logistic regression analysis, only abnormal creatinine clearance (<90ml/min/1/73m^2) was independently associated with composite cardiac abnormalities [odds ratio 2.43 (1.03-5.94)].

Conclusions: The prevalence of composite cardiac abnormalities was 54.7%, isolated structural and isolated functional cardiac abnormalities were present in 83.8% and 62.9% of the newly diagnosed T2DM participants respectively. LVDD and T wave abnormalities being the most prevalent .Abnormal creatinine clearance (<90ml/min/1/73m^2) was independently associated with the composite cardiac abnormalities.

Recommendations: Amongst newly diagnosed T2DM patients, early assessment for cardiac abnormalities is crucial, especially in the presence of abnormal creatinine clearance (<90ml/min/1.73m^2).

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body Mass Index
BP	Blood Pressure
CHD	Coronary Heart Disease
CVDs	Cardiovascular Diseases
DOPC	Diabetic Out-Patient Clinic
ECG	Electrocardiogram
ECHO	Echocardiogram
FPG	Fasting Plasma Glucose
HbA1C	Glycosylated Haemoglobin
IDF	International Diabetic Federation
LMIC	Low and Middle Income Countries
LVDD	Left Ventricular Diastolic Dysfunction
LVH	Left Ventricular Hypertrophy
LVSD	Left Ventricular Systolic Dysfunction
MTRH	Moi Teaching and Referral Hospital
OGLA	Oral Glucose Lowering Agents
RBS	Random Blood Sugar
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization
WHR	Waist Hip Ratio

OPERATIONAL DEFINITION OF TERMS

Cardiac abnormalities:

For the purpose of this study were defined as a **composite of structural and functional abnormalities as** assessed for by electrocardiography and /or echocardiogram.

Composite cardiac abnormalities:

Consisted the presence of both structural and functional abnormalities as seen on electrocardiography and/or echocardiography in a participant

The specific disorders that were sought for included:

- Rhythm abnormalities
- Conduction abnormalities
- Wall motion abnormalities- akinesia, hypokinesia or dyskinesia
- Myocardial mass changes- left /right ventricular hypertrophy
- Left ventricular chamber size abnormalities
- Valvular abnormalities
- Left ventricular systolic dysfunction and diastolic dysfunction
- Evidence of new or old myocardial ischemia /infarction

A. Structural abnormalities in this study were defined as presence of either:

- **Evidence of Myocardial ischemia on:**

  a. **Echocardiographic criteria**: Regional Wall motion abnormalities

b. **ECG criteria** : ST-T changes on ≥2 contiguous leads and /or T wave aberrations on contiguous leads

- ***Left ventricular remodeling as evidenced by*:**

a. ECG criteria :LVH determined by Cornell's criteria (S wave in in V3+ R in aVL) LVH present IF >20mm in females and > 28mm in males OR R >12mm in aVL) and /or

b. ECHO criteria : LVH as evidenced by left ventricular wall thickness of >11mm for females and >12mm in males in diastole

B. Functional abnormalities in this study were defined as presence of either:

1. ***Left ventricular dysfunction as evidenced b*y:** left ventricular diastolic dysfunction (LVDD) and/ or left ventricular systolic dysfunction(LVSD) on ECHO

2. ***Arrhythmias as evidenced by ECG*** - sinus tachycardia (heart rate >100beats per minute) , sinus bradycardia (heart rate < 60 beats per minute), atrial fibrillation, atrial flutter, premature ventricular contraction, premature atrial contraction or atrio-ventricular blocks

3. ***Conduction abnormality as evidenced by*** **either:** Bundle branch blocks or QT prolongation (>480ms in male, >470ms in female)(AHA,2011)

Newly diagnosed Type 2 diabetes mellitus patient:

- For the purpose of this study was:

– A **patient with a confirmed diagnosis of type 2 diabetes mellitu**s by ADA, 2020 criteria

AND

- Who at the time of diagnosis was **≥35 years, managed on OGLA and/or insulin** (rationale being T2DM has a wide variation in age of diagnosis but the risk increases with age, especially after age 35;ADA recommends annual diabetes screening tests for people aged≥ 35 years

AND

- **Whose diagnosis was made within a period of ≤ 6months** before screening for inclusion into this study

Diabetes mellitus diagnostic criteria according to American Diabetes Association (ADA, 2020)

- Symptoms of diabetes plus random blood sugar (RBS) ≥ 11.1mmol/L

OR

- Fasting plasma glucose (FPG) ≥7.0mmol/L

OR

- Glycosylated hemoglobin (HbA1C) ≥6.5%

OR

- 2 hour post load plasma glucose ≥ 11.1mmol/L

Hypertension

Based on the International Society of Hypertension (ISH, 2020) guidelines, any blood pressure measurement of ≥140/90 mmHg was considered high.

Known hypertensive patient

A patient who reported a history of hypertension, which was also confirmed from the patients file or was on anti-hypertensive medication

Glycemic control

This was based on glycemic targets as recommended by American Diabetic Associations (ADA, 2020). HbA1C ≤ 7% was considered to be on target.

Lipid profile

The cut offs were based on ADA, 2020 guidelines and the following figures were considered abnormal:

- Low Density Lipoprotein (LDL) >2.6mmol/l;
- Triglycerides >1.7mmol/l
- HDL was considered low if <1.3mmol/l for female, and <1.0mmol/l for male patients.

Body Mass Index (BMI)

This was calculated as weight in kilograms divided by height in (m^2). The degree of obesity was classified based on National Institute of Health (NIH) cut offs as follows;

- Underweight (BMI of<18.5)
- Normal (BMI of 18.5-24.9)
- Overweight (BMI of 25-30)
- Obese (BMI of >30)

Waist Hip Ratio (WHR)

The WHR was calculated by dividing waist circumference by hip circumference. According to World Health Organization, a healthy waist to hip ratio is 0.9 or less in men and 0.85 or less for women. Waist hip ratios were categorized as:

- Low risk - <0.80 in females and <0.95 in males
- Moderate risk - 0.81-0.84 for females and 0.96-1 for males

- High risk - > 0.85 for females and >1 males

Waist circumference

The waist circumference measured at the end of normal expiration by standard protocol with the patient standing up straight, using a tape measure applied snugly around the uppermost lateral border of iliac crest.

Based on World Health Organization (WHO) it was considered abnormal if >88cm for female and >102cm for male patients.

Hip circumference

The hip circumference was measured with the patient standing up straight, using a tape measure applied snugly around the widest part of the hips and recorded in centimeters.

Estimated Glomerular Filtration Rate (eGFR)

This was calculated using Chronic Kidney Disease -Epidemiology Collaboration (CKD-EPI 2021) formula

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, (ADA guidelines, 2020).

The estimated global prevalence of diabetes in 2019 was 9.3% affecting approximately 463 million people), this prevalence is expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al.,2019).Within the Sub- Sahara ,the estimated age adjusted prevalence of diabetes was 4.7%(19.4 million) in 2019 and is estimated to rise to 5.1% (28.6 million) by 2030 and 5.2% (47.1 million) by 2045 in people aged 20-79 years,(IDF atlas,2019).The world health organization estimates the prevalence of diabetes in Kenya at 3.3%, with the projection of reaching 4.5% by the year 2025 (WHO/Kenya STEPwise survey,2015) . Diabetes Mellitus encompasses various subtypes such as Type 1 Diabetes, Type 2 Diabetes, gestational diabetes, and other less common forms, each with its distinct etiological factors and clinical characteristics. Type 2 Diabetes Mellitus accounts for around 90% of all diabetes mellitus cases,(IDF Atlas,2019).The chronic nature of diabetes underscores its potential to impact multiple organ systems, including the cardiovascular system, kidneys, eyes, and nervous system, highlighting the systemic implications of sustained hyperglycemia. The rising prevalence of diabetes mellitus on a global scale mirrors a parallel surge in the incidence of its associated long-term micro and macro complications. Type 2 Diabetes Mellitus is a well-recognized risk factor for clinical and subclinical cardiovascular disease; with the presence of diabetes being associated with a threefold higher CVD mortality risk, and about a two-fold excess risk for a wide range of vascular

diseases, independently from other conventional risk factors (Church., et al 2009), (Sara., et al 2010). This recognition reinforces the imperative for a comprehensive approach to managing diabetes that extends beyond glycemic control to encompass robust cardiovascular risk management strategies that include preventive measures, early detection, and targeted interventions to mitigate the profound impact of T2DM on the cardiovascular system.

Frequently, T2DM is preceded by a long latent asymptomatic phase; the pre-diabetes period which is characterized by chronic hyperglycemia and a high burden of cardio-metabolic risk factors. T2DM may go undiagnosed for many years because the hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms. Despite the absence of overt symptoms, individuals with undiagnosed diabetes remain at an elevated risk of developing both macro-vascular and micro-vascular complications,ADA,2020).Pre-diabetes is recognized as an independent risk factor for cardiovascular disease in T2DM (ADA,2020, Huang, Y., et al, 2016) with the CVD risk increased up to 15years prior to the clinical diagnosis (Stampfer .,et al,2002).

T2DM independently causes structural and functional cardiac abnormalities, shown to be predictors of future cardiovascular events and premature death. These cardiac abnormalities are collectively referred to as diabetic cardiomyopathy; an entity defined by left ventricular hypertrophy(LVH), Left ventricular systolic dysfunction(LVSD) and Left ventricular diastolic dysfunction(LVDD) in the absence of significant CHD or systemic hypertension(Somaratne ., et al,2011). Coronary heart disease, left ventricular dysfunction and LVH are implicated as the causes of cardiac death in diabetic patients (Elley .,et al, 2008).

Cardiac abnormalities associated with T2DM can be non-invasively assessed by ECHO and ECG (ESC 2019). Early recognition of these abnormalities would guide timely interventions to retard, delay or prevent complications. Despite this, data on the profile of cardiac abnormalities amongst newly diagnosed T2DM patients in our setting is still limited. Available studies in done in different clinical set ups have shown newly diagnosed T2DM patients to have varying prevalence of abnormal ECHO and resting ECG abnormalities (Muddu et al.,2016, Harms et al., 2014,Bedane DA et al,2021)

This study therefore, sought to determine the prevalence and correlates of cardiac abnormalities on ECG and ECHO amongst newly diagnosed T2DM patients in Moi Teaching and Referral Hospital (MTRH).

1.2 Problem statement

The burden of rising cases of diabetes mellitus is a growing public health concern in Kenya, with an estimated prevalence of 3.3% and is projected to rise to 4.56% by 2025 (750,000 persons).

T2DM is a progressive disease and is associated with both micro-vascular complications such as diabetic retinopathy, nephropathy and neuropathy and macro-vascular complications such as coronary heart disease, cardiomyopathy, arrhythmias and sudden death, cerebrovascular disease and peripheral artery disease.

Diabetes related macro-vascular complications increase the overall risk of premature death in this patient population.

The long latent pre-symptomatic period coupled with clustering of risk factors (such as; obesity, dyslipidemia, dysglycemia, hypertension, micro/macro-albuminuria) predispose T2DM patients to high prevalence of CVD already at the time of diagnosis.

In the San Antonio heart study there was evidence that the risk of CVD starts to increase long before the onset of clinical diabetes (SN Haffner .,et al, 1990).

Structural heart disease exists in T2DM and even when asymptomatic, it is associated with poor prognosis. In the detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study, 22% of asymptomatic patients with T2DM had evidence of ischemia on stress myocardial imaging.

DM related cardiovascular disease complications increase the overall risk of premature death and remain the leading cause death in T2DM accounting for two thirds of diabetic mortalities; this despite treatment guidelines targeting traditional CVD risk factors in this subset of patients. Moreover, despite evidence that cardiovascular disease may occur prior to clinical diagnosis of T2DM; current clinical guidelines do not provide guidance on early evaluation for cardiovascular disease amongst newly diagnosed T2DM patients.

There is still need for optimal cardiovascular disease risk stratification among newly diagnosed T2DM patients, to allow for early optimization of available preventive and therapeutic measures for better cardiovascular disease outcomes.

This study therefore set out to determine the prevalence and correlates of cardiac abnormalities amongst newly diagnosed T2DM seen at the MTRH, diabetic outpatient clinic and medical wards.

1.3 Justification

At the Moi Teaching and Referral hospital ,diabetic outpatient clinic, cardiovascular abnormalities amongst newly diagnosed T2DM patients has not been studied hence the prevalence of both structural and functional cardiac abnormalities in this patient population is not known.

With early diagnosis of cardiovascular abnormalities, early application and optimization of both preventive strategies and treatment measures including use of anti-glycemic agents with cardiovascular benefits can be instituted.

Timely institution of appropriate interventions for specific cardiovascular abnormalities has associated benefits of disease modification, retarding disease progression and reduced morbidity and mortality from cardiovascular disease in T2DM.

Electrocardiograms and echocardiograms offer a noninvasive modality for diagnosis of cardiac function and structural changes and determine even subtle cardiac abnormalities in T2DM.

Clinical predictors would further help identify the subset of newly diagnosed T2DM patients with a higher likelihood of CVD, and this will confer cost effectiveness while increasing the yield of abnormal studies through targeted application of diagnostic ECG and ECHO in this patient group.

The findings from this study may be used to inform strategies of improving cardiovascular disease assessment in patients with newly diagnosed T2DM including development of protocols on application of ECHO and ECG at diagnosis of T2DM in our set up. This study will also serve as a baseline reference for development of other related studies.

1.4 Research question

1. What is the prevalence of cardiac abnormalities amongst newly diagnosed type 2 diabetes mellitus patients seen MTRH?
2. What are the socio- demographic, clinical and laboratory correlates of cardiac abnormalities amongst newly diagnosed type 2 diabetes mellitus patients seen at MTRH?

1.5 Objectives

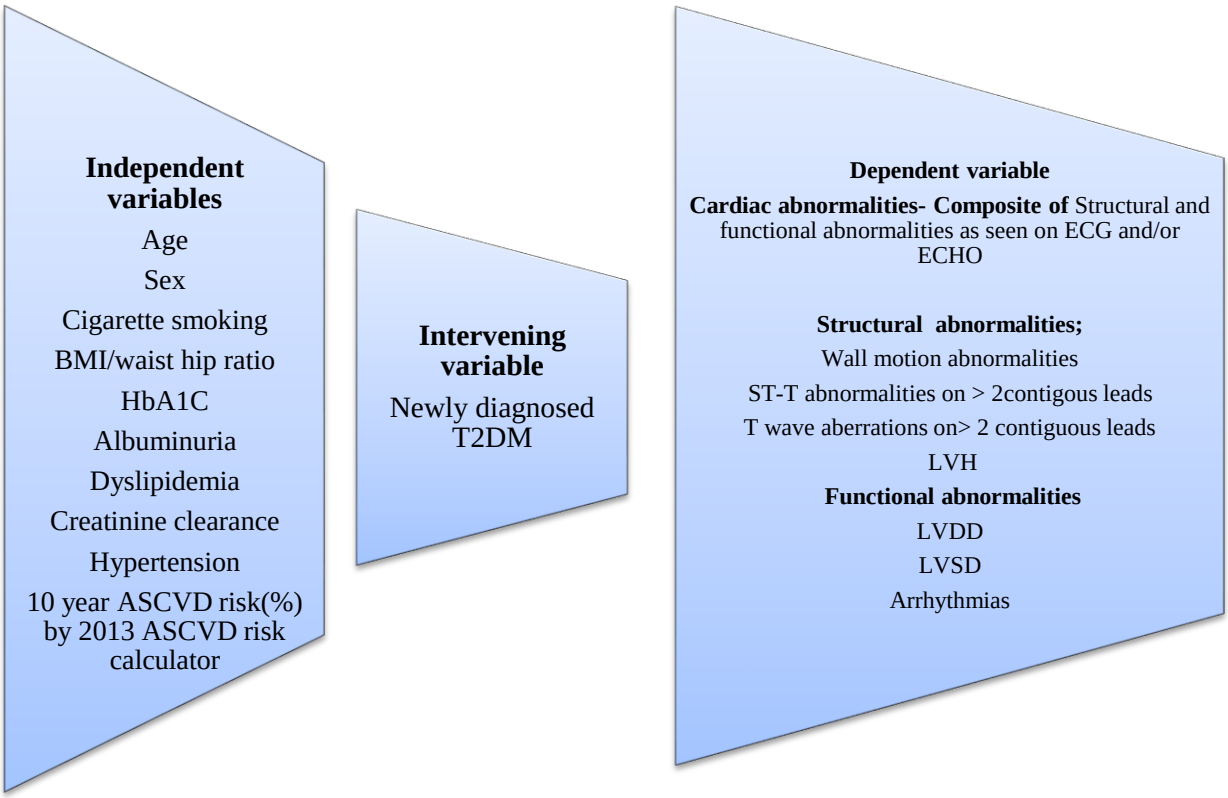
1.5.1 Broad objective

- To determine the prevalence and correlates of cardiac abnormalities amongst newly diagnosed T2DM patients seen at MTRH.

1.5.2 Specific objectives

1. To determine the prevalence of cardiac abnormalities amongst newly diagnosed type 2 diabetes mellitus patients seen at the DOPC and medical wards in MTRH.
2. To describe the socio-demographic, clinical and laboratory correlates of cardiac abnormalities amongst newly diagnosed T2DM patients seen at the DOPC and medical wards in MTRH.

1.6 Conceptual Framework



CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Background

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, resulting in elevated blood glucose levels.

Epidemiology and Global Impact:

The prevalence of T2DM has surged globally, evolving into a significant public health concern.

Global Prevalence and Incidence of Type 2 Diabetes Mellitus: According to recent statistics from the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes in 2021, with type 2 diabetes accounting for around 90% of these cases. The IDF estimates project a further increase to 643 million adults living with diabetes by 2030 if current trends persist. *International Diabetes Federation (IDF) (2019) IDF Diabetes Atlas, 9th edn. Brussels, Belgium*

The global prevalence of T2DM has been increasing, largely due to changes in lifestyle and an aging population.

Sub-Saharan Africa: Sub-Saharan Africa is experiencing a rapid increase in the prevalence of T2DM, primarily due to urbanization, changes in diet, and lifestyle factors. Limited access to healthcare, poor disease management and lack of awareness contribute to the challenges in controlling the disease burden in this region.

According to the IDF, in 2019, it was estimated that around 20 million people were living with diabetes in Sub-Saharan Africa.

Kenya: In Kenya, the prevalence of diabetes has been rising steadily over the years, driven by urbanization, sedentary lifestyles, and unhealthy diets. According to the Kenya STEPwise Survey for Non-Communicable Diseases Risk Factors 2015, the

prevalence of diabetes among Kenyan adults was estimated to be around 3.3%.WHO estimates that this prevalence will rise to 4.5% by 2025.

The Kenyan Ministry of Health and other organizations have been implementing various initiatives to increase awareness, improve access to care, and promote healthy lifestyles to combat the increasing prevalence of T2DM in the country.

This surge in diabetes prevalence exerts an immense burden on healthcare systems, leading to increased healthcare expenditures, reduced workforce productivity, and a higher risk of complications, including cardiovascular diseases, kidney failure, neuropathy, and blindness. Developing regions, particularly in low- and middle-income countries, bear a disproportionate share of this burden due to limited access to healthcare resources and rising urbanization with associated lifestyle changes.

One of the most alarming associations with type 2 diabetes is its strong correlation with cardiovascular diseases (CVD). The intertwining relationship between these conditions is profound and intricate. Individuals diagnosed with type 2 diabetes face a significantly heightened risk of developing various cardiovascular complications. Cardiovascular diseases encompass a broad spectrum of abnormalities, including coronary artery disease, myocardial infarction (heart attacks), stroke, peripheral arterial disease, and heart failure.

This correlation between type 2 diabetes and CVD stems from shared risk factors and pathophysiological mechanisms. Insulin resistance, a hallmark of type 2 diabetes, contributes to endothelial dysfunction, chronic inflammation, impaired vasodilation and abnormal lipid metabolism, culminating in atherosclerosis (the hardening and narrowing of arteries) paving the way for heart disease and stroke. Hyperglycemia, elevated blood glucose levels characteristic of diabetes, further exacerbates endothelial

damage, oxidative stress, and inflammation, all of which play pivotal roles in the development and progression of cardiovascular diseases.

Dyslipidemia, often observed in individuals with type 2 diabetes, involves abnormal lipid profiles characterized by elevated triglycerides and decreased high-density lipoprotein cholesterol. This lipid imbalance also contributes to the formation of atherosclerotic plaques, narrowing blood vessels, and increasing the risk of myocardial infarction and other cardiovascular events.

The gravity of this relationship underscores the critical importance of early detection and proactive management of cardiac abnormalities in individuals newly diagnosed with type 2 diabetes. Detecting cardiac complications in their latent stages holds immense potential to curtail the progression of cardiovascular diseases in these patients. Early intervention strategies targeting risk factors such as hypertension, dyslipidemia, and hyperglycemia can significantly mitigate the incidence and severity of subsequent cardiac issues.

Several diagnostic modalities play pivotal roles in identifying cardiac abnormalities in these patients. Electrocardiography, echocardiography, stress testing and cardiac biomarkers aid in; assessing cardiac function, detecting abnormalities and gauging the risk of cardiovascular events. Moreover, regular monitoring of blood pressure, lipid profiles, and glucose levels becomes imperative in managing and mitigating potential cardiac risks.

Beyond diagnostics, lifestyle modifications serve as cornerstone measures in both diabetes management and cardiovascular risk reduction. Dietary interventions, emphasizing balanced nutrition and controlling calorie intake, coupled with regular physical activity, exert profound positive effects in managing blood glucose levels and reducing cardiovascular risk factors.

Pharmacological interventions also play a crucial role in the integrated management of type 2 Diabetes and associated cardiac abnormalities. Medications targeting glucose control, blood pressure regulation, and lipid management are fundamental in preventing the progression of CVD in diabetic patients.

In conclusion, the escalating prevalence of type 2 diabetes globally has accentuated its association with cardiovascular diseases. The significance of early detection and proactive management of cardiac abnormalities amongst newly diagnosed type 2 diabetic patients cannot be overstated. The integration of diagnostic modalities, lifestyle modifications, and pharmacological interventions forms the cornerstone in reducing the burden of cardiovascular complications in this vulnerable population.

2.2 Overview of Diabetes Mellitus definitions and Key Characteristics

Diabetes mellitus is the most commonly occurring metabolic disorder globally. Various genetic and environmental factors have been implicated in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia.

Classification of Diabetes Mellitus

Diabetes mellitus classification is important for determining appropriate therapy. According to American diabetic association guidelines of 2021; Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance)

3. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Difficulties in distinguishing diabetes type may occur in all age-groups at onset but the diagnosis becomes more obvious over time.

Patients with all forms of diabetes are at risk for developing the same chronic complications, although the rates of progression may differ.

2.2.1 Diagnostic tests for diabetes mellitus

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria

ADA Criteria for the diagnosis of diabetes mellitus

1. Classic symptoms of hyperglycemia or hyperglycemic crisis PLUS a random plasma glucose ≥200 mg/dl (11.1 mmol/L). Random is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

2. FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h post load glucose 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

4. A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP (National Glyco-hemoglobin Standardization Program) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Notably, when using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment, age, race/ethnicity, pregnancy status, genetic background, and anemia/ hemoglobinopathies.

In the absence of unequivocal hyperglycemia (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]) these criteria should be confirmed by repeat testing of the abnormal test from the same sample or in two separate test samples on a different day. The third measure (OGTT) is not recommended for routine clinical use.

2.3 Type 2 diabetes mellitus overview

Type 2 diabetes, previously referred to as “noninsulin-dependent diabetes” or “adult-onset diabetes,” is a chronic metabolic disorder that predominantly manifests in adulthood, although it is increasingly affecting younger populations due to epidemiological and lifestyle transitions .It accounts for 90–95% of all diabetes mellitus cases. The hallmark characteristics of type 2 diabetes include hyperglycemia, insulin

resistance, and dysregulation of glucose metabolism. It arises when the body becomes resistant to the effects of insulin, leading to impaired glucose uptake by cells. Concurrently, the pancreatic β-cells fail to produce adequate insulin to compensate for this resistance, resulting in elevated blood glucose levels, known as hyperglycemia. Presentation ranges from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive

Symptoms such as increased thirst, frequent urination, fatigue, and blurred vision often accompany the condition, although some individuals may remain asymptomatic for a considerable period, leading to delayed diagnosis.

2.3.1 Primary Causes and Risk Factors

Type 2 Diabetes represents a multifaceted condition influenced by genetic, lifestyle, and environmental factors.

Genetic and Environmental Factors:

While genetic predisposition plays a role in the development of type 2 diabetes, environmental factors significantly contribute to its onset. Sedentary lifestyles, unhealthy dietary patterns high in processed foods and sugar, and obesity are key environmental determinants driving the escalating prevalence of the disease. Additionally, ethnic background and family history of diabetes significantly influence an individual's susceptibility to developing type 2 diabetes.

Insulin Resistance and Beta-cell Dysfunction:

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes. It is often associated with a strong genetic predisposition or family history in first-degree relatives, more so than type 1 diabetes and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American).However; the genetics of type 2 diabetes is poorly understood.

The associated insulin secretory defects are multi- factorial and related to inflammation and metabolic stress among other contributors, including genetic factors.

Insulin resistance characterized by reduced responsiveness of cells to insulin, especially in muscle, liver, and adipose tissue, is a fundamental pathophysiological feature of type 2 Diabetes. Concurrently, pancreatic beta cells struggle to produce sufficient insulin to overcome this resistance, leading to inadequate insulin secretion and exacerbating hyperglycemia.

Lifestyle Factors

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity .Obesity, particularly visceral adiposity, contributes significantly to insulin resistance and the development of type 2 Diabetes. Adipose tissue dysfunction leads to the release of inflammatory cytokines and adipokines, further impairing insulin action. Sedentary lifestyles exacerbate this condition, as physical activity plays a crucial role in maintaining glucose homeostasis and insulin sensitivity. It also occurs more frequently in women with prior gestational diabetes mellitus (GDM), in those with hypertension or dyslipidemia.

2.3.2 Clinical Presentation of Type 2 Diabetes Mellitus

The progression from normal glucose metabolism through pre-diabetes to overt diabetes is marked by distinct clinical presentations, each carrying significant clinical implications for both individuals and healthcare providers.

Understanding the clinical presentation of T2DM from pre-diabetes to advanced stages is essential for timely intervention and effective management. Each stage presents unique opportunities for preventive strategies and tailored interventions aimed at reducing the risk of complications and improving long-term outcomes for individuals affected by type 2 Diabetes.

Pre-diabetes:

Type 2 diabetes mellitus diagnosis is frequently preceded by a long latent period of pre diabetes and goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms.

Pre-diabetes represents an intermediate stage in the progression towards T2DM and is characterized by higher-than-normal blood glucose levels but not meeting the criteria for diabetes. Clinical indicators of pre-diabetes include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated HbA1c levels of 5.7–6.4%

Clinical presentations of pre-diabetes may include subtle symptoms such as fatigue, increased thirst, and mild weight gain. However, it is often asymptomatic, making routine screening crucial. American Diabetes Association recommends consideration for testing for pre-diabetes and/or type 2 diabetes in asymptomatic adults of any age with overweight or obesity and one or more additional risk factors for diabetes,(ADA,2020 guidelines).

The clinical significance of identifying pre-diabetes lies in its role as a precursor to T2DM. Pre-diabetes is also associated with presence of traditional risk factors for cardiovascular disease which include; obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. Individuals with pre-diabetes are at an increased risk for developing micro-vascular and macro-vascular complications including cardiovascular disease (CVD) due to the long pre-diabetic period and clustering of these risk factors.

Pre-diabetes is potentially a reversible state. ADA recommends early interventions at this stage including; lifestyle modifications such as adopting a healthy diet, weight management and increased physical activity to reduce the risk of progression to overt diabetes, potentially revert to normo-glycemia and mitigate the this risk of cardiovascular disease

Early Stage Type 2 Diabetes:

In the early stages of type 2 diabetes, patients may exhibit mild or nonspecific symptoms such as increased thirst, frequent urination, unexplained weight changes, fatigue, and blurred vision. However, many individuals might remain asymptomatic during the initial phase, making early detection challenging. Diagnosis is typically made through routine screening or when patients present with complications associated with sustained elevated blood glucose levels.

The ADA emphasizes the importance of early diagnosis through regular screenings, especially for individuals with risk factors such as obesity, family history, or sedentary lifestyles.

Early diagnosis and intervention in type 2 diabetes are crucial for preventing complications. At this stage, lifestyle changes remain foundational, but pharmacological interventions might also be initiated as per ADA guidelines to achieve glycemic control reduce the risk of cardiovascular events.. Regular monitoring of blood glucose levels, blood pressure, lipid profile, and kidney function becomes imperative to prevent or delay the onset of complications.

Regular monitoring and patient education are crucial to achieving treatment goals.

Advanced Stage Type 2 Diabetes:

As type 2 diabetes progresses, symptoms become more pronounced and complications may arise. Clinical presentations may include severe hyperglycemia, recurrent infections, slow wound healing, and peripheral neuropathy. Patients might also experience severe fatigue, persistent thirst and frequent urination. Additionally, complications such as diabetic retinopathy, nephropathy, and cardiovascular diseases become more prevalent.

The clinical implications of advanced T2DM are profound, with an increased risk of macro-vascular and micro-vascular complications. Intensive glycemic control remains a key focus. ADA recommends a multidisciplinary approach involving healthcare professionals from various specialties and stresses the importance of personalized treatment plans, considering individualized glycemic targets, addressing comorbidities and managing associated complications. Management extends beyond glycemic control to encompass comprehensive care targeting cardiovascular risk reduction, kidney protection, vision preservation, and neuropathy management

Conclusion:

Clinical guidelines play a pivotal role in shaping evidence-based practices, highlighting the importance of a holistic approach to diabetes care. The American Diabetes Association (ADA) specifically, provides essential guidelines that underscore the clinical aspects of T2DM, aiding in the early recognition and management of the disease continuum. The ADA guidelines emphasize a patient-centered approach that acknowledges individual differences and preferences. They stress the importance of a comprehensive care plan tailored to the individual's needs, setting treatment goals based on patient characteristics, preferences, and potential risks of complications. ADA also recommends lifestyle modifications as the foundation of management across all stages. Early detection and intervention, coupled with personalized treatment plans are key in mitigating the clinical implications at each stage of T2DM, ultimately improving patient outcomes and quality of life. ***American Diabetes Association. "Standards of Medical Care in Diabetes—2022." Diabetes Care, Volume 45, Supplement 1, 2022.***

2.4 Type 2 diabetes mellitus associated cardiovascular disease

Background

Type 2 Diabetes significantly impacts cardiovascular health through multifaceted physiological mechanisms, significantly increasing the risk of developing cardiac abnormalities. T2DM is a well-recognized risk factor for clinical and subclinical atherosclerotic CVD and T2DM patients have co-existent traditional CVD risk factors or established CVD at diagnosis

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide. CVD affects approximately 32.2% of all T2DM and accounts for 2/3 of diabetic mortality (Einarson., et al, 2018) Overall, people with T2DM have 2 to 4 times increased risk of

cardiovascular morbidity and mortality than individuals without diabetes. T2DM independently confers a 2 and 3 fold excess risk for vascular diseases and CVD mortality respectively (Church., et al 2009, Sarwar ., et al 2010) .

Newly diagnosed T2DM patients are particularly vulnerable, as their condition may not yet be well-managed, leading to potential adverse cardiovascular outcomes. People with T2DM have much earlier and more extensive process of accelerated atherosclerosis, more vulnerable and larger volume atherosclerotic plaques and coronary artery lumen with a smaller diameter, compared to people without DM. This results to chronic micro-and macro-vascular complications generated by alteration of the endothelium at all arterial vascular territory levels.

Macro-vascular T2DM complications include clinical and subclinical cardiovascular disease. Cardiovascular disease can manifest as distinct phenotypes encompassing structural, functional cardiac abnormalities or both.

The main structural heart disease associated with diabetes is atherosclerotic coronary artery disease (CAD), left ventricular hypertrophy, valve abnormalities and diabetic cardiomyopathy .Diabetic cardiomyopathy is characterized by altered myocardial function in the absence of significant CAD or systemic hypertension. The condition is associated with important clinical consequences, such as increased susceptibility to hypertension-mediated damage, an increased mortality rate after acute myocardial infarction, and progression to symptomatic heart failure.

Left ventricular hypertrophy and systolic dysfunction that is often asymptomatic and may lead to congestive heart failure .Other independent adverse functional cardiac effects include diastolic dysfunction, autonomic neuropathy, endothelial dysfunction and increased arterial stiffness and reduced myocardial contractility.

The risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in non-diabetic patients with a history of previous MI.

People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type, whereas prior myocardial infarction (MI) is often a major factor in HFrEF. (Lam, C.S., et al 2018)

2.4.1 Risk factors for cardiac abnormalities in Type 2 DM

Diabetes is characterized by the presence of risk factors and common important epigenetic, genetic, and cellular signaling mechanisms that lead to or accelerate the development of CV disease and progression.

Risk factors for CVD in T2DM include both modifiable and non-modifiable .Diabetes mellitus in itself confers an independent risk for atherosclerotic cardiovascular disease (ASCVD) (ADA, 2020 guidelines).

People with type 2 diabetes mellitus (T2DM) have a higher cardiovascular morbidity and mortality, and are disproportionately affected by CVD compared with non-diabetic subjects (Gu .,et al,1999).

Cardio-vascular disease is elevated in T2DM due to a complex combination of various traditional and non-traditional risk factors, that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial function to clinical events (Fonseca .,et al 2004).

Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which includes abdominal obesity, hypertension, hyperlipidemia, and hypercoagulability. These factors act to promote CVD occurrence in T2DM. Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of

ischemic disease, stroke, and death. This risk increases with the increase of fasting glycaemia since the stages of pre-diabetes.

The main risk factors for CVD in T2DM are insulin resistance/ hyperinsulinemia, hyperglycemia, dyslipidemia, hypercholesterolemia, hypertension, smoking, obesity/overweight, all of which cause endothelial dysfunction.

Cardiovascular risk factors in diabetes mellitus can be classified as: Traditional and non-traditional risk factors as shown on the table below, (Iciar., et al,2014).

Table 1: Traditional and non-traditional risk factors

Traditional risk factors	Nontraditional risk factors
Dyslipidemia	Insulin resistance and Hyperinsulinemia
Hypertension	Postprandial Hyperglycemia
Obesity	Glucose variability
Abdominal obesity	Micro albuminuria
Physical inactivity	Hematological factors
Cigarette smoking	Thrombogenic factors
	Inflammation C-reactive protein
	Homocysteine and vitamins
	Erectile dysfunction
	Genetics and Epigenetics

Other cardiovascular risk factors in DM include; a family history of premature coronary disease, chronic kidney disease, and the presence of albuminuria.

Furthermore, in the 2013 European Society of Cardiologists guidelines noted that the clustering of vascular risk observed in association with insulin resistance has led to the

view that cardiovascular risk appears early, before the development of T2DM, whereas the solid interactions between hyperglycemia and micro vascular disease suggests that this risk is not apparent until frank hyperglycemia appears, (Ryden et al.,2013).

Cardiovascular disease occurs following complex interactions of traditional and non-traditional risk factors in diabetes mellitus as noted in the flow chart below, (Iciar et al.,2014).

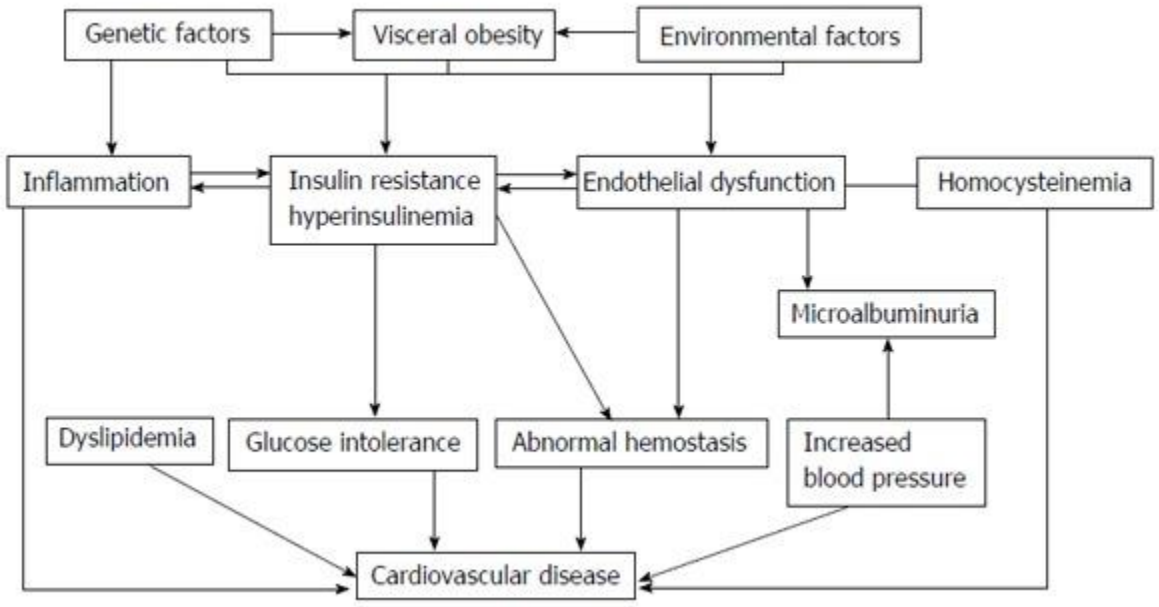


Figure 1: Risk factors for cardiac abnormalities in type 2 diabetes

2.4.2 Pathophysiology of cardiac abnormalities in type 2 diabetes

The pathophysiology of cardiac abnormalities in individuals newly diagnosed with Type 2 Diabetes Mellitus (T2DM) is a complex and multifactorial process that involves various metabolic and cardiovascular disturbances. Understanding the intricate pathophysiological mechanisms linking T2DM and cardiac abnormalities is critical for the development of effective prevention and management strategies to mitigate the risks associated with these complications.

The underlying mechanisms include;

1. **Insulin Resistance**: Insulin resistance is a central component of T2DM and has significant implications for the heart. T2DM patients often exhibit impaired insulin signaling in cardiac myocytes. This can lead to increased fatty acid uptake by the heart, resulting in lipotoxicity and cardiac dysfunction (Ormazabal et al.,2018).

2. **Hyperglycemia**: Elevated blood glucose levels contribute to oxidative stress, inflammation, and the formation of advanced glycation end-products (AGEs), which can damage cardiac tissues. AGEs can promote fibrosis and inflammation in the heart, impairing its function (Ramasamy et al., 2005).

3. **Dyslipidemia**: Dyslipidemia is common in T2DM and can lead to atherosclerosis. Increased levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, coupled with reduced high-density lipoprotein cholesterol (HDL-C), contribute to coronary artery disease (CAD) and myocardial infarction (Taskinen et al., 2003).

4. **Inflammation**: Chronic low-grade inflammation is a hallmark of T2DM. Inflammatory markers such as C-reactive protein (CRP) and pro-inflammatory cytokines are elevated. Inflammation can promote endothelial dysfunction and atherosclerosis, leading to cardiac abnormalities (Tsalamandrins etal.,2019)

5. **Oxidative Stress**: Hyperglycemia and insulin resistance contribute to increased oxidative stress. This oxidative stress damages cardiac cells and impairs their function. It is also linked to inflammation and the release of pro-inflammatory cytokines (Giacco & Brownlee, 2010).

6. **Endothelial Dysfunction**: In T2DM, the endothelium becomes dysfunctional, leading to impaired vasodilation and increased vascular tone. Reduced nitric oxide bioavailability contributes to hypertension and cardiac complications (Krentz, Clough, & Byrne, 2007).

7. **Micro vascular and Macro vascular Complications**: T2DM is associated with both micro vascular and macro vascular complications. Micro vascular complications can lead to myocardial ischemia, while macro vascular complications increase the risk of CAD and peripheral vascular disease (Tziomalos, Athyros, & Mikhailidis, 2011).

8. **Left Ventricular Hypertrophy (LVH)**: T2DM contributes to increased cardiac workload due to hypertension and fluid retention. This can lead to LVH, which impairs cardiac function and is associated with a higher risk of heart failure (Tadic et al., 2020).

9. **Autonomic Neuropathy**: Autonomic neuropathy affects the autonomic nervous system, which controls heart rate and blood pressure. Abnormal autonomic regulation can lead to arrhythmias and cardiac conduction abnormalities (Vinik et al., 2003).

10. **Thrombosis and Coagulation Abnormalities**: T2DM is associated with a prothrombotic state, increasing the risk of thrombosis and cardiovascular events. Altered coagulation and platelet function contribute to atherosclerotic plaque formation and instability (Böger & Hecher, 2008).

2.4.3 Phenotypes of cardiac abnormalities in Type 2 Diabetes Mellitus

Structural Cardiac Abnormalities
Left Ventricular Hypertrophy (LVH):

LVH is a prevalent structural anomaly frequently observed in individuals with type 2 diabetes. This condition entails an enlargement of the left ventricle's muscular wall due to persistent pressure overload, often linked to hypertension and insulin resistance. Prolonged exposure to a hyperglycemic state can potentially modify the structure and function of the myocardium. Among diabetic patients, there appears to be an augmentation in LV mass, with a study indicating that a 1% increase in HbA1C level contributes to a 3.0 g rise in LV mass. However, further investigations are necessary to evaluate the duration of elevated HbA1C that may contribute to the increase in LV mass (Gupta et al., 2015).

In patients with diabetes mellitus (DM), LV hypertrophy is predominantly eccentric, although both forms of hypertrophy may coexist (Bluemke et al., 2008). As the disease advances, remodeling can transition from eccentric to concentric (Calchera et al., 2008). Another characteristic of diabetic cardiomyopathy is left ventricular diastolic dysfunction (Boyer et al., 2004; Huynhk et al., 2014). Initial signs of diastolic dysfunction in DM patients involve prolonged and delayed LV filling as well as LV relaxation (Nagueh et al., 2016).

At the cellular level, remodeling of the extracellular matrix (ECM) leads to myocardial fibrosis, typically observed in the later stages of the disease. In the early stages, myocytes appear to be hypertrophic rather than fibrotic (Heerebeek et al., 2008).

Diabetic Cardiomyopathy

This encompasses a spectrum of structural changes in the heart independent of other known cardiac diseases. It includes myocardial fibrosis, impaired contractility, and diastolic dysfunction. Diabetic cardiomyopathy has the potential to lead to heart failure even in the absence of coronary artery disease or hypertension.

In 2013, the American College of Cardiology Foundation, the American Heart Association, and the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes defined diabetic cardiomyopathy as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus. In its early stages, diabetic cardiomyopathy includes a hidden subclinical period characterized by structural and functional abnormalities, including left ventricular (LV) hypertrophy, fibrosis, and cell signaling abnormalities. These pathophysiological changes of cardiac fibrosis and stiffness and associated subclinical diastolic dysfunction often evolve to heart failure with normal ejection fraction and eventual systolic dysfunction accompanied by heart failure with reduced ejection fraction,

Hyperglycemia, systemic insulin resistance, and impaired cardiac insulin metabolic signaling are major clinical abnormalities in diabetes mellitus, and all are involved in the pathogenesis of diabetic cardiomyopathy (Jia G .,et al, 2016)

Pathophysiological mechanisms of diabetic cardiomyopathy

Hyperglycemia, insulin resistance, and hyper-insulinemia induce cardiac insulin resistance and metabolic disorders that increase mitochondria dysfunction, oxidative stress, advanced glycation end products (AGEs), impairment of mitochondria Ca^{2+}

handling, inflammation, activation of renin–angiotensin–aldosterone system (RAAS), autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, as well as micro vascular dysfunction. These pathophysiological abnormalities promote cardiac stiffness, hypertrophy, and fibrosis, resulting in cardiac diastolic dysfunction, systolic dysfunction, and heart failure.

Free Fatty Acid Accumulation

Elevated levels of free fatty acids result from diabetes mellitus and obesity, accumulating primarily as triglycerides in adipose tissue. Increased intake and β-oxidation of fatty acids are employed to maintain ATP production levels, but over time, β-oxidation becomes insufficient, leading to the buildup of free fatty acids (FFA) (Nunes S et al., 2012). The deposition of ectopic fat in organs other than adipocytes in visceral and subcutaneous fat induces dysfunction in cells and organs, such as the liver, pancreatic β cells, skeletal muscle, and myocardium, through mitochondrial function deterioration, a phenomenon referred to as lipotoxicity (Mahabadi AA et al., 2013).

Fat accumulation occurs in the heart and myocardium, with pericardial fat divided into external pericardial fat and internal epicardial fat. High epicardial fat mass is identified as an independent predictor of coronary artery disease development (Mahabadi AA et al., 2013). Myocardial FFA accumulation leads to diminished myocardial energy production, reduced myocyte contractility, and lipoapoptosis (Pappachan et al., 2013).

Calcium (Ca2+) signaling alterations play a crucial role in myocardial contraction. In type 1 diabetes, reduced expression of sarcolemmal L-type Ca2+ channels (LTCC) results in decreased Ca2+ influx during an action potential, impacting myofibril activation and contraction (Lu Z et al., 2007). Similarly, in type 2 diabetes mellitus (T2DM), there is diminished LTCC density and Ca2+ current (ICa) density, along with

reports of depressed ryanodine receptor (RyR) activity, a Ca2+ release channel (Pereira L et al., 2006; Howarth FC et al., 2011 & 2012; Lu Z et al., 2011). Studies also indicate that acute hyperglycemia regulates RyR activity, leading to CaMKII-dependent diastolic sarcoplasmic reticulum (SR) Ca2+ leak from RyRs, contributing to SR Ca2+ load depletion observed in the early stages of diabetes (Yaras N et al., 2005; Bais SZ et al., 2012; Bidasce KR et al., 2003; Erickson et al., 2013).

Increased Oxidative stress

Prolonged hyperglycemia induces oxidative stress in pancreatic β-cells (Lenzen S et al., 1996). Elevated glucose levels stimulate the mitochondrial electron transport chain, leading to the overproduction of reactive oxygen species (ROS) and exacerbating advanced glycation end product (AGE) formation (Yuan T et al., 2019; Brownlee et al., 2001). Through the polyol pathway, high glucose levels metabolize into sorbitol using NADPH (nicotinamide adenine dinucleotide phosphate) and NAD+ (nicotinamide adenine dinucleotide), increasing the activity of the polyol pathway and elevating the NADH/NAD+ ratio, thereby promoting ROS overproduction (Vedantham et al., 2012).

AGEs prominently exist in the diabetic heart, potentially playing a role in the development of diabetic cardiomyopathy. The AGE receptor (RAGE), a member of the immunoglobulin superfamily, initiates various signaling pathways upon ligand binding (Bierhaus A et al., 2005). The interaction between AGE and RAGE stimulates NADPH oxidase-1, contributing to ROS production in diabetes (Chen J et al., 2016). These processes collectively lead to cardiac fibrosis and hypertrophy (Faria A et al., 2017). Hyperglycemia, oxidative stress, and the hexosamine biosynthetic pathway, providing substrates for proteoglycan synthesis and O-linked glycosylation of specific proteins, are associated with cardiomyocyte apoptosis (Rajamani et al., 2010).

Mitochondrial Dysfunction

The heart relies significantly on mitochondria for production of adenosine triphosphate (ATP) through the oxidation of fatty acids and glucose (Zhou B et al., 2018). In a diabetic state where the insulin production or action is reduced, the mitochondria shift to using fatty acids as an ATP source instead of glucose, potentially increasing reactive oxygen species (ROS) (Jia G et al., 2015). Dysfunctional calcium handling, involving excessive calcium influx or reduced calcium efflux, can activate the mitochondrial permeability transition pore (mPTP), leading to mitochondrial dysfunction (Gorski et al., 2015).

Elevated oxidative stress and mitochondrial dysfunction can result in cellular, protein, and nucleic acid damage, ultimately leading to cell apoptosis. Despite the heart's high ATP consumption, it maintains a relatively low ATP reserve. In pathological conditions, fatty acids only contribute 50-70% of the energy required by the human heart (Zhang L et al., 2010). Mitochondria can adapt their ATP production source based on nutrient availability, with insulin playing a role in this energy source selection (Stanley WC et al., 2005). Excessive ATP consumption depletes the ATP reservoir, and insufficient ATP production may contribute to reduced cardiac function (Covian R et al., 2018).

Evolution of Diabetic Cardiomyopathy to Clinical Heart Failure

Diabetic cardiomyopathy is usually asymptomatic in the early stages of its evolution. One of the earliest manifestations is LV hypertrophy and decreased LV compliance characterized by impaired early diastolic filling, increased atrial filling, and prolonged iso-volumetric relaxation.LV dilation and symptomatic heart failure occur after the development of systolic dysfunction,(Jia G., et al,2016)

Diagnosis

Diabetic cardiomyopathy manifests in two distinct stages. The early stage is characterized by left ventricular concentric hypertrophy, heightened myocardial stiffness, increased atrial filling pressure, and compromised diastolic function. In contrast, the late stage is marked by a rise in cardiac fibrosis, further deterioration in diastolic function, and the emergence of systolic dysfunction. Diagnosing diabetic cardiomyopathy lacks defined criteria, biochemical markers, or physical characteristics. Pathological changes during disease progression are often asymptomatic, necessitating thorough examination for detection. Tissue Doppler imaging and strain rate imaging are employed in stress testing to assess left ventricular dysfunction. The ratio of the medial mitral annulus (e′) to the early passive transmitral inflow velocity (E) has proven to be a reliable indicator of left ventricular filling pressure, serving as a valuable prognostic biomarker in diabetic patients (Di Bonito et al., 2005).

Atherosclerosis and Coronary Artery Disease (CAD):

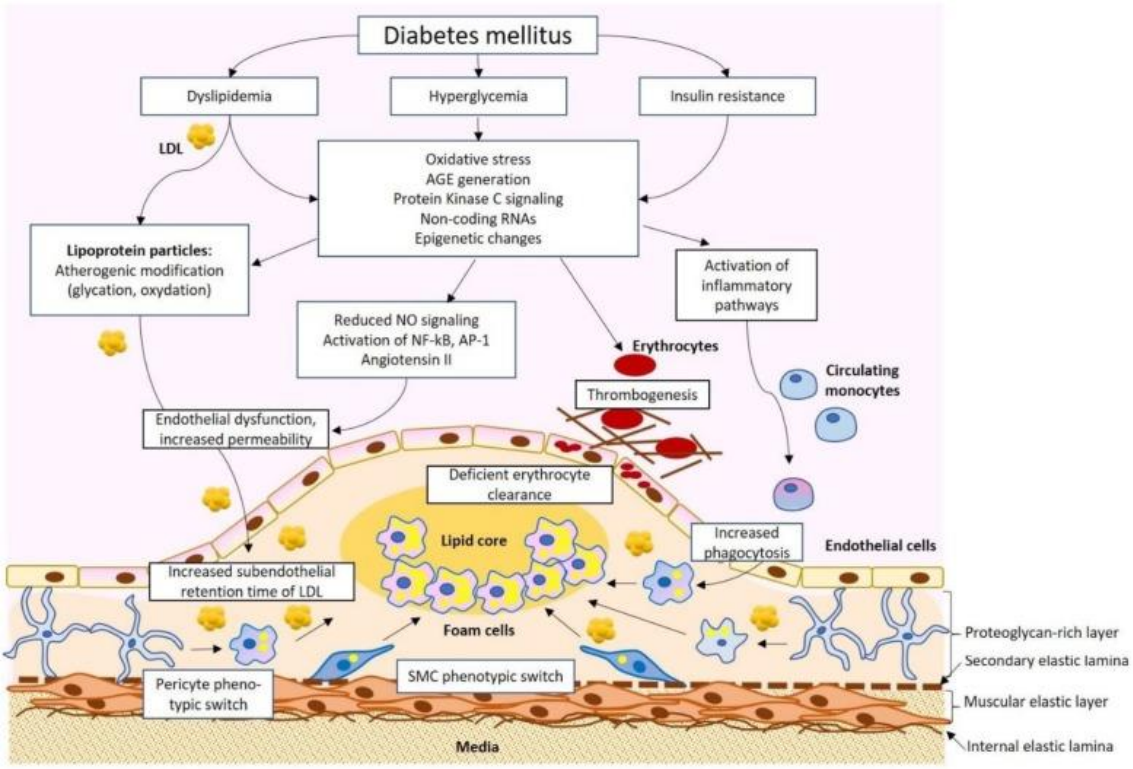


Figure 2: Atherosclerosis and Coronary Artery Disease (Anastacia et al., 2020)
A simplified schema of the patho-physiological connection of diabetes mellitus and atherosclerosis.Dyslipidemia, hyperglycemia, and insulin resistance result in a spectrum of physiological changes, including the formation of atherogenic low-density lipoprotein (LDL), advanced glycation end products (AGE), and activation of pro-inflammatory signaling that impact different cell types of the arterial wall, resulting in atherosclerotic lesion development. SMC, smooth muscular cells.

Diabetes accelerates the progression of atherosclerosis, leading to the narrowing of coronary arteries and increased risk of myocardial infarction. CAD is a prevalent structural abnormality in diabetic patients due to endothelial dysfunction, inflammation, and plaque formation.

Valvular Abnormalities: Type 2 diabetes may contribute to calcific aortic valve disease and affect mitral valve function. These valvular abnormalities can lead to stenosis or regurgitation, impacting cardiac function.

Functional Cardiac Abnormalities:

Diastolic Dysfunction: Diastolic dysfunction in Type 2 diabetes mellitus represents a complex interplay of various metabolic, inflammatory, and structural factors. Diabetic patients frequently exhibit impaired relaxation and increased stiffness of the ventricles during diastole, known as diastolic dysfunction. This leads to inadequate ventricular filling, contributing to heart failure with preserved ejection fraction (HFpEF).

Mechanisms of Diastolic Dysfunction in Type 2 Diabetes:

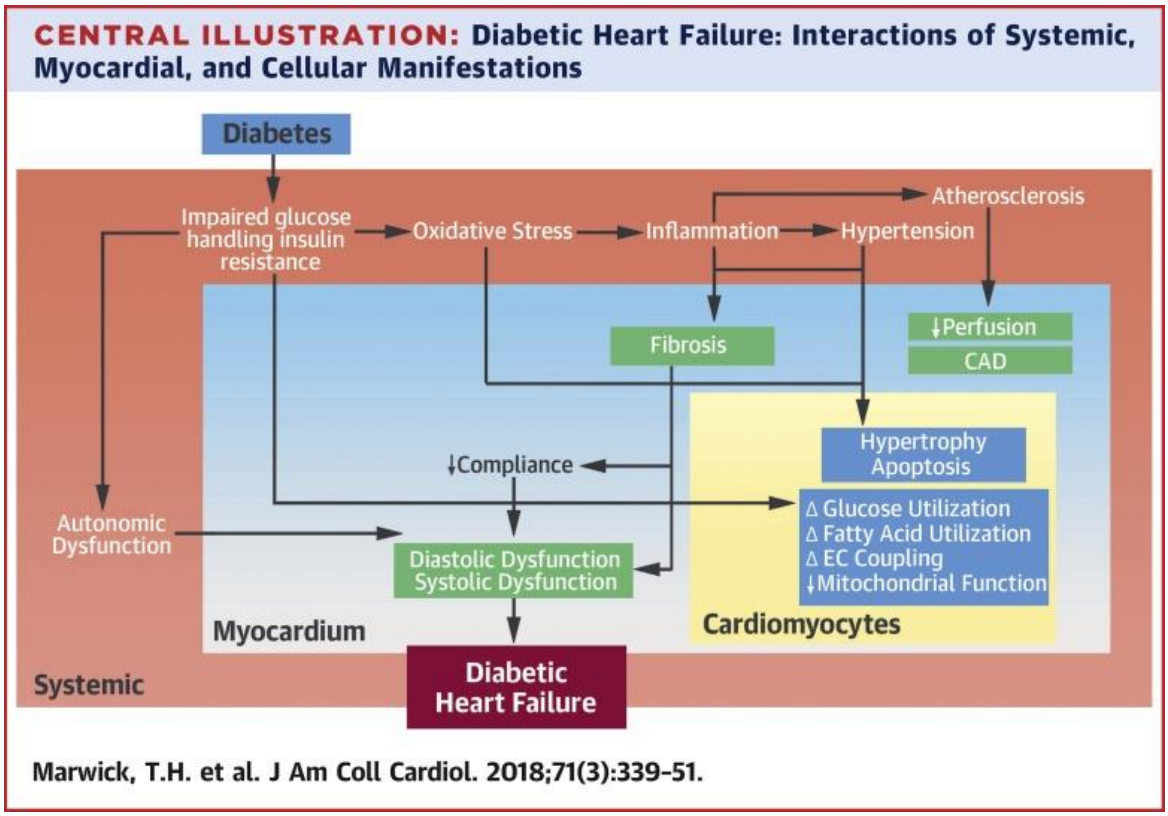


Figure 3: Mechanisms of Diastolic Dysfunction in Type 2 Diabetes

Insulin Resistance and Hyperglycemia: Insulin resistance, a hallmark of T2DM, is a key contributor to diastolic dysfunction. The insulin-resistant state impacts the heart by altering cellular metabolism, leading to impaired relaxation during diastole. Hyperglycemia, elevated blood glucose levels characteristic of diabetes, further exacerbates these changes by promoting oxidative stress and inflammation.

Myocardial Fibrosis: Chronic exposure to insulin resistance and hyperglycemia triggers myocardial fibrosis, characterized by the accumulation of collagen in the heart tissue. Fibrosis increases the stiffness of the myocardium, impairing its ability to relax during diastole.

Inflammation and Oxidative Stress: Persistent low-grade inflammation and oxidative stress are prevalent features of T2DM. These factors contribute to endothelial

dysfunction, impairing the ability of blood vessels to dilate and affecting the compliance of the heart chambers during diastole.

Advanced Glycation End Products (AGEs): The formation of AGEs, a result of prolonged exposure to high glucose levels, has been implicated in diastolic dysfunction. AGEs contribute to cross-linking of collagen fibers, further increasing myocardial stiffness.

Obesity and Adipose Tissue Dysfunction: Obesity, a common comorbidity in T2DM, exacerbates diastolic dysfunction. Adipose tissue dysfunction leads to the release of pro-inflammatory cytokines and adipokines, contributing to cardiac remodeling and impaired relaxation.

Clinical Implications of Diastolic Dysfunction in Type 2 Diabetes:

Heart Failure with Preserved Ejection Fraction (HFpEF): Diastolic dysfunction is a major contributor to heart failure with preserved ejection fraction (HFpEF) in T2DM patients. HFpEF is characterized by impaired filling of the heart during diastole, leading to symptoms of heart failure such as dyspnea and fatigue.

Increased Risk of Cardiovascular Events: T2DM patients with diastolic dysfunction face an increased risk of adverse cardiovascular events, including myocardial infarction and stroke. The compromised cardiac function elevates the overall cardiovascular burden in this population.

Reduced Exercise Tolerance: Diastolic dysfunction impairs the heart's ability to respond to increased demands during physical activity, resulting in reduced exercise tolerance in T2DM patients.

Autonomic Neuropathy

Cardiac autonomic dysfunction is a critical complication in type 2 diabetes mellitus (T2DM), significantly impacting cardiovascular health. The complex interplay of various mechanisms contributes to the disruption of autonomic nervous system (ANS) regulation of the heart, leading to profound cardiac abnormalities. Diabetes-associated autonomic neuropathy affects the nerves controlling the heart, leading to abnormal heart rate variability, exercise intolerance, and altered responses to physiological stress.

Mechanisms of Cardiac Autonomic Dysfunction in T2DM:

1. **Hyperglycemia-Induced Oxidative Stress:**

   Prolonged hyperglycemia leads to the generation of reactive oxygen species (ROS) and oxidative stress. This oxidative burden damages autonomic nerves, impacting their signaling and function within the cardiac tissue. *Citation:* Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. Nat Rev Neurol. 2011;7(10):573-583.

2. **Alterations in Neurovascular and Neurohumoral Regulation:**

   Dysregulation of neurovascular and neurohumoral control disrupts the balance between sympathetic and parasympathetic activity. The impaired release and action of neurotransmitters, such as acetylcholine and norepinephrine, affect cardiac rhythm and contractility. *Citation:* Maser RE, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab. 2005;90(10):5896-5903.

3. **Advanced Glycation End Products (AGEs) and Inflammation:**

   The formation of AGEs due to chronic hyperglycemia contributes to autonomic nerve damage. AGEs interact with receptors, triggering inflammatory pathways that exacerbate nerve injury and impair autonomic function in the heart.(*Citation:* Jakus V, Rietbrock N. Advanced glycation end-products and the progress of diabetic vascular complications. Physiol Res. 2004;53(2):131-142.)

4. **Endothelial Dysfunction and Vascular Changes:**

   T2DM-induced endothelial dysfunction affects coronary microvasculature and contributes to impaired coronary blood flow regulation. This alteration in vascular function compromises the ANS control over coronary perfusion.(*Citation:* Basha H, Shantsila A, Wrigley BJ, Lip GY. Evaluation of coronary microvascular dysfunction in heart failure with preserved ejection fraction and implications for future research. Int J Cardiol. 2018;251:41-46.)

Clinical Implications and Manifestations:

1. **Altered Heart Rate Variability (HRV):**

   Autonomic dysfunction in T2DM disrupts HRV, leading to an imbalance in sympathetic and parasympathetic activity. Reduced HRV is associated with increased cardiovascular morbidity and mortality in diabetic individuals.(*Citation:* Vinik AI, Maser RE, Ziegler D. Autonomic imbalance: prophet of doom or scope for hope? Diabet Med. 2011;28(6):643-651.)

2. **Arrhythmias and Cardiac Conduction Abnormalities:**

    - Dysregulated autonomic control predisposes T2DM patients to arrhythmias and conduction abnormalities. This includes increased susceptibility to atrial fibrillation, ventricular arrhythmias, and conduction delays.(*Citation:* Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years' experience in diabetes. Diabetes Care. 1985;8(5):491-498.)

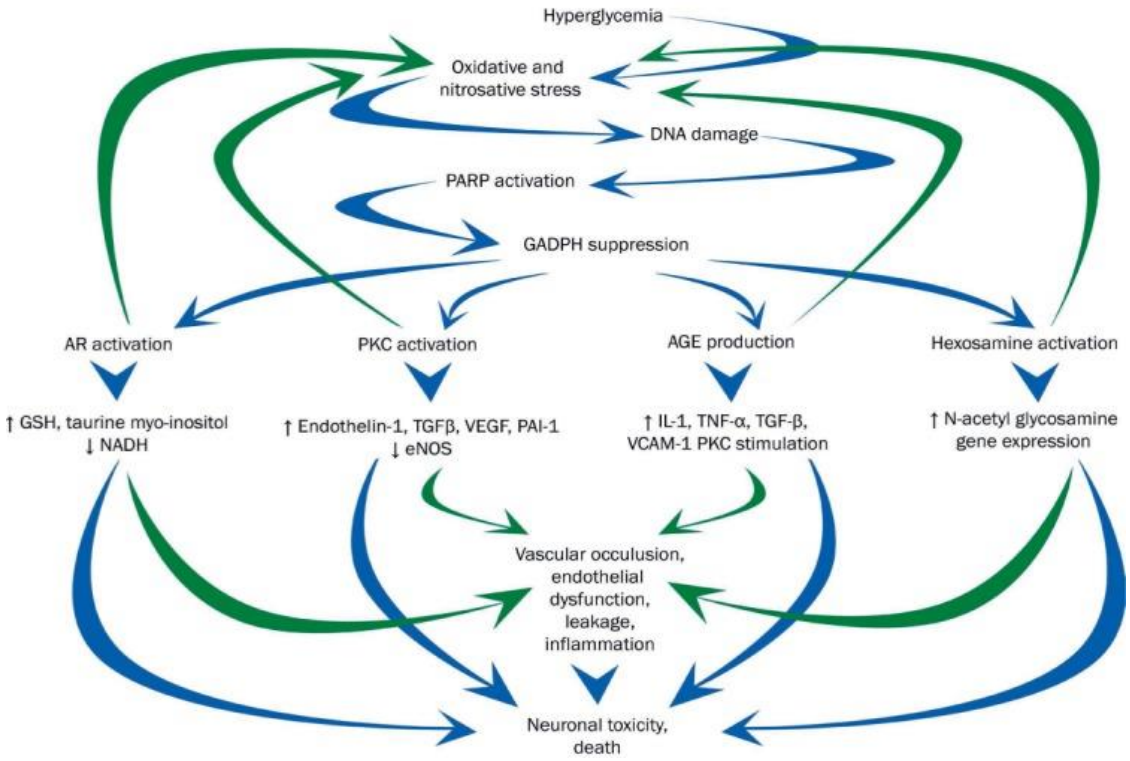


Figure 4: Arrhythmias and Cardiac Conduction Abnormalities
Summary of the mechanisms that relate hyperglycemia to microvascular complications such as neuropathy in patients with diabetes.(Tahrani AA et al.,2014) PKC: protein kinase C; AGE: advanced glycation end-products; PARP: poly ADP-ribose polymerase; GAPDH: glyceraldehyde-3 phosphate dehydrogenase; GSH: glutathione; NADH: nicotinamide adenine dinucleotide; TGF-β: transforming growth factor beta;

VEGF: vascular endothelial growth factor; PAI-1: plasminogen activator inhibitor-1; eNOS: endothelial nitric oxide synthase; IL-1: interleukin 1; TNF-α: tumor necrosis factor alpha; VCAM-1: vascular cell adhesion molecule 1

Endothelial Dysfunction:

Dysfunction in the endothelium, the inner lining of blood vessels, is a functional abnormality in T2DM. It impairs vasodilation, promotes vasoconstriction, and contributes to hypertension and atherosclerosis.

Mechanisms of Endothelial Dysfunction in Type 2 Diabetes:

1. **Hyperglycemia-Induced Oxidative Stress:**

   Prolonged exposure to elevated glucose levels induces oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidants to neutralize them. This oxidative stress damages endothelial cells, impairing their function. (*Citation:* Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615-1625.)

2. **Advanced Glycation End Products (AGEs):**

   Hyperglycemia leads to the formation and accumulation of AGEs, which interact with endothelial cells, impairing their function. AGEs induce inflammation, oxidative stress, and alter the extracellular matrix, contributing to endothelial dysfunction. (*Citation:* Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. Cardiovasc Res. 1998;37(3):586-600.)

3. **Inflammation and Cytokine Dysregulation:**

   Chronic low-grade inflammation is a hallmark of T2DM. Inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukins, disrupt endothelial function by promoting vasoconstriction, reducing nitric oxide (NO) bioavailability, and activating pro-thrombotic pathways (.*Citation:* Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? Diabetologia. 1998;41(10):1241-1248.)

4. **Insulin Resistance:**

   Insulin resistance, a core feature of T2DM, contributes to endothelial dysfunction. Insulin normally stimulates the production of nitric oxide (NO) in endothelial cells, promoting vasodilation. In insulin-resistant states, this response is impaired, leading to vasoconstriction and reduced NO bioavailability. (*Citation:* Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev. 2007;28(5):463-491).

Cardiac Abnormalities Linked to Endothelial Dysfunction:

1. **Atherosclerosis and Coronary Artery Disease (CAD):**

   Endothelial dysfunction is a key initiating factor in the development of atherosclerosis. Impaired endothelial function leads to decreased NO production, promoting inflammation and the formation of atherosclerotic plaques. In T2DM, this process accelerates, increasing the risk of CAD.(*Citation:* Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004;109(23_suppl_1):III-27-III-32.)

2. **Microvascular Complications:**

   Endothelial dysfunction extends to the microvasculature, contributing to microvascular complications in T2DM. In organs such as the kidneys and eyes, impaired endothelial function contributes to nephropathy and retinopathy.(*Citation:* Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137-188.)

3. **Diabetic Cardiomyopathy:**

   Endothelial dysfunction also plays a role in the development of diabetic cardiomyopathy. Reduced NO bioavailability and increased oxidative stress contribute to myocardial fibrosis, inflammation, and impaired contractility, leading to heart failure.(*Citation:* Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010;11(1):31-39.)

Reduced Myocardial Contractility:

Diabetes can impact myocardial contractility, reducing the heart's ability to efficiently pump blood. This reduced contractility contributes to heart failure and diminished exercise tolerance.

Understanding these phenotypes of structural and functional cardiac abnormalities is critical in the early identification and management of cardiac complications amongst newly diagnosed type 2 diabetic patients. Regular cardiac assessments, including echocardiography, stress testing, and cardiac biomarker evaluations, are vital for detecting these abnormalities and initiating appropriate interventions aimed at preventing further progression and reducing cardiovascular risks.

2.5.4 Prevalence of Cardiac Abnormalities amongst newly diagnosed T2DM

CVD, including myocardial infarction, stroke, angina, heart failure, atherosclerosis and coronary artery disease, is present in 32.2% of people with T2DM. The most frequent type of CVD seems to be the CAD (21.2%), males having higher rates (18.7%) than females (14.3%) (Einarson et al.,2018)

CVD is a major cause of death among people with diabetes (IDF, 2017 atlas). Cardiovascular disease accounts for 50% of deaths in patients with diabetes (Tancredi et al,2015).

People with T2DM are disproportionately affected by CVD compared with non-diabetic subjects, and adults with diabetes have a higher prevalence rate of CVD than adults without diabetes, (Haffner et al.,1998),(Sarwar et al.,2010).

Adults with diabetes historically have a higher prevalence rate of CVD than adults without diabetes and the risk of CVD increases continuously with rising fasting plasma glucose levels, even before reaching levels sufficient for a diabetes diagnosis, (Singh et al,2013)

Along with the increasing T2DM prevalence, the attributable risk of CVD due to T2DM was noted to have increased from 5.4% in the period 1952–1974 to 8.7% in the period 1975 and 1998(In the Framingham Heart Study)

A national wide database survey in primary care in Denmark noted the prevalence of CVD in T2DM to be high at 21.4%,while a systematic literature review of scientific evidence from across the world on prevalence of CVD in diabetes conducted between 2007-2017,estimated that globally overall cardiovascular disease affects approximately 32.2% of all persons with type 2 diabetes,(Rungby et al., 2017),(Einarson et al., 2018).

Another study noted that diabetes-related cardiovascular disease complications in Africa are on the rise and are regularly associated with classic cardiovascular risk factors. Coronary heart disease may affect 5% to 8% of type 2 diabetic patients and cardiomyopathy, up to 50% of all patients, (Kegne, et al.,2015).

Numerous studies have documented the prevalence of cardiac abnormalities amongst newly diagnosed T2DM patients. A study conducted by Xu et al. (2018) found that newly diagnosed T2DM patients had a significantly higher prevalence of cardiac abnormalities, such as left ventricular diastolic dysfunction, compared to non-diabetic individuals. The prevalence of diastolic dysfunction was found to be 38% in the T2DM group, as opposed to only 17% in the control group. Diastolic dysfunction is a common early marker of cardiac involvement in T2DM, and its higher prevalence amongst newly diagnosed patients highlights the importance of early cardiac assessment.

Similarly, a systematic review by Lee et al. (2019) found that newly diagnosed T2DM patients had a higher prevalence of coronary artery disease (CAD) compared to non-diabetic individuals. The prevalence of CAD in this population was estimated to be around 8.7%, highlighting the increased risk of coronary artery disease even in the early stages of T2DM.

These findings emphasize the importance of regular cardiac evaluation in individuals newly diagnosed with T2DM, as they are already at a higher risk of cardiac abnormalities. Early detection and intervention can be crucial in preventing or managing these issues effectively

2.4.5 Diagnostic Techniques for Detecting Cardiac Abnormalities in T2DM Patients

Cardiac screenings by electrocardiograms (ECGs), echocardiography, and stress tests, are essential in the management of T2DM patients (Lachin et al., 2019).

Early detection of cardiac abnormalities in T2DM patients is crucial for timely intervention. However, challenges persist in the early diagnosis of cardiac abnormalities. Subclinical disease may go unnoticed until advanced stages. Advanced diagnostic tools have emerged to aid in this endeavor. Non-invasive imaging techniques, such as cardiac magnetic resonance (CMR) and computed tomography angiography (CTA), offer high sensitivity and specificity for the detection of CAD and structural cardiac abnormalities (Zhu et al., 2018).These modalities are however still very expensive and not widely available. More affordable and widely available noninvasive imaging techniques with electrocardiogram and echocardiogram can be applied to diagnose structural and functional cardiac abnormalities in type 2 diabetes

ECG abnormalities can be classified into minor and major on Minnesota coding. The minor abnormalities categories include minor QS pattern abnormalities, minor ST-segment abnormalities, complete right bundle branch block, or premature atrial or ventricular contractions. The major abnormalities category includes major QS pattern abnormalities, major ST-segment abnormalities, complete left bundle branch block or intra-ventricular block, or atrial fibrillation or flutter.

The presence of resting ECG abnormalities are common in all people with type 2 diabetes (29.1%), including those without a history of CVD (24.0%), and their prevalence is related to traditional cardiovascular risk factors such as older age, male sex, hypertension, lower HDL cholesterol, higher BMI, and smoking behavior (Harms et al., 2021) .

Another study found that 26% asymptomatic diabetics had ECG abnormalities, 70% patients with ECG changes had poor glycemic control, increased triglyceride and decreased High Density Lipoprotein (HDL) levels. The most commonly observed

abnormality being ST-T changes, followed by Left Atrial Enlargement (LAE), Left Ventricular Hypertrophy (LVH), Left Bundle Branch Block (LBBB) and Right Bundle Branch Block (RBBB), (Gupta et al., 2017).

Furthermore, another study concluded that the presence of an ECG abnormality can predict the occurrence of a future cardiovascular event in patients withT2DM more accurately than risk factors alone with relative risk (RR) of a cardiovascular event in a patient with an ECG abnormality as 8.28 (95% confidence interval [CI], 3.36-20.42). This finding could be helpful in selecting subgroups of high-risk diabetic patients (MacFarlane et al., 2007)

Echocardiographic abnormalities in T2DM patients are also common. In a study that included a total of 1030 patients with type 2 diabetes found that echocardiographic abnormalities were present in 513 (49.8%) patients, mainly driven by a high prevalence of diastolic dysfunction 178 (19.4%), left ventricular hypertrophy 213 (21.0%) and left atrial enlargement, 200 (19.6%), (Jorgensen et al., 2016).

The prevalence increased markedly with age and was equally distributed among the sexes. In that study, electrocardiographic abnormalities, age, body mass index, known coronary heart disease, hypertension, albuminuria, diabetes duration and creatinine were associated with abnormal echocardiography along with dyspnea and characteristic chest pain.

In a study done in Uganda, at Mulago referral hospital, among newly diagnosed adult diabetic patients; the prevalence of an abnormal echocardiogram was 67.8 % (95% CI 60%-74%). Diastolic dysfunction, systolic dysfunction, LVH and wall motion abnormalities were present in 55.0%, 21.8%, 19.3% and 4.0% of all the participants respectively. In this study, the factors associated with an abnormal echocardiogram

were mainly traditional CVD risk factors including age, hypertension and increased waist circumference, (Muddu et al,2016).

2.5 Assessment for cardiac abnormalities in type 2 diabetes

The European Society of Cardiology Guidelines,2019, recommendations include;

The assessment of cardiovascular risk in individuals with diabetes and pre-diabetes encompasses several key components. Standard evaluations include the routine assessment of microalbuminuria to identify patients at risk of developing renal dysfunction or cardiovascular disease (CVD). For patients with diabetes mellitus (DM) or suspected CVD, a resting electrocardiogram (ECG) is recommended. Additional tests, such as transthoracic echocardiography, coronary artery calcium (CAC) score, and ankle–brachial index (ABI), may be considered for detecting structural heart disease or modifying risk in those at moderate or high risk of CVD. However, the routine assessment of novel biomarkers is not advised for cardiovascular risk stratification.

Electrocardiography plays a pivotal role in identifying silent myocardial infarction (MI), with a prevalence of 4% in individuals with DM. This silent MI has been correlated with an elevated risk of CVD and all-cause mortality, particularly in men. Furthermore, prolonged corrected QT interval is associated with increased cardiovascular mortality in Type 1 DM, while an increasing resting heart rate is linked to the risk of CVD in both Type 1 and Type 2 DM. Additionally, reduced heart rate variability, indicative of diabetic cardiovascular autonomic neuropathy, is associated with an elevated risk of fatal and non-fatal coronary artery disease.

Echocardiography stands out as the primary choice for evaluating structural and functional abnormalities linked to DM. Asymptomatic DM patients often exhibit increased left ventricular (LV) mass, diastolic dysfunction, and impaired LV

deformation, all of which are associated with a poorer prognosis. This comprehensive approach to cardiovascular risk assessment aims to identify potential issues early on, enabling timely intervention and management in individuals with diabetes or pre-diabetes.

2.6 Therapeutic and preventive options available

The ADA standard practice guidelines, 2020, recommend several measures for prevention of cardiovascular disease in patients with diabetes and pre-diabetes.

Recommendation on Lifestyle modification

Initiating and sustaining lifestyle changes constitute a cornerstone in the prevention of Diabetes Mellitus (DM) and its associated cardiovascular (CV) complications. Among these pivotal changes, a reduction in calorie intake emerges as a crucial strategy, especially for individuals with DM, to effectively lower excessive body weight. The significance of this approach lies not only in addressing weight concerns but also in mitigating the risk factors that contribute to the progression and exacerbation of diabetes.

A dietary pattern that has garnered substantial attention for its cardiovascular benefits is the Mediterranean diet. When supplemented with olive oil and/or nuts, this dietary regimen has demonstrated a remarkable ability to reduce the incidence of major cardiovascular events in individuals with DM. The incorporation of heart-healthy fats from olive oil and nuts, combined with the rich array of fruits, vegetables, whole grains, and lean proteins characteristic of the Mediterranean diet, creates a synergistic effect that promotes overall cardiovascular health.

Complementing dietary modifications, engaging in regular moderate-to-vigorous physical activity is a fundamental recommendation for both the prevention and control of DM. Accumulating at least 150 minutes of such activity per week serves as a guideline to optimize metabolic function, enhance insulin sensitivity, and contribute to weight management. This commitment to physical activity is not only instrumental in preventing the onset of DM but also plays a pivotal role in the comprehensive management of the condition for those already diagnosed.

Collectively, these lifestyle interventions represent a multifaceted approach to DM prevention and control, extending beyond the immediate metabolic concerns to address the broader spectrum of cardiovascular health. By fostering habits such as prudent dietary choices, regular physical activity, and weight management, individuals can significantly reduce the risk of developing DM and its associated cardiovascular complications.

Recommendation on control of dyslipidemia

Statins prove highly effective in preventing cardiovascular (CV) events and lowering CV mortality, demonstrating a favorable safety profile with minimal adverse events. Given the heightened risk profile of patients with Diabetes Mellitus (DM), the utilization of intensive statin therapy is recommended on a personalized, case-by-case basis. Presently, statins stand as the forefront therapy for lipid-lowering in the management of patients with DM. The addition of ezetimibe or a proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitor, either in conjunction with a statin or as an alternative for individuals with documented statin intolerance; further contributes to reducing low-density lipoprotein cholesterol (LDL-C) levels in patients with DM. This

comprehensive approach not only enhances LDL-C reduction but also plays a pivotal role in improving overall CV outcomes and diminishing CV mortality.

For patients with DM classified as being at very high CV risk, the recommended target for LDL-C is <1.4 mmol/L (<55 mg/dL), with a minimum LDL-C reduction of 50%. Similarly, for those at high CV risk, the target LDL-C is <1.8 mmol/L (<70 mg/dL), accompanied by a reduction of at least 50%. In cases where DM patients have a moderate CV risk, the goal is to achieve an LDL-C target of <2.6 mmol/L (<100 mg/dL). These target values and reduction percentages serve as critical benchmarks in tailoring lipid management strategies to the specific risk profiles of individuals with DM, thereby optimizing their cardiovascular health outcomes.

Recommendations on control of hypertension

The blood pressure (BP) goal is to target systolic BP (SBP) to 130 mmHg in patients with DM and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 − 139 mmHg.The diastolic BP (DBP) target is <80 mmHg, but not <70 mmHg. Optimal BP control reduces the risk of micro- and macro vascular complications. Guidance on lifestyle changes must be provided for patients with DM and hypertension. Evidence strongly supports the inclusion of an angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin receptor blocker (ARB) in patients who are intolerant to ACEI. BP control often requires multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium channel blocker or diuretic. Dual therapy is recommended as first-line treatment. The combination of an ACEI and an ARB is not recommended. In pre-DM, the risk of new-onset DM is lower with RAAS blockers than with beta-blockers or diuretics. Patients

with DM on combined antihypertensive treatments should be encouraged to self-monitor BP.

Recommendations on Glycemic control

HbA1c target for most adults is <7.0% (<53 mmol/ml).More-stringent HbA1c goals of <6.5% (48 mmol/ml) may be suggested on a personalized basis if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Less-stringent HbA1c goals of <8% (64 mmol/mol) or ≤9% (75 mmol/mol) may be adequate for elderly patients

Combined reduction in HbA1c, SBP, and lipids decreases CV events by 75%.

Other recommendations include:

In DM patients at high/very high CV risk, use of antiplatelet medication for platelet inhibition can be used as a secondary preventive measure. In this patient population smoking cessation should be encouraged. Furthermore physical activity that includes moderate-to-vigorous exercises for ≥150 min/week, with combined aerobic and resistance training should be prescribed.

There should be aim for weight stabilization in overweight or obese patients with DM, based on calorie balance, and weight reduction in subjects with impaired glucose tolerance, to prevent the development of DM.

As regards to dietary habits, reduction of caloric intake is recommended in obese patients with T2DM to lower body weight; there is no ideal percentage of calories from carbohydrate, protein, and fat for all people with DM

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study site

This study was conducted at the Moi Teaching and Referral Hospital (MTRH) diabetic outpatient clinic (DOPC) and in the adult medical wards. The Hospital is located in Eldoret town, Uasin Gishu County, which is approximately 300 Kilometers northwest of the Kenyan capital, Nairobi. MTRH is a tertiary (level 6) health facility with a bed capacity of 1000, serving as a teaching hospital for Moi University college of health sciences, Public Health, Nursing, Dentistry and others middle level colleges including Kenya Medical Training Center (KMTC), Eldoret and University of Eastern Africa Baraton School of Nursing. It is the second largest referral hospital after Kenyatta National Hospital with a catchment population of approximately 25 million people. It serves 23 counties in western and north rift region (comprising of both urban and rural population), Eastern Uganda, and parts of southern Sudan. The diabetic clinic runs three times per week on Monday, Thursday and Friday. The clinic personnel includes a multidisciplinary team made up of an endocrinologist/ diabetologist, general physicians, internal medicine residents, clinical officers, nutrionists , diabetes specialist and non-specialist nurses and diabetic foot care health educator. There is an average of 90 patients being seen per week of which approximately 9 are newly diagnosed. Remember, individualized care is crucial, and adjustments may be necessary based on the patient's unique needs, preferences, and response to treatment. The typical care of a newly diagnosed diabetes patient involves comprehensive management to control blood glucose levels, prevent complications, and promote overall well-being. A general outline of the typical care for a newly diagnosed diabetic patient in an outpatient diabetic clinic includes: Medical assessment with comprehensive medical history to gather information about the patient's medical history, family history, lifestyle, and any

symptoms related to diabetes, a physical examination to assess weight, blood pressure, and signs of complications or comorbidities. The provider gives diabetes education on the nature of the disease, its complications, and the importance of self-management. Teaches the patient to recognize and respond to hypo- and hyperglycemia, addresses lifestyle modification: smoking and alcohol cessation if applicable. Promote stress management techniques. If needed, oral anti-diabetic medications or insulin therapy are initiated and patient is taught the about proper medication administration, dosage, and potential side effects .Patient then subsequently gets educated on self-monitoring of blood glucose (SMBG) using a glucose meter and set target blood glucose levels for fasting and postprandial periods. Work up to screen for diabetes-related complications (e.g., eye exams, foot exams, lipid profile, kidney function tests) is requested. The patient is then referred to a registered dietitian to create an individualized meal plan and lay emphasis on the importance of a balanced diet with controlled carbohydrate intake. A diabetes educator finally reviews the patient to encourage regular physical activity tailored to the patient's fitness level and discusses the benefits of exercise in managing blood glucose levels and overall health. The educator also assesses the patient's mental health, provides resources or referrals for psychosocial support, addresses any emotional or psychological challenges related to diabetes management, encourages the patient’s active involvement in managing their condition and provides resources for diabetes support groups and community resources.

A scheduled regular follow-up appointment to monitor progress and adjust treatment plans and evaluate glycemic control through A1C testing is then given as the patient exits the clinic.

3.2 Study design

A cross sectional study design was employed to conduct this study

3.3 Study population

All adult patients with a confirmed diagnosis of newly diagnosed Type 2 Diabetes Mellitus patients seeking care at Diabetic outpatient clinic or admitted in the medical wards at MTRH

3.4 Sampling technique

Consecutive sampling technique of newly diagnosed T2DM patients, meeting the study inclusion criteria, was done from November 2021 to July, 2022.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

Patients with the age of ≥35 years (rationale being T2DM has a wide variation in age of diagnosis but the risk increases with age, especially after age 35;ADA recommends annual diabetes screening tests for people aged≥ 35 years) diagnosed with T2DM according to ADA 2020 diagnostic criteria (Symptoms of diabetes plus random blood sugar (RBS) ≥ 11.1mmol/L **OR** fasting plasma glucose (FPG) ≥7.0mmol/L **OR** glycosylated hemoglobin (HbA1C) ≥6.5% **OR** 2 hour post load plasma glucose ≥ 11.1mmol/L) within a period of up to 6months before screening for inclusion into this study and willingness to sign an informed written consent.

3.5.2 Exclusion criteria

- Women of child bearing age with a clinically confirmed pregnancy (assessment based on last menstrual period and subsequent pregnancy determine test **IF** history of amenorrhea) with no prior history of overt diabetes diagnosis before current gestation). Rationale – study focused on T2DM and did not intend to include cases of gestational diabetes mellitus, pregnancy also modifies other risk factors for cardiac disease including hypertension

- Patient with a reported or documented history of /or currently receiving cardio-toxic medications (Drugs included: cytotoxic agents (doxorubicin/ anthracyclines) ,alkylating agents, antimetabolites, tyrosine kinase inhibitors, monoclonal antibodies (trastuzumab , rituximab). Rationale- confounding factor for cardiovascular abnormalities attributable to T2DM

- Severely ill to participate as deemed by researcher ;included a participant who was too ill to give a consent or one unable to stand for anthropometric measures

3.6 Sample Size Determination

Objective 1: Prevalence of cardiac abnormalities
Sample size was derived using the Fisher et al, (1998) formulae

$$n=\frac{Z^2(1-\alpha/2).Pq}{d^2}$$

n= minimum sample size required

z= confidence interval at 95% (standard value of 1.96)

p= estimated prevalence of echocardiographic abnormalities among newly diagnosed adult diabetic patients (Muddu, et al, 2014) 67.8%

d= margin of error (0.05)

The sample size calculation was based on a study done in Uganda at Mulago referral hospital that looked at the prevalence of echocardiographic abnormalities among newly diagnosed adult diabetic patients .The study found the overall prevalence of an abnormal echocardiogram as 67.8 % (95% CI 60%-74%). Muddu, et al,2014.

$$n=\frac{1.96^2 \times 0.678 \times 0.322}{0.05^2}$$

n= 335 patients

Adjustment for missing or incomplete data of 10% = n=$\mathbf{335}/(\mathbf{1}-\mathbf{0.1}) = \mathbf{372}$

1. **The 10% adjustment on sample size calculation was included to mitigate for incomplete laboratory data in case of insufficient sample, loss of samples or poor quality blood samples.**

- Data from MTRH Record Office, 648 newly diagnosed cases of DM from June 2019 to June 2020. Those classified as new cases of T2DM were 279 in 6 months.
- Modified Fisher's formula $n = \frac{no}{1+(no-1)/N}$
- Finite sample $= \frac{372}{1+(372-1)/279}$=160

0bjective 2: Factors correlated with cardiovascular abnormalities

The minimum sample size (N) based on logistic regression model was obtained using the formula suggested by Peduzzi et al 1996 formula for correlate factors **(N=10K/p)**

N= the sample size

K= no of independent variables

P= number of events or prevalence of condition of interest as determined from previous studies (pre study estimate of the proportion)

The number of independent variables in this study were 10; age, gender, cigarette smoking status, BMI, HbA1c, albuminuria, dyslipidemia, Creatinine clearance, hypertension and calculated 10 year atherosclerotic cardiovascular disease risk. p was derived from a study by Muddu et al, 2014, where prevalence was 67.8%.the calculated sample size was

P= 67.8 %(0.678)

10 is constant

N= 10*10/0.678

N= 143

Settling for the higher sample size determined which was 160.

3.7 Study Procedure

3.7.1: Patient Recruitment

The principal investigator and the research assistant trained on good clinical practices sought for patients eligible for recruitment into the study every weekday from the medical inpatient wards and on diabetic outpatient clinic days, (Monday, Wednesday and Friday) between November 2021 and June 2022. All patients who met the inclusion criteria were approached and the rationale for study explained .Those who agreed to participate were consented and recruited into the study.

3.7.2 Consenting

The consenting process was carried out by the principal investigator or the research assistant. Literate participants were provided with written consent form in English (appendix 2A)or Kiswahili (appendix 2B).Participants who could not read had the consent read and explained to them and a translator was sought when necessary; consent was provided by thumb print. Data collection was done after an informed written consent was obtained.

3.7.3 Clinical and laboratory procedures

The principal investigator and research assistant administered the structured questionnaires which were utilized to collect socio-demographic clinical and laboratory data(Appendix 1).The patients' self-reported bio data and a comprehensive medical history of current and past illnesses, including : duration of diabetes, history of hypertension, co-morbidities, history of cigarette smoking as well as medication use including diabetic medication, use of ACE inhibitors or ARBs, and lipid lowering agents was taken. The blood pressure, weight, height, waist and hip circumference measurements were taken before patients were taken to the phlebotomy area (Appendix 3, 4, and 5). Measurement of blood pressure was performed using Omron M2 compact

upper arm blood pressure monitor (Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015). The arm cuff position was maintained at the heart level during rest in a seated position and readings taken after at least 30 minutes of being seated in the waiting area.

Blood pressure measurement was taken by the examiner with the arm rested on the table. The cuff was wrapped on the arm with the bottom of the cuff one centimeter above the elbow, while allowing for finger breadth allowance on application of the cuff. The machine was switched on, the cuff inflated and the blood pressure reading recorded. Three blood pressure readings were taken at least one minute apart with the average of the last two being recorded as per the American Heart Association recommendation (Muntner et al., 2019). Patients, who reported history of hypertension, had their records verified. The patients who were not known hypertensive but with BP readings of systolic above 140mmHg and diastolic of more than 90mmHg had their files reviewed and if they had high Blood pressure >140/90mmHg during their last visit they were classified as hypertensive.

Patient's weight was then taken and recorded to the nearest half kilograms (kg) using a standard weighing scale with the patients dressed in light clothing and without shoes. Height was taken against a vertical scale with the patient standing upright and without shoes and recorded to the nearest centimeter (cm). Body Mass Index (BMI) was then be calculated as weight in kg /height in (m2) and the degree of obesity classified based on National institute of Health (NIH) cut offs (National Institutes of Health (NIH) National Heart, Lung, and Blood Institute, 1998).Waist circumference was measured using the standard protocol by palpating the upper right hipbone of the patient until the uppermost lateral border of the iliac crest was located; where this was not palpable the greatest gluteal circumference was measured by applying tension to the tape to ensure

it was snug, without causing indentation to the skin. This was taken at the end of a normal expiration and the measurement was approximated to the nearest 0.5cm waist circumference. The hip circumference was measured with the patient standing up straight, using a tape measure applied snugly around the widest part of the hips and recorded in centimeters. The waist hip ratio was then calculated by dividing waist circumference by hip circumference. According to World health organization, a healthy waist to hip ratio is 0.9 or less in men and 0.85 or less for women

At the phlebotomy area, blood samples for glycated hemoglobin (HbA1C), non-fasting lipid profile, serum creatinine were drawn under sterile conditions, adhering to established standard operating procedures for collection, storage and transport. The procedure for drawing blood is explained in Appendix 6. Random spot urine samples were taken for estimation of albuminuria based on urine albumin-creatinine ratio. A routine urinalysis by dipstick was also done.

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease-Epidemiology Consortium) equation.

All laboratory investigations were carried out at the iso certified MTRH laboratory according to standard laboratory and clinical guidelines/practices. The procedures were carried out by the principal investigator, research assistant and a trained laboratory technician.

Patients then proceeded to the cardiology diagnostic unit where standard 2D transthoracic echocardiograms with spectral and color flow Doppler were done in standard lateral decubitus position by certified MTRH ECHO technicians **on a 2D CX 50 Echo machine**. **Echo parameters assessed for were** *Systolic and diastolic function, chamber morphology, valve morphology and function and wall motion function.*

Written reports were generated and soft copy recordings of the stored in a study dedicated archive for review by a board certified cardiologist.

Resting 12 lead ECGs on paper speed of 25mm/s, Gain setting of 10Mv were also done by Principal investigator (PI), with the help of certified MTRH technicians. Print out of the best quality recording generated for interpretation by PI as per the American heart association/ American college of cardiologists recommendations for electrocardiogram interpretation and counterchecked by a board certified cardiologist. **ECG parameters assessed for included;** *Cardiac axis, heart rate, P wave, PR interval, QRS duration, Cornell voltage criteria, ST-T segment changes, T wave changes*

The procedures of ECG and ECHO are described in appendices 8 and 9

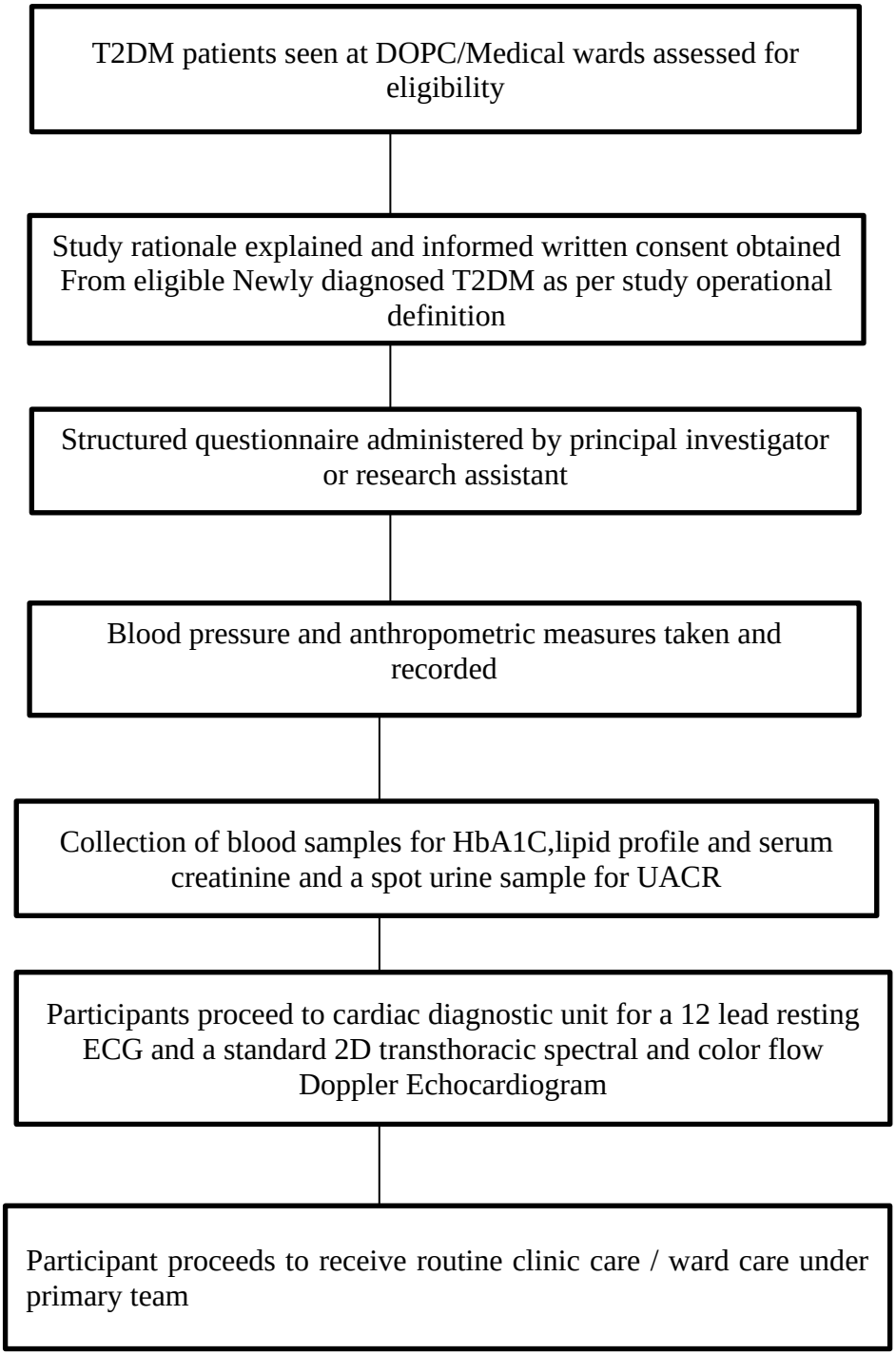


Figure 5: Study procedure

3.8 Study variables

The independent variables were age, sex, history of cigarette smoking, BMI, WHR, HbA1C, albuminuria, dyslipidemia, creatinine clearance, hypertension and calculated 10year atherosclerotic cardiovascular disease risk using the ACC/AHA 2013 risk calculator.

The dependent variables was **Cardiac abnormalities as defined by a Composite of** Structural and functional abnormalities as seen on ECG and/or ECHO

Structural abnormalities included;

Myocardial ischemia as evidenced by: wall motion abnormalities, ECG: ST-T abnormalities on > 2contigous leads and / or T wave aberrations on> 2 contiguous leads

AND/OR

Left ventricular remodeling as evidenced by; ECHO and /or ECG left ventricular hypertrophy as assessed by Cornell's criteria (S in V3+ R in aVL. LVH was considered present when >20mm in female and > 28mm in male OR R >12mm in aVL (sensitivity 40%, specificity 90%) most accurate criterion for LVH

Functional abnormalities were defined as;

Left ventricular dysfunction evidenced by: Left ventricular diastolic dysfunction and or left ventricular systolic dysfunction as assessed by echocardiogram

AND/OR

Arrhythmias and conduction abnormalities as evidenced by; sinus tachycardia, sinus bradycardia, atrial fibrillation, atrial flutter, premature atrial tachycardia ,premature ventricular tachycardia ,left bundle branch blocks and /or QT prolongation as assessed for by a 12 lead resting echocardiogram

3.9 Data Management

3.9.1 Materials and Data collection

A structured interviewer administered questionnaire was used to collect demographic and clinical information. The only unique identifier that the questionnaire contained was the subject's birth dates and the study number to ensure confidentiality of the patient information was maintained. Laboratory results were recorded on a data collection sheet. Once completed, questionnaires and data collection sheets were checked for errors and completeness then data was entered, cleaned and stored into an MS Excel file which was encrypted and password protected. Questionnaires and all other data collection forms were stored in a secure cabinet only accessible to principal investigator. De identified data was then shared with statistician for purpose of analysis

3.9.2 Data cleaning

Data was cleaned during collection, data entry and analysis. Data collection sheets and questionnaires were checked for completeness and errors at the end of each week during data collection. Missing data was excluded from the analysis.

3.9.3 Data protection and security

Paper records were kept under lock and key only accessible to the PI. Computer was password protected, with up-to-date Kaspersky antivirus, internet firewall protected and with a backup. Data validation was done through the same application. Thereafter the data was converted into a database and exported to R statistical package version 4.3.1 for analysis.

3.9.4 Data analysis

Objective 1 and Objective 2

Categorical variables were summarized using frequencies and the corresponding percentages. Continuous variables were summarized using measures of central tendency

Descriptive statistics such as the mean and corresponding standard deviation were used to summarize continuous variables such as age, BMI, HbA1c and estimated GFR levels.

Frequencies and the corresponding percentages were used to summarize categorical variables such as gender, occupation, hypertension history, smoking and alcohol use history.

HbA1C levels, WHR categories, GFR categories, UACR categories, ASCVD risk, BMI, echocardiographic and electrocardiogram findings were categorized using clinically acceptable limits.

Good glycemic control was defined as an HbA1C $\leq$ 7% while poor control was defined as HbA1C >7%.

BMI (kg/m^2) was categorized as underweight <18.5, normal 18.5-24.9, overweight 25.0 – 29.9, obese$\geq$30.0- 39.9 and extreme obesity$\geq$ 40.

Low Density Lipoprotein (LDL) was abnormal if >2.6mmol/l; Triglycerides abnormal if >1.7mmol/l and HDL was considered low if <1.3mmol/l for female, and <1.0mmol/l for male . Study participants were stratified based on their estimated 10-year atherosclerotic cardiovascular disease risk (ASCVD) using American College of Cardiology/American Heart Association, 2013 (ACC/AHA) risk calculator. Participant were either at Low risk <5 %, borderline risk 5% to 7.4%, intermediate risk 7.5% to 19.9% or high risk >20%

Continuous variables were compared using independent samples t-test if Gaussian assumptions hold or using two-sample Wilcoxon rank-sum test if the Gaussian assumptions got violated.

Bivariate and multivariate Logistic regression were used to analyze the association between independent and dependent variables **(composite of structural and functional abnormalities)**. **Exploratory analysis** for the sub groups of isolated structural and functional cardiac abnormalities was also done.

Bivariate logistic regression model was used to calculate the unadjusted odds ratios (OR) with corresponding 95% confidence intervals. Variables with significant statistical association in bivariate analysis were entered into multivariable model. These variables included hypertension, GFR and calculated 10 year ASCVD risk. Multivariate logistic regression model was then used to calculate the adjusted odds ratios with 95% confidence intervals to assess for strength of association .Statistical significance was considered when **P value was <0.05**.Results were then presented using frequency tables, pie charts and graphs.

3.10 Ethical considerations and quality assurance

Ethical and institutional approvals were obtained from IREC **(IREC/2021/83, approval no.FAN:0003933)** and MTRH administration to carry out the study. The purpose of the study was clearly explained to eligible participants in English or Kiswahili prior to inclusion into the study. Written informed consents were obtained from the participants. No incentive or inducements were given to the participants. Fidelity to predetermined study procedures was maintained. The laboratory samples were analyzed at the ISO Certified MTRH laboratory.ECGs were interpreted as per AHA/ACC recommendations for standardization and interpretation of ECGs and subsequently ECG interpretations done by PI and archived ECHO recordings were **reviewed by a board certified cardiologist.** The results obtained and clinical data relevant to management of participant was shared with the primary doctor to institute appropriate management and patients requiring additional interventions were referred for appropriate cardiology care. All patient information was kept confidential by storing data in key-locked cabinet only accessible to the principal investigator. There was no conflict of interest in this study.

CHAPTER FOUR

4.0 RESULTS

4.1 Recruitment Schema

There were 192 patients eligible for enrollment in the study from the medical wards and diabetic out-patient clinics which run on Monday, Thursday and Friday every week.23 participants were excluded; 20 participants had been on follow up longer than 6 months and 3 were severely ill. Of the remaining 169 participants, 9 declined consent leaving 160 participants who were subsequently recruited in the study. The recruitment procedure is illustrated in the schema below.

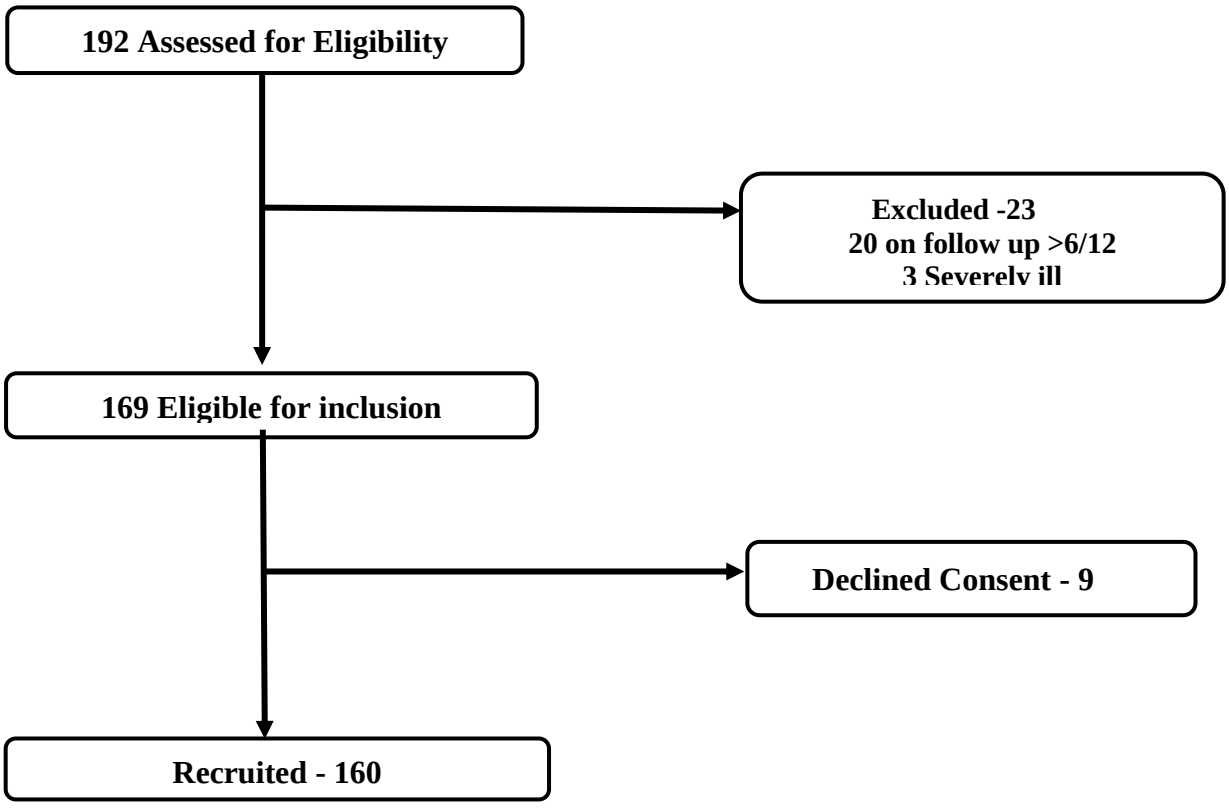


Figure 6: Recruitment Schema

4.2 Socio demographic characteristics

A total of 160 participants were enrolled in the study, 85 were females representing 53.1%. The mean age of the participants was 56.89 years (SD 11.26) with the youngest being 35 and the oldest being 81years. Participants who had a positive history of tobacco smoking were 39(24.4%) while 51 (31.9%) had history of alcohol use. Out of the total participants, 143(89.3%) had a form of occupation, 6 (3.75%) were unemployed and 11(6.87%) were retirees.

These findings are illustrated in the table below.

Table 2: Socio-demographic characteristics of the participants

Variable	Overall (N=160)
Age (in years)	
Mean (SD)	56.89 (11.26)
Range	35.00 - 81.00
Sex	
Male	75 (46.9%)
Female	85 (53.1%)
Occupation	
Farming	63(39.4%)
Business	29(18.1%)
Informal employment	41(25.6%)
Formal employment	41(11.9%)
Unemployed	8(5%)
Smoking history	
Non-smoker	121 (75.6%)
Smoker	38 (23.8%)

Variable	Overall (N=160)
Former smoker	1 (0.6%)
History of Alcohol use	
Never used	109 (68.1%)
Currently user	51 (31.9%)

4.3 Clinical characteristics

4.3.1 Medical History

The mean duration since diagnosis of diabetes was 3.64(1.19) months with a range of 1 and 6months.Fourty four (27.5%) participants had a known diagnosis of hypertension. Only 4(2.6%) patients had other previously diagnosed comorbidities. These findings are summarized in the table below

Table 3: Medical History

Duration since diagnosis	
Mean (SD)	3.64 (1.19)
Range	1.00 - 6.00
Known hypertensive	
No	116 (72.5%)
Yes	44 (27.5%)
Co -existent comorbidities	
None	156 (97.4%)
COPD	1 (0.6%)
Cor Pulmonale	2 (1.2%)
Ischemic CVA	1 (0.6%)

4.3.2 Medication History

For glycemic control, most participants 89(55.6%) were on oral anti-diabetic agents, only 66(41.2%) were on a combination of insulin and an oral anti diabetic agent while only 5(3.1%) were on insulin only. All those on an oral anti-diabetic agent had metformin as part of their treatment regimen, while those on insulin therapy all had pre mixed insulin Mixtard 70/30. Out of the 44 on anti -hypertensive agents; 22(13.8%) were on an ACE/ARB, while 25(15.6%) and 15(9.4%) were on a CCB and diuretics respectively.

Only 17(10.6%) participants were on a lipid lowering agent with 10% being on a statin based therapy. These findings are summarized on table 4 below

Table 4: Medication History

Variable	N=160
Anti-diabetic medications	
Orals	89 (55.6%)
Insulin only	5 (3.1%)
Oral + Insulin	66 (41.2%)
Anti-hypertensive medications	
None	116 (72.5%)
ACE/ARB	22 (13.8%)
BB	0 (0.0%)
CCB	25 (15.6%)
Diuretic	15 (9.4%)
Lipid lowering medication	
None	143 (89.4%)
Statin	16 (10.0%)
non-statin	1 (0.6%)

4.3.3 Anthropometric measures

The mean BMI was 26.50 (SD 3.68) with most participants being either overweight(46.9%) or obese(18.1%).This results are represented, as shown in the bar chart and table 5 below.

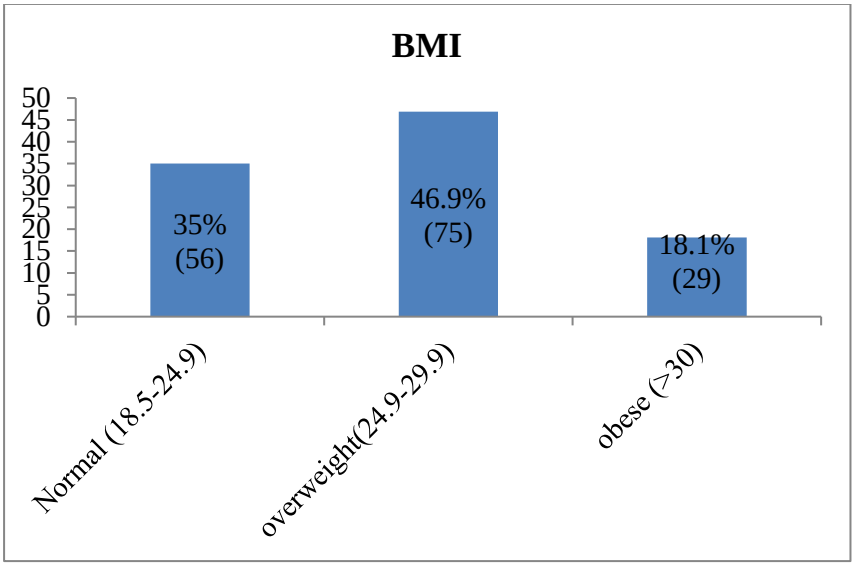


Figure 7: Anthropometric measures

Table 5: Table Showing Anthropometric Characteristics

Variable	N=160
BMI	
Mean (SD)	26.50 (3.68)
Range	18.90 - 38.80
BMI in categories	
Normal	56 (35.0%)
Obese	29 (18.1%)
Overweight	75 (46.9%)

Waist Hip Ratio:

Abnormal waist hip ratio was observed in 40(25%) participants with 34 (21.2%) and 6(3.8%) being in the high risk and moderate risk categories respectively. Abnormal waist hip ratio was defined as less than 0.80 and less than 0.95 for low risk, 0.81-0.84 and 0.96-1 for moderate risk and greater than 0.85 or greater than 1 in females and in males respectively. These findings are illustrated in the pie chart below.

Waist hip Ratio in categories	
High risk	34 (21.2%)
Low risk	120 (75%)
Moderate risk	6 (3.8%)

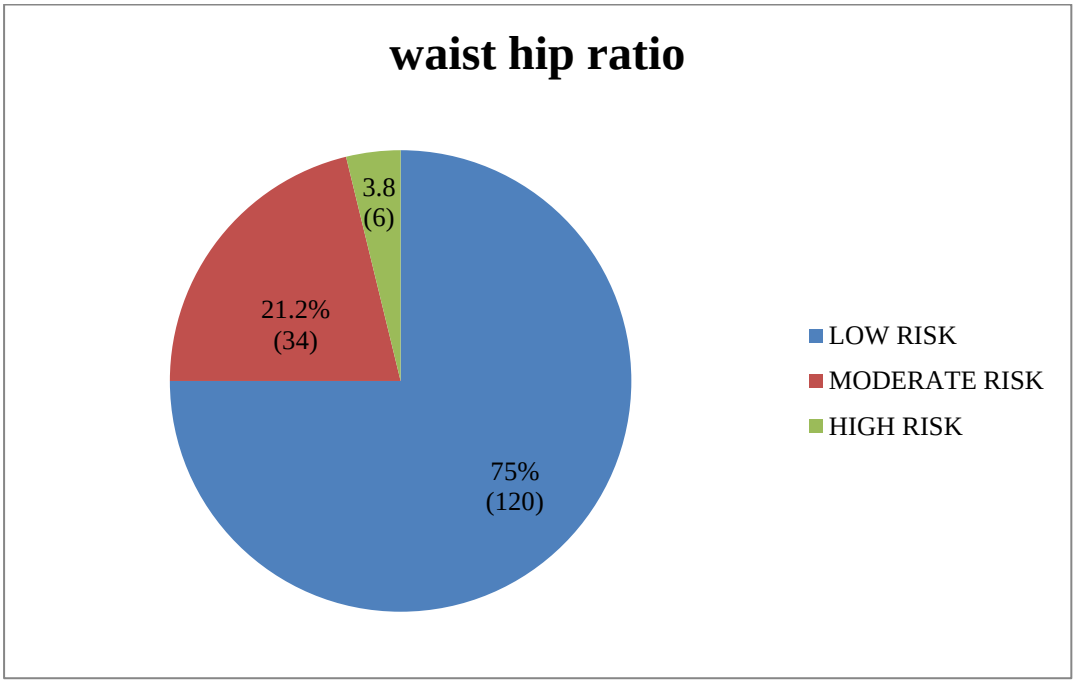


Figure 8: Pie Chart Showing Waist Hip Ratio categories

4.3.4 Laboratory Findings and blood pressure measurements

The mean HbA1C was 8.99(SD 4), 95 (59.4%) participants had an HbA1c of >7%, 61 participants (38.1%) participants had hypertriglyceridemia of>1.7, 39(24.4%) had hyperlipidemia with LDL-C of >2.6.Majority of the participants above the age of 40 years, 145(90.6%) were not on a lipid lowering agent. Majority of the participants 75(46.9%) had an estimated glomerular filtration rate of > 90ml/min/1.73m^2.Majority of the participants112 (70. %) had albuminuria, with 51(31.9%) having micro-albuminuria (UACR 30-300) and 61(38.1%) having macro-albuminuria (UACR >300).The mean systolic and diastolic pressures were 130.77mmhg and 75.84mmhg respectively. Majority of the participants 59(37.8%) had a calculated 10year atherosclerotic cardiovascular disease risk of >20% .These results are illustrated in the table below.

Table 6: Laboratory findings and Blood pressure measurement

Variable	**N=160**
HbA1C	
Mean (SD)	8.99 (4)
Total_cholestrol	
Mean (SD)	3.85 (0.99)
LDL_C	
Mean (SD)	1.92 (0.95)
HDL_C	
Mean (SD)	0.97 (0.45)
Triglycerides	
Mean (SD)	1.55 (0.81)
UACR	
<30	47 (29.4%)
30-300	52 (32.5%)

Variable	N=160
>300	61 (38.1%)
LDL	
<2.6	121 (75.6%)
>=2.6	39 (24.4%)
Triglycerides	
<=1.7	99 (61.9%)
>1.7	61 (38.1%)
HDL	
High	44 (27.5%)
Low	116 (72.5%)
Participants Over 40 years on statin	
No	143 (89.4%)
Yes	17 (10.6%)
GFR	
>=90	75 (46.9%)
60-89	55 (34.4%)
45-59	27 (16.9%)
30-44	3 (1.9%)
ASCVD risk (n=156)	
<5%	46 (29.5%)
5%-7.5%	12 (7.7%)
7.5-20%	39 (25.0%)
>=20%	59 (37.8%)
Systolic BP	
Mean (SD)	130.77 (15.05)
Diastolic BP	
Mean (SD)	75.84 (12.07)

4.4 Prevalence of cardiac abnormalities among newly diagnosed T2DM at MTRH

The prevalence of **composite cardiac abnormalities** as defined in this study (**composite of** Structural and functional abnormalities as seen on ECG and/or ECHO) was (87) **54.7 %(95%CI 47-63**)

Isolated functional cardiac abnormalities were present in **(134) 83.8**% (95%CI 77-89) of the participants.

Left ventricular Diastolic dysfunction in 66.87%

Left ventricular systolic dysfunction in 15%,

Arrhythmias (evidenced by an ECG with either sinus tachycardia/ bradycardia, atrial fibrillation/ flutter/ PAC / PVC/ and/ or AV blocks) in 31.87% and

Conduction abnormalities (evidenced by Bundle branch blocks and/or QT prolongation) present in 31.87%

Isolated structural cardiac abnormalities were present in (**100)62.9 %**(95%CI 55-70) of the participants.

Regional Wall motion abnormalities were present in 13.2%

ST-T changes on ≥2 contiguous leads in 6.90%

T wave aberrations on contiguous leads in 51% and

Left ventricular remodeling as evidenced by **LVH in** 17.50%

These results are illustrated in the bar graphs below

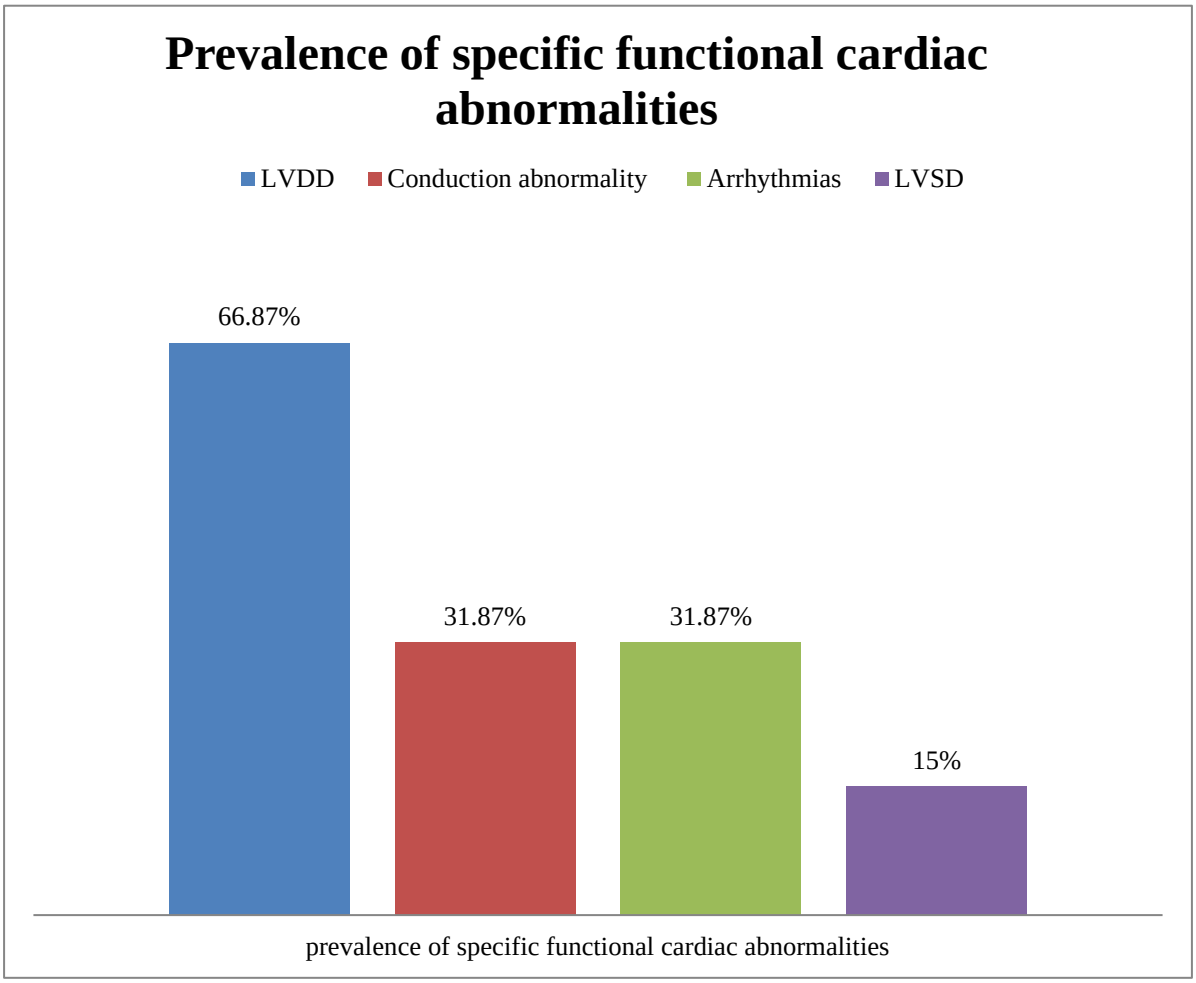


Figure 9: Prevalence of specific functional cardiac abnormalities

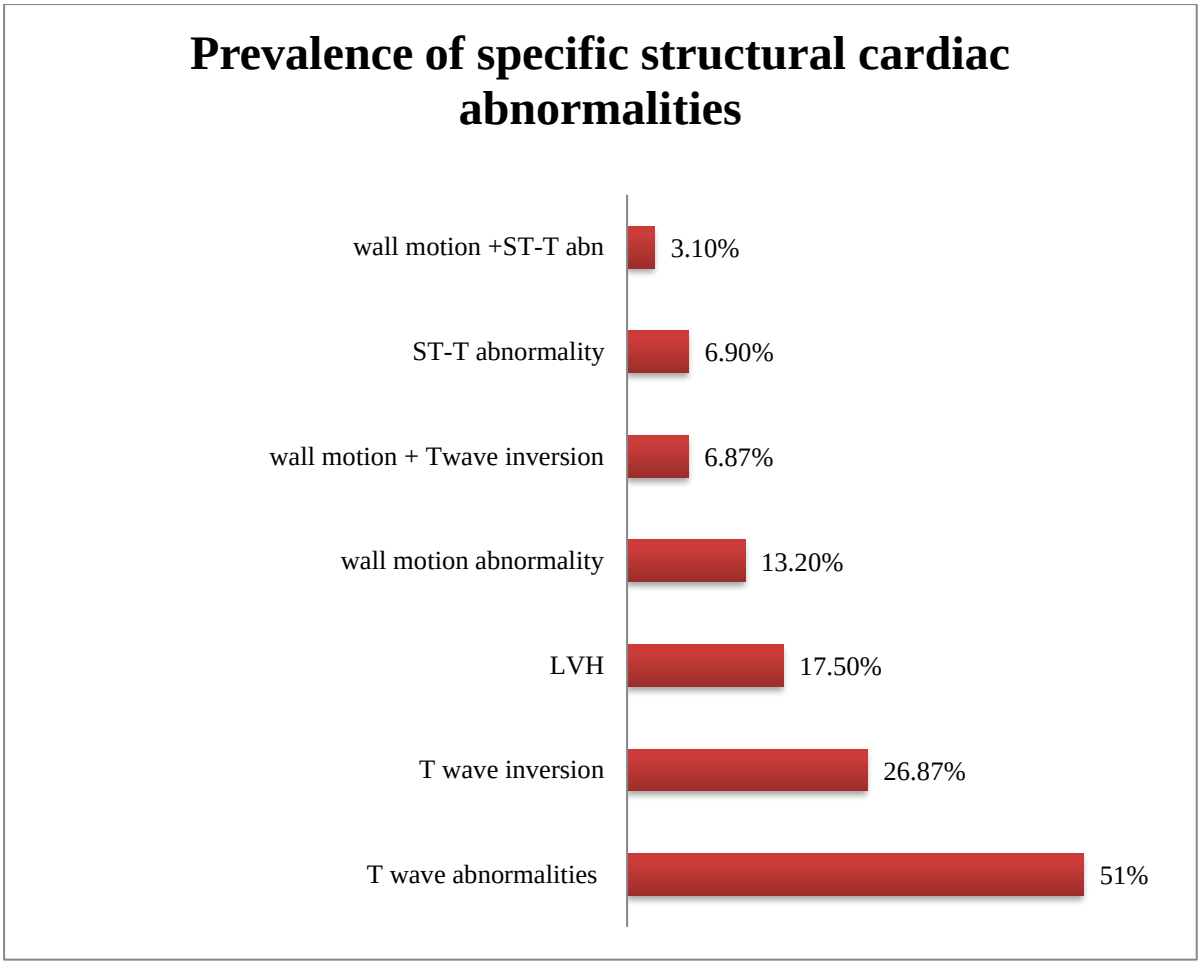


Figure 10: Prevalence of specific structural cardiac abnormalities

ECHOCARDIOGRAPHIC ABNORMALITIES

Table 7: Prevalence of Echocardiographic abnormalities among newly diagnosed T2DM patients at MTRH

Characteristic	Normal	Abnormal	95%CI
Isolated diastolic function	52 (32.7%)	107 (67.3%)	59.42, 74.52
Isolated Systolic function	136 (85.0%)	24 (15.0%)	9.85, 21.49
Combined systolic and diastolic	47 (29.6%)	112 (70.4%)	62.70, 77.40
Wall motion	139 (86.9%)	21 (13.1%)	8.31, 19.36
Chamber	97 (60.6%)	63 (39.4%)	31.75, 47.40
Valve function	88 (55.0%)	72 (45.0%)	37.14, 53.05

Table 8: Prevalence of specific Echocardiographic abnormalities among newly diagnosed T2DM patients at MTRH

Variable	N=160
Wall motion	
None	139 (86.9%)
Hypokinesia	19 (11.9%)
Dyskinesia	2 (1.2%)
Akinesia	0 (0.0%)
Left ventricular Systolic function	
>50	136 (85.0%)
40-50	11 (6.9%)
<40	13 (8.1%)
Left ventricular Diastolic function	
Normal	53 (33.1%)
Abnormal	107 (66.9%)
Right ventricular systolic function	
Normal	135 (84.4%)
Reduced(mild/mod/severe)	24 (15.6%)
Chamber Abnormalities	
Atrial abnormalities	
None	114 (71.2%)
Right atrium	31 (19.4%)
Left atrium	4 (2.5%)
Both atria	11 (6.9%)
Ventricular abnormalities	
None	99 (61.9%)
Right ventricle	33 (20.6%)
Left ventricle	16 (10.0%)
Both	12 (7.5%)

Variable	N=160
Valve abnormalities	
Mitral valve	
Normal	120 (75.0%)
Abnormal	40 (25.0%)
Aortic valve	
Normal	146 (91.2%)
Abnormal	14 (8.8%)
Tricuspid valve	
Normal	102 (63.8%)
Abnormal	58 (36.2%)
Pulmonary valve	
Normal	148 (92.5%)
Abnormal	12 (7.5%)

ELECTROCARDIOGRAPHIC (ECG) Abnormalities

Table 9: Prevalence of ECG abnormalities among newly diagnosed T2DM patients at MTRH

Characteristic	Normal	Abnormal	95%CI
Axis deviation	130 (81.2%)	30 (18.8%)	13.02, 25.67
Poor R Wave progression	121 (75.6%)	39 (24.4%)	17.94, 31.78
STT Abnormality	149 (93.1%)	11 (6.9%)	3.48, 11.97
T Wave aberration	78 (48.8%)	82 (51.2%)	43.23, 59.22
Atrial conduction abnormalities	155 (96.9%)	5 (3.1%)	1.02, 7.14
Ventricular conduction abnormalities	131 (81.9%)	29 (18.1%)	12.49, 24.98
Arrhythmias	109 (68.1%)	51 (31.9%)	24.74, 39.69

Table 10: Prevalence of specific Electrocardiographic abnormalities among newly diagnosed T2DM patients at MTRH

Variable	N=160
Q wave	
Normal	158 (98.8%)
Abnormal	2 (1.2%)
QTc interval	
Normal	132 (82.5%)
Prolonged	28 (17.5%)
QRS deviation	
None	130 (81.2%)
LAD	17 (10.6%)
RAD	13 (8.1%)
Tall amplitude	
No LVH	118 (73.8%)
LVH	42 (26.2%)
R wave progression	
Normal	121 (75.6%)
Poor	39 (24.4%)
ST-T abnormality category	
Normal ST segment	149 (93.1%)
ST elevation	11 (6.9%)
ST depression	0 (0.0%)
T-Wave category	
Normal T wave	78 (48.8%)
Peaked T wave	24 (15.0%)
Depressed T waves	7 (4.4%)
Biphasic T waves	8 (5.0%)
Inversion (TWI)	43 (26.9%)
Atrio-ventricular conduction defects	
None	155 (96.9%)
1st degree	4 (2.5%)
Mobitz 1	0 (0.0%)
Mobitz 2	0 (0.0%)
3rd degree	1 (0.6%)
Ventricular conduction abnormality	
None	131 (81.9%)
RBBB	17 (10.6%)
LBBB	12 (7.5%)

Arrhythmia category	
Sinus tachycardia	
No	125 (78.1%)
Yes	35 (21.9%)
Sinus bradycardia	
No	157 (98.1%)
Yes	3 (1.9%)
Atrial fibrillation	
No	157 (98.1%)
Yes	3 (1.9%)
Atrial flutter	
No	160 (100.0%)
Yes	0 (0.0%)
Premature atrial contraction	
No	157 (98.1%)
Yes	3 (1.9%)
Premature ventricular contraction	
No	148 (92.5%)
Yes	12 (7.5%)

4.5 Factors associated with cardiac abnormalities

Binary and multivariate logistic regression analyses were applied to test for associations between independent factors and cardiac abnormalities (composite of structural and functional abnormalities).Exploratory analysis was also done for the sub groups of isolated structural and functional cardiac abnormalities .Variables with significant association in bivariate analysis were entered into a multivariable model. Statistical significance was considered when P value was <0.05 .Strength of association on multi variable analysis was subsequently calculated as adjusted odds ratio with 95% CI (confidence intervals)

4.5.1 Logistic regression analysis for factors associated with composite Cardiac abnormalities among newly diagnosed T2DM patients at MTRH

On bivariate analysis ,the factors that were associated with the composite cardiac abnormalities were presence of hypertension with unadjusted odds ratio of 2.07 95%CI(1.01-4.41) p value of 0.05,abnormal glomerular filtration rate (<90ml/min/1.73m2) with an unadjusted odds ratio of 2.42 95%CI(1.28-4.66), P value of 0.007 and abnormal calculated 10 year atherosclerotic cardiovascular risk(>5%) with an unadjusted odds ratio of 3.15 95%CI(1.20-8.94),P value of 0.019.When this factors were subjected to a multivariate logistic regression analysis, only abnormal glomerular filtration rate (<90ml/min/1/73m^2) was independently associated with the composite cardiac abnormalities with an adjusted odds ratio of 2.43 ,95% CI (1.03-5.94)]. These results are displayed on table 8 below

Table 8: Factors associated with composite Cardiac abnormalities among newly diagnosed T2DM patients at MTRH

Variable	No (N=72)	Yes (N=87)	p value	UOR	95%CI	AOR	95%CI
Age			0.064				
Mean (SD)	54.06 (14.60)	58.30 (14.05)		1.02	1.00, 1.04	1	0.95, 1.05
Gender			0.515				
Male	36 (50.0%)	39 (44.8%)		1		1	
female	36 (50.0%)	48 (55.2%)		1.23	0.66, 2.31	1.03	0.36, 2.92
Known. HTN			**0.05**				
No	58 (80.6%)	58 (66.7%)		1		1	
Yes	14 (19.4%)	29 (33.3%)		2.07	1.01, 4.41	1.6	**0.64, 4.15**
Smoking			0.157				
non-smoker	51 (70.8%)	70 (80.5%)		1		1	
smoker	21 (29.2%)	17 (19.5%)		0.59	0.28, 1.23	0.77	0.13, 4.10

Alcohol use			0.2491				
never used	46 (63.9%)	63 (72.4%)		1		1	
currently user	26 (36.1%)	24 (27.6%)		0.67	0.34, 1.32	1.39	0.27, 7.58
BMI			0.65				
Abnormal	48 (66.7%)	55 (63.2%)		1		1	
Normal	24 (33.3%)	32 (36.8%)		1.16	0.61, 2.25	1.73	0.74, 4.16
WHR			0.964				
High risk	15 (21.1%)	18 (20.7%)		1		1	
Low risk	53 (74.6%)	66 (75.9%)		1.04	0.47, 2.25	1.13	0.42, 3.03
Moderate risk	3 (4.2%)	3 (3.4%)		0.83	0.14, 5.09	2.2	0.25, 24.1
UACR			0.156				
Abnormal	47 (65.3%)	65 (75.6%)		1		1	
Normal	25 (34.7%)	21 (24.4%)		0.61	0.30, 1.21	0.49	0.20, 1.18
GFR			**0.007**				
Abnormal	47 (65.3%)	38 (43.7%)		1		1	
Normal	25 (34.7%)	49 (56.3%)		2.42	1.28, 4.66	**2.43**	**1.03, 5.94**
HbA1C			0.719				
<=7	31 (43.1%)	35 (40.2%)		1		1	
>7	41 (56.9%)	52 (59.8%)		1.12	0.60, 2.12	1.42	0.61, 3.32
LDL			0.325				
<2.6	57 (79.2%)	63 (72.4%)		1		1	
>=2.6	15 (20.8%)	24 (27.6%)		1.45	0.70, 3.08	0.93	0.34, 2.50
Trig			0.652				
<=1.7	43 (59.7%)	55 (63.2%)		1		1	
>1.7	29 (40.3%)	32 (36.8%)		0.86	0.45, 1.64	0.49	0.19, 1.18
ASCVD			**0.019**				

Abnormal	40 (74.1%)	63 (90.0%)	3.15	1.20,8.94	**3.23**	**0.75,15.1**
Normal	14 (25.9%)	7 (10.0%)	1		1	

4.5.2 Exploratory logistic regression analysis for factors associated with structural Cardiac abnormalities among newly diagnosed T2DM patients at MTRH

On bivariate analysis ,the factors that were associated with structural cardiac abnormalities were abnormal glomerular filtration rate (<90ml/min/1.73m2) with an unadjusted odds ratio(UOR) of 2.29, 95%CI(1.19-4.52), P value of 0.014 and abnormal calculated 10 year atherosclerotic cardiovascular risk(ASCVD >5%) with an unadjusted odds ratio of 3.02 ,95%CI(1.17-8.29),P value of 0.021.When subjected to a multivariate logistic regression analysis, both factors maintained association but this was not statistically significant .Abnormal glomerular filtration rate (<90ml/min/1/73m^2) had an adjusted odds ratio(AOR) of 2.11 ,95% CI (0.89-5.14) and ASCVD risk >5% ,AOR of 2.01 95%CI 0.46-9.15). These results are displayed on table 9 below.

Table 9: Factors associated with structural Cardiac abnormalities among newly diagnosed T2DM patients at MTRH

Variable	No (N=72)	Yes (N=87)	p value	UOR	95%CI	AOR	95%CI
Age			0.993				
Mean (SD)	56.39 (13.44)	56.37 (15.03)		1	0.98, 1.02	1.02	0.97, 1.08
Gender			0.785				
Male	27 (45.8%)	48 (48.0%)		1		1	
Female	32 (54.2%)	52 (52.0%)		0.91	0.48, 1.74	0.88	0.30, 2.51
Known.HTN			0.275				
No	46 (78.0%)	70 (70.0%)		1		1	
Yes	13 (22.0%)	30 (30.0%)		1.52	0.73, 3.29	1.67	0.65, 4.45
Smoking			0.969				
non-smoker	45 (76.3%)	76 (76.0%)		1		1	
Smoker	14 (23.7%)	24 (24.0%)		1.02	0.48, 2.20	0.28	0.03, 1.71
Alcohol use			0.583				
never used	42 (71.2%)	67 (67.0%)		1		1	
currently user	17 (28.8%)	33 (33.0%)		1.22	0.61, 2.49	3.92	0.69, 32.6
BMI			0.789				
Abnormal	39 (66.1%)	64 (64.0%)		1		1	
Normal	20 (33.9%)	36 (36.0%)		1.1	0.56, 2.18	1.85	0.78, 4.55
WHR			0.948				
High risk	13 (22.0%)	20 (20.2%)		1		1	

Low risk	44 (74.6%)	75 (75.8%)		1.11	0.49, 2.43	1.28	0.48, 3.43
Moderate risk	2 (3.4%)	4 (4.0%)		1.3	0.22, 10.4	1.94	0.22, 20.9
UACR			0.307				
Abnormal	39 (66.1%)	73 (73.7%)		1		1	
Normal	20 (33.9%)	26 (26.3%)		0.69	0.34, 1.41	0.57	0.23, 1.38
GFR			**0.014**				
Abnormal	39 (66.1%)	46 (46.0%)		**2.29**	**1.19,4.52**	**2.11**	**0.89,5.14**
Normal	20 (33.9%)	54 (54.0%)		1		1	
hba1c			0.865				
<=7	25 (42.4%)	41 (41.0%)		1		1	
>7	34 (57.6%)	59 (59.0%)		1.06	0.55, 2.03	1.43	0.61, 3.38
LDL			0.185				
<2.6	48 (81.4%)	72 (72.0%)		1		1	
>=2.6	11 (18.6%)	28 (28.0%)		1.7	0.79, 3.86	1.03	0.38, 2.82
Trig			0.425				
<=1.7	34 (57.6%)	64 (64.0%)		1		1	
>1.7	25 (42.4%)	36 (36.0%)		0.77	0.40, 1.48	0.57	0.22, 1.38
ASCVD			**0.021**				
Abnormal	36 (73.5%)	67 (89.3%)		**3.02**	**1.17,8.29**	**2.01**	**0.46,9.15**
Normal	13 (26.5%)	8 (10.7%)		1		1	

4.5.3 Exploratory analysis for factors associated with functional cardiac abnormalities among newly diagnosed T2DM patients at MTRH

On bivariate analysis ,the factors that were associated with functional cardiac abnormalities were age with UOR 1.08, 95%CI (1.04-1.12) P value <0.001,female gender with UOR 2.48, 95%CI (1.05-6.19) P value 0.039,hypertension with UOR 3.38,95%CI(1.10-14.8) ,P value of 0.046, abnormal glomerular filtration rate (<90ml/min/1.73m2) with an unadjusted odds ratio(UOR) of 2.8, 95%CI(1.15-7.56), P value of 0.026 and ASCVD risk>5% with UOR of 3.75,95%CI (1.03-12.8),P value 0.027 .When subjected to a multivariate logistic regression analysis, only abnormal glomerular filtration rate (<90ml/min/1.73m2) maintained a statistically significant association with an adjusted odds ratio(AOR) of 8.98, 95%CI (1.65- 81.1). However the confidence interval was very wide which makes the point estimate less precise. These results are displayed on table 10 below.

Table 10: Factors associated with functional Cardiac abnormalities among newly diagnosed T2DM patients at MTRH

Variable	No (N=26)	Yes (N=134)	p value	UOR	95%CI	AOR	95%CI
Age			< **0.001**				
Mean (SD)	44.31 (13.25)	58.85 (13.47)		**1.08**	**1.04, 1.12**	1.02	0.88, 1.08
Gender			**0.039**				
Male	17 (65.4%)	58 (43.3%)		1		1	
Female	9 (34.6%)	76 (56.7%)		**2.48**	**1.05, 6.19**	**6.93**	**0.91, 65.9**
Known.HTN			**0.046**				
No	23 (88.5%)	93 (69.4%)		1		1	
Yes	3 (11.5%)	41 (30.6%)		**3.38**	**1.10, 14.8**	**2.81**	**0.32, 62.8**
Smoking			0.20				
non-smoker	15 (57.7%)	106 (79.1%)		1		1	
Smoker	11 (42.3%)	28 (20.9%)		0.36	0.15, 0.88	1.82	0.12, 27.5
Alcohol use			0.30				
never used	13 (50.0%)	96 (71.6%)		0.4	0.17,0.94	0.64	0.05,8.16
currently user	13 (50.0%)	38 (28.4%)		1		1	
BMI			0.621				
Abnormal	18 (69.2%)	86 (64.2%)		1.26	0.52,3.26	2.29	0.44,16.9
Normal	8 (30.8%)	48 (35.8%)		1		1	
WHR			0.993				
High risk	5 (20.0%)	28 (20.9%)		1		1	
Low risk	19 (76.0%)	101 (75.4%)		0.95	0.29, 2.61	0.44	0.05, 2.73

UACR			0.119				
Abnormal	15 (57.7%)	97 (72.9%)		1		1	
Normal	11 (42.3%)	36 (27.1%)		0.51	0.21, 1.23	0.23	0.04, 1.18
GFR			**0.026**				
Abnormal	19 (73.1%)	66 (49.3%)		**2.8**	**1.15,7.56**	**8.98**	**1.65,81,1**
Normal	7 (26.9%)	68 (50.7%)		1		1	
hba1c			0.236				
<=7	8 (30.8%)	58 (43.3%)		1		1	
>7	18 (69.2%)	76 (56.7%)		0.58	0.23, 1.39	0.37	0.04, 2.16
LDL			0.504				
<2.6	21 (80.8%)	100 (74.6%)		1		1	
>=2.6	5 (19.2%)	34 (25.4%)		1.43	0.53, 4.54	0.58	0.09, 4.19
Trig			0.399				
<=1.7	18 (69.2%)	81 (60.4%)		1		1	
>1.7	8 (30.8%)	53 (39.6%)		1.47	0.61, 3.81	0.6	0.10, 3.34
ASCVD			**0.027**				
Abnormal	8 (61.5%)	96 (85.7%)		**3.75**	**1.03,12.8**	**11.1**	**0.90,189**
Normal	5 (38.5%)	16 (14.3%)		1		1	

4.6 Correlation between cardiac abnormalities and factors with statistical significance

In summary, on a multi-variable adjusted analysis model, only abnormal glomerular filtration rate (<90ml/min/1/73m^2) was independently associated with the composite cardiac abnormalities with an adjusted odds ratio of 2.43 ,95% CI (1.03-5.94).On further exploratory analysis done for factors associated with the sub groups of isolated structural and functional cardiac abnormalities, none of the independent factors showed a statistically significant association with structural cardiac abnormalities on multivariate logistic analysis. Abnormal glomerular filtration rate (<90ml/min/1.73m2) was independently associated with isolated functional cardiac abnormalities with an adjusted odds ratio (AOR) of 8.98, 95%CI (1.65- 81.1). However the confidence interval was very wide which limits the precision of the effect estimate.

CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

This study revealed a notable prevalence of cardiac abnormalities in individuals seen in Moi Teaching and Referral Hospital, Eldoret with newly diagnosed Type 2 diabetes mellitus (T2DM). The most prominent abnormalities were; presence of features indicative of myocardial ischemia and myocardial dysfunction, including left ventricular diastolic dysfunction (LVDD), left ventricular hypertrophy (LVH), wall motion abnormalities (WMA), and T wave abnormalities

In this study, cardiac abnormalities were defined as a composite of structural and/or functional disorders of the heart observed through electrocardiographic and/or echocardiographic imaging studies.

A. Structural abnormalities were defined by presence of either;

- ***Myocardial ischemia as evidenced*** *by* : Regional Wall motion abnormalities and/or ST-T changes on ≥2 contiguous leads and /or T wave aberrations on contiguous leads OR;
- ***Left ventricular remodeling as evidenced by*** **:** ECG LVH- Cornell's criteria and /or ECHO LVH

B. Functional abnormalities were defined by presence of either;

- ***Left ventricular dysfunction as evidenced by*****:** Diastolic and/ or systolic dysfunction on ECHO (LVDD and LVSD) OR ;
- ***Arrhythmias evidenced by; ECG*** - sinus tachycardia/ bradycardia , atrial fibrillation/ flutter/ PAC / PVC/AV blocks OR;
- ***Conduction abnormality evidenced by*****;** Bundle branch blocks and / or QT prolongation

Incidence of cardiovascular disease (CVD), the leading cause of mortality globally is 2-3 times higher in Type 2 diabetes Mellitus (T2DM) individuals than in those without. Overall CVD affects approximately 32.2% of all T2DM patients (Einarson et al., 2018). Cardiovascular disease represents the main cause of morbidity and mortality in subjects with T2DM in whom it occurs approximately 15 years earlier than in people without diabetes(GL Booth et al.,2006, Low wang et al.,2016).

The disproportionately higher risk for CVD in this population has been attributed to coexistence of shared cardio-metabolic risk factors including insulin resistance, hypertension, dyslipidemia and obesity (Gaede P et al.,2003).Frequently DM associated cardiovascular disease remains silent possibly due to diabetes associated autonomic neuropathy, therefore patients remain undiagnosed and untreated until the disease is very advanced.

Studies have shown newly diagnosed DM patients to have varying prevalence of an abnormal echocardiogram (ECHO) and resting ECG abnormalities (Muddu et al.,2016, Harms et al., 2014,Bedane DA et al.,2021)

Verona Newly Diagnosed Type 2 Diabetes Study 9 (VNDS 9) found that approximately 50% of patients with newly diagnosed T2DM had clinical or preclinical manifestations of micro-vascular and/or macro-vascular disease while a study on cardiovascular complications in diabetes mellitus done in sub Saharan Africa found that approximately 50% of patients may present with echocardiographic abnormalities at diagnosis, (Kegne et al., 2015).

5.2 Prevalence of cardiac abnormalities

This study demonstrated a high prevalence of both structural and functional cardiac abnormalities amongst newly diagnosed type 2 diabetes mellitus patients. Among the

160 patients studied (with a mean age of 56.8 years, median duration since diagnosis of diabetes 4 months and a mean HbA1c of 8.99%); ECG abnormalities exhibited a high prevalence at 79.4% (95% CI: 72.35%-84.99%) (127) while ECHO abnormalities were present in (114) 71.3%(95% CI 63.7-77.8).

The overall prevalence of composite cardiac abnormalities, encompassing both structural and functional aspects, was 54.7% (95% CI 47-63). This study's findings align with those of a cross sectional study of 130 T2DM patients with a mean age of 56 by Sardesai et al. (2022) in India, who reported a similar prevalence of 53.8%. In contrast, Muddu et al. (2016) in Mulago, Uganda, found a slightly higher prevalence of 67.8%. The variance in results may stem from differences in study populations and criteria used for assessing cardiac abnormalities. Notably, Muddu's study included both Type 1 and Type 2 diabetes participants and solely employed echocardiography for assessment, while our study focused exclusively on newly diagnosed T2DM individuals, employing both ECG and ECHO modalities, thereby adopting a more stringent definition of cardiac abnormalities.

Despite the relatively short duration of diabetes diagnosis (mean duration of 3.69 months) in our participants, the high prevalence of cardiac abnormalities in our study aligns with evidence suggesting an increased cardiovascular risk in T2DM well before the clinical diagnosis is made (Stampfer et al., 2002). The prolonged latent pre-diabetes period, identified as an independent risk factor for cardiovascular disease (ADA, 2020; Huang Y et al., 2016), underscores the critical importance of early cardiovascular assessment in T2D

Upon further stratification of cardiac abnormalities assessed for; this study found isolated functional cardiac abnormalities to be present in **(134)83.8**%(95%CI 77-

89),while isolated structural cardiac abnormalities were present in (**100)62.9 %**(95%CI 55-70) .T2DM is a well-established independent risk factor for CVD and directly contributes to a distinct form of structural and functional cardiac abnormalities collectively referred to as diabetic cardiomyopathy characterized by; left ventricular hypertrophy (LVH) (thickening of the heart muscle/ enlargement of the heart chambers), left ventricular systolic dysfunction (LVSD) (reduced contractile function)and left ventricular diastolic dysfunction (LVDD) (impaired relaxation and filling of the heart)in the absence of significant coronary artery disease or systemic hypertension, (Somaratne et al.,2011), all of which increase the risk of heart failure, myocardial infarction, arrhythmias, and other cardiovascular complications.

Left ventricular diastolic dysfunction (LVDD) emerged as the most frequently occurring functional cardiac abnormality with a prevalence 66.87% (107)(95%CI 59.42-74.52) .This mirrored results from previous studies done by , Ojji., et al,2008 who found a prevalence 71%,Boyer et al ,2004 with a prevalence of 75% and Ayman et al,2021 whose study found a prevalence of 61%.LVDD represents impaired left ventricular relaxation and increased ventricular stiffness and represents one of the first pre-clinical reversible manifestations associated with diabetic cardiomyopathy (Freire CM., et al 2007). Left ventricular diastolic dysfunction may progress to diastolic heart failure (HF), however, timely recognition and intervention may help avoid or significantly delay onset of LVDD associated HF. In contrast, a study done in 2016 in Denmark, found a much lower prevalence of LVDD at 19.4% .This significant disparity could be attributed to the differences in clinical settings and their participant clinical characteristics. In the Danish study, participants were recruited from specialized endocrine clinics; a significant number of participants were on medications with CVD

risk modification and had a better glycemic control with a mean HbA1c of 7.1% in comparison to a mean of 8.99% in our study.

Further findings indicated a substantial prevalence of arrhythmias (including sinus tachycardia, sinus bradycardia, atrial fibrillation, premature atrial contraction and premature ventricular contraction) with a prevalence of 31.87% (95% CI: 24.74%-39.69%.

Left ventricular systolic dysfunction was present in 15% (95%CI 9.85-21.49) of our study participants. This finding was comparable to what Muddu et al., 2016 found - 21.8%. LVSD represents a pre- clinical phase of heart failure of reduced ejection fraction, a clinical entity associated with poor outcomes. Left ventricular dysfunction and left ventricular hypertrophy (LVH) are implicated as the causes of cardiac death in T2DM (Elley et al., 2008).Identification of LVSD at an early pre –clinical stage is useful in improving survival in T2DM as there currently exists proven treatment for LVSD that delays and or prevents progression to symptomatic heart failure ,including the anti-glycemic agents from the sodium glucose co-transporter 2 inhibitors class of medications.

Among participants with structural cardiac abnormalities; T wave abnormalities were the most frequent exhibiting near-equal prevalence between abnormal occurrences (51.2%; 95% CI: 43.23%-59.22%) and normal occurrences (48.8%; 95% CI: 40.78%-56.78%). Our findings are comparable to what was found in a cross sectional study of 258 participants in Ethiopia by Sinamaw et al.,2021, who found a prevalence of 57%. T wave abnormalities are indicative of abnormal ventricular repolarization, a crucial phase in the cardiac cycle. In the context of Type 2 diabetes mellitus (T2DM), these abnormalities may not only be linked to structural alterations such as left ventricular

hypertrophy (LVH) but can also serve as a potential harbinger of myocardial ischemia or injury. T wave abnormalities can manifest as the sole indicator of myocardial ischemia or injury, especially when there is T wave inversion exceeding 1mm on contiguous leads or when dynamic changes are evident in electrocardiograms performed at different time points.

The identification of left ventricular hypertrophy (LVH) in 17.50% of our study participants mirrors the prevalence reported by Muddu et al. in 2016, who found a similar occurrence of 19.3%. This consistent finding may be attributed to the well-established association between Type 2 diabetes mellitus (T2DM) and the development of LVH. T2DM is recognized as an independent risk factor for cardiovascular diseases, and its chronicity often leads to a cascade of structural changes in the heart, including LVH. The prolonged exposure to hyperglycemia, insulin resistance, and the associated hemodynamic alterations in T2DM contributes to cardiac remodeling, characterized by the thickening of the heart muscle, ultimately resulting in LVH. The similarities in LVH prevalence between our study and Muddu et al.'s investigation could be indicative of a common pathophysiological mechanism underlying LVH development amongst newly diagnosed T2DM patients.

In contrast, our study identified wall motion abnormalities in 13.1% of participants (95% CI 8.31-19.36), a notably higher prevalence compared to a study conducted by Nguyen et al. in 2011 among an African population, which reported a prevalence of hypokinesia at 6.1%. Several factors may contribute to this discrepancy. Firstly, differences in the criteria used to define and assess wall motion abnormalities may impact prevalence rates. Our study applied both ECG and echocardiography modalities, whereas the study by Nguyen et al. primarily utilized echocardiography. The inclusion of ECG, which assesses electrical activity, might have led to a more comprehensive

identification of wall motion abnormalities, explaining the higher prevalence observed in our study.

Regarding ST-T abnormalities, our findings indicated a relatively low prevalence of 6.9% (3.48-11.97) in the study participants. The infrequent occurrence of ST-T abnormalities may be indicative of the early stage of cardiac involvement in our newly diagnosed T2DM cohort. These electrocardiographic changes are often associated with myocardial ischemia or injury, which may not have fully manifested in our participants during the early phases of diabetes diagnosis. The low prevalence could also be influenced by a relatively short duration of T2DM since diagnosis.

The significance of the findings in this study is underscored by existing data from a prospective study, as reported by Harms et al., in 2023. Their research indicates that the identification of a baseline cardiac abnormality in individuals with T2DM correlates with a substantial 3-4 fold increase in the incidence of future major adverse cardiac events (MACE), encompassing heart failure or coronary heart disease. This association highlights the predictive value of early cardiac abnormalities in determining long-term cardiovascular outcomes in T2DM patients. Further this re-affirms the urgency in early assessment and recognition of cardiac abnormalities in individuals newly diagnosed with T2DM and becomes a pivotal cornerstone for timely management strategies, offering a window of opportunity to potentially modify the trajectory of poor outcomes associated with cardiovascular complications

5.3 Factors associated with cardiac abnormalities

5.3.1: Factors associated with the composite, functional and structural cardiac abnormalities

In a multivariable adjusted analysis there was a significant independent association between abnormal estimated Glomerular Filtration Rate (eGFR) - defined as less than 90% - and composite cardiac abnormalities. Individuals with an eGFR below 90% exhibited a 2.4 times higher odds of experiencing composite cardiac abnormalities. This observation aligns with the findings of previous studies conducted by Jorgensen et al. in 2016 in Denmark, Piyush et al. in 2008 in Australia, and Nyuyen et al. in 2011.

The existing body of literature underscores the consistency of our results, as prior research has demonstrated a correlation between renal dysfunction and the manifestation of various metabolic and hemodynamic abnormalities, ultimately impacting long-term cardiovascular prognosis. Specifically, a decline in glomerular filtration rate and the presence of micro-albuminuria have been linked to a range of pro-atherogenic factors. These include insulin resistance, lipid abnormalities, hyperhomocystinemia, endothelial dysfunction, and chronic inflammation. The convergence of these factors, in conjunction with hemodynamic abnormalities, contributes to a heightened risk for adverse cardiovascular outcomes. The identification of abnormal eGFR as an independent factor associated with composite cardiac abnormalities emphasizes the importance of monitoring renal function in assessing and managing cardiovascular risk.

Calculated 10 year ASCVD (Atherosclerotic Cardiovascular Disease) risk of $\geq 5\%$ and history of hypertension showed a trend towards higher odds (3 times and 2 times higher odds respectively) of having the composite cardiac abnormality however, after

adjusting for other factors these associations did not meet a statistically significant threshold.

Further, on exploratory analysis; Abnormal eGFR (estimated Glomerular Filtration Rate) and an increasing ASCVD (Atherosclerotic Cardiovascular Disease) risk of >5% , demonstrated higher odds for both isolated structural and isolated functional cardiac abnormalities. This finding suggests a potential link between renal function impairment and heightened ASCVD risk with these specific cardiac abnormalities. Additionally, female gender, a history of smoking, and a diagnosis of hypertension were associated with higher odds of isolated functional cardiac abnormalities. Nonetheless, similar to the aforementioned associations, statistical significance was not met which implied that while these factors might show a trend towards certain cardiac abnormalities, their independent impact remains uncertain in our study cohort.

Existing evidence provides context to our findings, indicating that an elevated 10-year ASCVD risk is linked to subclinical heart remodeling, as well as a significant increase in systolic and diastolic dysfunction (Cauwenberghs et al., 2019).Moreover, corroborating our results, previous research by Muddu et al. in 2016, Piyush et al. in 2008, and Dzudie et al. in 2012 also found hypertension to be associated with cardiac abnormalities. Hypertension, known for causing vascular remodeling and dysfunction, is implicated in left ventricular hypertrophy and is as a recognized risk factor for myocardial infarction (MI). Additionally, hypertension accelerates myocardial architectural changes resulting from diabetes mellitus, further emphasizing the intricate interplay between these cardiovascular risk factors.

5.4 Factors that showed no statistical association with cardiac abnormalities

5.4.1 Socio-demographic factors

The mean age of the participants in this study was 56.4 years (SD11) with a range of 35-81. This is in keeping with the International Diabetes Federation (IDF) 2018 fact sheet which reports that the highest prevalence of Diabetes in Africa is among adults aged 55-64 years. In contrast to the findings of Muddu et al., 2016 (mean age 46 years), Jorgensen et al.,2016(mean age 65.5) and Sardesai et al., 2021(mean age 56.3) ;this study found no statistical association between age and the cardiac abnormalities studied. Several factors could contribute to the lack of association between age and cardiac abnormalities amongst newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients in this study. Some of the factors in this study that might explain a lack of association include: Firstly, majority of the cohort predominantly comprised of younger individuals within an age range of (35-60 years) at 52.5%, however, Jorgensen et al., 2016 ,in their study demonstrated that the prevalence of cardiac abnormalities increases sharply with age and that abnormal echocardiography has a very high prevalence in patients with type 2 diabetes >75 years of age, driven mainly by left ventricular hypertrophy, left atrial enlargement and diastolic dysfunction. Further the small sample size(n=160) might lack the statistical power needed to identify significant correlations, especially if the effects of age are modest or influenced by other variables. Unlike in the other studies where participants were stratified into categorical age groups, this study considered age as a continuous variable in the analysis. Age-related changes in cardiac function may not follow a linear pattern, stratifying the analysis by age groups could reveal age-specific patterns in the development of cardiac abnormalities. It's possible that associations become more evident in specific age brackets. Other factors, such as comorbidities, genetic predispositions, or lifestyle variables, may play a more dominant role in influencing cardiac abnormalities in the

early stages of T2DM. These factors could overshadow the potential impact of age in this specific context. The effects of age on cardiac health can be heterogeneous among individuals. Some may exhibit early cardiac changes, while others may maintain better cardiovascular function despite aging. This heterogeneity can contribute to the lack of a consistent association in this studied population. Furthermore the relatively short duration since the diagnosis of diabetes in the study population might mean that age-related changes in cardiac function have not yet manifested prominently. Over a more extended period, the impact of age on cardiac abnormalities might become more apparent.

This study consisted of a relatively balanced representation of both males and females with a slight female predominance at 53.1% (85). This distribution aligns with the anticipated epidemiological pattern of Type 2 Diabetes Mellitus (T2DM) as outlined in the International Diabetes Federation (IDF) fact sheet. Within this cohort, females exhibited a slightly higher prevalence of cardiac abnormalities compared to their male counterparts. Despite this trend, similar to findings reported by Muddu et al., 2016 , our study, like theirs, revealed no statistically significant association between gender and the occurrence of cardiac abnormalities.

This is deviates from what Harms et al.,2020, and Sellers MB et al.,2014 found. Differences in methodological approaches might explain this disparity. This study did not employ sub-group analysis and sensitivity testing specifically designed to explore relationships between gender and various types of cardiac abnormalities. The absence of such targeted analyses may obscure potential gender-specific patterns in cardiac outcomes. Furthermore, the limited sample size of in this study constrained our ability to conduct robust exploratory analyses that could unveil subtle associations. The lack of statistical significance in our study underscores the necessity for larger sample sizes

and incorporation of more comprehensive analyses to explore gender-specific associations with the diverse spectrum of cardiac abnormalities in individuals newly diagnosed with Type 2 Diabetes Mellitus.

Among other factors studied; history of alcohol use and smoking status did not show a significant association with abnormality. However, it is worth noting that the prevalence of cardiac abnormalities was higher among smokers compared to non-smokers and former smokers.

5.3.2 Clinical characteristics

The urinary albumin-to-creatinine ratio (UACR) categories presented a trend suggestive of a potential association with cardiac abnormalities. Notably, individuals categorized within higher UACR ranges (>30) exhibited higher odds of having cardiac abnormalities compared to those in the reference category (<30). Despite the observed trend, this association did not attain statistical significance within our study cohort. This differs from what Jorgensen .,et al 2016 and the Strong heart study found ,who found strong associations between albuminuria and occurrence of cardiac abnormalities. In contrast to our study, Jorgensen et al. and the Strong Heart Study employed a more stringent definition of albuminuria, requiring persistence through measurements of urine albumin excretion conducted on two consecutive occasions or via a 24-hour urine albumin excretion rate, performed initially and repeated in cases of elevated levels. Our study, however, relied on a spot measurement of albuminuria at a specific point in time. This methodological disparity raises the possibility that spot albuminuria might not capture transient fluctuations or subtle changes in renal function that could be intricately linked with the manifestation of cardiac abnormalities. The variability in albuminuria levels could also contribute to a lack of association, as the impact on cardiac abnormalities may be more evident with sustained levels of albuminuria. The

intermittent nature of spot measurements might not fully encapsulate these nuances. Continuous or more frequent monitoring of albuminuria could potentially offer a more accurate reflection of renal status, enabling a more precise understanding of its relationship with cardiac abnormalities. Moreover, it is worth considering that spot albuminuria might have a more prominent association with specific cardiac abnormalities, such as diastolic dysfunction, as opposed to systolic dysfunction. Focusing on specific cardiac parameters, rather than a broad definition of abnormalities, could unveil more targeted associations. To better understand the intricacies of the association between UACR and cardiac abnormalities, future studies with larger sample sizes and extended follow-up durations are warranted. This approach will not only enhance the statistical power to detect subtle associations but also allow for a more comprehensive exploration of the temporal dynamics of this relationship.

The median duration since the diagnosis of diabetes within this cohort was 4 months, ranging from 0 to 6 months. No significant association was observed between the duration of diabetes mellitus and the prevalence of cardiac abnormalities. This aligns with the findings reported by Muddu et al., where the mean duration was noted to be 3 months. The concurrence of these results suggests that individuals newly diagnosed with Type 2 Diabetes Mellitus (T2DM) may still be in the early stages of the disease, yet cardiac abnormalities may take time to manifest, particularly those linked to long-term diabetic complications. Consequently, the duration of diabetes in this context may not have been of sufficient length to reveal a significant association with the prevalence of cardiac abnormalities.

Among the 160 participants, notable proportions exhibited dyslipidemia markers: 24.4% with LDL-C exceeding 2.6, 38.1% with Triglycerides > 1.7, and a predominant 72.2% presented with low HDL levels (male < 1mmol/l and female < 1.3) at 72.5%.

Surprisingly, only 9.4% of individuals above 40 years, with one or more additional cardiovascular disease (CVD) risk factors, were undergoing lipid-lowering therapy in adherence with ADA 2020 guidelines recommending statin therapy alongside lifestyle interventions for this demographic. A follow up knowledge, attitude and practice survey would better evaluate this finding to assess for and address the existing gaps in practice. Despite these statistics, no statistically significant association emerged between dyslipidemia and the presence of cardiac abnormalities. These findings diverge from those reported by Olamayegun et al.,in 2021.Possible explanations for the absence of an observed association could be multifaceted: Dyslipidemia encompasses multifactorial components, and the singular focus on LDL-C, Triglycerides, or HDL levels might overlook the interplay among lipid fractions that contribute to cardiac abnormalities and the study might have had limitations in sample size, study duration, or insufficient adjustment for confounding factors, potentially affecting the ability to detect a significant relationship.

The mean HbA1c for this cohort was 8.99% .Majority of the participants at 59.4% had not achieved the target HbA1c of < 7% as per the ADA 2020 guideline recommendation. However there was no demonstrable association between glycemic control and cardiac abnormalities. Muddu et al, had similar findings.

Further**,** no associations were observed with body mass index (BMI) categories (normal, obese, overweight) or waist circumference both in crude and adjusted analysis. This stands in contrast to the findings reported by Muddu et al in 2016, Piyush et al in 2008, and Jorgensen et al in 2016, all of whom found an association between obesity and cardiac abnormalities. Correlation between obesity, waist circumference, and cardiac abnormalities may vary among individuals. The lack of association in this study may be due to random variation with the observed results occurring by chance, but also

the short study time frame and categorization of individuals into different groups may contribute to these varying results.

5.5 Study Strengths and Limitations

5.5.1 Strengths

- The participants in this study were evaluated with both ECHO and ECG allowing for comprehensive cardiac assessment.
- Extensive laboratory evaluation for recognized risk factors was done and this provided good CVD risk prediction.

5.5.2 Limitations

- The definition of T2DM was based on ADA criteria rather than the gold standard of insulin secretory function testing. Younger participants with T2DM may have been excluded given the recent trends of younger patients being diagnosed T2DM.Missclassication and inclusion of some T1DM and maturity onset diabetes of the young (MODY) may have occurred; however the higher cut-off recruitment age of 35years minimized this chance.
- This was a cross sectional study - Associations in cross-sectional study do not imply cause-effect relationship and future studies with matched control of non –diabetic patients would best indicate attribution of diabetes to the cardiac abnormalities ,however the study gives a snapshot of the problem and lays a foundation for longitudinal studies.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

- Overall this study found the prevalence of cardiac abnormalities among newly diagnosed T2DM patients in MTRH **significantly high at 54.7%**
- **Left ventricular diastolic dysfunction** and **T wave abnormalities** were the most common functional and structural abnormalities respectively
- Abnormal GFR was independently associated with **2 times higher odds of cardiac abnormalities**
- **Hypertension** and **increasing 10 year ASCVD risk** showed non statistically significant higher odds of cardiac abnormalities

6.2 Recommendations

- Due to the high prevalence of cardiac abnormalities amongst newly diagnosed T2DM patients at MTRH; early non-invasive assessment (by ECG and ECHO) for cardiac abnormalities amongst newly diagnosed T2DM should be done
- Evaluation for cardiac abnormalities amongst newly diagnosed T2DM patients should be done at baseline when; The estimated GFR is <90ml/min and considered in comorbid hypertension or those with ASCVD risk >5%

REFERENCES

ACC Guidelines Committee. (2014). Reply: 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. *Journal of the American College of Cardiology*, *63*(25 Part A), 2886-2886.

Association, A. D. (2020). Cardiovascular disease and risk management: Standards of medical care in diabetes- 2020. *Diabetes Care*, *43*(Supplement 1), S111–S134. https://doi.org/10.2337/dc20-S010

Atlas, I. D. (2017). Brussels: International Diabetes Federation; 2015. *International Diabetes Federation*.

Boston, U. Framingham Heart Study. Cardiovascular Disease (10-year risk) Boston2015 [cited 2015 20th March].

Boyer, J. K., Thanigaraj, S., Schechtman, K. B., & Pérez, J. E. (2004). Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *American Journal of Cardiology*, *93*(7), 870–875. https://doi.org/10.1016/j.amjcard.2003.12.026

Chawla, A., Chawla, R., & Jaggi, S. (2016, July 1). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, Vol. 20, pp. 546–553. https://doi.org/10.4103/2230-8210.183480

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023

Church, T. S., Thompson, A. M., Katzmarzyk, P. T., Sui, X., Johannsen, N., Earnest, C. P., & Blair, S. N. (2009). Metabolic syndrome and diabetes, alone and in combination, as predictors of cardiovascular disease mortality among men. *Diabetes care*, *32*(7), 1289-1294.

Cosentino, F., Grant, P. J., Aboyans, V., Bailey, C. J., Ceriello, A., Delgado, V., … Chowdhury, T. A. (2020). 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European Heart Journal*, *41*(2), 255–323. https://doi.org/10.1093/eurheartj/ehz486

Devereux, R. B., Roman, M. J., Paranicas, M., O'Grady, M. J., Lee, E. T., Welty, T. K., … Howard, B. V. (2000). Impact of Diabetes on Cardiac Structure and Function. *Circulation*, *101*(19), 2271–2276. https://doi.org/10.1161/01.CIR.101.19.2271

DZuDiE, A., CHOuKEM, S., Africa, F. K.-… journal of, & 2012, undefined. (n.d.). Prevalence and determinants of electrocardiographic abnormalities in sub-Saharan African individuals with type 2 diabetes. *Ncbi.Nlm.Nih.Gov*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3721941/

Einarson, T. R., Acs, A., Ludwig, C., & Panton, U. H. (2018, June 8). Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovascular Diabetology*, Vol. 17, p. 83. https://doi.org/10.1186/s12933-018-0728-6

Einarson, T. R., Acs, A., Ludwig, C., & Panton, U. H. (2018, June 8). Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovascular Diabetology*, Vol. 17, p. 83. https://doi.org/10.1186/s12933-018-0728-6

Elley, C. R., Kenealy, T., Robinson, E., & Drury, P. L. (2008). Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: A large prospective cohort study. *Diabetic Medicine*, *25*(11), 1295–1301. https://doi.org/10.1111/j.1464-5491.2008.02581.x

Ford, E. S., Zhao, G., & Li, C. (2010). Pre-Diabetes and the Risk for Cardiovascular Disease. A Systematic Review of the Evidence. *Journal of the American College of Cardiology*, *55*(13), 1310–1317. https://doi.org/10.1016/j.jacc.2009.10.060

Fowler, M. J. (2008, April 1). Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*, Vol. 26, pp. 77–82. https://doi.org/10.2337/diaclin.26.2.77

Fox, C. S., Pencina, M. J., Wilson, P. W. F., Paynter, N. P., Vasan, R. S., & D'agostino, R. B. (2008). Lifetime Risk of Cardiovascular Disease Among Individuals With and Without Diabetes Stratified by Obesity Status in the Framingham Heart Study org/licenses/by-nc-nd/3.0/ for details. *DIABETES CARE*, *31*(8). https://doi.org/10.2337/dc08

Gæde, P., Vedel, P., Larsen, N., Jensen, G. V. H., Parving, H.-H., & Pedersen, O. (2003). Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *New England Journal of Medicine*, *348*(5), 383–393. https://doi.org/10.1056/nejmoa021778

Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition - Diabetes Research and Clinical Practice. (n.d.). Retrieved August 25, 2020, from https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(19)31230-6/fulltext

Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., … Yeboah, J. (2019, June 18). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, Vol. 139, pp. E1082–E1143. https://doi.org/10.1161/CIR.0000000000000625

Gu, K., Cowie, C. C., & Harris, M. I. (1999). Diabetes and decline in heart disease mortality in US adults. *Jama*, *281*(14), 1291-1297.

Gupta, S., Gupta, R. K., Kulshrestha, M., & Chaudhary, R. R. (2017). Evaluation of ECG abnormalities in patients with asymptomatic type 2 diabetes mellitus. *Journal of Clinical and Diagnostic Research*, *11*(4), OC39–OC41. https://doi.org/10.7860/JCDR/2017/24882.9740

Haas, A. V., & McDonnell, M. E. (2018, March 1). Pathogenesis of Cardiovascular Disease in Diabetes. *Endocrinology and Metabolism Clinics of North America*, Vol. 47, pp. 51–63. https://doi.org/10.1016/j.ecl.2017.10.010

Haffner, S. M., Lehto, S., Rönnemaa, T., Pyörälä, K., & Laakso, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England journal of medicine*, *339*(4), 229-234.

Harms, P. P., van der Heijden, A. A., Rutters, F., Tan, H. L., Beulens, J. W. J., Nijpels, G., & Elders, P. (2021). Prevalence of ECG abnormalities in people with type 2 diabetes: The Hoorn Diabetes Care System cohort. *Journal of*

Diabetes and Its Complications, *35*(2). https://doi.org/10.1016/j.jdiacomp.2020.107810

Harms, P. P., van der Heijden, A. A., Rutters, F., Tan, H. L., Beulens, J. W. J., Nijpels, G., & Elders, P. (2021). Prevalence of ECG abnormalities in people with type 2 diabetes: The Hoorn Diabetes Care System cohort. *Journal of Diabetes and Its Complications*, *35*(2), 107810. https://doi.org/10.1016/j.jdiacomp.2020.107810

Henning, R. J. (2018). Type-2 diabetes mellitus and cardiovascular disease. *Future Cardiology*, *14*(6), 491–509. https://doi.org/10.2217/fca-2018-0045

Huang, Y., Cai, X., Mai, W., Li, M., & Hu, Y. (2016). Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *Bmj*, *355*.

Introduction: Standards of medical care in diabetes-2020. (2020, January 1). *Diabetes Care*, Vol. 43, pp. S1–S2. https://doi.org/10.2337/dc20-Sint

Jørgensen, P. G., Jensen, M. T., Mogelvang, R., Von Scholten, B. J., Bech, J., Fritz-Hansen, T., … Jensen, J. S. (2016). Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. *Diabetes and Vascular Disease Research*, *13*(5), 321–330. https://doi.org/10.1177/1479164116645583

Kengne, A. P., & Mbanya, J. C. (2004). Cardiovascular risk profile of newly diagnosed type 2 diabetic patient at the central Hospital of Yaounde [final dissertation, end-of-specialisation in internal medicine]. *Yaounde: The University of Yaounde*, *1*.

Litwak, L., Goh, S. Y., Hussein, Z., Malek, R., Prusty, V., & Khamseh, M. E. (2013). Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. *Diabetology and Metabolic Syndrome*, *5*(1), 1–10. https://doi.org/10.1186/1758-5996-5-57

Lorenzo-Almorós, A., Tuñón, J., Orejas, M., Cortés, M., Egido, J., & Lorenzo. (2017, February 23). Diagnostic approaches for diabetic cardiomyopathy. *Cardiovascular Diabetology*, Vol. 16, p. 28. https://doi.org/10.1186/s12933-017-0506-x

Macfarlane, P. W., & Norrie, J. (2007). The value of the electrocardiogram in risk assessment in primary prevention: Experience from the West of Scotland Coronary Prevention Study. *Journal of Electrocardiology*, *40*(1), 101–109. https://doi.org/10.1016/j.jelectrocard.2006.05.003

Martín-Timón, I. (2014). Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World Journal of Diabetes*, *5*(4), 444. https://doi.org/10.4239/wjd.v5.i4.444

Muddu, M., Mutebi, E., & Mondo, C. (2016). Prevalence, types and factors associated with echocardiographic abnormalities among newly diagnosed diabetic patients at Mulago hospital. *African Health Sciences*, *16*(1), 183–193.

Nathan, D. M., Meigs, J., & Singer, D. E. (1997). The epidemiology of cardiovascular disease in type 2 diabetes mellitus: How sweet it is . . . or is it? *Lancet*, *350*(SUPPL.1), 4–9. https://doi.org/10.1016/s0140-6736(97)90021-0

Nguyen, M. T., Cosson, E., Valensi, P., Poignard, P., Nitenberg, A., & Pham, I. (2011). Transthoracic echocardiographic abnormalities in asymptomatic diabetic patients: association with microalbuminuria and silent coronary artery disease. *Diabetes & metabolism*, *37*(4), 343-350.

Prineas, R., Crow, R., & Zhang, Z. (2009). *The Minnesota code manual of electrocardiographic findings*. Retrieved from https://books.google.com/books?hl=en&lr=&id=T2sNcqGEXYoC&oi=fnd&pg=PR4&ots=8aQj_v3cPR&sig=ahJ-NaJ49tBBdwcKDtDrz7Zwgwk

Rungby, J., Schou, M., Warrer, P., Ytte, L., & Andersen, G. S. (2017). Prevalence of cardiovascular disease and evaluation of standard of care in type 2 diabetes: a nationwide study in primary care. *Cardiovascular Endocrinology*, *6*(4), 145–151. https://doi.org/10.1097/XCE.0000000000000135

Ryden, L., Grant, P. J., Anker, S. D., Berne, C., Cosentino, F., Danchin, N., … Zamorano, J. L. (2014). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - Summary The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in col. *Diabetes and Vascular Disease Research*, *11*(3), 133–173. https://doi.org/10.1177/1479164114525548

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., ... & IDF Diabetes Atlas Committee. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, *157*, 107843.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., … Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *157*. https://doi.org/10.1016/j.diabres.2019.107843

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., … Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice, 157*. https://doi.org/10.1016/j.diabres.2019.107843

Sarwar, N., Gao, P., Kondapally Seshasai, S. R., Gobin, R., Kaptoge, S., Di Angelantonio, E., … Wormser, D. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet*, *375*(9733), 2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9

Sharma, H., Lencioni, M., & Narendran, P. (2019, March 1). Cardiovascular disease in type 1 diabetes. *Cardiovascular Endocrinology and Metabolism*, Vol. 8, pp. 28–34. https://doi.org/10.1097/XCE.0000000000000167

Singh, G. M., Danaei, G., Farzadfar, F., Stevens, G. A., Woodward, M., Wormser, D., … Danesh, J. (2013). The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: A pooled analysis. *PLoS ONE*, *8*(7). https://doi.org/10.1371/journal.pone.0065174

Somaratne, J. B., Whalley, G. A., Bagg, W., & Doughty, R. N. (2008). Early detection and significance of structural cardiovascular abnormalities in patients with Type 2 diabetes mellitus. *Expert Review of Cardiovascular Therapy*, Vol. 6, pp. 109–125. https://doi.org/10.1586/14779072.6.1.109

Somaratne, J. B., Whalley, G. A., Poppe, K. K., ter Bals, M. M., Wadams, G., Pearl, A., ... & Doughty, R. N. (2011). Screening for left ventricular hypertrophy in patients with type 2 diabetes mellitus in the community. *Cardiovascular diabetology*, *10*(1), 1-8.

Srivastava, P. M., Calafiore, P., MacIsaac, R. K., Patel, S. K., Thomas, M. C., Jerums, G., & Burrell, L. M. (2008). Prevalence and predictors of cardiac hypertrophy and dysfunction in patients with Type 2 diabetes. *Clinical Science*, *114*(3–4), 313–320. https://doi.org/10.1042/CS20070261

Tancredi, M., Rosengren, A., Svensson, A. M., Kosiborod, M., Pivodic, A., Gudbjörnsdottir, S., … Lind, M. (2015). Excess mortality among persons with type 2 diabetes. *New England Journal of Medicine, 373*(18), 1720–1732. https://doi.org/10.1056/NEJMoa1504347

Tougouma, S. J. B., Kambiré, Y., Bado, J., Yaméogo, A. A., Yaméogo, T. M., Sidibé, S., … Ouédraogo, M. (2018). Electrocardiography coupled with transthoracic echocardiography at rest in the diagnosis of cardiac impairments in type 2 diabetics: Lessons learned from a cross-sectional case series in Burkina Faso. *Pan African Medical Journal*, *31*. https://doi.org/10.11604/pamj.2018.31.169.15798

Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., ... & Schutte, A. E. (2020). 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*, *75*(6), 1334-1357.

Wamai, R. G., Kengne, A. P., & Levitt, N. (2018). Non-communicable diseases surveillance: overview of magnitude and determinants in Kenya from STEPwise approach survey of 2015. *BMC Public Health*, *18*(3), 1-8.

Wang, Y., & Marwick, T. H. (2016, September 1). Update on Echocardiographic Assessment in Diabetes Mellitus. *Current Cardiology Reports*, Vol. 18. https://doi.org/10.1007/s11886-016-0759-0

Young, L. H., Wackers, F. J. T., Chyun, D. A., Davey, J. A., Barrett, E. J., Taillefer, R., … Inzucchi, S. E. (2009). Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes the DIAD study: A randomized controlled trial. *JAMA - Journal of the American Medical Association*, *301*(15), 1547–1555. https://doi.org/10.1001/jama.2009.476

Zhang, Z. M., Prineas, R. J., Soliman, E. Z., Baggett, C., Heiss, G., & ARIC Research Group (2012). Prognostic significance of serial Q/ST-T changes by the Minnesota Code and Novacode in the Atherosclerosis Risk in Communities (ARIC) study. *European journal of preventive cardiology*, *19*(6), 1430–1436. https://doi.org/10.1177/1741826711426091

APPENDICES

Appendix 1: Data Collection Form

Diabetes Type: 2

Biodata

IP.NO…….. Serial number……..

Age……..…years Gender……

Ethnicity……. Residence…….

Occupation……..…

If female, LMP: **……**

Medical History

Duration of diabetes (months)…….

H/O Hypertension:…….Yes/No

Family & social history

H/O Smoking:……Yes/No

H/O alcohol use……Yes/No

H/O Diabetes in the family……..Yes/No

Treatment history:

Glycaemic control agent (tick appropriate)

A. Insulin.....type ……

B. Oral hypoglycemic agents; types: ……

C. Both Insulin and oral hypoglycemic: types: …….

D. Diet control….

Anti- Hypertensive agent (tick appropriate)

A. Yes……..name…….B No……

Lipid lowering agents (tick appropriate)

A. Yes……..name…….B No……

List other drugs:……

EXAMINATION

General:

Pallor Jaundice Edema

Dehydration Lymphadenopathy

Height……..…cm **Weight:**……kg

BMI ……kg/m2 **Hip Circumference……..**cm **Waist Circumference**……cm **Waist Hip Ratio…….**

Vital signs: BP: ……/……mmHg Pulse:……../min

Temp: …….oC SPO2: ……..%

LABORATORY RESULTS

Test	**Results**	**Date**
HbA1C		
Serum creatinine		
Lipid profile **Total cholesterol** **LDL-C** **HDL-C**		
Urinalysis		
UACR		

Appendix 2: Consent Form Information
English

My name is Dr Stella Murugi Gichovi. I am a medical doctor currently pursuing a Master's degree in Internal Medicine at Moi University. I would like to recruit you today into my research which is looking at the prevalence and correlates of cardiovascular abnormalities among newly diagnosed type 2 diabetes mellitus patients that are receiving care at MTRH.

Purpose of the study:

The purpose of this study is to establish the prevalence(number of individuals with the condition under study that includes both new and existing cases) and correlates (examined clinical findings that predict the possibility of having the outcome under the study) of cardiac abnormalities among newly diagnosed type 2 diabetes mellitus patients seen at MTRH in order to institute appropriate measures to manage the condition early enough.

What does the study involve?

In this study, you will be asked to provide your socio-demographic information which includes age, sex, marital status, occupation, level of education among others. You will have several anthropometric measures taken ,including weight,height,waist circumference and hip circumference. Your vital signs including your blood pressure, pulse rate and temperature will be taken. You will undergo imaging with echocardiography and electrocardiography to assess for cardiac abnormalities. Then, blood samples will be drawn from you and taken to the laboratory for a lipid profile, serum creatinine and HbA1c .A random urine sample will be taken for a urine dipstick and Urine-Albumin-Creatinine-Ratio.

There are minimal risks involved in this study. These include but not limited to pain at the injection site and swelling at the site of the injection.

Your participation in this study is voluntary and you can withdraw at any stage should you change your mind during the course of study. Your refusal to participate or withdrawal from the study will not in any way affect future care and treatment in this facility. All information obtained will be treated with utmost confidentiality.

Consent form

I _____, having been explained to and well understood the nature and purpose of this study by_____, do hereby voluntarily agree to participate in the study. I agree to willingly answer the questions honestly and undergo the laboratory investigations that have been explained to me.

Signature (Patient)_____

Date._____

If you need further clarifications, feel free to contact IREC using the address below.

The Chairman IREC,

Moi Teaching and Referral Hospital,

PO Box 3,

Eldoret.

Tel: 33471/2/3

You can also contact me (Dr. Stella Murugi Gichovi) on 0727 865 202

Appendix 3: Kiswahili

Jina langu ni Stella Murugi Gichovi. Mimi ni daktari ambaye ni msomi wa shahada ya juu (Masters) ya udaktari (Internal medicine)katika chuo kikuu cha Moi. Nimekuona leo kwa sababu ninafanya utafiti wa kuangalia kiwango cha shida za muundo na utenda kazi wa moyo katika wagonjwa ambao wameguduliwa na tatizo la ugonjwa wa kisikuari wanaopata matitabu katika hospitali ya rufaa ya MTRH.

Lengo kuu la utafiti huu ni kutambua shida za matatizo ya muundo na utendakazi wa moyo na sababu za hatari ambazo zinatabiri uwezekano wa kupata maradhi ya moyo katika wagonjwa wa shida ya kisukari.. Hii itatuwezesha kuweka mikakati bora ya matibabu kabla ugonjwa huu kuleta madhara zaidi mwilini.

Katika utafiti huu, utahitajika kutueleza maswala kadha wa kadha kukuhusu. Kwa mfano, miaka, jinsia, kiwango ulichokifikia cha masomo, kazi unayoifanya kujikumu maisha na kadhalika. Utahitajika pia kupimwa urefu,uzito,mduara wa nyonga,mduara wa kiuno,shinikizo la damu,joto na mapigo ya moyo.utahitajika pia kutolewa damu itakayopelekwa mahabara kwa utafiti tofauti,ikiwemo,wasifu wa lipid, HbA1C na kretini ya serum.Pia utahitajika kutoa sampuli ya mkojo itakayofanyiwa utafiti wa dipstick,kretini na albumin.Kisha utafanyiwa picha mbili za moyo,ECHO na ECG

Utafiti huu hauna madhara kuu kwako mbali na uchungu utakaosikia unapotolewa damu ama uvimbe mdogo mahala utakapotolewa damu. Hata hivyo, uvimbe huu hautakawia kwa muda mrefu.

Una huru wa kukubali ama kukataa kuwa katika utafiti huu. Unaweza pia kujiondoa wakati wowote unapohisi. Kukataa kwako ama kujiondoa katika utafiti huu hautadhuru jinsi utakavyohudumia katika hospitali hii sasa wala siku za usoni.

Unajulishwa kwamba kushiriki kwako katika utafiti huu ni kwa hiari yako na sio kwa kulazimishwa na unaweza jiondoa katika utafiti huu wakati wowote. Habari zote tutakazopata kuhusiana nawe na afya yako italindwa na uaminifu wote

Mimi_____baada ya kufafanuliwa na kuelezwa na_____ kiini cha utafiti huu na jinsi utakavyotekelezwa nimekubali kushiriki katika utafiti huu bila kushurutishwa.Nakubali kuyajibu maswali yote kwa uaminifu na pia kutolewa damu itakayopelekwa kwenye mahabara kwa uchunguzi.

Sahihi (mshiriki)_____

Tarehe _____

Iwapo uhatihatiji maelezo zaidi, usikose kuwasiliana na IREC ukitumia anwani ifuatayo

Mwenyekiti wa IREC

Moi Teaching and Referral Hospital,

Sanduku la Posta 3,

Eldoret.

Simu: 33471/2/3

Unaweza pia wasiliana nami (Dr. Stella Murugi Gichovi) ukitumia nambari ya simu ifuatayo: **0727865202**

Appendix 4: Procedure for Measuring Blood Pressure

Blood pressure will be taken using an Omron M2 compact upper arm blood pressure monitor

The patient should be in a quiet place, in a relaxed sitting position with no tight fitting clothing on the upper arm, or any thick clothing such as a sweater.

The patient sits upright with the back straight and places the arm on the table so that the cuff is on the same level as the heart. The cuff is wrapped on the right arm such that the bottom of the cuff is at least 1cm above the elbow. It is then fastened snugly. The start button on the machine is then pressed and automatically the cuff begins to inflate and the machine takes a reading. The blood pressure results as well as a heart rate reading are then displayed on the screen.

Should an error occur, the cuff is deflated and the process is repeated. High blood pressure readings are confirmed manually using a mercury sphygmomanometer.

Appendix 5: Procedure for Drawing Blood

The procedure is explained to the patient and verbal consent sought.

Universal precautions will be observed.

A tourniquet is applied at a distal site about 5cm proximal to the selected site of venipuncture. The patient makes a fist without pumping the hand. The phlebotomist puts on a pair of clean gloves. The selected site is cleaned thoroughly with methylated spirit or providence Iodine starting with the center and working outward. It is then allowed to dry.

The patient's arm is grasped firmly using the thumb to keep the skin taut and to anchor the vein. Blood will be drawn and transferred to a blood collection bottle.

An alcohol impregnated swab is then applied under pressure at the site of blood collection. Pressure is applied for a whole minute then the site is reassessed for continued bleeding. The area is dressed with a dry gauze and tape.

Appendix 6: The ECG Procedure

1. Explain the procedure to the participant and obtain verbal consent
2. The participant will be asked to remove any objects that may interfere with the procedure.
3. The participant will be asked to remove clothing from the waist up while ensuring the privacy of the subject by covering with a gown and exposing only the necessary areas.
4. The participant will lie flat on the procedure bed and will be asked to remain still throught the period of the procedure to avoid interference with the tracing.
5. Electrodes will be attached to the subject's chest, arms, and legs.
6. The lead wires will be attached to the skin electrodes.
7. Once the leads are attached, identification information about the subject will be keyed into the machine's computer.
8. The E.C.G. tracing will then be started.
9. Once the tracing is completed, the technician will disconnect the leads and remove the skin electrodes.
10. The ECG findings will be interpreted by the P.I. and confirmed by a study dedicated cardiologist.

Appendix 7: ECG parameters to be recorded and analyzed

Key aspects in the interpretation of the 12-lead ECG will include the heart rate, the heart rhythm (both atrial and ventricular), the electrical axis (both the P-wave axis and the QRS axis), the intervals,the relationship of P waves to QRS complexes and analysis of the QRS morphology and ST and T-wave segments.

ECG paper commonly moves at 25 mm/second; thus, each small box (1 mm) is equivalent to 0.04 seconds (40 milliseconds), and each large box (5 mm) is equivalent to 0.2 seconds (200 milliseconds). Normal ECG values for waves and intervals are as follows:RR interval: 0.6-1.2 seconds ,P wave: 80 milliseconds ,PR interval: 120-200 milliseconds ,PR segment: 50-120 milliseconds ,QRS complex: 80-100 milliseconds ,ST segment: 80-120 milliseconds ,T wave: 160 milliseconds ,QT interval: 420 milliseconds or less if heart rate is 60 beats per minute (bpm)

ECG PARAMETER	**PATIENT'S ECG FINDING**	**Abnormality if any**
Heart rate		
Heart rhythm	Normal or Abnormal	
Electrical axis P wave axis QRS axis		
PR interval		
PR segment		
QRS complex		
ST segment		
T wave		
QTc interval		
Left bundle branch block	Y/N	
Right bundle branch block	Y/N	
RVH	Y/N	
LVH	Y/N	

Appendix 8: 2D Doppler Echocardiography technique

1. Doppler Echocardiography

Method; -Explain the procedure to the participant ,obtain verbal consent, Exposure of the upper body and cover with gown, Position the patient in the left lateral position, Apply gel on the probe

The positioning of the probe in appropriate windows:

I. Long parasternal axis

II. Short Axis LV/AOV- R.V. Outflow tract

III. Apical four chambers view

IV. Apical two chambers view

V. Apical five-chamber view

VI. Subcostal- IVC

A qualified technician will record the echocardiography images and the interpretation/review done by the cardiologist and PI

Echocardiography Findings:

Part A.

1. ECHO Number:..... DATE……

2. Previous ECHO

Report:.....

.....

.....

3. Brief clinical

history.....

.....

Part B.

Situs:

Venous Return:

Great Arteries:

Valves:

Chambers:

Septa:

Pericardium:

LV Systolic Function:

Wall

Motion:.....

E.F. %..... (calculation using simplified Simpson's biplane method)

.....

LV Diastolic Function Grade:

PART C.

M-Mode Measurements:

A.O	**L.V.I.D.D.**	**I.V.S.D.**	**R.V**	**E.F%**
L.A	**L.V.ID.S.**	**L.V.P.W.D**	**F.S%**	
H.R.:	**S.V.:**	**E.S.V:**	**E.D.V.:**	

Conclusion:

Additional Comments:

ECHO Reported by:..... Date:.....

Appendix 9: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2021/83
Approval Number: 0003933
27th July, 2021

Dr. Stella Murugi Gichovi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Murugi,

PREVALENCE AND CORRELATES OF CARDIOVASCULAR ABNORMALITIES AMONG NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

This is to inform you that ***MTRH/MU-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN: 0003933.*** The approval period is **27th July, *2021- 26th July, 2022.***
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MTRH/MU-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MTRH/MU-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MTRH/MU-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from ***MOH at the recommendation of NACOSTI*** for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MTRH/ MU-IREC.***

Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
27 JUL 2021
APPROVED
P. O. Box 4606-30100 ELDORET

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 10: Hospital Approval (MTRH)

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

28th July, 2021

Dr. Stella Murugi Gichovi
Moi University
School of Medicine
P.O. Box 4606-30100
ELDORET-KENYA

PREVALENCE AND CORRELATES OF CARDIOVASCULAR ABNORMALITIES AMONG NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

You have been authorised to conduct research within the jurisdiction of Moi Teaching and Referral Hospital (MTRH) and its satellites sites. You are required to strictly adhere to the regulations stated below in order to safeguard the safety and well-being of staff, patients and study participants seen at MTRH.

1. The study shall be under Moi Teaching and Referral Hospital regulation.
2. A copy of MTRH/MU-IREC approval shall be a prerequisite to conducting the study.
3. Studies intending to export human bio-specimens must provide a permit from MOH at the recommendation of NACOSTI for each shipment.
4. No data collection will be allowed without an approved consent form(s) to participants unless waiver of written consent has been granted by MTRH/MU-IREC.
5. Take note that **data** collected must be treated with due confidentiality and anonymity.

The continued permission to conduct research shall only be sustained subject to fulfilling all the requirements stated above.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
28 JUL 2021
SIGN.....
P. O. Box 3-30100, ELDORET

28/07/2021
DR. WILSON K. ARUASA, *EBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

c.c. - Senior Director, Clinical Services
- Director of Nursing Services
- HOD, HRISM