Risk Factors and Complications Associated with Diabetes Mellitus in Patients with Heart Failure: A Case-Control Study.

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DECLARATION

I, Caroline Cherotich Mutai, declare that this proposal is my original work and has not been presented for any degree award in any other institution or university

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DEDICATION

This dissertation is dedicated to:

1. God Almighty for His mercies and grace throughout my master period
2. My parents, for your support, prayers and sacrifices you gave during this time
3. My siblings, for the constant encouragement, love, prayer and support
4. Dr. Ombui Davis, for the love, encouragement, support and constant reminder that I can do this.

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I am grateful to my family and friends for being there during this period. Your prayers and constant support are highly appreciated. This work is a reminder that I am blessed with a support team that I would always go back to for help.

LIST OF ABBREVIATIONS

AHA : American Heart Association

ACC : American College of Cardiology

ACE : Angiotensin converting enzyme

AF : Atrial fibrillation

AKUH : Aga Khan University Hospital

ARBS : Angiotensin II Receptor Antagonist

ATLAS : Assessment of Treatment with Lisinopril and Survival in heart failure

BPM : Beats Per Minute

CA : Coronary Angiogram

CAD : Coronary artery disease

CCB : Calcium channel blockers

CHD : Coronary heart disease

CHF : Congestive Heart Failure

CKD : Chronic kidney disease

CT : Computed Tomography

COPD : Congestive obstructive pulmonary disease

CVD : Cardiovascular disease

DBP : Diastolic blood pressure

DCM : Dilated cardiomyopathy

DM : Diabetes mellitus

EDMS : Electronic Data Management System

HBA1c : Glycosylated Hemoglobin

HCM : Hypertrophic cardiomyopathy

HF : Heart failure

HFmrEF : Heart Failure with mid-range Ejection Fraction

HFpEF : Heart Failure with preserved Ejection Fraction

HFrEF : Heart Failure with reduced Ejection Fraction

KNH/UoN ERC: Kenya National Hospital/University of Nairobi Ethics and Research Committee

NYHA : New York Heart Association

LMICs : Low- and middle-income countries

SD : Standard deviation

OR : Odds Ratio

RAAS : Renin-angiotensin Aldosterone System

SBP : Systolic blood pressure

WHO : World Health Organization

DEFINITION OF OPERATIONAL TERMS

Heart Failure

Heart failure based on the standardized diagnostic criteria, according to the American Heart Association/American College of Cardiology and the European College of Cardiology guidelines, is defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood". The guidelines underscore that it is largely a clinical diagnosis that is based on a careful history and physical examination.

Heart failure with reduced ejection fraction (HFrEF) is defined as the inability of the left side of the heart to contract effectively and therefore less oxygen-rich blood is pumped out of the body. It is sometimes referred to as systolic heart failure.

Diabetes Mellitus

Diabetes mellitus according to the Kenyan National Clinical guidelines for the management of diabetes, has been defined as a chronic metabolic disorder that is characterized by sustained elevated blood glucose (hyperglycemia) resulting from defects in insulin secretion, action or both. Diabetes mellitus was determined by blood tests using the fasting blood glucose and a glycosylated hemoglobin A1c (HbA1c) more than or equal to 6.5 mmol/l.

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ABSTRACT

Introduction

Globally, heart failure (HF) is among the leading causes of morbidity and mortality within the spectrum of adults with cardiovascular diseases. Its prevalence has been said to sharply increase in the western population, 10% of 75-year-old and above have HF, which is an increase from 1% in 40-year-old. It is responsible for about 30% of all hospital admission in Sub-Saharan Africa and 7% in general areas. Heart failure (HF) patients have a higher probability of having pre-existing co-morbidities or developing concomitant diseases such as diabetes mellitus (DM), predominantly type 2 diabetes. These patients face a substantial risk of in-hospital mortality and re-hospitalization. DM, majorly type 2 diabetes, affects nearly 390 million people worldwide, which is expected to increase. Majority of the patients suffering from HF have DM. This close relationship to some extent is because of commonality of some of the risk factors for HF, such as hypertension, obesity, sleep apnea, advanced age, and dyslipidemia, are also found in patients with DM. Research done on this topic was done nearly 20 years ago and therefore there is paucity of data.

Objective: To determine the risk factors and complications associated with DM in HF patients

Methodology: This was a case control study based in Nairobi County, at the Heart Clinic and Diabetes clinic in Aga Khan University Hospital Nairobi (AKUHN). All patients with HF with an EF of ≤ 40% and DM (a fasting blood glucose of >7.5mmol/l and HbA1c of >6.5 mmol/l) were included in the study. Data collection was undertaken after approval from the Kenyatta National Hospital/UoN-Ethics and Research Committee (KNH/UoN-ERC) and NACOSTI. Recruitment of participants into the study was done using a systemic random sampling with the first participant chosen randomly. Once a case was chosen, a control within five years the age of the case was chosen. The controls are age-matched individuals with HFrEF without DM. Collection of data was done using a structured questionnaire and secondary data was collected from both electronic and medical records. Questions were checked for completeness and were entered into MS excel ready for analysis. Data was then analyzed using R and R-studio.

Associations were assessed using the odds ratio (OR) and statistically significant findings were considered significant at a p-value of <0.05.

Results: A total of 377 participants were recruited into the study, 143 cases and 234 controls. In social demographic findings, the mean age for the entire population with HF was 59.1 years with an SD of 11.17. The median age was 61 years. In the whole population, there were 29.4% and 30.3% of women in the case and control groups respectively. Among the cases and control group, men and women comprised 70.6% and 69.7%, respectively. In univariable analysis, there was no statistically significant association between sex and ethnicity with DM (P-0.842 and P-0.567) respectively. Obesity was determined by BMI and was categorized into underweight, normal weight, overweight and obese. Being underweight had a positive non-statistically significant association with DM (p-value = 0.152). Level of Education, hypertension, Heart attack, CAD, Holter, myocardial perfusion tests, ischemic cardiomyopathy, non-ischaemic cardiomyopathy, anaemia and peripartum cardiomyopathy were associated with the onset of DM among HF patients with a p value of less than 0.20 (P-0.20). In multivariable analysis, those who were hypertensive had approximately three times the odds of developing DM among HF patients at an adjusted odds ratio of (aOR – 2.78 95% CI: 1.73-4.46). Heart attack and CAD were not statistically significantly associated with DM (aOR-1.22, 95% CI: 0.65-2.28) and (aOR-1.17 95% CI: 0.66-2.08) respectively. Those who had ischemic cardiomyopathy were not likely to develop DM (aOR-1.13, 95% CI: 0.71-1.81) while peripartum cardiomyopathy and atrial fibrillation showed a statistically significant association with DM (aOR-0.12, 95% CI: 0.01-0.99) (aOR- 0.08 95% CI: 0.01-0.68) respectively.

Conclusion: DM patients are twice as likely to develop microvascular and macrovascular complications compared to non-DM patients. Hypertension, Atrial Fibrillation, Peripartum cardiomyopathy were identified as some of the complications of DM in HF Patients. Therefore, DM patients should undergo regular screening for these complications and early interventions be carried out.

Recommendation: Further investigation to be carried out with a larger population in order to determine the strength of association of the risk factors and complications of DM in HF patients.

CHAPTER ONE

INTRODUCTION

Heart failure (HF), is a global public health problem that affects about 26 million people and its prevalence is steadily increasing has been seen to increase. Its burden has been felt most in terms of mortality rates, the expenses that come with treatment methods and its associated negative impact on the quality of life of those suffering from HF (1) has been described as a "cardiac disorder that impairs the ability of the ventricle to fill or eject blood. This disorder can be structural or functional." which is further aggravated by insufficient cardiac output to fulfill the body's metabolic needs. This definition is stated by the American Heart Association guidelines (AHA)/ American college of Cardiology (ACC) guidelines (2) HF is further classified according to its functional capacity based on its ejection fraction, diastolic function, and the natriuretic peptide level. HF has been classified into three subtypes: HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF) and HF with mid-range ejection fraction (HFmrEF) (3). In this study, we will concentrate on patients with HFrEF with ejection fractions of less than 40%.

Background of the study

Diabetes mellitus (DM) is commonly found in patients who have HF, especially those who have a preserved ejection fraction. The Kenyan National Clinical Guidelines for the Management of Diabetes, has defined DM as a metabolic disorder that has been defined to be chronic and is characterized by high blood glucose (hyperglycemia) due to lack in insulin secretion, action or both (4). DM has been broken down to two types, type 1 and type 2.

Patients who have both conditions, HF and DM, have a greater death rate compared to those who only have one of the two conditions (5). Furthermore, the prevalence of DM is increasing globally. According to an article by Danaei et al. who conducted a worldwide study in 199 countries addressing trends of DM at a national, regional and global level revealing, an increase in the age standardized prevalence of DM among adult men from 8.3% in 1980 to 9.8% (95%

confidence interval [CI], 8.8-11.2) , while the age standardized prevalence in women was 9.2% (95% CI 8.0-10.5) in 2008 up from 7.5% (95% CI, 5.8-9.6) in 1980 (6).

In a recent report by International Diabetes Federation (IDF) of 2017(7) , it was estimated that 425 million adults (20-79 years) whole world had DM and if this shift continues, by 2045, 629 million people will have DM. DM, mainly type 2 affects 390 million people worldwide which is expected to rise to 600 million by 2030 (8). Urbanization, population increase, the rise in obesity and lack of physical exercise are some of the contributing factors (9).

In Africa, approximately 41 million people will have DM by 2045 which is an increase from 16 million in 2017. Low and middle-income countries (LMICs) account for 80% of all DM cases (10). The frequency of DM in both rural and urban areas in Kenya is 3.5% to 5% as reported by population-based studies, with a higher proportion among those in urban settings(11,12).

HF is a potentially fatal disease and has been considered as a global health problem. HF, in the western population, affects over two percent of its population and is expected to increase in its prevalence from one percent in 40-year-old individuals to 10% in 75-year-old and above(13). Its projected prevalence is more worrisome as it was estimated to increase to 46% in people 18 years and above from 2012 to 2030 resulting to more than eight million HF individuals in the United States (14,15). The prevalence of HF among 25-49-year-old was reported to be 1.36%, 50-59-year-old to be 2.93% 60-69-year-old to be 7.63%, 70-79-year-old to be 12.67% and 16.14% in patients above the age of 80 in the late 1990 in Portugal. This was reported by the Epidemiology of HF learning (EPICA) (16). The estimated prevalence of HF in the Middle East more specifically Oman, has been estimated to be 5.17 per 1,000 individuals (17).

HF has been known to be more prevalent in the old and its incidence in people over the age of 60 years is increasing; increasing morbidity, hospital admission and death rate of these individuals. In the United States, the annual occurrence of HF among individuals above the age of 65 years has been estimated to be 10 cases per 1,000 individuals, which is expected to double every decade thereafter. This age group represents a prevalence of 75% of HF cases. In a population of individuals who are less than 50 years of age, HF is more common in black patients than in white patients with an incidence rate of 20 times more in black than in white (3,18). The reduction in

occurrence of HF in adults can be achieved by addressing some of the important factors at an early age such as obesity, hypertension, and systolic dysfunction (19).

DM and HF commonly coexist in a patient, this is due to the fact that most of the risk factors for HF overlap in DM patients, such as chronic kidney disease, sleep apnoea, anaemia, obesity, hypertension (HTN), advanced age, dyslipidemia, and coronary heart disease (20) The presence of both has markedly increased the morbidity and mortality of HF patients. Cardiovascular disease accounts for two-thirds of lives lost among diabetic patients. Ischaemic heart disease accounts for nearly 40%, other types of heart diseases account for 15% such as congestive heart failure (CHF), and 10% are from stroke (21).

The management of blood sugar levels may influence the occurrence of HF in patients who are diagnosed with type 2 DM. This is because they have an increased chance of developing HF irrespective of the existence of coronary artery disease (CAD) and HTN (22,23).

HF development in DM patients is attributed to many factors but is largely due to: extracellular fluid volume expansion, CAD, HTN and diabetic cardiomyopathy (22).

The existence of DM in HF patients with preserved ejection fraction has increased their risk for hospitalization, morbidity, and mortality especially if the microvascular problems of diabetes are present. DM is usually present in 35-45% of chronic HF patients (24,25)

A systematic review done in Sub Saharan Africa of HF and diabetes revealed that HF is responsible for about 30% of hospital admissions in a specialized cardiovascular unit and 3-7% in general medicine (26,27) . Data on the prevalence of DM in HF patients in Kenya was done nearly 20 years ago in Kenyatta National Hospital (KNH) among 13-year-old patients admitted with clinical diagnosis of CHF. Ninety-one patients were studied (44 males and 47 females). Results revealed that 3.3% of all medical admission in KNH constituted CHF (26).

This study, therefore, will seek to determine the risk factors and complications associated with DM in HF patients. It will also determine the association between obesity, alcohol use and cigarette smoking with DM and determine the cardiovascular complication associated with DM. The study will assess the types of cardiomyopathies associated with DM. There are very few

studies done in Kenya, creating a huge knowledge gap in the subject matter. The study will therefore contribute to knowledge on DM and HF.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This chapter puts forward the risk factors associated with HF and DM. These include coronary hypertension and cardiomyopathy. The chapter also looks at coronary artery disease, obesity, and renin angiotensin receptor blocker system.

2.2 Diabetes, Coronary Heart Disease and Heart Failure

The appearance, severity and advancement of coronary heart disease (CHD) are negatively overelaborated by type 2 diabetes. The chances of cardiovascular disease (CVD) in individuals who have diabetes is higher than in those who do not have diabetes (27). Patients with diabetes have a lot of problems due to CVD. Adults who have diabetes and suffer from CHD account for nearly one third to a half; this is entirely dependent on the setting and method of diagnosis. The prevalence of cardiac disease based on the ECG and echocardiogram has been estimated to be one to two times more in diabetic patients and most of the cardiac events in diabetic patients are usually silent. Type 2 diabetes patients who suffer CHD events per year are approximately 1-3%; a rate that is double that in non-diabetic individuals. In the springtime of life, such events occur in diabetic individuals than in non-diabetic individuals (28)

Generally, the cause of most of mortality in patients with type 2 diabetes is CHD (29). The frequency of HF, angina pectoris, sudden cardiac death and re-infarction disability among diabetic patients is at least double that which has been observed in those patients who do not have diabetes.

2.3 Cardiomyopathy

Cardiomyopathy, according to the American Heart Association (AHA), has been described as a disease of the heart muscles that restricts the heart from pumping blood to the rest of the body (30). The World Health Organization (WHO) defined cardiomyopathy as the “heart muscle

diseases of unperceived causes" to differentiate between cardiomyopathy and cardiac dysfunction. This difference can be due to known cardiovascular issues like hypertension, ischaemic heart disease, or valvular disease. However, in clinical practice, the term "cardiomyopathy" has also been correlated to diseases that have a cardiovascular cause (eg, "ischaemic cardiomyopathy" and "hypertensive cardiomyopathy". Later in 1995, WHO in conjunction with the International Society and Federation of Cardiology (ISFC) task force considered the aetiology of the heart muscle as an addition to the definition of cardiomyopathy. Therefore, cardiomyopathies were defined as "diseases of the myocardium associated with cardiac dysfunction." They different types of cardiomyopathies were categorized according to anatomy and physiology of which each has many different causes (31).

1. Cardiomyopathies that are associated with HF; include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, and unclassified cardiomyopathy.
2. The unclassified cardiomyopathy has been divided further to left ventricular non-compaction and takotsubo cardiomyopathy.

2.31.Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a serious factor in patients with diabetes and has been described as ventricular dysfunction that occurs independent of vascular or valvular pathology (32). Diabetes has been linked to changes in the heart anatomy and purpose, including unreasonable left ventricular hypertrophy (LVH), perivascular and interstitial fibrosis resulting in thickness of the heart, systolic and diastolic dysfunction and a greater risk of HF (33) The changes are known as cardiac small artery disease as they have more in common with vascular changes in other microvascular systems including the retina, the vaso nervorum, and the kidney than they do with other forms of cardiomyopathy (34). Some of the common factors that are involved in the small artery impairment that are related with diabetic cardiomyopathy including hyperglycemia, dyslipidemia, altered energy metabolism, dysregulated insulin signaling, inflammation, endoplasmic ventricular stress, mitochondrial dysfunction, oxidative stress and accumulation of advanced glycation end products (AGE's) and activation of the renin-angiotensin-aldosterone

system (RAAS). Direct effects are, however, seen in cardiac myocytes together with abnormal calcium resulting to defective myocardial relaxation.

2.3.2 Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) occurs when the ventricles enlarge and weaken. This condition starts in the left ventricle and after a while can affect the right ventricle. The weakened chambers of the heart usually do not pump blood effectively causing the heart to work harder over time. This type of cardiomyopathy can result in HF, valve disease, arrhythmia and a thrombus in the heart leading to heart attack. The aetiology of DCM has been divided into two groups, genetic and non-genetic. Those people who have genetic DCM are at high risk of complications such as the progression of systolic impairment (34). DCM has a close link to peripartum cardiomyopathy as some of the truncating variants in the genes were similar in those patients who presented with DCM. Peripartum cardiomyopathy is a type of cardiomyopathy that has an effect on women late in pregnancy or during the post-partum period. The incidence of peripartum cardiomyopathy varies from 1 in 100 to 1 in 300 depending on the geographic area (35).

2.4 Glycemic Control, Diabetes and Heart Failure

Type 2 diabetes in itself is a vital risk factor for HF independent of hypertension and CVD suggesting that glycemic control may influence the development of HF in diabetic patients. There has been strong epidemiologic evidence showing a strong association between poor glycemic control and the development of HF. Blood glucose control is primarily evaluated with the glycated haemoglobin (A1C) test (HbA1c), a count that was assessed in clinical trials to reveal benefits of improved glucose control (36). In a longitudinal study of type 1 diabetes in patients from a Swedish National Diabetes study, the risk of mortality from HF after adjusting for co-morbidities, other cardiovascular risk factors, age, duration of diabetes and sex, increased incrementally with higher updated mean glycated hemoglobin level (36). There is a non-linear relationship connecting mortality and HbA1c in diabetic patients and HF, with the decreased probability of death in patients with a small degree of weakened sugar control (HbA1c 7.0-7.8%) and a greater chance of mortality with elevated or lower HbA1c levels (37). Clinical trials that

have tested the outcome of glucose lowering have not had any impact on an individual developing HF and cardiovascular events (37)

The best treatment plan in DM and HF patients remains contentious. Metformin has been linked to a greater risk of lactic acidosis in HF and it is usually recommended that it be discontinued in HF patients. In a recent study, where metformin was combined with DPP-4i which is a second line glycemic control drug, it was seen to lower the risk of developing HF in diabetic patients in comparison to SU irrespective of the history of CVD of a patient (38). The DPP-4 inhibitors with saxagliptin have not been seen to increase or decrease the rate of ischemic events, but there has been an increased chance of hospitalization of patients with diabetes due to HF. Saxagliptin is known to enhance glucose control but other measures are necessary to lower the chances of cardiovascular events in diabetes patients (39). Adding sitagliptin to patients with type 2 diabetes and confirmed cardiovascular diseases, it did not appear to enhance the risk of adverse cardiovascular episodes or admission for HF and other adverse events (40).

The inhibitors of the type 2 sodium-glucose co-transporter (SGLT2) is also of heed in the obviation and control of HF, as its use seem to lower the risk of occurrence of HF events whether HF is present or not and other known or unknown comorbidities. A reduction in incident rate HF mortality was reported in a study between Empagliflozin and cardiovascular outcomes among type 2 diabetes patient (41).

2.5 Diabetes, Hypertension and Heart Failure

Hypertension is a recurrent comorbidity in patients with type 2 diabetes. Its prevalence is exorbitant in patients with diabetes than those without diabetes. The concurrence of hypertension and diabetes in individuals increases the incidence of CVD, mortality and incident HF (42). Hypertension has been viewed as the essential risk factor for HF and the steady medical care of hypertension in the community has reduced the occurrence of HF by roughly half (43,44). Although there is strong evidence that exists in the general population, little is known about the effects of lowering blood pressure and the new onset of HF events in patients who are diabetic (45).

Lower risk of HF has been associated with the use of diuretic based hypertensive therapy or RAAS blockers. Calcium channel agents or α1-blockade which remarkably reduces blood pressure have slightly magnified the risk of HF when compared with all other types of antihypertensive treatments (45,46) Lowering blood pressure in diabetic patients should be a priority (37).

DM and HF are managed using different classes of drugs to control blood sugar and HF symptoms. HF patients are not only treated for HF but they are also treated for hypertension and other cardiac conditions such as coronary artery disease. HF is managed by certain drug classes such as; diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers and sacubitril/valsartan (43). All these medications have an impact in the control of HF on the other hand; DM is managed using insulin, sulfonylureas, DPP4c inhibitors, meglitinides, SGLT2 inhibitors, GLP-1 receptor agonists, metformin and thiazolidinediones (4).

A number of studies on the different medications prescribed for the control of DM have reported that, the use of insulin and glitazone strengthens the risk of HF (47). These findings were also seen in the Framingham Heart Study where an increased risk of CHF was felt and was linked to the use of insulin among diabetic patients compared to those who were treated with diet or orally administered drugs (24). However, clinical trials such as EPHESUS-HF Trial and EMPHASIS-HF Trial has linked a higher prevalence of DM among patients with reduced ejection fractions who use eplerenone, a mineralocorticoid receptor antagonist, for the management of HF (48).

2.6 Heart Failure, Diabetes and the Renin Angiotensin Aldosterone System

ACE inhibitors are successful in lowering the probability of mortality and hospitalization of chronic HF patients and decreases the ejection fraction. The angiotensin receptor blockers (ARBs) were tested first and were linked to a smaller possibility of hospitalization in patients with chronic HF, in combination with candesartan, the risk was lower among patients who couldn’t take ACE inhibitors (49). In addition, ACE inhibitors contributes to the alteration of cardiac hypertrophy and with remarkably greater efficacy compared to a beta-blocker in patients

with hypertension and it reduces pulmonary congestion by a balanced reduction in cardiac preload and afterload in congestive heart failure (CHF) patients. It has also been shown to reduce endothelial dysfunction in HF patients and also in coronary artery disease (CAD) and type 2 diabetic patients (50).

RAAS blockade have been widely used as a treatment strategy for hypertension in patients with type 2 diabetes and has been seen to have a vascular -protective effect more than lowering blood pressure. In the RENAAL and LIFE studies, among DM patients, the use of losartan had a significant reduction in the occurrence of hospitalization for HF among diabetes patients with no prior history of HF who were at a high risk of renal and cardiovascular events (51). Additionally, in the ADVANCE trial, the reduction of mortality and any cardiovascular events were greatly reduced especially with the use of perindopril in combination with indapamide, which also automatically reduced HF events in type 2 diabetes patients (52).

2.7 Obesity, diabetes and heart failure

A high body mass is instrumental in the development of diabetes and HF (53). The higher the body mass the higher the risk for the development of HF and diabetes and the worse the clinical outcomes.

The comorbidities for DM and obesity along other comorbidities such as hypertension, dyslipidemia, and metabolic syndrome are common among HF patients and affect its clinical outcome. Although these clinical comorbidities are linked with the occurrence of incident HF, in the wider population, their contributory role in patients with already confirmed HF is not predictable and management of these patients is challenging (44).

The recent AHA and ACC guidelines for the management of overweight and obesity in adults stated the significance of treatment and curbing overweight and obesity on the likelihood for development of CVD and type 2 DM. It also gave guidelines on the CVD morbidity and mortality but did not give certain particular comments on prevention of HF or treatment of obesity among HF patients (2). A report from the recent Eight Joint National committee

addressing the management of hypertension did not also give definite guidelines for the management of the same comorbidities in HF patients (54).

In the management of DM, weight loss has been recommended for obese patients with type 2 diabetes which, in turn, lowers the risk for cardiovascular outcomes leading to improved glycemic control, quality of life and other obesity- related co-existing illnesses. One of the ways of weight loss management is through bariatric surgery where, according to a study done on the Swedish Obese Subjects (SOS) who had undergone this type of surgery and were followed up for a mean duration of 13.3 years, a reduction in the insulin level was seen (55).

It is, therefore, recommended that patients with DM who are obese adopt measures to reduce weight together with regular physical exercise, diet and lifestyle modification. However, these measures have not been proven to reduce new diagnosis of HF or improve its end result in the event it should manifest in patients. The improvement in weight and increase in physical activity in diabetic patients was not linked with a decrease in HF and this was evident in the LOOK-AHEAD study (RRR 0.80, 95% CI, 0.61- 1.04, p=0.10) (56).

2.8 Chronic Kidney Disease, Heart Failure and Diabetes

Chronic kidney disease (CKD) patients have a higher rate of developing detrimental health outcomes such as HF, which has been widely known as a cardio-renal syndrome. Besides, it is commonly found in patients who have diabetes and just about half of those patients have diabetes, type 2. CKD is usually described by a reduction in the glomerular filtration rate (eGFR) to less than 60 ml/min/1.73m^2, an elevation in the albumin creatinine ratio or urinary albumin excretion.

Type 2 diabetes should be taken seriously due to its renal complications such as diabetic nephropathy; damage that results from diabetes, and which can consequently lead to kidney failure (57). According to a report on the US renal data system, there has been an increased incidence in the number of renal dysfunctions among type 2 diabetes patients (58).

2.9 Diabetes, Heart Failure and Anaemia

Anaemia is closely related to diabetes (59) due to the high occurrence of CKD in diabetes patients, causing a functional erythropoietin deficiency (60). Most diabetic patients have anaemia compared to renal disease patients. Patients with diabetes with stage III CKD had anaemia translating to 30%. This rate is double that of patients without diabetes as reported in the Kidney Early Evaluation Program (KEEP) (61). Diabetes people in the general population had a two times chance of having anaemia in comparison to those without diabetes but with an equivalent magnitude of renal impairment. This was observed in the third National Health Nutrition Examination Survey (NHANES-III) (62).Diabetic patients develop anaemia earlier in their life and that is more severe in diabetic patients compared to patients with renal impairment from other causes (63).

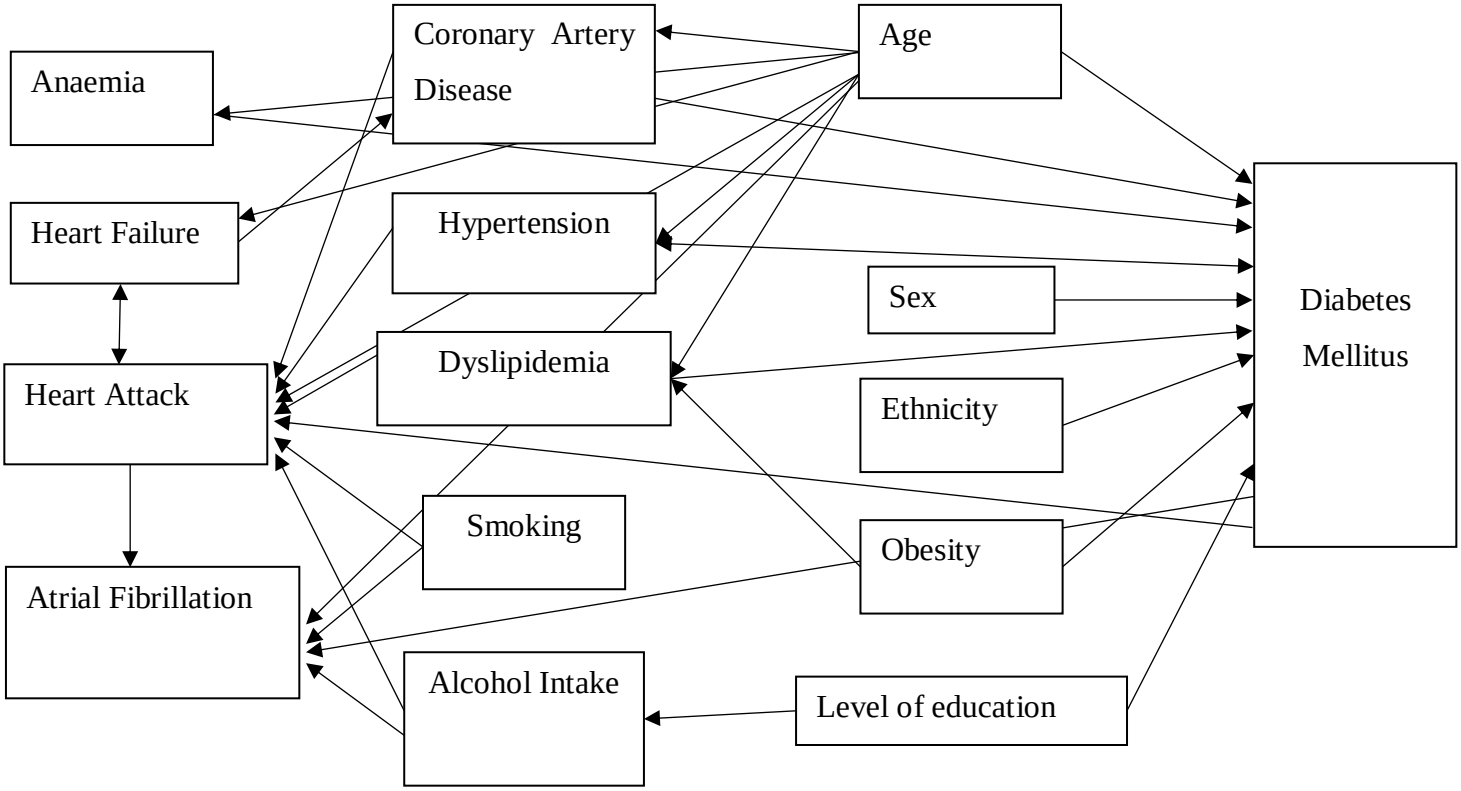
2.10 Association between Alcohol use, heart failure and diabetes

The association between DM and alcohol consumption has been viewed as having a U-shaped relationship. Studies done have revealed 30% risk reduction in incident DM among patients who have moderate consumption of alcohol and no risk reduction in heavy alcohol consumers (64). This relationship was evident among Swedish Population and US. Alcohol consumption and its association in DM is based on the type of alcoholic beverage being consumed.

2.11 Association between cigarette smoking, heart failure and diabetes

Cigarette smoking is one of the modifiable risk factors associated with DM and HF. There is an inverse relationship between smoking and DM. Epidemiological data in the western population has documented a relationship between smoking and the risk of DM (65). The number of packs smoked in a day increases the risk of developing DM as has been revealed in a cohort study conducted in China (66).

2.12 Conceptual Framework



The conceptual framework gives a summary of some of the risk factors and outcomes of DM. The independent variables are factors that lead to the occurrence of DM if not well controlled. The intermediary variables including HF are some of the outcomes of uncontrolled DM for a long period of time. Some factors such as dyslipidemia can lead to the development of DM if not well controlled. The arrow that face towards DM explain some of the risk factors that eventually lead to DM.

2.13 Statement of the Problem

HF has become a global public health concern affecting approximately 26 million people worldwide with its prevalence increasing. Its burden is felt in morbidity, mortality, the economic distress that comes with the treatment methods and even the quality of life of those who suffer from HF. Patients who have HF have a higher likelihood of hospitalization and re-

hospitalization. HF mainly affects individuals of advanced age. In the western population, about 2% of its population have been affected by HF with a sharp increase of its prevalence from 1% in 40-year-old individuals to 10% above the age of 75 (44).

HF and DM can co-exist in a patient and this is said to increase the mortality of patients with most of them having sudden deaths. All the common risk factors for HF, such as hypertension, coronary artery disease, obesity, advanced age and sleep apnea also cluster in patients who have DM. There is a knowledge gap about the risk factors and complications of DM in HF patients especially in Kenya. In addition, the process that underlies the connection between HF and DM is not well understood.

2.14 Justification

HF for many years has been a major public health concern with its prevalence at 46% in the United States (Savarese & Lund, 2017). In Sweden, the annual age adjusted prevalence increased from 1.61% to 1.72% and from 2.15% to 2.18% respectively, from 2010 to 2014 (67). HF affects women and men from diverse cultures and has been known to be a complication in diabetes patients leading to high morbidity and mortality. Patients who have DM have been known to have sudden deaths. Epidemiologic studies, such as longitudinal and randomized control studies, have linked the relationship between cardiovascular mortality with type 2 DM (68,69). Population-based studies done among diabetes patients have closely linked risk factors in DM patients with those in HF patients (70).

Few studies have been done in Kenya and Africa. The last study on the prevalence of diabetes in HF patients in Kenya was done 20 years ago. Therefore, there is need to investigate this issue further to add to the existing knowledge. to increase the prevention of complications and better prognosis for patients with HF and DM.

2.15 Research Question

What are the risk factors and complications associated with DM in HF patients?

2.16 Null Hypothesis

There is no difference in risk factors and cardiovascular complications between patients with and those without DM among HF patients.

2.17 Alternative hypothesis

There is a difference in risk factors and complications between patients with and those without DM among HF patients.

2.18 Objectives of the study

Broad Objective

To determine the risk factors and complications associated with DM in HF patients.

Specific Objectives

Among HF patients:

1. To determine the association between obesity, alcohol use and cigarette smoking with DM.
2. To determine the cardiovascular complications associated with DM.
3. To determine the types of cardiomyopathies associated with DM.

3.0 CHAPTER THREE: METHODOLOGY

3.0 METHODOLOGY

3.1 Research Design and Methodology

This chapter includes the study area, the study design, study population, sample size and sample size determination, data collection procedures, the inclusion and exclusion criteria, study variables and ethical consideration.

3.2 Study Design

This was a hospital-based individually matched case-control study to determine the risk factors and complications associated with DM among patients with HF. The choice of the study design was appropriate for assessing the association between the different risk factors and outcomes with DM, considering that both DM and HF are rare conditions. The study design was also appropriate since the focus was on clinical history, which could be derived from the medical records. In addition, the co-existence of DM and HF is rare and there is a paucity of information about the risk factors for DM in HF patients.

3.3 Study area description

The study took place in Aga Khan University Hospital (AKUH), which has been in existence for over 50 years serving families in Kenya, East Africa and Africa at large. It is the first referral hospital in Kenya to receive an accreditation from the Joint Commission International of the United States of America (JCIA). AKUH is a comprehensive tertiary teaching hospital and treated patients enjoy a team-based approach that guarantees a high-level standard of care and has set the standard for comprehensive healthcare and modern education in East Africa. The hospital has a bed capacity of 254. AKUH has satellite clinics in Kenya but our study site is the main hospital at third parklands. A well-equipped hospital with state-of-the-art facilities and well-trained staff has earned the hospital a good reputation over the past years. The hospital has various departments such as the Department of Medicine, Accident and Emergency, Dental Clinic, Family Medicine, and Children's hospital, Anaesthesia and Pain Management, and

Pharmacy. It has a well-functioning medical records unit, where all the patient medical files are stored and also has a data management system known as the electronic data management system (EDMS), an online platform where patients' medical history is fed so that any doctor can access the information without using the physical file. The hospital's referral system is comprised of specialized medical care and diagnostic services from different hospitals and clinics in the area.

AKUH offers an array of services ranging from medical services to diagnostic services. The heart clinic, where our participants will be selected from, is located at the doctors' plaza on the ground floor. The doctors' plaza has private clinics and offices, but our participants were from the hospital and not the private doctors' clinics. The heart clinic, which is supervised by specialized cardiologists, offers state-of-the-art non-invasive cardiac diagnostic facilities and investigations. A cardiologist reports the findings within 24 hours and a report submitted to the referring physicians. The heart clinic receives referrals from different parts of Kenya, East Africa and other parts of the world who come to be treated for various cardiac issues including HF.

The heart clinic operates from Monday to Friday. The clinic hours are from 9 a.m. to 5 p.m. with two cardiologists running the clinic at different times. About 60 patients are seen in a day, out of whom 10 to 15 are HF patients. Some of the services offered at the clinic are ambulatory blood pressure monitoring, echocardiogram, electrocardiogram, holter monitoring, exercise stress testing and dobutamine stress echocardiogram. It is a requirement that each patient that comes to the clinic must undergo some routine blood tests (including fasting blood sugar, serum cholesterol level, full haemogram, and kidney function tests) routine urine test and other diagnostic tests depending on the doctor. Cardiac patients, including HF patients, have to do an echocardiogram.

These tests are carried out by well-trained personnel and supervised by the cardiologist. AKUH was, therefore, chosen because of the availability of facilities for comprehensive diagnosis and good record keeping. These will facilitate the identification of study participants and data collection.

3.4 Study Population

The study population was outpatients aged 30 to 75 years, who had HF and had been undergoing treatment at the heart clinic or diabetes clinic in AKUH for six months or more. These criteria were chosen in order to avoid misclassification of participants to ensure we recruited chronic HF and not acute HF patients. The age range 30 to 75 years was chosen because heart failure progresses with age and it is rare in young people. This age range was also appropriate because most type 2 diabetes is usually diagnosed at an older age (40 years and above) compared to type 1. Majority of Type 1 diabetes are diagnosed at the age of less than 40 years while type 2 diabetes is diagnosed at 45 years of age on average but the development of the condition depends on too many factors to accurately predict diagnosis on an individual basis. Cases of HF were identified using the heart clinic database, which includes a section for diagnosis. Cases and controls had same eligibility criteria (stated below), except that cases had DM. The ratio of cases to controls was 1:3, this was in order to maximize the power of the study.

Case Definition

1. Patients who had an ejection fraction of ≤ 40% as determined by an echocardiogram.
2. Adults of 30 to 75 years.
3. Diagnosis of HF for ≥ 6 months.
4. With DM as determined by both a fasting blood glucose of > 7 mmol/l, and an HbA1c of > 6.5 at the time of diagnosis.

Control Definition

1. Patients who had an ejection fraction of ≤40% as determined by an echocardiogram.
2. Adults who were 30 to 75 years old.
3. Diagnosis of HF for ≥ to 6 months.
4. Without DM

3.5 Inclusion and Exclusion Criteria

The inclusion criteria for cases

1. Those who attended the heart clinic or diabetes clinic in AKUH, Nairobi.
2. Clinically diagnosed with HF and had an echocardiographic ejection fraction of < 40%.
3. Clinical diagnosis of diabetes with a fasting plasma glucose of above 7 mmol/l, and HbA1c of >6.5 mmol/l during diagnosis.
4. Patients aged 30 to 75 years.

The inclusion criteria for controls

1. Patients who attended the heart clinic in AKUH, Nairobi.
2. Clinically diagnosed with heart failure and had an echocardiographic ejection fraction of ≤ 40%
3. Patients aged 30 to 75 years

Exclusion criteria for controls and cases

1. Those who do not consent to take part in the study
2. Those who were too ill to take part in the study

3.6 Sample size determination and calculation

Using the case control sample size calculation to determine the sample size for the study. We used R software and R studio to calculate the required sample size. The total sample size was 376 participants.

The sample size was derived as follows (Kasiulevičius et al., 2006);

$$N1 = \frac{(Z_{\alpha+}Z\beta)^2 pq(r+1)}{r(p1-p2)^2}$$

$$P_1 = \frac{P2OR}{1+P2(OR-1)}$$

Where:

$N_2 = rN_1$

N_1 = No. of exposed (or no. of cases in Case-control (CC) studies)

N_2 = No. of unexposed (or no. of controls in CC studies)

Z_α = critical value associated with significance level 1.96. Value for a 2 tailed test

$Z\beta$ = the value of $Z\beta$ required for power= $1-\beta$: $Z_{0.20} = -0.84$ Beta is always in the lower tail so it's negative and only one-tailed.

P1 = Proportion of heart failure patients with diabetes mellitus (cases)

q1= 1-P_1

P2 = Proportion of heart failure patients without diabetes mellitus

$$q2 = 1 - p2.$$

$$\bar{p} = \frac{P1+rP2}{r+1}$$

$$\bar{q} = 1 - \bar{p}$$

R= Ratio of unexposed to exposed (or ratio of controls to cases in CC studies).

Therefore,

The odds ratio for heart failure and DM association was estimated at 2.0.

Ratio of cases to control = 1:3

Power = 80%

Confidence interval of 0.95

Proportion of controls exposed is 0.5

Therefore, the required sample size was 94 cases and 282 controls (total = 376)

3.7 Sampling procedures

Participants with HF were identified using a systematic random sampling with the first participant chosen as a random sample. The next participant was chosen using an interval of six from the list of daily patients' medical records. Once a case of a given age was selected, a control within five years of age of the case was identified. The attending nurse provided the daily list of the patients. Age matched controls were identified who had HF but not DM. The attending nurse who reviewed the medical records of the patients identified both the controls and the cases.

Recruitment of participants was done every day of the clinic (Monday to Friday from 9am to 5pm) at the heart clinic and Diabetes clinic. Consent was sought from the triage nurse to approach potential participants since she was aware of the condition of the patient and therefore would know whether it is appropriate to ask them to participate in the study. However, none of the participants was excluded on this basis because none was considered too ill to participate.

3.8 Recruitment and consenting procedures

The principal investigator and a trained research assistant carried out recruitment. All patients who attended the heart clinic and diabetes clinic who met the eligibility criteria were recruited into the study. The attending nurse did matching of the participants based on age (the age of the control had to be within five years the age of the case). Patients' medical records were reviewed to assess whether they met the eligibility criteria. Ethical concerns and the purpose and process of the study were explained to the participants. Confidentiality was maintained by using codes instead of patient names on the data extraction tools. A written consent was signed by willing participants.

3.9 Variable and method of measurement

The study variables included independent and dependent variables;

Independent variables included:

1. History of an established risk factor for HF; myocardial infarction, valvular disease, diabetic cardiomyopathy, hypertension (by diagnosis of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg)
2. Obesity was determined by the BMI of a patient, which was calculated by dividing the weight in kilograms, and the height in meters squared. Obesity was classified according to the WHO classification criteria using the body mass index (BMI) cut off with <18.5kg/m^2 as underweight, 18.5 to 24.9kg/m^2 as normal weight, 25.0 to 29.9kg/m^2 as overweight and ≥30kg/m^2 as obese
3. Anemia determined by hemoglobin level estimated form the laboratory samples taken for a full haemogram was measured in grams per deciliter. Anaemia was categorized into three, no anaemia (Hb ≥11g/dl), severe anemia (<8.0g/dl) and moderate anaemia (8.0 – 10.9 g/dl).
4. Dyslipidemia was defined as those who had high cholesterol values; HDL and LDL. For those who had low HDL were defined to be at risk of cardiovascular complication. HDL was categorised into two, normal (>1.05mmol/l) and low (<1.04mmol/l). LDL was classified into three categories; Normal (0-3.34 mmol/l), Borderline (3.35-4.0 mmol/l) and high (>4.0 mmol/l).
5. Atrial fibrillation as determined by an electrocardiogram and Holter monitor.
6. Smoking status determined by a yes or no response and the frequency was determined by the number of sticks smoked per day.
7. The number of units taken in a day or week determined alcohol intake, which was determined by a yes or no response and the quantity was determined according to the dietary Guidelines for Americans 2015-2020

The outcome variable was

1. DM status with a fasting blood glucose of above 7 mmol/l, and HbA1c of > 6.5 mmol/l.

3.10 Data Collection Procedure

Data was collected from both the electronic medical records (EMR) and physical patient charts by the researcher or research assistant. The EDMS was used to obtain the clinical history of the participants.

The questionnaire was in English (Appendix 1). This comprised demographic questions such as sex, date of birth, Ethnicity, tribe, age, education level, physical examination which comprised of blood pressure measurements, weight, height, waist circumference which was used to determine central obesity. Medical history of the participants covered questions on previous heart attack, date on diagnosis of DM and some of the routine blood tests done. Collection of information from participants was done using a structured questionnaire. The same questionnaire was administered to all interviewees and they received exactly the same interview stimulus. Questions were very specific with a fixed range of answers. The structured questionnaire had multiple-choice questions in which the researcher provided choices of answers and dichotomous questions had only two response alternatives, yes or no. The array of information collected gave us a broader perspective of the various factors that possibly affected and determined the occurrence of DM in HF patients. Secondary data on type of medication and initial diagnosis of HF and DM was obtained from the hospital records. Interviews were done with participants to elicit information concerning the drugs used and tests done for the evaluation of coronary artery disease.

Questionnaires were then checked for completeness and missing information was sought from the medical records. All the data collected were initially entered into the Micro Soft Excel and later transferred to Stata version 13.0 for analysis.

3.11 Quality Assurance

A pilot study was done to test the questionnaire for easy understanding and appropriate corrections made. The research assistant was trained on how to administer the questionnaire and how to carry out the interview and to adhere to the questions and answer format strictly with the same degree of questioning for both cases and controls. This minimized information biases. Selection bias was minimized by ensuring the attending nurse is well informed about the inclusion and exclusion criteria for both the controls and cases. This was also verified by the researcher or research assistant.

We consulted the attending nurse on the status of the patient before consent was sort. Ethical considerations were explained and what the study entails was made clear to the attending nurse. The instruments used for measuring the BMI, weight and blood pressure were automated and are usually calibrated every week. To reduce information bias, the same set of questions was used for both cases and controls.

3.12 Ethical Consideration

Ethical approval was obtained from the Kenyatta National Hospital-University of Nairobi Ethical Review Committee (KNH/UoN-ERC, Appendix II), Aga Khan Ethics Research Committee and NACOSTI (Appendix III). The Director for Cardiac Services at AKUH gave permission to conduct the study. A written informed consent was given by the attending nurse in the clinic.

Written informed consent was sought from each participant after a detailed explanation of the purpose of the study before the interviews. The researcher and research assistant-maintained confidentiality by not sharing the medical information of the participants and by undertaking the interviews in a private space. Information collected was stored safely in a password-protected computer and kept confidential; there was the use of codes instead of participants' names.

All the information collected, was stored in a computer with passwords and encryption that was accessible to the researcher only.

3.13 Data analysis and management

Questionnaires were edited, coded, entered into Microsoft excel and kept safe in a password-protected computer. Data analysis was done using the Stata version 13.0 (Stata Corporation, College Station, Texas, USA) statistical software. Descriptive statistics was used to outline the baseline demographic and clinical characteristics of cases and controls. The study considered factors such as age, gender, education level, race as socio-demographic factors. The descriptive statistics reported means, median, interquartile ranges, and standard deviations. Baseline characteristics were stratified by type 2 diabetes (cases) and none type 2 diabetes (control). Continuous data were presented as mean, median, and standard deviation (SD). Categorical data were reported as proportions and percentages. In Univariable analysis, each risk factor was tested against the odds of DM and assessment was done using logistic regression at a liberal P-value of ($P \leq 0.20$). The P-value was chosen in order to eliminate potential confounders from the model. Statistically significant variables in the univariable analysis were moved to the multivariable analysis. In the multivariable analysis, those variables with a greater than 5% ($P > 0.05$) level of significance were eliminated using backward step-wise approach. The none significant variables were eliminated from the model if their exclusion in the model did not result in 30% change in the effects of the remaining variables. The non-significant continuous variables were categorized into two or more categories and were tested again for significance. The two-way interaction was fitted between the remaining variables in the final model and their significance was assessed. Assessment of the goodness of fit of the logistic model was done using the Hosmer-Lemeshow test with a P-value of > 0.05 being suggestive of a good fit. Findings were presented in tables.

3.14 Study Limitations and Minimization

The study recruited participants from AKUH, limiting the generalizability of the findings and recruitment of HF patients. Since it is a hospital-based case-control study, it excluded other patients who have HF who do not come to the facility and concentrating on a sub-set of the population. It is also subject to biases such as recall bias, which was mitigated by asking questions related to the event leading to the diagnosis of DM. This would help jog the memory of the patient. Information bias was mitigated by checking the hospital records of the patient and

interviewer bias was mitigated by ensuring the researcher was trained on how to carry out the interview and administer the questionnaire. This was a hospital-based study, where e both cases and controls were recruited from the same clinic; therefore, minimizing recall bias. In addition, the questionnaire included questions that promoted recall. In addition, medical records were used to obtain information on past exposures.

To minimize confounding by age, controls were age-matched to cases. This was controlled from the design stage and during multivariable analysis. Selection bias was minimized by having controls and cases from the same hospital with similar referral patterns and clear eligibility criteria.

Case-control studies are prone to have interviewer bias. This was reduced by training research assistants to complete the questionnaires in a standard manner. We also used a standardized questionnaire with closed-end, easy to understand questions with appropriate response options for participants.

4.0 CHAPTER FOUR: RESULTS

4.1 Introduction

Presentation of research findings and interpretation are highlighted in this chapter. It is arranged into sections. The first section is a presentation of demographic characteristics of study participants (cases and controls). In the subsequent sections are results from the analysis of the association between obesity, alcohol use and cigarette smoking with DM, cardiovascular complications associated with DM in HF patients, types of cardiomyopathies associated with DM among HF patients, and cardiovascular evaluation among DM and non-DM patients with HF. The findings are presented in tables and include crude odds ratios (ORs), and adjusted ORs.

4.2 Sociodemographic characteristics of study participants

Data collection was conducted from July 2020 to December 2020 at the AKUH. A total of 377 (143 cases and 234 controls) participants were recruited into the study (a case – control ratio of 1:3). Socio-demographic characteristics of study participants are shown in Table 1.

Table 1: Socio-demographic characteristics of study participants

Characteristic	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	Chi Square test	P-value
Age (years)	30-44	3 (2.1)	42 (18)	χ^2 (3)-27.95	<0.001
	45-54	24 (16.8)	46 (19.7)		
	55-64	48 (33.6)	79 (33.8)		
	65+	68 (47.6)	67 (28.6%)		
	Mean	62.7	56.8		
	Range	-	-		
	Median	64	58		
	Standard Deviation	8.9	11.8		
Sex	Female	42 (29.4)	71 (30.3)	χ^2(1)- 0.0399	0.842
	Male	101 (70.6)	163 (69.7)		
Ethnicity	Asians	23 (16.1)	32 (13.7)	χ^2(2) - 1.2100	0.546
	Black	117 (81.8)	193 (82.5)		
	White	3 (2.1)	9 (3.8)		
Level of education	No Education	31 (22)	36 (15.4)	χ^2(4)- 4.8474	0.303
	Primary	28 (20)	39 (17)		
	Secondary	8 (6)	11 (5)		
	Certificate	1 (0.7)	5 (2.1)		
	Tertiary	75 (52)	143 (61.1)		

Socio-demographic factors

The average age was 59 years (standard deviation, SD = 11.17) among the controls and 64 years (SD = 8.99) among the cases was not statistically different (p <0.001).

Among the ethnic groups, Kikuyu were the majority at 68% (n=73) among the cases and 46% (n = 79) among the controls. Ethnicity among cases and controls was of no differences (p = 0.546). There was also no difference in gender distribution and level of education between cases and controls (p = 0.9 and p = 0.5, respectively).

4.3 Association between obesity, alcohol use and cigarette smoking with DM among HF patients

Table 2 presents the association of obesity, alcohol use, cigarette smoking and serum cholesterol levels with DM among HF patients.

Obesity was classified according to WHO classification criteria using the body mass index (BMI) cut off as <18.5kg/m^2 as underweight, 18.5 to 24.9kg/m^2 as normal weight, ≥25.0 to 29.9kg/m^2 as overweight and ≥30kg/m^2 were classified as obese. In the respondents' group, comprised only three categories; normal, underweight and obese. In the univariable analysis, the inclusion of BMI as a continuous variable resulted in an insignificant association and therefore, it was categorized into three groups and was re-assessed for significance as a categorical variable.

Dyslipidemia was defined as those who had high cholesterol values; HDL and LDL. For those who had low HDL were defined to be at risk of cardiovascular complication. HDL was defined into two, normal (>1.05mmol/l) and low (<1.04mmol/l). LDL was defined into three categories; Normal (0-3.34 mmol/l), Borderline (3.35-4.0 mmol/l) and high (>4.0 mmol/l).

Univariable analysis was carried out using logistic regression at a liberal P-value of ≤0.20. Those who were underweight had a higher odds of developing DM among HF patients (OR-0.537 95% CI: 0.230-1.257) compared to normal weight patients. HDL and LDL did not show any association with DM. In multivariable analysis, none of the assessed variables had an association with DM at a p-value of ≤0.05 after adjusting for age, smoking status, gender, heart attack and CAD.

Table 2: Association between cholesterol level, BMI, Alcohol use and smoking with DM

Characteristic	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	OR[1]	95% CI	p-value	aOR[2]	95% CI	p-value
BMI	Normal (18.6–24.9)	86 (60.1)	133 (56.8)	Ref			Ref		
	Underweight (≤18.5)	8 (5.6)	23 (9.8)	0.537	0.230-1.257	0.152	0.578	0.242-1.383	0.218
	Obese (≥30)	49 (34.3)	78 (33.3)	0.971	0.620-1.521	0.9	1.047	0.655-1.672	0.847
Alcohol Intake	No	132(92.3)	216 (92.3)	Ref			Ref		
	Yes	11(7.7)	18 (7.7)	1.00	0.458-2.183	1.00	1.07	0.476-2.405	0.870
Smoking	No	136 (95.1)	219 (93.6)	Ref			Ref		
	Yes	7 (4.9)	15 (6.4)	0.751	0.299-1.890	0.544	0.651	0.249-1.701	0.382
HDL	Normal (>1.05)	42 (29.4)	48 (20.5)	Ref			Ref		
	Low (<1.04)	46 (32.2)	57 (24.4)	0.922	0.522-1.6273	0.78	1.08	0.573-2.040	0.809
LDL	Normal (0-3.34)	64 (44.8)	74 (31.3)	Ref			Ref		
	Borderline (3.35-4.0)	12 (8.4)	15 (6.4)	0.999	0.672-1.485	0.997	1.278	0.622-2.626	0.504

[1]BMI category of overweight was not included because there were no participants that fell into this category.
[2]OR1 – Crude Odds Ratio,
[3]OR2- Odd ratio adjusted for age, smoking, heart attack, CAD, alcohol use,
Triglycerides and total cholesterol could not be included in the analysis because all the values were within normal
BMI = Body Mass Index, OR=Odds Ratio, CI=Confidence Interval, TCL=Total Cholesterol, LDL=Low Density lipoprotein, HDL=High Density lipoprotein
.

4.4 Association between cardiovascular complications and DM in HF patients.

Table 3: Association between cardiovascular complications and DM in HF patients

Characteristic	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	OR[1]	95% CI	p-value	aOR[2]	95% CI	p-value
Heart Attack	No	100 (69.9)	184 (78.6)	Ref			Ref		
	Yes	43 (30.1)	50 (21.4)	1.582	0.984-2.544	0.058	1.22	0.652-2.282	0.533
Hypertension	No	43 (30.1)	133 (56.8)	Ref			Ref		
	Yes	100 (69.9)	101 (43.2)	3.062	1.970-4.761	P<0.001	2.782	1.734-4.461	P<0.001
Anaemia	No Anaemia	128 (89.5)	221 (94.4)	Ref			Ref		Ref
	Severe	4 (2.8)	5 (2.1)	1.381	0.364-5.236	0.635	1.68	0.405-7.001	0.473
	Moderate	11 (7.7)	8 (3.4)	2.374	0.931-6.055	0.070	3.10	1.108-8.669	0.031
CAD	No	86 (60.1)	166 (70.9)						
	Yes	57 (39.9)	68 (29.1)	1.618	1.044-2.507	0.031	1.169	0.6577-2.078	0.594
Atrial Fibrillation	No	119(83.2)	185 (79.1)	Ref			Ref		Ref
	Yes	1(0.7)	16 (6.8)	0.097	0.0130-0.742	0.025	0.08	0.0107-0.679	0.02

[1]BMI category of overweight was not included because there were no participants that fell into this category.
[2]Triglycerides and Total cholesterol could not be included in the analysis because all the values were within normal
[3]BMI = Body Mass Index, OR=Odds Ratio, CI=Confidence Interval, LDL=Low Density lipoprotein, HDL=High Density lipoprotein

Table 3 shows the association between DM and cardiovascular complications in HF patients. Hypertension was described as a systolic blood pressure of >140mmHg and or a diastolic blood pressure of >90 mmHg. In the case and control groups, those who had hypertension were 69.9% (n=100) and 43.2% (n=101), respectively. Crude ORs showed that participants with hypertension were three times more likely to have DM compared to those without hypertension (OR-3.06; 95% CI: 1.73 – 4.46). The findings were similar in multivariable analysis, after adjusting for age, BMI, cigarette smoking status, history of heart attack, CAD and alcohol use.

Those who reported to have had heart attack among the respondents 30.01% (n=43) were cases and 21.4% (n=50) were controls. CAD was defined as those who had had a history of coronary bypass graft surgery (CABG), 39.9% (n=57) were cases and 29.1% (n=68) were controls.

In univariable analysis, history of heart attack and CAD were all positively associated with DM but the association was not statistically significant (OR-1.58; 95% CI: 0.984– 2.544 and (OR-1.62; 95% CI: 1.044 – 2.507) respectively. The associations were weaker in multivariable analysis (aOR-1.22; 95% CI: 0.652 – 2.282 and (aOR-1.169; 95% CI: 0.66 – 2.208).

Anaemia was categorized into three, no anaemia, severe anemia (<8.0g/dl) and moderate anaemia (8.0 – 10.9 g/dl). In the crude analysis, significant association was observed between moderate anemia and DM (OR -2.374 95% CI: 0.931-6.055). Those who had moderate anaemia had approximately three times the odds of developing DM in multivariable analysis (aOR-3.099; 95% CI: 1.108-8.669).

Atrial fibrillation (AF) as diagnosed on the ECG and Holter as having more than 100 beat per minute (bpm). Among the cases 99.17% (n=119) were diagnosed with AF and 93.53% (n=188) controls had AF. A statistically significant inverse association was seen between DM and AF in crude analysis (OR-0.010; 95% CI: 0.01-0.74). The findings were almost similar in multivariable analysis after adjusting for age, hypertension status and history of peripartum cardiomyopathy.

4.5 Cardiovascular Evaluation among DM and Non-DM patients with HF

Cardiovascular evaluation is usually done on HF patients to evaluate the status of the heart. The association between the tests shown in Table 5 with DM were assessed using logistic regression. An Echocardiogram was done for all participants (both cases and controls).

Positive non-statistically significant associations were observed between DM and having had a Holter or stress echocardiogram (OR –2.05; 95% CI: 0.86-4.88 and OR –1.66; 95% CI: 0.47-5.84, respectively). No association was observed between DM and having had a coronary angiography, CT coronary angiography or EST

Table 4: Cardiovascular Evaluation.*OR[1] – Crude Odds Ratio, ECG – Electrocardiogram; EST – Exercise Stress Test; CT Coronary

Characteristic	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	OR[1]	95% CI	p-value	aOR[2]	95% CI	p-value
ECG	No	23 (16.1)	33 (14.1)	Ref			Ref		Ref
	Yes	120 (83.9)	201 (85.9)	0.857	0.480-1.527	0.6	0.66	0.352-1.241	0.198
Coronary Angiogram	No	69 (48.3)	150 (64.1)	Ref			Ref		Ref
	Yes	74 (51.7)	84 (35.9)	1.024	0.328-3.191	0.968	1.645	0.987-2.743	0.056
CT-Coronary Angiogram	No	138 (96.5)	226 (96.6)	Ref			Ref		Ref
	Yes	5 (3.5)	8 (3.4)	1.024	0.328-3.192	0.968	0.65	0.199-2.155	0.488
EST	No	131 (91.6)	215 (91.9)	Ref			Ref		Ref
	Yes	12 (8.4)	19 (8.1)	1.037	0.487-2.205	0.926	0.88	0.393-1.983	0.764
Stress Echocardiogram	No	138 (96.5)	229 (97.9)						
	Yes	5 (3.5)	5 (2.1)	1.659	0.471-5.835	0.43	1.58	0.422-5.909	0.497
Myocardial Perfusion Test	No	138 (96.5)	232 (99.1)	Ref			Ref		Ref
	Yes	5 (3.5)	2 (0.85)	4.202	0.805-21.957	0.089	2.752	0.501-15.108	0.243
Holter	No	131 (91.6)	224 (95.7)						
	Yes	12 (8.4)	10 (4.3)	2.052	0.862-4.88	0.104	2.01	0.6733-6.022	0.21

Angiogram =Computed tomography Coronary Angiogram

**** aOR[2]- Adjusted Odds Ratio (adjusting for age, heart attack, hypertension, cardiomyopathy)***

Among the respondents who had undergone coronary angiogram (CA), 48.25% (n=69) were cases and 64.10% (n=150) were controls. Of the factors assessed in the univariable analysis, Holter (OR-2.05, 95% CI: 0.862-4.88) and Myocardial perfusion test (OR-4.202, 95% CI: 0.805-21.957) were associated with DM among HF patients at P≤0.20 (Table 2). In the multivariable analysis, these variables were included for further testing. In the multivariable analysis, after adjusting for age, heart attack, hypertension and cardiomyopathy, myocardial perfusion test (aOR-2.752, 95% CI: 0.501-15.108) and Holter (aOR- 2.01, 95% CI: 0.6733-6.022) did not show any significant association with DM. CA did not have a significant association with DM (aOR-1.024 95% CI: 0.328-3.191).

4.6 Types of Cardiomyopathies associated with DM among HF patients

The study assessed the association between different types of cardiomyopathies with DM. In crude analysis, statistically non-significant positive association between DM and ischemic cardiomyopathy was observed (OR-1.53; 95% CI: 0.99 – 2.36), and an inverse association between DM and non-ischemic cardiomyopathy (OR-0.65; 95% CI: 0.42 – 1.01). In the multivariable analysis, non-ischemic and ischemic cardiomyopathy did not have any significant association with DM at a p-value of <0.05.

An assessment of the association between the different types of non-ischemic cardiomyopathy with DM was also carried out. Among cases 33.6% (n=48) had non-ischemic cardiomyopathy and 43.6% (n= 102) controls had non-ischemic cardiomyopathy. Idiopathic dilated cardiomyopathy had a statistically non-significant inverse association with DM in univariable analysis (OR- 0.87; 95% CI: 0.57 – 1.35). The same association was seen in multivariable analysis. Similarly, peripartum cardiomyopathy had a positive association with DM that was statistically significant (OR-0.89; 95% CI: 0.011-0.682). In multivariable analysis, those patients who had peripartum cardiomyopathy had 0.12 (aOR=0.12; 95% CI: 0.0147-0.9944) odds of developing DM compared to those who did not have peripartum cardiomyopathy.

Table 5: Types of cardiomyopathy associated with DM among HF Patients.

Characteristic	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	OR[1]	95% CI	p-value	aOR[2]	95% CI	p-value
Ischaemic Cardiomyopathy	No	48 (33.6)	102 (43.6)	Ref			Ref		Ref
	Yes	95 (66.4)	132 (56.4)	1.529	0.992-2.357	0.054	1.136	0.713-1.811	0.589
Non-Ischaemic Cardiomyopathy	No	95 (66.4)	132 (56.4)	Ref		Ref			Ref
	Yes	48 (33.6)	102 (43.6)	0.654	0.424-1.008	0.054	0.879	0.551-1.401	0.589
Peripartum cardiomyopathy	No	142 (99.3)	217 (92.7)	Ref			Ref		Ref
	Yes	1(0.7)	17 (7.3)	0.898	0.011-0.682	0.02	0.121	0.014-0.994	0.049
Idiopathic Dilated Cardiomyopathy	No	98 (68.5)	153 (65.4)	Ref			Ref		Ref
	Yes	45 (31.5)	81 (34.6)	0.86	0.556-1.352	0.53	0.93	0.591-1.492	0.791
Alcoholic Cardiomyopathy	No	143 (100)	232 (99.1)	Ref			Ref		Ref
	Yes	0	2 (0.9)	-		-			-

*Alcoholic cardiomyopathy could not be carried out in multivariable analysis because of the small number of participants.

4.7 Current Medications among HF and DM patients

An analysis was carried out to assess the relationship between DM and different classes of drugs used in the management of HF. The findings are presented in Table 6. Factors included in the logistic regression model were hypertension, age, CAD, anaemia, heart attack, ischaemic cardiomyopathy and BMI. In both univariable and multivariable analyses, users of lipid lowering drugs were about five times more likely to have DM compared to non-users (OR- 4.93; 95% CI: 3.11-7.80 and OR- 4.62; 95% CI: 2.63 - 8.12, respectively). Positive but statistically non-significant associations were observed between use of ARB or calcium channel blockers and DM (OR-1.47; 95% CI: 0.84-2.57 and OR-2.14, 95% CI: 0.10- 4.96, respectively). On the other hand, an inverse association was observed between DM and use of spironolactone in both univariable and multivariable analyses (OR- 0.61; 95% CI: 0.36 – 1.01 and aOR- 0.57; 95% CI: 0.33 – 0.99, respectively). Non-statistically significant inverse associations were also observed between DM and use of diuretics, ACE inhibitors or beta-blockers.

Table 6: Current drugs for treatment of HF and HTN

Drug class	Categories	Cases (n=143) No. (%)	Controls (n-=234) No. (%)	OR	95% CI	P-Value	aOR	95% CI	P-Value
Diuretics	**No**	48 (33.6)	75 (32.1)	Ref	Ref		Ref	Ref	Ref
	Yes	95 (66.4)	159 (67.9)	0.933	0.599-1.453	0.761	1.17	0.725-1.897	0.517
Ace Inhibitor	**No**	87 (60.8)	133 (56.8)	Ref			Ref		
	Yes	56 (39.2)	101 (43.2)	0.847	0.55-1.295	0.445	0.875	0.562-1.363	0.555
ARB	**No**	116 (81.1)	202 (86.3)	Ref			Ref		
	Yes	27 (18.9)	32 (13.7)	1.469	0.838-2.574	0.179	1.103	0.605-2.010	0.748
Calcium Channel Blocker	**No**	127 (88.8)	221 (94.4)						
	Yes	16 (11.2)	13 (5.6)	2.141	0.997-4.956	0.051	1.629	0.713-3.728	0.247
Beta Blockers	**No**	31 (21.7)	48 (20.5)						
	Yes	112 (78.3)	186 (79.5)	0.932	0.561-1.551	0.787	1.199	0.698-2.061	0.511
Spironolactone	**No**	116 (81.1)	169 (72.2)						
	Yes	27 (18.9)	65 (27.8)	0.605	0.364-1.005	0.052	0.572	0.329-0.994	0.047
Lipid Lowering	**No**	37 (25.9)	148 (63.2)						
	Yes	106 (74.1)	86 (36.8)	4.93	3.11-7.802	0.00	4.619	2.629-8.116	<0.001

*ARB=Angiotensin Receptor Blocker, ACE Inhibitor=Angiotensin-converting-enzyme inhibitor.

[1]OR- Crude Odds Ratio
[2]CI -Confidence Interval.
[3] aOR- Adjusted Odds Ratio (age, heart attack, hypertension)

In the drug class for HF, most patients were put on Sacubitril Valsartan 23.7% (n=34) and among the control group; there were 26.07% (n=61). No association was observed between Sacubitril valsartan and DM (OR-0.91; 95% CI – 0.56-1.48).

Table 7: Heart failure drug class

Variable	Categories	Cases (n=143) No. (%)	Controls (n=234) No. (%)	OR[1]	95% CI	p-value
Isosorbide Mononitrate	No	139 (97)	230 (98)	Ref		
	Yes	4 (2.8)	4 (1.7)	1.65	0.407 – 6.722	0.481
Ivabradine	No	136 (95)	211 (90)	Ref		
	Yes	7 (4.9)	23 (9.8)	0.47	0.197 – 1.131	0.092
Sacubitril Valsartan	No	109 (76)	173 (74)	Ref		
	Yes	34 (24)	61 (26)	0.88	0.53 – 1.47	0.619

Isosorbide Mononitrate and Ivabradine showed a non-statistical positive association with DM (OR-1.65; 95% CI – 0.30 - 9.02) and (OR-0.47; 95% CI – 0.197 – 1.131). In multivariable analysis, the findings did not change after adjusting for age, hypertension and heart attack, (aOR-1.36; 95% CI – 0.316 - 5.195). In multivariable analysis after adjusting for hypertension and heart attack, Ivabradine did not show any association with DM (aOR-0.70, 95% CI: 0.273-1.786).

The model had a good fit (P=0.2107).

CHAPTER FIVE

DISCUSSION

5.1 Introduction

A summary of findings and conclusions in line with the objectives of the study has been provided in this chapter. It also provides key contributions of the study to knowledge, as informed by the findings. A comparison between our results and other authors' findings are made in order to understand their similarities and differences.

5.2.1 Discussion

In the whole study group of patients with and without DM, we found the most common ischemic etiology among these group of patients was peripartum cardiomyopathy with 1 (0.7%) of the cases and 17 (7.3%) of the controls had peripartum cardiomyopathy. Non-ischemic cardiomyopathy showed to be a significant predictor of DM among HF patients with those who have peripartum cardiomyopathy having higher odds of developing DM (aOR-0.12 95% CI: 0.0147-0.9944). Peripartum cardiomyopathy (PPCM) was also found to be significantly associated with DM in a population-based cohort study of women with a birth of at least one live in Canada and Korea. The study suggested the presence of PPCM and its association with DM was due to confounding factors such as vascular risk factors such as hypertension during pregnancy (71,72)

Hypertension has been noted to be a common comorbidity in type two diabetics. Its prevalence was said to be higher in type 2 diabetic patients than those without and was described as those patients who had a systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg (54). In logistic regression, association between DM and hypertension was statistically significant (aOR-2.782; 95% CI: 1.734-4.461). This same association was seen in a study by Passarella, et. al who noted that the occurrence of hypertension in DM patients increases their likelihood of developing HF and CVD. An article by Vasilis et al revealed that 16% out of the 46% of the study subjects who had DM were all hypertensive indicating an increased risk of developing hypertension among DM patients (73).

AF is a rising global burden and has had significant public health implications. Patients who have stroke and HF experience a higher chance of morbidity due to AF as well as increased mortality. In the global burden of disease study of 2010, a systematic review of epidemiological data revealed that individuals with higher risk of developing AF were in the older age group (74). A population-based study revealing evidence of an increased prevalence of AF in the general population supported this. DM is an established risk factor for AF and has been reported to be associated with a higher chance of new onset AF. In our study, those who had DM had a higher odds of developing AF compared to those who did not have (aOR- 0.08, 95% CI: 0.011-0.68) These results were supported by a nation-wide population-based cohort study carried out in Korea for 7 years, revealing a higher risk of AF among type 2 diabetics patients (HR 1.16 95% CI 1.12 – 1.20) (75).

A meta-analysis of Cohort and case control studies revealed a 40% greater risk of occurrence of new onset AF among type 2 DM patients compared to those without (76). In a Swedish National diabetes registry, which included 421,855 patients with type 2 diabetes and 2,131,223 controls, 35% of the cases had a bigger risk of AF compared to the controls (55).

Ischemic cardiomyopathy did not have a strong association with DM among HF patients. This varied across sex and ethnicity. The odds of developing ischemic cardiomyopathy among DM patients was low and therefore showed a non-statistically significant association with DM (aOR -1.137, 95% CI: 0.713- 1.812). Ischemic etiology (ischemic cardiomyopathy) was also reported by Adam C Powel et al. in a review of patients who had undergone CRT-D and were admitted for HF between February of 2013 and February of 2014 and found 64.3% of 1303 patients had ischemic etiology (P-0.02), which is similar to the findings of this study (77). Ischemic events can range from cardiomyopathy to heart attack in this group of patients.

Patients who have DM, have a higher likelihood of developing macrovascular complications compared to those who do not have DM. Macrovascular complication include MI and stroke. DM is a known risk factor for acute myocardial infarction (AMI) and therefore majority of patients who have DM will eventually have AMI. In our study AMI was defined as having heart attack and out of the 377 participants, 43 (30.07%) of the cases had had previous heart attack and 50 (21.37%) of the controls had heart attack. There was no association between heart attack and DM in the multivariable analysis (aOR-1.22, 95% CI: 0.562- 2.282). However, in the Framingham study, DM patients had a two to four times greater risk of

developing AMI (78) . The FRagmin during Instability in Coronary artery disease (FRISC) II trial also observed positive association between heart attack and DM (OR-3.12, 95% CI: 2.09 - 4.66) (Norhammar et al., 2004). In this regard, the lack of statistically significant association in our study could be attributed to the small sample size and choice of study design as most of the studies conducted were population-based studies and clinical trials, however, the direction of effect was the same as that of the other studies.

Smoking status and the development of DM has been a controversial subject as other studies find an association and others do not. In our study, there was no association of smoking status with DM among patients who were smoking (OR-0.751; 95% CI: 0.299-1.890) modifying the relationship between HF and DM. However, in a cohort study to determine the relationship of cigarette smoking, alcohol use and risk of developing DM among men who were followed up for 6 years. The study revealed current cigarette smoking doubles the risk of diabetes among healthy population of men (42).

Obesity is the leading cause of type 2 DM. Individuals who have a higher BMI have a higher risk of developing DM and HF. Studies such as the Swedish Obese Subjects (SOS) showed that among patients who underwent a bariatric surgery for weight loss there was a significant reduction in insulin levels, which influenced significantly their clinical outcome. In our study, we however, determined that those who were defined to be obese did not have an association with DM (aOR 1.047 95% CI 0.655- 1.672) after adjusting for age, ethnicity and alcohol intake. In another study in Taiwan those who were termed to be underweight, where patients were followed up for one year to ascertain the relationship between low BMI and type 2 diabetes and results were significant (79). This association can be attributed to reverse causality, because one of the components of management of DM is to reduce weight.

Alcohol use in our study and its association with DM was not statistically significant (OR-1.00, 95% CI: 0.458- 2.183) while in other studies, it has been noted that alcohol consumption in large amounts has resulted in higher incidence of DM due to poor glycemic control (80). However, the relationship between DM and alcohol use is a complex subject and therefore studies differ in the outcomes and this makes it difficult to compare results across studies (80). It has been stated in an article by Albert Van de Wiel, that light to moderate alcohol intake may lower the incidence of type 2 DM while those who are considered as heavy drinkers have a higher chance of developing DM and therefore indicating a dose

response relationship (81). However, this association cannot be ascertained in this study as their diabetic status might have led to lifestyle modification.

Patients who have diabetes have a higher chance of developing cardiovascular complication such as HF and heart attack. DM alone can promote myocardial damage even in the absence of hypertension and valvular ischemic heart diseases. This condition has been referred to as diabetic cardiomyopathy (82). DM has been known to be the major cause of accelerated atherogenesis and atherothrombosis observed in population studies such as the Danish population-based study on 3.3 million people indicating that patients without a history of CAD had the same 5-year cardiovascular mortality as non-DM with a history of MI (83). It is therefore advisable for patients who have DM to undergo regular cardiovascular evaluation in order to curb adverse outcomes. In this case, cardiovascular evaluation encompassed an array of tests done on HF patients such as coronary angiogram, stress echocardiogram, myocardial perfusion tests, ECG and CT-Angiogram. Coronary angiogram, which aids in the diagnosis of CHD among patients who are diabetic, did not have any association with DM (OR- 1.024, 95% CI: 0.328-3.191). However, an association was seen in a cohort study by Jorgensen et al who in his paper on the trends in pharmacotherapy, comorbidities and demographics in patients referred for CA in Sweden showed an increase in the number of CA done on diabetes patients (84). Medical management of HF patients with reduced ejection fraction protects them from adverse cardiovascular outcome. Current guidelines strongly recommend HF patients be treated with multiple medications proven to improve clinical outcomes. The target dose and drug classes typically used for HF with reduced ejection fraction is, ACEI, Sacubitril /valsartan, beta blockers, angiotensin receptor blocker (ARBs) have recently set out to provide additional morbidity and mortality reduction over other drug classes such as Enalapril (85).

Results revealed that out of the 143 cases, 34 (2.8%) patients were using Sacubitril valsartan that was not statistically associated with DM. Beta-blockers, calcium channel blockers and ARB had a positive association with DM in the univariable analysis. In the multivariable analysis, these drugs did not have any significant association with DM. The percentage of patients getting the target dose were ACEi (OR=0.847), Beta-blocker (OR=0.93), and sacubitril/valsartan (OR=0.88). None of the above medication showed any association with the occurrence of DM. In a randomized control studies, treatment of HF with high dose Lisinopril resulted in a reduction of mortality and HF hospitalization among type 2 diabetes

patients in the Assessment of Treatment with Lisinopril and Survival in heart failure (ATLAS) trial. Also, in a meta-analysis of CIBIS-2, MERIT-HF and COPERNICUS, patients with type 2 DM ($n = 1883$) had reduced mortality when treated with beta-blockers (86).

Strengths and limitations of the study

Our study is subject to a number of limitations. First, the sample was from one hospital and population and therefore the results cannot be conclusive or indicate what is in the wider population. Second, this being a case control study, there was the risk of some biases. Information sort from the patient was limiting and therefore with the use of EDMS, we were able to get medical information of the patients. Matching of cases and controls allowed us to control for potential confounders from the design to the analysis stage. Some key demographic data was still missing from the questionnaire such as duration of diabetes, which was an important determinant on the occurrence of HF in this group of patients, number of units of alcohol intake, and missing cholesterol values. Fourth, the study also could not control for other complications such as chronic kidney disease and cancer, which might have led to development of HF. These data were not collected as we were looking at cardiovascular complications and associations with DM. Fifth, there was the risk of selection bias, which was reduced by having both controls and cases from the same hospital with similar referral patterns. Training of research assistant on how to carry out the interview minimized interviewer bias. The study design enabled us to show the association of risk factors among HF patients. Statistically they were not significant but a positive association was seen and therefore it calls for studies to be done with a bigger population and sample size.

CHAPTER SIX

6.1 Conclusion

Hypertension being a major complication of DM showed significant statistical association with DM in our study. DM patients experience increased peripheral artery resistance caused by vascular remodeling and increased body fluid volume associated with insulin resistance-induced hyperinsulinemia and hyperglycemia. Both of these elevate systemic blood pressure. Uncontrolled sugars for a long period of time increases the risk of developing hypertension. Therefore, glycemic control among this group of patients is vital. Our results are consistent with a study by Passarella et al who also noted an increased risk of developing HTN among DM patients (42).

Other positive correlation with DM was dyslipidemia among these patients. High cholesterol values intensifies the likelihood of occurrence of DM in patients with HF. The association of high cholesterol values was also seen in our study with 13% (n=19) of the cases and 7.3% (n=17) of controls exhibiting high TCL. MI is a cardiovascular complication among DM patients and they are at risk of developing MI compared to those without as seen in our study and other studies done across the world. Patients with DM need to undergo regular cardiac evaluation as MI can silently occur.

Ischemic events are common among DM patients. In our study, we observed that a majority of these patients had non-ischemic cardiomyopathy. This was however noted in other studies where non-ischemic cardiomyopathy is the most common complication among these groups of patients especially diabetic cardiomyopathy, dilated cardiomyopathy and peripartum cardiomyopathy. Risk factors that play a vital role in the onset of DM are weight, hypertension, ethnicity and dyslipidemia. Medical management of HF with reduced ejection fraction should be with multiple medications, which improves their cardiovascular outcomes as compared with one class of drugs. Therefore, from our findings, DM is associated with development of complication such as hypertension and heart attack and therefore, healthcare practitioners should approach treatment of these patients from a multifactorial point in order to lower the mortality and morbidity of these patients due to cardiovascular outcomes. Thus, in future, studies on the risk factors for DM in HF patients should be carried out with a larger

population to look into the association of DM and the specific risk factors to improve the management of HF patients.

6.2 Recommendations

1. Further investigation to be carried out with a larger population in order to determine the strength of association of the risk factors for DM with HF.
2. Regular screening and lifestyle modification of HF patients known to exhibit risk factors such as obesity, alcohol intake, and smoking for DM should be encouraged.
3. In our study, we did not factor in chronic kidney disease as a diabetes complication and therefore further association study can be carried out with this in mind.
4. In our study, we did not factor in cancer as a factor that can lead to development of DM among cancer patients and therefore an association study can be carried out with this in mind.
5. The duration of diabetes should be factored in and therefore further studies should be carried out with this in mind
6. Screening for heart attack should be done among HF patients who have DM, as they are two to three times more likely to develop ischemic events compared to those who do not have DM.

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APPENDICES

RISK FACTORS FOR DIABETES MELLITUS IN HEART FAILURES/N_____

Date of Birth: __ __/ __ __/_____ Gender: Male [ ] Female [ ]

Telephone No: _____Email: _____

VITALS

Blood Pressure: _____ Height: _____Current weight: _____

Weight at 18 _____, Weight before HF diagnosis _____

Waist Circumference_____ BMI: _____

1. What is your ethnicity?

   White [ ] Indian [ ] Pakistani [ ] Bangladesh [ ] Black African [ ]

   Other Asian [ ] Not Stated [ ]

2. What is your highest level of education?

   Primary [ ] Secondary [ ] University [ ] Higher Diploma [ ]

   Certificate [ ] Post Graduate [ ]

3. Do you smoke? YES [ ] NO [ ]

   If Yes, How many sticks per day?

   Less than 10 [ ] 10-19 [ ] Above 20 [ ]

4. Do you take alcohol?

   Yes [ ] No [ ]

5. Have you had a heart attack?

   Yes [ ] No [ ]

6. What was your HbA1c level when you were diagnosed with Diabetes mellitus?
   7-10 [ ] 11-13 [ ] 14-15 [ ] Above 15 [ ]

7. What was your haemoglobin level?
   7-10 [ ] 11-13 [ ] 14-15 [ ] Above 15 [ ]

8. Are you on blood pressure medicine?
   Yes [ ] No [ ]

9. What are you current medications? (Tick all that apply)
   Ace Inhibitor [ ] ARB [ ] Beta Blocker [ ] Diuretics [ ] Anti-Coagulants [ ]
   Insulin [ ] Metformin [ ] DPP4i [ ] SGLT2 inhibitor [ ]
   Salfonylurea [ ] Lipid Lowering Agents [ ]

10. Are you being treated for coronary artery disease?
    Yes [ ] No [ ]

11. What was your haemoglobin level at the time of heart failure diagnosis?
    7-9 [ ] 10-11 [ ] 12-13 [ ] 14-15 [ ] Above 15 [ ]

12. What is your cholesterol level during diagnosis of heart failure?
    HDL [ ] LDL [ ] Total cholesterol [ ]

13. What test has been done for cardiovascular evaluation?
    Coronary Angiography [ ] CT Coronary Angiography [ ] EST [ ]
    Stress Echocardiogram [ ] Myocardial perfusion test [ ]

14. What type of cardiomyopathy were you diagnosed with?
    Ischemic cardiomyopathy [ ] Non-ischemic cardiomyopathy [ ]

15. If non-ischemic which of the following:

Alcoholic cardiomyopathy [ ] Peripartum cardiomyopathy [ ]

anthracycline related [ ] Takotsubo [ ] idiopathic dilated [ ] Other [ ]

16. Was an ECG done at the time of heart failure diagnosis?

Yes [ ] No [ ]

If yes, what was the rhythm?

Sinus [ ] Atrial Fibrillation [ ] Other [ ]

Appendix II: Participant Information and Consent Form

Title of Study: Risk Factors for Diabetes Mellitus in Heart Failure Patients

Principal Investigator: Caroline Cherotich Mutai

Postgraduate Student

School of Public Health

University of Nairobi

Introduction:

My name is Caroline Cherotich Mutai, a masters student in the School of Public Health, College of Health Sciences, University of Nairobi. I am conducting a study about the risk factors for diabetes mellitus in heart failure patients. I would like to invite you to participate in this study which will give insight into the various risk factors associated with diabetes mellitus among heart failure patients. It is therefore, very important that you understand the following general principles which will apply to all participants in our study:

17. Your decision to participate is entirely voluntary.
18. You maywithdrawfromthestudyatanytimewithoutnecessarilygivingareasonforyourwithdrawal.
19. Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities.
20. After you have read/listened to the explanation, please feel free to ask me any questions that will allow you to clearly understand the nature of the study.
21. All information obtained from this study will remain confidential and your privacy will be upheld. Identification will be by number only; no names will be used in this study or in its future publications.
22. We will give you a copy of this form for your records.

May I continue? YES / NO

What is this study about?

The researcher listed above are interviewing individuals who have heart failure and Diabetes Mellitus. The purpose of the interview is to find out the risk factors for diabetes mellitus in heart failure patients. Participants in this research study will be asked questions about their medical history. Participants will also have the choice to undergo tests such as blood pressure taking and measurement of their weight and height.

There will be approximately 376 participants in this study randomly chosen. We are asking for your consent to consider participating in this study.

What will happen if you decide to be in this research study?

If you agree to participate in this study, the following things will happen:

A trained interviewer in a private area where you feel comfortable will interview you.

The interview will last approximately 15 minutes. The interview will cover topics such as demographic; age, phone number, date of birth and sex, family history, education level, ethnicity and medical history.

After the interview is over we may wish to contact you for any missing information, if you are agreeable to this.

We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others.

Are there any risks, harms discomforts associated with this study?

You will not be exposed to any risks or hazards beyond standard care by taking part in this study. We will be collecting clinical information and physical measurements as is routine in medical practice.

Are there any benefits being in this study?

There may be no immediate benefit to you should you decide to take part in this study. However, information gathered will help us improve the future care of patients with heart failure and its complications.

Will being in this study cost you anything?

There will be no additional cost involved for participating in the study and you will not receive any compensation for your participation.

Will you get refund for any money spent as part of this study?

Since there will be no money spent in taking part in the study, there will be no refund made to you.

What if you have questions in future?

If you have further questions or concerns about participating in this study, please call or send a text message to Caroline Mutai at 0722117997.

For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

What are your other choices?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time.

STATEMENT OF CONSENT

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with the investigator. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

I agree to participate in this research study YES [ ] NO [ ]

Participant printed name:…….

Participant signature: …….. Date: ……

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: ……Date: …….

Signature: _____

Role in the study: …… (*I.e. study staff who explained informed consent form.*

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27th May 2020

KENYATTA NATIONAL HOSPITAL APPROVED 27 MAY 2020 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Mutai Caroline Cherotich
Reg. No. H57/11517/ 2018
School of Public Health
College of Health Sciences
University of Nairobi

Dear Caroline

RESEARCH PROPOSAL –RISK FACTORS FOR DIABETES MELLITUS IN PATIENTS WITH HEART FAILURE: A CASE CONTROL STUDY (P1001/12/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 27th May 2020 – 26th May 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. 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*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
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REPUBLIC OF KENYA

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Date of Issue: **11/July/2020**

RESEARCH LICENSE

This is to Certify that Ms.. Caroline Cherotich Mutai of University of Nairobi, has been licensed to conduct research in Nairobi on the topic: Risk Factors for Diabetes Mellitus in Patients with Heart Failure: A Case Control Study for the period ending : 11/July/2021.

License No: **NACOSTI/P/20/5754**

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Francis
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Risk Factors and Complications Associated with Diabetes Mellitus in Patients with Heart Failure: A Case-Control Study.

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23.11.2022