PREVALENCE AND DETERMINANTS OF DYSLIPIDEMIAS AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

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A research dissertation submitted in partial fulfilment of the requirements for the award of the degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of the University of Nairobi.

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DECLARATION OF ORIGINALITY

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This is to certify that this research dissertation has been submitted for review with our approval as the University supervisors.

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DEDICATION

I dedicate this work to all the renal transplant recipients attending transplant clinic at Kenyatta National Hospital

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ABBREVIATIONS AND ACRONYMS

ACVD-Atherosclerotic cardiovascular disease

AZA- Azathioprine

BMI- Basal Metabolic Index

CAD- Coronary artery disease

CHF- congestive heart failure

CKD- Chronic Kidney Disease

CNIs- Calcineurin Inhibitors

CVD- Cardiovascular Disease

ESRD- End-stage Renal Disease

GFR- Glomerular filtration rate

HCT- Haematocrit

HDL- High-density lipoproteins

HTN- Hypertension

KDIGO- Kidney disease: Improving Global Outcomes

KDOQI- Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidaemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative

KNH- Kenyatta National Hospital

LDL- Low-density lipoproteins

LP-Lipoprotein

LVH- Left Ventricular Hypertrophy

MI- Myocardial infarction

MOH- Ministry of Health (Kenya)

MPA- Mycophenolates

MTORs- the Mammalian target of rapamycin inhibitors

NODAT- New-onset diabetes after transplantation

PTH- Parathyroid Hormone

RTRs-Renal Transplant Recipients

TC- Total cholesterol

TLC- Therapeutic Lifestyle changes

VLDL- Very low-density lipoproteins

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DEFINITION OF TERMS

Atherosclerosis is the thickening and loss of elasticity of arterial walls as a result of the formation of atherosclerotic plaques within the intima of the arteries. These plaques are made up of smooth muscle cells, cells of inflammation, foam cells, extracellular lipids and a fibrous cap.

Calcineurin inhibitors are a group of immunosuppressive medicines that selectively inhibit Calcineurin. This will ultimately reduce the proliferation of T-lymphocytes. They are used for immunosuppression in solid organ transplantation. They include cyclosporine and tacrolimus.

Cardiovascular disease refers to a disease condition that causes damage to the heart or blood vessels. This may include coronary artery disease, stroke, peripheral vascular disease and Congestive heart failure.

Chronic Graft Failure is the progressive decline in renal graft function during the course of at least three months characterized by interstitial fibrosis, glomerulosclerosis, arteriosclerosis and tubular atrophy, without evidence of any specific aetiology such as recurrent glomerulonephritis, renal artery stenosis or obstruction

Chronic Kidney Disease is kidney damage or a decreased glomerular filtration rate of less than 60ml/min/1.73m2 for at least 3 months.

Drug-drug interaction is a phenomenon where one drug interacts with another when they are administered concurrently. This leads to an alteration in their pharmacological effect

Dyslipidaemia refers to any abnormality in plasma lipoprotein concentration or composition.

End-stage renal disease is severe irreversible kidney damage/failure which is characterized by proteinuria and glomerular filtration rate (GFR) of less than 15ml per minute

Functional graft failure is the death of a renal transplant recipient with a functioning renal graft (1) provided that death is not preceded by a return to dialysis or nephrectomy of the graft and serum creatinine at the last follow up clinic was less than 4mg/dl.

High-density lipoproteins are complex molecules comprising of multiple proteins and lipid particles this class of lipoproteins has relatively high density. Their major function is to transport cholesterol from the tissues to the liver where it is excreted.

Hyperinsulinaemia is higher than expected blood insulin levels relative to the level of blood glucose that is defined by plasma insulin level that is higher than 2 μU/mL and serum glucose concentration less than 60mg/dl

Hypertriglyceridemia is blood level of triglycerides greater than 150mg/dl or greater than 1.7mmol/L

Low-density lipoproteins are complex molecules comprising of multiple proteins and lipid particles that have a relatively low density. Their main function is to transport cholesterol from the liver to body tissues.

mTOR inhibitors are a group of chemotherapeutic agents that inhibit IL-2 mediated signal transduction resulting in cell cycle arrest in the G1-phase. They are used as anticancer agents and also to prevent graft rejection by blocking T-cell and B-cell activation by cytokines. They include sirolimus and everolimus.

Nephrology Clinic is a specialist clinic dealing with all medical conditions affecting the kidney

Proteinuria is a phenomenon characterized by the presence of plasma proteins in the urine and indicates the presence of kidney disease.

Renal Transplant is a surgical procedure that involves the replacement of a diseased or damaged kidney with a functional kidney from a donor

Very low-density lipoproteins are complex molecules made up of triglycerides, cholesterol and proteins. They are synthesized in the liver and are mainly used to transport triglycerides in blood from the liver to body tissues.

ABSTRACT

Introduction: Dyslipidaemia is a common and a major modifiable risk factor for cardiovascular disease in renal transplant recipients and is usually multifactorial. The major risk factor for atherosclerotic cardiovascular disease in renal transplant recipients is dyslipidaemia which is multifactorial. Cardiovascular disease is the leading cause of functional graft failure in this cohort of patients. Management of dyslipidaemias in renal transplant recipients Management of dyslipidaemia in these patients is usually complicated by concerns over safety of statins and other lipid lowering drugs because of interactions with other drugs. This study aimed to assess the prevalence, predictors and management of dyslipidaemia in Renal Transplant recipients attending clinic in a tertiary hospital in Kenya

Objective: The study aimed to evaluate the types, prevalence, predictors and management of lipid disorders in renal transplant recipients attending the nephrology clinic at Kenyatta National Hospital

Methods: A cross-sectional survey was done. A total of 110 adult renal transplant recipients on follow up at the nephrology clinic at Kenyatta National Hospital were universally consecutively selected and interviewed using a structured questionnaire and data was abstracted from their medical files. Descriptive statistics were presented in the form of frequencies, proportions, tables, charts and other figures where necessary. Bivariable and multivariable logistic regression models were developed to evaluate associations between dyslipidaemias and participants' characteristics while adjusting for possible confounding by other covariates. For both the bivariable and multivariable models, the odds ratios, the 95% confidence intervals and the associated p-values were reported. The level of significance was set at $P \leq 0.05$.

Results: The mean age of the participants was 43.4±13.4 with a male gender predominance at 64%. Hypertension and Diabetes were the most prevalent comorbidities at 93% and 31% respectively. The overall prevalence of dyslipidaemia was 72% and the most prevalent types were elevated LDL-C and elevated non-HDL-C each at 44%. A partly 12% of the participants were on a statin and atorvastatin was the most commonly used at 10%. Lifestyle modification strategies used by participants included dietary modification (30%), weight reduction (58%), engaging in a form of physical activity (64%), smoking cessation/abstinence (99%) and limitation of alcohol intake (99%). Variables that were

significantly associated with the overall presence of dyslipidaemia included weight gain (P=0.003), dietary modification (P=0.001) and physical activity (P=0.04). Dietary modification (P=0.004) was the only independent predictor of dyslipidaemia

Conclusion: The prevalence of dyslipidaemia was high. Seven types of dyslipidaemias were identified and the most prevalent types were elevated LDL-C and Elevated non-HDL-C. Statins and Lifestyle modification strategies were used for the management of dyslipidaemia. However, their usage was low among the participants. Dietary modification, engaging in physical activity, obesity weight gain and time on dialysis before transplant were significant predictors of dyslipidaemia. Predictors for hypercholesterolemia included weight gain, physical inactivity, body mass index (BMI), Obesity weight reduction and dietary modification.

CHAPTER ONE: INTRODUCTION

1.1 Background

In the year 2017, the Ministry of Health Kenya estimated that about 4 million Kenyans had chronic kidney disease (CKD). A significant number of these patients end up progressing to end-stage renal disease (ESRD). The prevalence of end-stage renal disease patients in Kenya on either hemodialysis or peritoneal dialysis was reported in 2013 as 20 persons for every million people and 0.5 for every million people respectively (2). The optimal management of ESRD is renal transplantation (3). About 370 ESRD patients had received renal transplantation either locally or abroad in the year 2013 (2). Thus, the number of Renal Transplant Recipients (RTRs) is on the rise. Interestingly the main cause of death in RTRs is a cardiovascular disease (CVD) which account for up to 55% of the cases (4,5). Therefore it is important that the management of modifiable risk factors of cardiovascular disease is optimized in order to reduce death with a functional graft.

Kidney transplant recipients are more likely to develop CVD compared to age-matched general population (6,7). The significant higher risk is partly as a result of the presence of traditional cardiovascular risk factors such as hypertension, dyslipidaemias, diabetes, physical inactivity, smoking and older age (3).

Dyslipidaemia is a common observation among RTRs with reported prevalence as high as 80% in some studies (8). It is an independent predictor for the development of coronary heart disease in this cohort of patients (9). Dyslipidaemias in RTRs enhances atherogenesis which leads to coronary artery disease. CAD is a major cause of death among long-term renal transplantation survivors and hence functional graft loss (10).

Hyperlipidemia in RTRs is also implicated in increased risk of chronic graft loss. High serum lipids will adversely affect graft function either directly or indirectly (11). Persistent hyperlipidemia will cause gradual thickening of the intima of graft blood vessels and thus lead to gradual narrowing down of arteries. This will eventually cause ischemia and ultimately graft failure. These lesions histologically resemble atherosclerotic plaques and contain lipoproteins which are present as foam cells (11). Additionally LDL modified

through oxidation appear to be toxic to mesangial cells and this may have a deleterious effect on the extracellular matrix components (12).

Dyslipidaemia observed in RTRs is usually multifactorial. It is mainly caused by pre-transplant dyslipidemia, side effects of immunosuppressive medication such as corticosteroids, cyclosporine, tacrolimus, sirolimus, everolimus and co-morbidity with glucose intolerance or DM (8,13). Additionally, other contributing factors include familial predisposition, age, obesity, reduced renal function, proteinuria, gender, lack of exercise, smoking and concomitant use of diuretics or non-selective B-blockers without intrinsic sympathomimetic activity and weight gain. Dyslipidaemia can be safely and effectively managed in these patients through careful selection of lipid-lowering therapy and therapeutic lifestyle changes (TLC) (14).

An unpublished local study establishes that there is a high burden of dyslipidemia among RTRs attending nephrology clinics in Nairobi (15). Further findings show that most of these patients with dyslipidemia are not achieving adequate control. Interestingly only about a fifth of those with dyslipidemia were on a statin. This study aimed to assess the risk factors and management of dyslipidemia among RTRs attending the nephrology clinic at KNH.

1.2 Problem statement

Worldwide, RTRs are more likely to develop CVD compared to the healthy population (5,6). Cardiovascular disease is among the leading causes of mortality among RTRs which leads to functional graft failure. Amongst the most common CVDs in RTRs is an atherosclerotic cardiovascular disease (ACVD). Dyslipidaemia in RTRs is common and is a major contributing factor to ACVD including coronary artery disease (CAD) (14). CAD is a major cause of morbidity and mortality among RTRs (7). Additionally, dyslipidemia is a significant predictor of chronic graft failure hence contributing to graft loss and reduced patient survival (16). Kidney transplant recipients are commonly on chronic treatment with drugs which cause and/or worsen dyslipidemia such as corticosteroids, Calcineurin inhibitors, and mTOR inhibitors. This further compounds the management of dyslipidemia in these patients. Immunosuppressive drugs such as cyclosporine, which is commonly used by RTRs are known to interact with a number of lipid-lowering drugs such as statins, niacin, bile acid sequestrants and fibrates. This further complicates the management of dyslipidemia in RTRs (8). A local study established a prevalence of dyslipidemia of about 73% among RTRs attending nephrology clinic in Nairobi (15). Evidence from research in other countries has suggested that lipid abnormalities independently contribute to chronic allograft failure and hence graft loss (17,18). Unfortunately, no local study had assessed the types, prevalences, predictors and management of dyslipidemia in this group of patient. This study was done to highlight the burden of dyslipidemias their predictors and management among RTRs attending nephrology clinic at KNH. Thus the results of this study will help improve patient survival by optimizing management of dyslipidemia in these patients.

1.3 Purpose of the study

This study highlighted the predictors of dyslipidemia among renal transplant recipients attending the nephrology clinic at KNH. The study also evaluated the management of dyslipidemia in the same cohort of patients. This will help the multidisciplinary healthcare team to improve the care of renal transplant recipients. Improved management of dyslipidemia will enhance the survival of renal transplant recipients and hence graft survival by decreasing the occurrence of atherosclerotic cardiovascular disease and chronic allograft failure.

1.4 Objectives

1.4.1 Main Objective

The main objective was to evaluate the prevalence, determinants and management of lipid disorders in renal transplant recipients attending the nephrology clinic at Kenyatta National Hospital

1.4.2 Specific Objectives

The specific objectives were as follows

i. To determine the prevalence, and types of dyslipidaemias among RTRs attending Nephrology Clinic at KNH
ii. To investigate the predictors of dyslipidaemias among RTRs attending Nephrology clinic at KNH
iii. To identify the types of lipid-lowering drugs and lifestyle modifications used in the management of dyslipidaemias in RTRs attending nephrology clinic at KNH

1.5 Research questions

i. What are the types and prevalence of dyslipidaemias among RTRs attending nephrology clinic at KNH?
ii. What are the predictors of dyslipidaemias among RTRs attending Nephrology clinic at KNH?
iii. What are the types of lipid-lowering drugs and lifestyle modifications used in the management of dyslipidaemias among RTRs attending Nephrology clinic at KNH?

1.6 Rationale/ Study Justification

Cardiovascular-related mortality is the leading cause of functional graft failure among RTRs. Dyslipidaemia, which is common in RTRs happens to be one of the most important risk factors for atherosclerotic CVD including CAD. Hence it is imperative that dyslipidemia is managed optimally in these patients to enhance patient and graft survival. This study identified predictors associated with dyslipidemia among RTRs attending nephrology clinic at KNH. The study findings will help develop policy guidelines and

protocols on the management of dyslipidemia among RTRs which will, in turn, improve survival of patients and hence graft survival. The study findings are also expected to help clinicians optimize the management of dyslipidemia among RTRs in KNH which will eventually improve kidney transplant recipients' survival and hence graft survival.

1.7 Study Delimitations

The study sample was derived from RTRs attending nephrology clinic at KNH. This is because there are very few transplant clinics in the country and KNH nephrology clinic has the highest number of post renal transplant patients. Additionally, the study focused on predictors and management of dyslipidaemias. The study highlighted the characteristics associated with dyslipidemia in kidney transplant recipients attending the nephrology clinic at KNH.

1.8 Conceptual Framework

Dyslipidaemia in renal transplant recipients is a function of several factors. Some risk factors are unique to transplant recipients while others apply even to the general population. Generally, serum lipid levels tend to increase with age (19).

Thiazide diuretics, reduced renal function, diabetes, glucose intolerance, and obesity contribute to post-transplant insulin resistance and hence insulinemia (13,20–22). Hyperinsulinaemia as a result of insulin resistance will stimulate hepatic triglyceride-rich LP production. It also causes reduced VLDL turnover rate and also reduced post-prandial TG clearance rate. This eventually leads to increased TC, LDL cholesterol, and triglycerides.

Proteinuria causes reactive synthesis of protein in the liver including lipoproteins and also lower blood levels of lipoprotein lipase thus reduced dissimilation of LDL. The net result is increased plasma LDL and VLDL.

Cardioselective or noncardioselective β-blocker without intrinsic sympathomimetic activity monotherapy for hypertension normally leads to elevated serum TGs and decreased HDL. These drugs have little or no effect on TC and LDL (22).

Immunosuppressive drugs used in RTRs are also heavily implicated in dyslipidemia that is usually observed in these patients (8,13,23). A high cumulative dose of prednisolone is an independent risk factor for high VLDL, TC, TGs and reduced HDL. mTOR inhibitors increase LDL, VLDL, and non-HDL (8). Tacrolimus increases both serum cholesterol and triglycerides(13). Cyclosporine increases serum cholesterol, triglyceride levels, and LDL cholesterol.

Lack of exercise may cause weight gain which may lead to obesity. Obesity is independently associated with occurrence of metabolic syndrome and hence insulin resistance (8).

Most if not all of these factors are in a complex interaction in RTRs further complicating management of dyslipidemia in this group of patients

Therapeutic lifestyle modifications and use of lipid-lowering drugs are the two main strategies for managing dyslipidaemia in RTRs.(14) Dyslipidaemia if unchecked will increase the risk of atherosclerotic complications including stroke, CHD, and Peripheral Arterial Disease (8,14,24). Additionally, chronic dyslipidemia may lead to chronic allograft nephropathy hence chronic graft failure

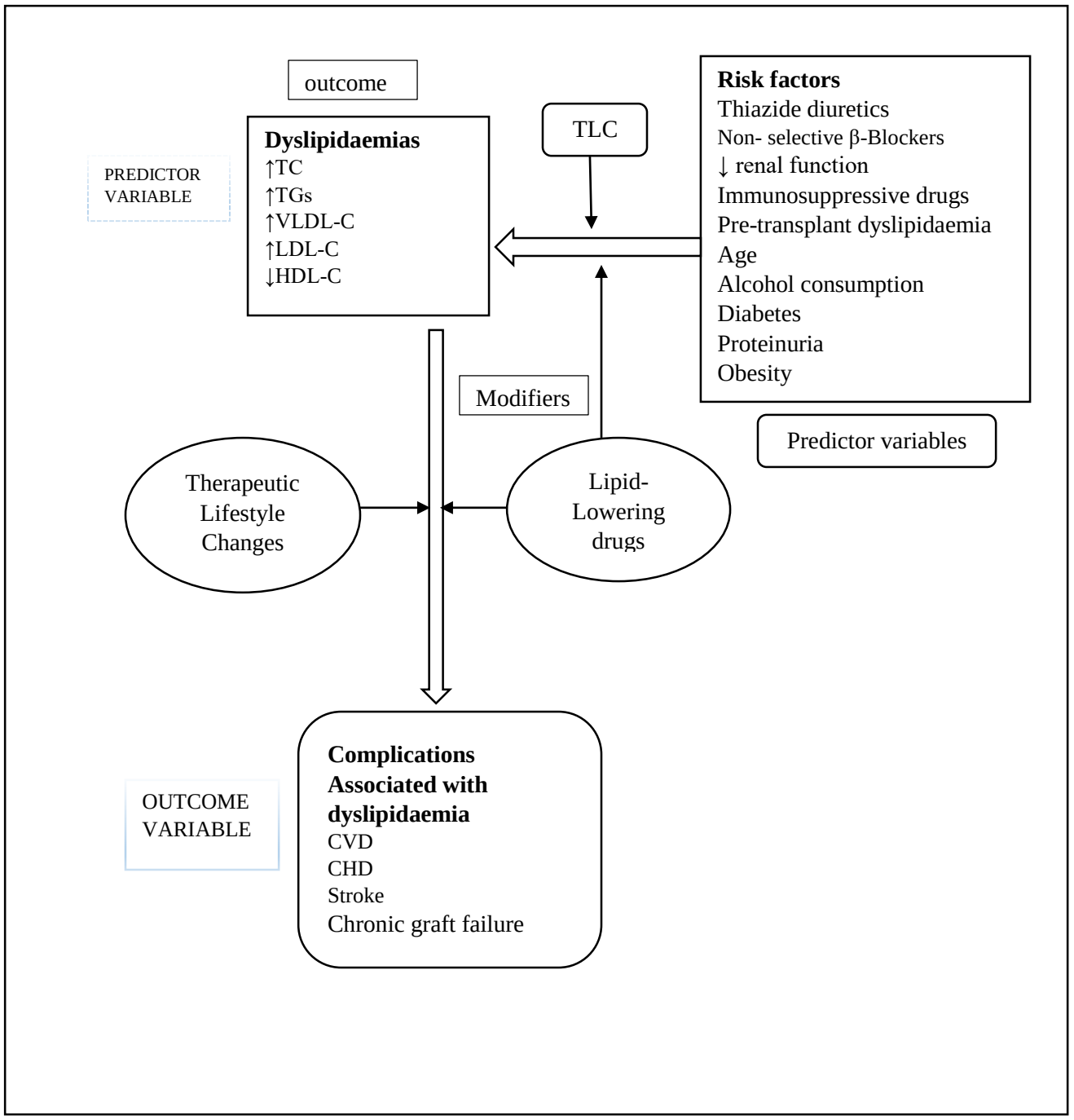

Figure 1. 1 Factors contributing to Dyslipidaemias and complications of dyslipidaemias in RTRs

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Dyslipidaemia in RTRs is a complex conundrum of several factors that contribute to the deranged serum lipids and also complicate management. Some comorbidities are often present in these patients which further contribute to dyslipidaemia and complicate management with lipid-lowering agents. Some of these comorbidities such as hypertension require drugs that are known to worsen dyslipidaemia such as non-selective β-blockers w and thiazide diuretics. These patients are usually on long-term therapy with immunosuppressive drugs that significantly contribute to dyslipidaemia. These drugs include cyclosporine, tacrolimus, Sirolimus, everolimus, and corticosteroids. Most RTRs tend to have comorbidities such as hypertension which require antihypertensive medication some of which may induce dyslipidaemia such as β-blockers and Thiazide diuretics. Thus unlike in the general population, it's more difficult to achieve adequate control of serum lipids in RTRs. These patients also tend to be on several drugs and hence increased the risk of drug interactions especially with the immunosuppressive agents or ADRs which further complicate management of dyslipidaemia. Hence lipid-lowering drugs have to be used judiciously in this cohort of the patient so as to optimize patient and graft outcomes. Additionally, most of the evidence on the management of dyslipidaemia is derived from studies conducted on the general population. There is limited evidence derived from studies on kidney transplant recipients. Some global and regional organizations have tried to come up with recommendations on management and targets for dyslipidaemia in RTRs.

2.2 Lipid disorders in kidney transplant recipients

Dyslipidaemia refers to abnormal lipoprotein concentration or constitution (composition) that is implicated in increased risk of ACVD. Lipid abnormality is a common feature in RTRs with a reported prevalence of about 30% to 80% (8,10,13,16,25). In 2012 a local study established a prevalence of about 73% (15).

In RTRs dyslipidaemia is a function of many factors and as such, there is no clear pattern of lipid abnormalities that are encountered in these patients (26). However, the most commonly encountered lipid abnormalities in RTRs include elevated plasma levels of TC, LDL-C, VLD-C, non-HDL-C, high levels of triglycerides and decreased levels of HDL-

C(26). Most guidelines usually focus on TC and/or LDL-C levels (27,28). The importance of reducing LDL-C levels in reducing the risk of ACVD has been established. However, a substantial number of ACVD events have occurred after achieving a significant decrease in LDL-C (27). Other lipids that are targeted by current clinical practice guidelines include HDL-C and Triglycerides (28). Available evidence suggests that a reduction in non-HDL-C levels may be more important than reducing LDL-C in predicting CVD events (29). Published results have shown that non-HDL-C concentration is more reliable in predicting CVD risk compared with LDL-C concentration (28,30).

Other Lipid abnormalities in RTRs include high TG: HDL ratio and high LDL-C: HDL-C ratio. A raised TG: HDL-C ratio (greater than 4) is a surrogate marker of the presence of small dense LDL which are known to be extremely atherogenic (28,31). This ratio should be measured in those RTRs with metabolic syndrome too. High LDL-C: HDL-C ratio together with elevated triglycerides levels has been depicted as atherogenic and has a correlation with the highest risk of CHD (32,33).

High serum TG levels is an independent predictor associated with CHD (34). High levels of TGs favour development of small thick LDL molecules are easily oxidized and also circulate for longer periods in plasma because they have low affinity to LDL lipoprotein receptor (10). This may explain the higher incidence of CVD in hypertriglyceridemia.

2.3 Drugs associated with dyslipidaemia in renal transplant recipients

2.3.1 Immunosuppressive Drugs

2.3.1.1 Corticosteroids

There is a correlation between raised cumulative dose of prednisolone and high levels of VLDL, TC, and TGs as well as a reduction in HDL (8,35). Corticosteroids have several effects which lead to these lipid abnormalities. Corticosteroids may induce insulin resistance (36) which enhances increased total cholesterol and serum TGs in addition to a reduction in HDL-C.

Hyperinsulinaemia induced by corticosteroids increases the activity of Acetyl CoA carboxylase and free fatty acid (FFA) synthase (36). This increases the biosynthesis of free

fatty acids. There will also be increased uptake of FFAs by the liver. FFAs act as a substrate for the biosynthesis of TGs and VLDL rich lipoproteins (25) and thus the levels of TGS and VLDL will be elevated. Insulin resistance will also cause increased biochemical activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, inhibition of lipoprotein lipase and down-regulation of LDL receptor activity (36,37). Decreased action of peripheral lipoprotein lipase which is supposed to degrade TGs leads to increase TG levels. These TGs will be available to the liver for synthesis of VLDL. VLDL is modified into IDL and LDL causing elevated levels of LDL-C (25).

2.3.1.2 Calcineurin inhibitors

Hypercholesterolemia is the most prevalent form of dyslipidaemia in RTRs on cyclosporine (36). Cyclosporine (CsA) independently affect TC, LDL-C and TGs (38) CsA is lipophilic and hence it is transported in plasma in association with lipoproteins(LPs)(36) Evidence suggest that it may require LDL receptors to enter cells. This interferes with the basic cholesterol feedback mechanism through the LDL receptor (36,39). CsA is thought to interfere with LDL configuration leading to the altered interaction of LDL with its receptor (25). The abnormal interaction could lead to hypercholesterolemia. Evidence suggests that there is an association between serum cholesterol levels and blood CsA levels (39). CsA inhibits 26-hydroxylase enzyme thus reducing the biosynthesis of bile acids from cholesterol and translocation to small bowel (8,36). Secretion of bile acids acts as a negative feedback for biosynthesis of cholesterol (39). As a result biodegradation of cholesterol is reduced. Additionally, it has been suggested that CsA increases the activity of HMG-CoA reductase thus enhancing collateral biosynthesis of cholesterol (36). CsA has a pro-oxidant effect on LDL-C(40) that is dose-dependent. Higher blood concentration of CsA increases the susceptibleness of LDL-C to oxidation. CsA is also associated with elevated non-HDL-C (28). CsA and corticosteroids may have an additive effect in raising cholesterol levels (8).

Tacrolimus has a similar effect to CsA on enhancing oxidability of LDL-C (40). Evidence suggests that those treated with tacrolimus tend to have significantly lower plasma TC and LDL-C levels compared with those treated with CsA (36). Switching patients to from CsA to tacrolimus is associated with decreased lipid parameters (41). However, the concomitant

use of tacrolimus and cyclosporine is independently associated with raised plasma levels of TC and TGs.

2.3.1.3 mTORs

Both sirolimus and everolimus cause a substantial rise in both plasma cholesterol levels and Serum TGs in a dose-dependent manner (42). There is an association between elevated serum levels of TGs and trough blood levels of sirolimus (43,44) Increase in the levels of TC and TGs is observed after about 2 weeks of exposure (36). The increase in both TC and TG levels as a result of the use of both sirolimus and everolimus is likely by a reduction in the breakdown of apolipoprotein B_{100}, suppression of insulin and insulin-like growth factor signals and/or modification of hepatic biosynthesis of lipids (42). Apolipoprotein B_{100} is found in both VLDL and LDL and is a ligand for LDL receptor. Sirolimus may inhibit uptake of LDL by blocking LDL receptor (42). Elevated levels of apolipoprotein C3 may inhibit lipoprotein lipase (42) resulting in increased levels of VLDL and LDL. Evidence suggests that dyslipidaemia is worse in concomitant use of sirolimus with CsA than with tacrolimus (42). There may be a dose-response effect.

2.3.2 β-blockers

Several β-blockers have been shown to elevate plasma levels of TGs as well as reduce HDL-C. These effects are most commonly seen in patients on unselective $\beta_{1\&2}$ adrenergic blockers devoid of intrinsic sympathomimetic activity (ISA) (39,40), rare in patients on selective β1 adrenergic blockers devoid of ISA and absent in patients on β blockers with ISA.

A few β blockers such as propranolol and sotalol may decrease the sensitivity of insulin and in prolonged use may induce glucose intolerance especially if used together with diuretics (22). Reduced insulin sensitivity impairs lipoprotein lipase action and thus decreases the removal of TGs from blood (22,45). Due to reduced adrenergic tone as a result of the use of β-blockers, the activity of lipoprotein lipase is reduced and this leads to the decreased breakdown of TG rich lipoproteins (22).

Post-synaptic α1 blockers may decrease TGs, LDL-C and TC/HDL-C ratio by a small fraction and also slightly improve insulin sensitivity, secretion, and glucose intolerance (22,46)

2.3.3 Diuretics

Thiazide diuretics may increase plasma TC, LDL-C as well as VLDL but rarely affect HDL-C and apolipoprotein A_1 and A_2 (20,47). This implies that LDL/HDL-C and TC/HDL-C ratios are usually elevated. Loop diuretics also seem to raise these ratios (20) Thiazides may also marginally increase TGs although the pre-menopausal state has been associated with a protective influence against dyslipidaemias associated with thiazides (20). at the Usual therapeutic dose of Indapamide of 2.5mg does not induce dyslipidaemia (20). It has been postulated that at high doses diuretics may stimulate sympathetic nervous system (SNS) activity causing an increase in circulating norepinephrine which consequently enhances lipolysis (22). Increased activity of SNS may also promote biosynthesis of cholesterol by the liver which is secreted as VLDL (22). Thiazide and loop diuretics may also impair insulin sensitivity leading to a state of Hyperinsulinaemia which promotes hypertriglyceridemia and reduces HDL-C (22). This effect may be dose-dependent. Thiazides may by marginal stimulation of SNS and inhibition of phosphodiesterase enzyme increase circulating levels of CAMP which consequently stimulate lipolysis (45).

2.4 Other risk factors associated with dyslipidaemia in RTRs

Evidence from several studies suggests that pre-existing dyslipidaemia before transplantation may be the most important predictor of lipid disorders in RTRs (10). This may be due to the presence of host factors both environmental and genetic which affect serum lipids.

Diabetes mellitus (DM) is a common comorbidity in RTRs. It's one of the leading causes of renal failure. New onset diabetes after the transplant is also common owing to the deleterious effects of prednisolone and CNIs. DM is associated with a state of cellular insulin resistance in the peripheral tissues leading to Hyperinsulinaemia which enhance the biosynthesis of VLDL (21) VLDL particle is progressively degraded to its component lipid particle and apolipoproteins which consequently cause increased formation of LDL and IDL both of which are atherogenic (21).

Persistent consumption of excess calories may lead to weight gain and eventually obesity which makes the body markedly resistant to insulin causing insulinemia (21). Normally in

obese patients, there is a reduction in the disposition of glucose in the adipose tissue which gradually leads to hyperlipidemic (21).

2.4 Complications associated with dyslipidaemia in renal transplant recipients.

2.4.1 Atherosclerotic cardiovascular disease (ACVD)

Atherosclerotic cardiovascular disease includes coronary heart disease (CHD), cerebrovascular accidents (transient ischaemic attack and ischaemic stroke), renal artery stenosis and atherosclerotic disease of the arteries that cause Ischaemia of the extremities (peripheral vascular disease) (14). The main pathological mechanism in all these diseases is atherosclerosis. Results of Studies from the general population strongly link dyslipidaemia with ACVD(14). Most studies done in RTRs suggest a similar association between dyslipidaemia and ACVD in this cohort of patients (14). Studies have implicated high levels of LDL, TGs and lower levels of HDL in the development of ACVD in RTRs (14). The results of ALERT trial further supported the association between dyslipidaemia in RTRs and ACVD. The ALERT extension trial which was a placebo-controlled randomized controlled trial (RCT) demonstrated the efficacy of statins (fluvastatin) in reducing the incidence of major Adverse cardiovascular events (MACE) in RTRs by lowering LDL-C and TGs in addition to increasing HDL-C (48). A large cohort study found that post-transplant myocardial infarction is quite common in RTRs with an incidence of about 11 % (49). This cohort study further found that dyslipidaemia was an independent predictor of post-transplant MI.

Evidence shows that high plasma cholesterol level which is present in RTRs increases the ultrasonographically measured carotid wall thickness (50). Plasma LDL-C may be implicated in increasing thickness of intimal medial complex thus contributing to the formation of atherosclerotic plaques in RTRs(51). Both LDL-C and HDL-C are predictors of increased carotid intima-medial thickness (IMT)which is a predictor of coronary artery disease (CAD) and stroke (52) RTRs usually have increased LDL-C and low levels of HDL-C.

LDL oxidation is thought to be the main activity in the pathogenesis of atherosclerosis and small dense LDL are more susceptible to oxidation than large dense LDL (53). Histological findings show the presence of oxidized LDL in atherosclerotic plaques (53).

Increased LDL-C, non-HDL -C and TGs in RTRs favour the formation of small dense LDL(13). Increased TGs in RTRs may enhance LDL oxidation which subsequently contributes to the development of ACVD in these patients (53). In RTRs there is increased LDL oxidation and this may possibly lead to the increased risk of ACVD (53)

2.4.2 Chronic Allograft failure

Hyperlipidaemia may affect graft function directly via oxidatively modified LDL. Oxidatively modified LDL which is common in RTRs may be cytotoxic to mesangial cells and thus adversely affect extracellular matrix components (12). Dyslipidaemia may also indirectly affect graft function through destructive effects on the blood vessels of the transplanted kidney (12). Persistent hyperlipidemic may cause progressive thickening of intima-media of the renal blood vessels which gradually causes progressive narrowing of these vessels and eventually leads to Ischaemia (12). Histologic findings in chronic allograft rejection have suggested that dyslipidaemia may be a significant cause of chronic allograft failure (12,37). These findings include concentric fibro-intimal proliferation in medium and large intrarenal arteries, foam cells and lipoprotein deposits in the vascular lesions (12,37). The lesions that are seen in chronic allograft dysfunction share similarities with the vascular lesions in systemic atherosclerosis. There is the presence of macrophages, foam cells lipoproteins, T-cells and smooth muscles in the lesions found on the vascular walls of kidneys with chronic allograft dysfunction (12). This suggests that atherosclerosis is integral in chronic allograft dysfunction.

2.5 Management of Dyslipidaemia in RTRs

The risk of primary or secondary CVD events is lowered in all populations by lipid-lowering therapy (54). Strategies for managing dyslipidaemia in RTRs include Therapeutic Lifestyle Changes (TLC) and Pharmacological management (14). Dietary modification alone does not significantly lower the lipid levels. RTRs should be considered as high-risk patients when starting lipid-lowering therapy and when considering the treatment targets (55). Therapeutic intervention should aim at assessment and treatment of multiple lipid abnormalities, not just a singular lipid disorder (29). Very few guidelines are available to guide the management of dyslipidaemia in this cohort of patients. They include KDOQI guidelines (14), KDIGO clinical practice guidelines on monitoring, management and

treatment of kidney transplant recipients (55,56) and Renal Association clinical practice guidelines on post-operative care of kidney transplant recipient (57)

2.5.1 Evaluation of dyslipidaemia in RTRs

A number of guidelines for management of dyslipidaemia in kidney transplant recipients recommend that all renal transplant recipients should have their fasting lipid levels measured on presentation, within the first two to three months post-transplant, two to three months following adjustment of treatment or other comorbidities that are known to lead to dyslipidaemia and annually thereafter (4,14,55,57). These patients should be assessed for fasting lipid levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (14). In patients with moderately raised TGs (200-499mg/dL) the level of non-HDL cholesterol should be determined as it correlates well with the level of remnants of VLDL and is reliable in predicting CVD risk(8). For the purposes of optimal management, dyslipidaemia in RTRs is classified as shown in table 1.1.

2.5.2 Pharmacological and non-pharmacological interventions for dyslipidaemia in RTRs

Kidney transplant recipients should initially be considered for treatment with therapeutic lifestyle changes (TLC) irrespective of the type of dyslipidaemia a(14). TLC includes dietary modification, weight reduction, increased physical activity, abstaining from alcohol consumption and treating hyperglycaemia if present (14). The treatment options and the goal will depend on the kind of dyslipidaemia being targeted as shown in Table 1.2 below.

Table 2. 1 Classification of dyslipidaemia as per Adult treatment panel III guidelines (14)

Lipid abnormality	**Serum level in mg/dL**
Total Cholesterol	
Desired	< 200
Moderately high	200-299
High	≥ 240
LDL-Cholesterol	
Desired	< 100
Near desired	100-129
Moderately raised	130-159
High	160-189
Very high	≥ 190
Triglycerides	
Normal	< 150
Sub-optimal	150-199
High	200-499
Very high	≥ 500
HDL- Cholesterol	
Low	< 40
To convert mg/dL to mmol/L, multiply triglycerides by 0.001129, and cholesterol by 0.02586	

Adapted from KDOQI clinical practice guidelines(14)

Table 2. 2 Goals and management options for dyslipidaemia in RTRs (14,55)

Lipid disorder	**Goal**	**Treatment to Initiate**	**Target not achieved**	**Alternative Therapy**
TG ≥ 500mg/dL	< 500mg/Dl	TLC	TLC + Fibrate	Fibrate OR Niacin
LDL-C 100-129mg/dL	LDL< 100mg/dL	TLC	TLC + Low dose Statin	Bile acid sequestrant OR Niacin
LDL-C ≥ 130mg/dL	LDL< 100mg/dL	TLC + Low dose Statin	TLC + maximum dose Statin	Bile acid sequestrant OR Niacin
TG ≥ 200mg/dL& Non-HDL ≥ 130mg/dL	Non-HDL < 130mg/dL	TLC + Low dose Statin	TLC + maximum dose Statin	Fibrate OR Niacin
To convert mg/dL to mmol/L, multiply triglycerides by 0.001129, and cholesterol by 0.02586.				

Adapted from KDOQI Clinical practice guidelines(14)

2.5.2.1 Management of Elevated Low-density lipoprotein cholesterol (LDL-C)

Dietary modification for 2-3 months should be considered initially for RTRs with moderately elevated LDL-C (100-129mg/dl or 2.59-3.34mmo/l) after which pharmacological management is initiated if therapeutic goals are yet to be achieved(14)

Treatment with Statins

All RTRs are at a significantly increased risk for ischaemic heart disease (IHD) and thus should be managed with target LDL-C level of less than 100mg/dl (55). Several RCTs in the general population have shown that reducing LDL-C indeed decreases Cardiovascular (CVD) events and death (8,14,55).

The most frequently prescribed lipid-lowering drugs in RTRs are the HMG-CoA reductase inhibitors (8). They can be safely and effectively used in these patients (8). Their ability to significantly reduce LDL-C and lowering of the risk of cardiovascular events has been demonstrated in RCTs (58). Statins are well tolerated in RTRs (8,14,58). The ALERT study

examined the effects of statins (fluvastatin) on cardiovascular disease (CVD) risk reduction in RTRs with a functional graft. These patients were followed up for six years. Although fluvastatin led to a non-significant 17 % reduction in cardiac death or non-fatal myocardial infarction (MI), it led to a significant 35 % reduction in relative risk of cardiac death or non-fatal MI (48). This study further confirmed that HMG-CoA reductase inhibitors are safe and effective in RTRs. The selection and dosage of statin prescribed should consider the simultaneous immunosuppressive drugs being used by a specific patient (57).

Statins competitively inhibit HMG-CoA reductase and are known to stimulate expression of LDL receptors thus increasing biodegradation of LDL which leads to lowering of LDL-C in the blood (8). They also cause a mild decrease in TGs and moderate elevation of HDL (8).

Statins may cause an elevation in liver function tests (LFTs) even though liver failure is extremely rare (8,58). In RTRs on statins, LFTs should be monitored upon initiation when the doses are changed and these drugs should be withdrawn if liver function tests are more than 3 times the normal upper limit (8). Statin-induced myopathy may present as isolated myalgia or muscle weakness, raised creatinine phosphokinase (CK), or rhabdomyolysis which is extremely rare (8,48,58). The risk of myopathy appears to be higher in the elderly, those with eGFR of < 30ml/min, patients on maximum dose of statin and those on concurrent therapy with inhibitors of cytochrome p450 isoenzymes such as azole antifungals, macrolides, non-dihydropyridine calcium channel blockers, amiodarone and warfarin among other (8).

Statins which are not metabolized by cytochrome p450 isoenzymes including fluvastatin, pravastatin, and pitavastatin are the safest (8). However, they have lower efficacy thus only suitable for mildly elevated LDL-C. Kidney transplant recipients usually have a high risk of CVD events and hence require more potent statins such as atorvastatin which is well tolerated in combination with tacrolimus and has a presumed benefit in reducing proteinuria (8,14,55). Atorvastatin is metabolized by cytochrome p450 system and hence maximal dose in RTRs should be 50% or less of the recommended maximum dose in the general population (55). This is especially so for patients on cyclosporine where the dose should be reduced by 50% and probably for tacrolimus too although there is insufficient

data for tacrolimus (8,55). Proteinuria and even renal failure associated with use rosuvastatin limit its use in RTRs. In case a patient on statins experiences minor adverse effects associated with them, dose reduction may be warranted (14,55) however, changing to another class of lipid-lowering drugs is advisable.

Combination Therapy with a Statin/ Alternatives to statins

In cases that are refractory to statins, a different class of drugs, for example, niacin or Ezetimibe may be considered. In patients with persistently high LDL-C that is refractory to statins, the addition of Ezetimibe is indicated (8,26). It is safe and effective in reducing total cholesterol and LDL fractions in RTRs (8,14,57). Ezetimibe is not usually used as a monotherapy unless the treatment goal is not reached even with optimized dose of statins or if patients can't tolerate statins (59). The only combination therapy with evidence of clinical benefits is Ezetimibe and statin (59). This combination is efficacious in reducing TC, LDL-C and TG levels safely in kidney transplant recipients on Calcineurin inhibitors as evidenced by a study in South Korea (60). Ezetimibe works by inhibiting intestinal absorption of cholesterol hence effective in patients with hyperlipidemic refractory to statin monotherapy or intolerant to statins.

Niacin can be used as an adjuvant therapy to help reduce LDL-C especially after optimization of statin therapy (8,14). Alternatively, it can be used as monotherapy in patients who cannot tolerate statins and who haven't achieved optimal control of LDL-C.

Bile acid sequestrants reduce both TC and LDL-C but they are not well tolerated and may increase TGs hence they are not routinely used in RTRs (59). If at all they have to be used these drugs must be used with extreme caution since they interfere with the pharmacokinetic properties of immunosuppressive drugs and should be administered at least one hour before or 4 hours after the dose of Calcineurin inhibitors.

Fibrates are effective in the reduction of TGs and LDL-C and also raising of serum HDL-C (8,14). Concurrent use with HMG CoA reductase inhibitors leads to increased risk of myotoxicity especially if gemfibrozil is used together with a statin (8,14) However, this effect is rarely seen with fenofibrate but unfortunately fenofibrate may cause a significant decline in renal function and thus should generally be avoided in RTRs (8,14).

2.5.2.2 Treatment of Hypertriglyceridemia in RTRs.

Severe triglyceridemia in RTRs (> 500mg/dl) is associated with significantly increased risk of pancreatitis and hence should be treated as a first priority in these patients (8,14). Hypertriglyceridemia may be seen more often in RTRs using immunosuppressant medications such as sirolimus or cyclosporine and this may warrant dose reduction or withdrawal of offending drug especially in severe hypertriglyceridemia (14). If hypertriglyceridemia is absent then normalization of LDL-C becomes the primary target of treatment (8). Patients with normal or low LDL-C with elevated non-HDL cholesterol (≥ 130mg/dl) and mildly elevated triglycerides (≥ 200 < 500mg/dl) should be treated similarly to those with elevated LDL-C thus HMG-CoA reductase inhibitors are preferred in such patients (8,14,55). Serum TGs < 150mg/dl is independently associated with a lower risk of current CHD event and thus LDL-C should not be the only consideration (34).

The initial recommended management strategy for hypertriglyceridemia in RTRs should involve the withdrawal of causative agent and/or TLC which involves modification of the diet, weight reduction, increased physical activity, abstaining from alcohol consumption and treatment of hyperglycaemia if present (8,14). Medication therapy with niacin should be considered if this treatment approach fails to achieve treatment targets (14). Niacin may cause side effects such as flushing, pruritus and nausea and hence patients should be monitored for such (8).

In patients who can't tolerate niacin, fibrates should be considered as the third option (8,14). Fibrates are effective in decreasing triglycerides but may cause elevation of serum creatinine which is more commonly observed with fenofibrate. National kidney foundation favours gemfibrozil as the preferred fibrate and further recommends 50% reduction in dose for RTRs with eGFR< 60ml/min/1.73m^2 and total avoidance in eGFR < 15ml/min/ 1.73m^2 (14).

2.5.2.3 Drug-drug interactions with lipid-lowering drugs in RTRs

Statins are metabolized by cytochrome P450 enzyme system and hence drugs that inhibit these microsomal enzymes are known to raise plasma levels of HMG CoA reductase inhibitors (8,14). In RTRs already on statin, add on therapy with a third agent metabolized by cytochrome p450 isoenzymes significantly raises the risk of myopathy and thus should

be avoided (8,14,58). Some drugs are raise the plasma levels of statins and hence should not be used or where absolutely important the dose of HMG CoA reductase inhibitor should be lowered or completely discontinued (14). These drugs include non-dihydropyridine calcium channel blockers (verapamil, diltiazem), azole antifungals (itraconazole, fluconazole), Macrolides (erythromycin), warfarin, serotonin reuptake inhibitors, niacin, fibrates, amiodarone, protease inhibitors, grapefruit juice and cyclosporine (8,14). In renal transplant patients who are receiving a statin and cyclosporine, it's more prudent to avoid a third agent that may increase the blood levels of the statin (8,14). It's important to consider the immunosuppressive regimen a transplant patient is on before deciding on the choice and dosage of a statin (57).

Bile acid sequestrants impair absorption of co-administered drugs such as mycophenolate acetate products and hence should generally be avoided in kidney transplant patients receiving Mycophenolates (8,14). These sequestrants may be used safely in patients on cyclosporine although it's advisable to give these medications at least 1 hour before or at least 4 hours after CsA is given (14).

2.6 Literature Gap

Most studies prior to this had focused on the risk factors for dyslipidaemia in RTRs without much focus on management. More importantly, few if any studies had evaluated dyslipidaemia in RTRs in Sub-Sahara region. This research provided information on the types, prevalence and predictors of dyslipidaemias among RTRs in a tertiary hospital within a resource-limited setting. Additionally, this study provided guidance on the pharmacological and non-pharmacological management of dyslipidaemia among RTRs in a resource-limited setting.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Research Design

This study was a cross-sectional survey that was carried out in the Transplant Clinic at Kenyatta National Hospital. This type of study is usually used when a researcher wants to describe the prevalence of an exposure or outcome and thus it was the most suitable for this research study which aimed to describe the prevalence of dyslipidaemia and Lipid-lowering drug use among RTRs attending transplant clinic at KNH.

3.2 Location of the Study

The study was conducted at the Kenyatta National Hospital (KNH) Renal Transplant clinic. KNH is located in Upper Hill area approximately 3 km from Nairobi Central Business District. It is the largest Public Training and Referral Hospital in Kenya with a bed capacity of about 2000 beds. It serves approximately 70,000 inpatients and about 550,000 outpatients annually. The hospital's catchment area includes the whole of Kenya and parts of East and Central Africa. It offers preventive, curative and clinical diagnostic health services. It is a training and research centre for different cadres of healthcare professionals including medical doctors, pharmacists, dentists, and nurses among many others. It has several specialized clinics including a nephrology clinic. KNH is one of the very few centres in the country where renal transplantation is done. The transplant clinic at KNH runs on Tuesday every week. About 15 to 20 kidney transplant recipients are reviewed during a given clinic day.

3.3 Target Population

The target population for the study was all adult renal transplant recipients attending transplant clinic at KNH and who had received renal transplantation at least 3 months before recruitment into the study.

3.4 Inclusion/Exclusion Criteria

3.4.1 Inclusion Criteria

Those included in the study were patients who;

1) Were renal transplant recipients who were 18 years and over
2) Were on follow up in the transplant clinic at KNH even those who had their transplant done in other centres
3) Had received a renal transplant at least 3 months before the date of recruitment into the study.
4) Voluntarily gave informed consent and signed the consent declaration form

3.4.2 Exclusion Criteria

1) All renal transplant recipients on follow up at the transplant clinic in KNH who were back on dialysis. This is because patients on dialysis are known to be at a higher risk for dyslipidaemia than those with a functional graft and hence their inclusion may have modified the effect thus giving a higher dyslipidaemia burden than may be the case.
2) Any patient who was mentally ill, had dementia or Parkinsonism. This is because these patients may not have had the capacity to give a voluntary well-informed consent because of impairment of their judgement.

3.5 Sampling

3.5.1 Sample Size

The sample size was determined using the method described by Naing *et al*(61). This is because the target population was a finite population. The targeted sample size was greater than 5% of the target population

$$n_1 = \frac{NZ^2p(1-p)}{d^2(N-1) + Z^2P(1-P)}$$

Where,

n, is sample size with finite population correction

N is population size (all RTRs on follow up at the transplant clinic) which is 156

Z is the z-statistic for a level of confidence. In this study, it will be 1.96 for a 95% level of confidence. The population is greater than 120 hence the decision to use 1.96.

p is the expected proportion/ prevalence of dyslipidaemia among RTRs attending transplant clinic at KNH which is estimated to be 73% (15)

d is the precision which in this study will be 0.05 because the expected prevalence of dyslipidaemia (73 %) lies between 10% and 90%.

Substituting these estimates into the equation gave a sample size of 103 patients.

$$n_1 = \frac{156 * 1.96^2 * 0.73(1 - 0.73)}{(0.05^2(156 - 1) + 1.96^2 * 0.73(1 - 0.73))}$$

$$n_1 = 103.19$$

To provide for a 5% contingency for non-response and incomplete records, an additional 7 participants were added to the calculated sample size which gave a target sample size of 110 participants

At the end of the study, 110 RTRs patients who met the inclusion criteria were recruited into the study.

3.5.2 Sampling Technique

Study participants were recruited using a universal consecutive sampling method because the calculated sample size was close to the number of RTRs who would have attended the transplant clinic during the 3 months of data collection. Normally an average of 5 to 13 RTRs were seen on every clinic day and because the clinic is held once every week on

Tuesdays about 120 patients were seen in those 3 months. Thus in 12 weeks' time, a sample size of 110 was achieved. Files of patients scheduled to attend the clinic on a given Tuesday were screened for eligibility by the principal investigator in the morning of every clinic day. The files for patients who met the eligibility criteria were tagged for ease of identification and their numbers recorded on a list. A tag bearing a different colour was used for every month to avoid duplicate recruitment. These tags were only removed after the end of the study. Usually, the files belonging to RTRs on follow up in the transplant clinic at KNH are usually stored in the transplant coordinator's office which is within the hospital's renal unit.

3.6 Participant Recruitment

On presentation at the clinic for regular follow up those participants that met the inclusion criteria were further screened for eligibility criteria using the eligibility form (Appendix 1). All eligible patients were approached by the investigator and informed on what the study was about Those who were willing to participate in the study and fitted into the eligibility criteria were taken through the informed consent process which was either the English version (Appendix 2A) or the Kiswahili version (Appendix 3A) after which those that consented were required to sign the consent declaration form (Appendix 2B/3B). At this point, a patient was considered duly recruited into the study and a questionnaire (Appendix 4) was administered by the principal investigator. This process was repeated during every transplant clinic date until the required sample size was achieved

3.7 Research Instruments

3.7.1 Eligibility screening form

This form would assist the principal investigator select kidney transplant recipients who met the inclusion criteria (Appendix 1)

3.7.2 Informed Consent Form and Consent Declaration Form

The informed consent form was used to inform eligible patients about the study (Appendix 2A; English version and Appendix 3A; Kiswahili version).Those eligible patients who were voluntarily ready and willing to participate in the study were required to sign the consent declaration form There were two versions of the same form including the English version (Appendix 2B) and for those patients who couldn't understand English, there was a Kiswahili version (Appendix 3B). Patients would also give consent through a proxy. The

proxy should have been a caregiver to the eligible patient and would include a legal guardian, spouse, parent, child or sibling in that order of priority.

3.7.3 Data Collection forms

Information from the patient was collected using a well-structured questionnaire (Appendix 4). Information on Serum levels of Triglycerides, Total cholesterol, LDL-cholesterol and non-HDL cholesterol, immunosuppressive drugs that the patient was on, , comorbidities that the patient had, other medications that the patient was receiving including thiazide diuretics, loop diuretics, and β-blockers was abstracted from the patient's file using the data abstraction form (Appendix 5). This was done after the patient had duly signed the consent declaration form (Appendix 2B/3B)

3.8 Pilot Study

The questionnaire was piloted on 3 eligible patients. This was necessary in order to establish the validity and reliability of the questionnaire. This helped ensure that the language used in the questionnaire could be clearly understood and that the questions were short, clear and concise. It also helped establish the time required to administer a single questionnaire and its ability to capture data as per the objectives of the study. Any flaws that were identified were corrected before the actual study began. The pilot was rolled out during the usual clinic day. Contamination was minimized by excluding data from the pilot study in the final analysis and also by excluding all the patients who participated in the pilot study from the main study.

3.9 Validity

To ensure the validity of the results of the study, research instruments including the questionnaire were structured in a way that ensured that the objectives of the study were met. The questions in the questionnaire were short, clear and concise. The language in the questionnaire was simple and clear. The research instruments were developed in such a manner to allow for standardized data collection. The sample size achieved was adequate and representative so as to allow the results to be generalizable to all adult RTRs in the country.

3.10 Reliability

Data collection tools were pre-tested on 3 eligible patients to determine the internal reliability of these tools. The pre-test tools were administered at the same time. Improvement and/or amendments were done in order to ensure the reliability of the instruments in meeting the objectives of the study.

3.11 Data Collection Techniques

Collection of data was done in two phases after an eligible participant had granted a written informed consent. Each patient was assigned a unique code to ensure confidentiality throughout the study

The first phase involved the completion of an interviewer-administered questionnaire where the principal investigator would systematically ask the study participant (respondent) the questions in the questionnaire. Each questionnaire was uniquely coded. The principal investigator conducted the interview at the patient's convenience guided by the structured questionnaire. In this phase data that was collected included information on Therapeutic Lifestyle changes (dietary modification, weight reduction, smoking, physical activity and alcohol intake), duration on dialysis before the transplant, duration post-transplant and patient's biodata. This data was entered into the uniquely coded questionnaire by the principal investigator and the research assistant.

The second phase involved the abstraction of data from the patient's file. Patient's bio-data was obtained from the patient and from the patient's medical records. Other data which was abstracted from the patient's medical records included the most recent data (one year or less) on Serum levels of Triglycerides, Total cholesterol, LDL-cholesterol, non-HDL cholesterol and creatinine, immunosuppressive drugs that the patient was on, their doses and blood levels if available, comorbidities that the patient had including diabetes, hypertension, ischaemic heart disease, history of stroke, TIA, MI other medications that the patient was receiving including, angina medication (nitrates, trimetazidine, ranolazine) thiazide diuretics, loop diuretics and non-selective β-blockers. Non-HDL cholesterol and LDL-cholesterol levels were not usually given readily by the laboratory. Non-HDL-C levels were calculated by subtracting the HDL-C levels from total cholesterol while LDL-

C was calculated using Friedewald formula (14) $\boldsymbol{LDL = TC - HDL - (TGs \div 5)\ in \frac{mg}{dL}}$

OR

$$\boldsymbol{LDL = TC - HDL - (TGs \div 2.19)\ in \frac{mmol}{L}}$$

Additionally, patient treatment charts were reviewed and drug interactions checked for every patient recruited into the study using Medscape version 4 drug interaction checker. This information was abstracted and recorded in the data abstraction form. The filled forms were kept under lock and key at all times with access limited to the principal investigator only to ensure that confidentiality was maintained.

3.12 Data Management

3.12.1 Data Acquisition

Standardized data collection tools (questionnaire and data abstraction form) were developed, piloted and amended before the actual study began. The data collection tools were completed by the principal investigator. Raw data was then be coded, cleaned, validated and entered into a pre-created and pre-validated Epi Info 7 database. Data was entered into the database every clinic day. In case of missing or discrepant data, the principal investigator would call the patient to verify and correct the information. Where missing information could not be obtained, this would be clearly indicated on the data collection form. Data was checked regularly for consistency, accuracy, and completeness. Any flaw was corrected promptly. The database was under password protection and only the principal investigator would access. Once data collection was complete, the PI went through the complete set of data to further clean it before exporting to STATA version 13 for analysis.

3.12.2 Data Handling

An Epi Info 7 database was created. This database was verified and put under password protection prior to the start of the data entry process. Raw data was interpreted and entered into the database in real time by the principal investigator so that in case of missing data, the steps in section **3.12.2** above would be undertaken. Once data collection was complete, the data in the database was exported and analysed using STATA version 13.0. Data was

backed up in two external hard drives that were password protected and only accessible to the principal investigator.

Descriptive and inferential statistics were used to analyse all variables. The main outcome of interest was dyslipidaemia in RTRs. Continuous variables such as age, were summarized into a mean and standard deviation Categorical variables were summarized as proportions and percentages. Prevalence of dyslipidaemias, and complications (ACVD) was presented as a percentage of all RTRs. Association between the dependent variable (dyslipidaemia) and various predictive variables (sociodemographic variables and clinical factors) was determined using Fischer's exact test and bivariable and multivariable logistic regression analysis. For all the analyses, the level of significance was set at 0.05.

3.12.3 Quality Assurance

The principal investigator ensured that data collected was accurate, legible, complete, contemporaneous, relevant, concise and easily analysable using STATA version 13.0 software. This was assured through data checks at the end of each day of data collection. These checks were performed in order to look for missing information, inappropriate use of abbreviations, compare sample data entry forms. Data quality was ensured through careful planning at all stages, engaging nephrology fellows for any clarification and paying attention to every detail. Any errors were identified and rectified.

3.13 Study Variables

The main outcome variable of interest in this study was be dyslipidaemia of any type. The predictive variables of interest in this study included immunosuppressive therapy, diuretic drug therapy, non-selective β-blocker without ISA (intrinsic sympathomimetic activity) therapy, diabetes, obesity, alcohol consumption, diet, physical activity, time on dialysis before transplantation. Confounding variables included age, gender, and smoking. Other outcome variables of interest included any atherosclerotic cardiovascular disease.

3.14 Ethical considerations

3.14.1 Ethical Approval

Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UON -ERC) before the commencement of the study

(see Appendix 6). Permission to conduct the study was also obtained from KNH Research Department and Renal Unit where the study was carried out.

3.14.2 Respect for persons

All those who will met the eligibility criteria were individually taken through the consent explanation form. The principal investigator ensured that the eligible patients got full information/ disclosure about the study including study objectives, procedures of selection, benefits, and risks. Any question or concern by the eligible patients was addressed to their satisfaction. Eligible participants were informed that the participation was voluntary and any participant was free to withdraw at any time without dire consequences. Once the eligible participants fully understood what the study was about they were required to voluntarily sign a consent declaration form without coercion or inducement. For those who couldn't write they were required to use their thumbprint. Consent would also be given voluntarily through a legal representative (proxy).

3.14.3 Confidentiality

Before consenting, eligible patients were assured of confidentiality and anonymity. Several strategies were used to maintain data confidentiality. Firstly, all paper documents relating to a patient were kept under lock and key in a safe cabinet. Secondly, all data collection forms did not have any participant unique identifier such as name or hospital number. Thirdly only the principal investigator had access to the safe cabinet where patient data forms were kept. Fourthly, all electronic data entered was under password protection with access limited to the Principal investigator only. Finally, any patient identifier information was securely stored separately from the rest of the data.

3.14.4 Risks Involved

In my opinion, there were no anticipated risks for participating in this study.

3.14.5 Benefits from the Study

The study participant benefited from expert advice by the PI on therapeutic lifestyle change (TLC) and comprehensive medication therapy management (MTM) as described in **Table 3.1** and **Table 3.2** below. Any significant drug interaction or untreated dyslipidaemia noted was reported immediately to the presiding nephrologist or nephrology fellow for corrective

action. The findings of this study were shared with the relevant authority in order to improve the care of RTRs at KNH and beyond.

Table 3. 1 Outline of expert advice on Therapeutic lifestyle changes

Area of Concern	**Specific Interventions**
Diet	-Saturated fats < 7% of total calorie intake -Monosaturated fats should make-up 20% of total calorie intake -Total fats should be 25-35% of total calorie consumption -Daily cholesterol <200mg per day - 50-60% of total calorie intake should be carbohydrates -20-30g of fibre (5 to 10g viscous/ soluble fibre) -2g of plant sterols/ sterols per day - match total calorie intake to total calorie needs
Increased Physical Activity	-A moderate daily activity that breaks a sweat for example digging -Regular daily walking for a distance of at least 2km -Regular physical exercise at least 4 days in a the week for 20-30 minutes (the physical activity should break a sweat) -An activity that will break a sweat includes brisk walking, Jogging, swimming, aerobics etc.
Weight Reduction	-BMI 25-28 kg/M^2 initially for obese patients -Waist circumference men< 40 inches (102cm) women < 35 inches (88cm) - Waist: ratio (men< 1.0) (women <0.8)
Alcohol	-As much as possible abstain - If not possible to abstain, consume in moderation with a limit of a drink per day with the approval of the physician
Smoking	-Stop smoking immediately - Use of nicotine alternatives to help in smoking cessation
Blood sugar	-Treat hyperglycaemia if present - Optimal glycaemic control for diabetic patients

Source: Clinical practice guidelines for managing dyslipidemias in kidney transplant patients(14)

Table 3. 2 Outline of expert advice on Comprehensive Medication Management

Area of concern	Specific interventions
Assessment of patient	-Review medication history -Getting , organization and interpretation of patient data -Prioritization of patient problems and unmet medication-associated needs
Evaluation of Medication therapy	-Assessment of appropriateness of current drug therapy -Identify medication-related problems (MRPs) and evaluate the need for interventions. Such MRPs include non-adherence, adverse drug reactions, dose too high and unnecessary therapy
Development and Initiation of plan	-Reassessment of patient's active medical problem list -Formulate a comprehensive care plan to achieve definitive outcomes -Education of patient and/or caregivers to ascertain discernment of the pharmacotherapy plan, optimization of adherence and therapeutic outcomes. -Come up with patient specific quantifiable goals and have time periods for monitoring and re-examination
Follow up and Monitoring	-Coordination with other caregivers to ascertain that the patient follow up and succeeding clinic visits are aligned with patients treatment-related needs -Reassessment and polishing of the pharmaceutical care plan to optimize therapy and assure individual treatment targets are accomplished. -Monitoring, modification, documentation and management of the pharmaceutical care plan

Source: American College of Clinical Pharmacy (ACCP)

CHAPTER FOUR RESULTS

4.1 Introduction

This chapter summarizes the key findings of the research based on the study objectives. The results have been presented in form of frequency tables, normal tables, pie charts and bar graphs. The association between variables is also demonstrated

4.2 Characteristics of Study participants

4.2.1 Sociodemographic Characteristics

A total of 110 study participants were recruited into the study and **Table 4.1** summarizes their sociodemographic characteristics.

Table 4. 1 Sociodemographic Characteristics

Variable	Category	Frequency n (%)
Sex	Male	70 (63.6%)
	Female	40 (36.4%)
Age (years)	18 - 34	32 (29.1%)
	35 - 54	50 (45.5%)
	55 - 64	21 (19.1%)
	65 and above	7 (6.4%)
	Mean ± SD	43.5 ± 13.4
BMI	Below 18.5 (Underweight)	3 (2.8%)
	18.5 – 24 (Normal)	65 (61.3%)
	24 – 29 (Overweight)	22 (20.8%)
	30 and Above (Obese)	16 (15.1%)
Marital status	Single	25 (23.4%)
	Married	82 (76.6%)
Employment status	Unemployed	20 (18.5%)
	Employed	88 (81.5%)
Education status	Primary	9 (8.4%)
	Secondary	31 (29%)
	Tertiary	67 (62.6%)
Where transplant was done	KNH	65 (59.1%)
	Other*	45 (40.9%)
Time on dialysis before transplant	Less than 1 Month	1 (0.9%)
	1-6 Months	7 (6.5%)
	More than 6 Months	100 (92.6%)
Smoking status	Smokers	1 (1.0%)
Alcohol Intake	Take alcohol	1 (1.0%)

*Nairobi Hospital, Aga Khan and India

The majority (70, 63.6%) of the study participants were males and fifty (45.5%) of them were between 35 and 55 years. The mean age was 43.4 years and the majority had attained secondary school level of education and beyond. Sixty-five (59.1%) had done their kidney transplantation at KNH. Only one patient was a smoker and a regular user of alcohol. About 90% of participants had been on dialysis for more than 6 months prior to transplantation.

4.2 Clinical Characteristics

4.2.1 Comorbidities

The comorbidities are summarized in **Figure 4.1**. The majority (102, 92.7%) had hypertension followed by diabetes at (34, 30.9%). The least common were lupus and polycystic ovary syndrome at (2, 1.9%) each. Two study participants had no comorbidity.

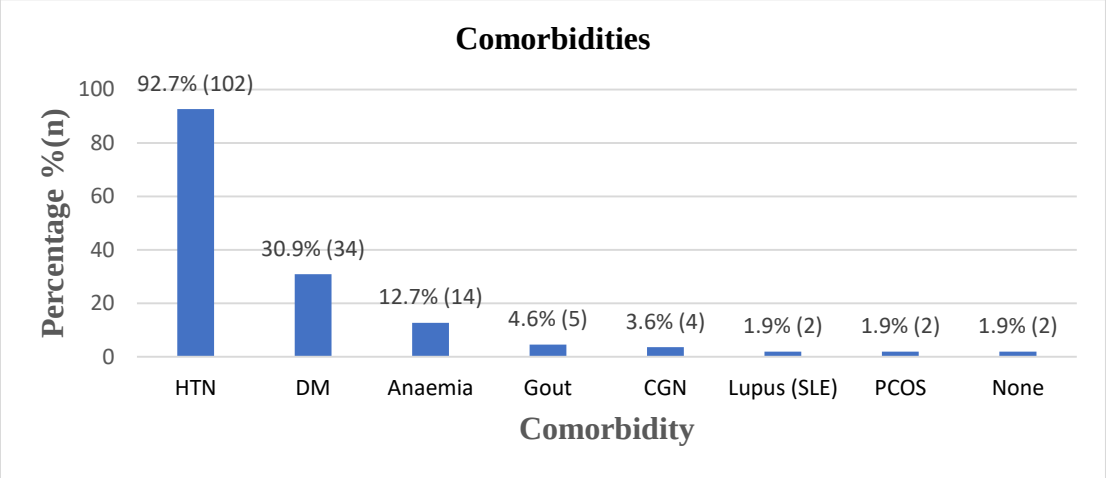

Figure 4. 1 Comorbidities of study participants (N=110)

KEY: *HTN= Hypertension, DM= Diabetes, CGN = Chronic Glomerulonephritis, SLE= Systemic Lupus Erythematosus and PCOS=Polycystic Ovary Syndrome*

4.2.2 Drugs used by Study participants

4.2.2.1 Immunosuppressive regimens

Figure 4.2 and **Figure 4.3** shows the patterns of immunosuppressant use among participants

Forty-four (40%) participants were on a combination of Tacrolimus, Mycophenolic acid and prednisolone and one (0.9%) was a combination of everolimus, Mycophenolate mofetil and prednisolone.

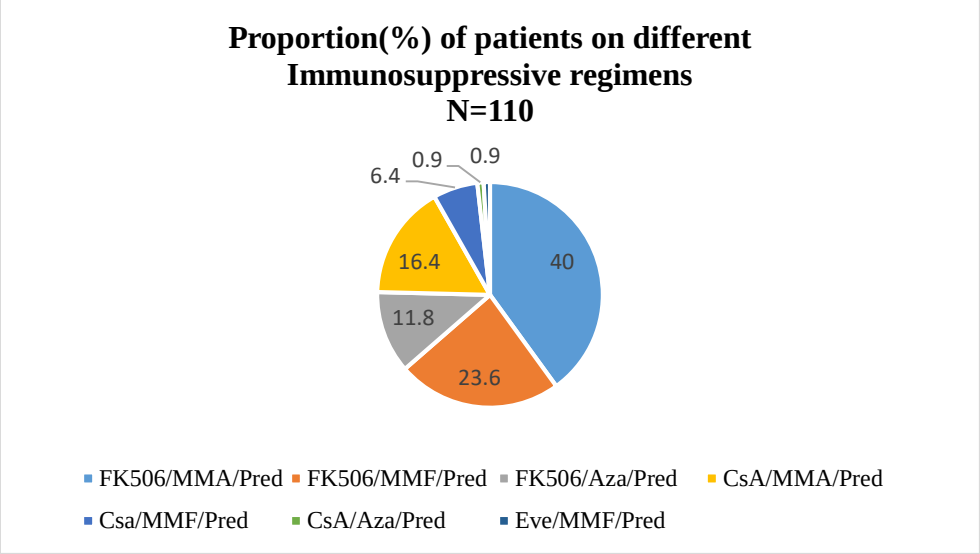

Figure 4. 2 Proportion (%) of patients on different Immunosuppressive regimens

KEY: *FK506=Tacrolimus, CsA=Cyclosporine, MMA= Mycophenolic Acid, MMF=Mycophenolate Mofetil, Pred=Prednisolone, Aza=Azathioprine and Eve=Everolimus*.

Prednisolone was universally used followed by Tacrolimus (83, 75.5%). Azathioprine and Everolimus were the least commonly used immunosuppressants. (**Figure 4.3**)

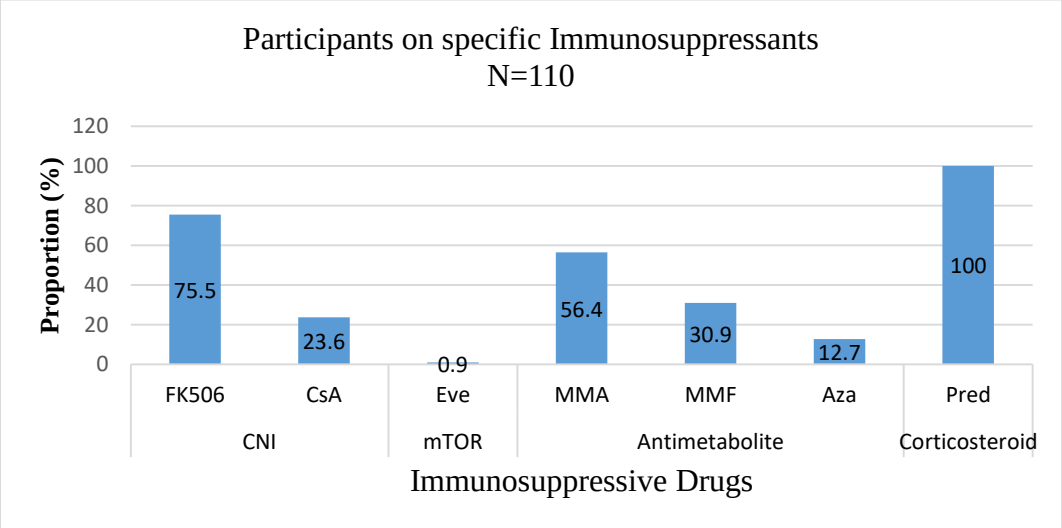

Figure 4. 3 Proportion of patients on specific Immunosuppressants

4.2.2.2 Antihypertensive Drugs used by the study participants

The types of antihypertensive medications used among the participants are depicted in **Figure 4.4** and **Table 4.2** below.

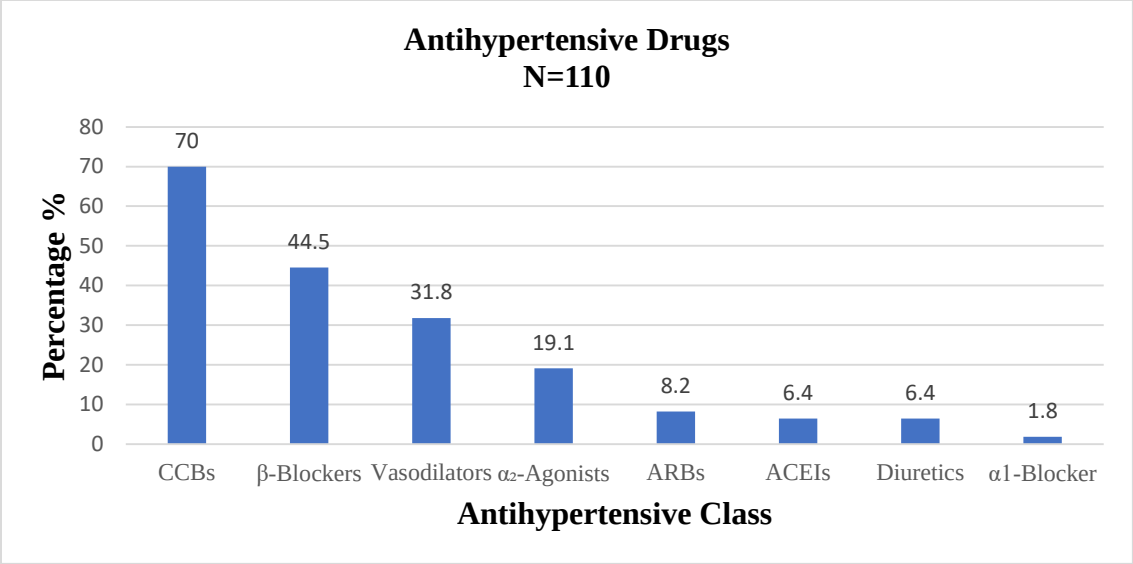

Figure 4. 4 Classes of Antihypertensive drugs prescribed among hypertensive participants

Key: *CCB=Calcium Channel blocker, ARB=Angiotensin Receptor Blocker, ACEI=Angiotensin Converting Enzyme inhibitor*

Dihydropyridine calcium Channel blockers were the most commonly prescribed antihypertensive drugs followed by β-Blockers, Hydralazine and methyldopa. Among those with hypertension, an α_2 agonist was also preferred. ACEIs, diuretics, and α1 blocker (Prazosin) were the least prescribed antihypertensive drugs among the participants

Table 4. 2 Antihypertensive drugs prescribed among the participants (N=110)

Broad class	Specific class	Drug	Frequency n (%)
β-Blocker	Selective β1 Blocker	Metoprolol	23 (20.9%)
		Nebivolol	10 (9.1%)
		Atenolol	7 (6.5%)
	Unselective β&α1 blocker	Carvedilol	9 (8.2%)
Alpha agonists & antagonists	α 2 agonist	Methyldopa	17 (15.9%)
		Clonidine	4 (3.7%)
	α1 blocker	Prazosin	2 (1.9%)
Peripheral Dilator	Arterial	Hydralazine	35 (33.0%)
CCBs	Dihydropyridine	Amlodipine	41 (37.6%)
		Nifedipine	35 (32.1%)
		Felodipine	1 (0.9%)
	Benzothiazepine	Diltiazem	1 (0.9%)
ARBs & ACEIs	ARB	Losartan	9 (8.3%)
	ACEI	Enalapril	7 (6.5%)
Diuretics	Loop Diuretics	Furosemide	2 (1.8%)
	Thiazides	HCTZ	2 (0.9%)
		Indapamide	1 (0.9%)
		Metolazone	1 (0.9%)
	K-Sparing	Spironolactone	1 (0.9%)

Key: *CCB=Calcium Channel blocker, ARB=Angiotensin Receptor Blocker, ACEI=Angiotensin Converting Enzyme inhibitor, HCTZ=Hydrochlorothiazide*

4.2.2.3 Types of Antidiabetic Drugs used

Insulin was the most commonly prescribed hypoglycemic drug while Sitagliptin and Vildagliptin were the least common as illustrated in **Figure 4.5**

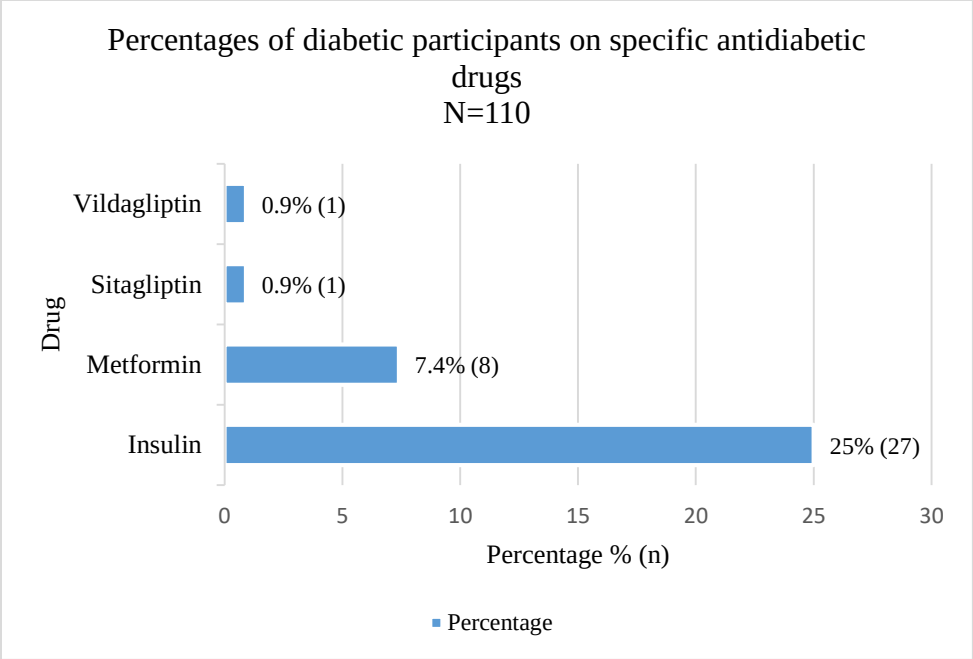

Figure 4. 5 Proportion of patients on specific hypoglycemic drugs

4.2.2.4 Lipid-Lowering Drugs

Among the study participants who were on a lipid-lowering drug, thirteen (12%) were on statins. Atorvastatin (11, 10.1%) was the most commonly prescribed statin whereas both rosuvastatin and fluvastatin were the least preferred as shown in **figure 4.6**

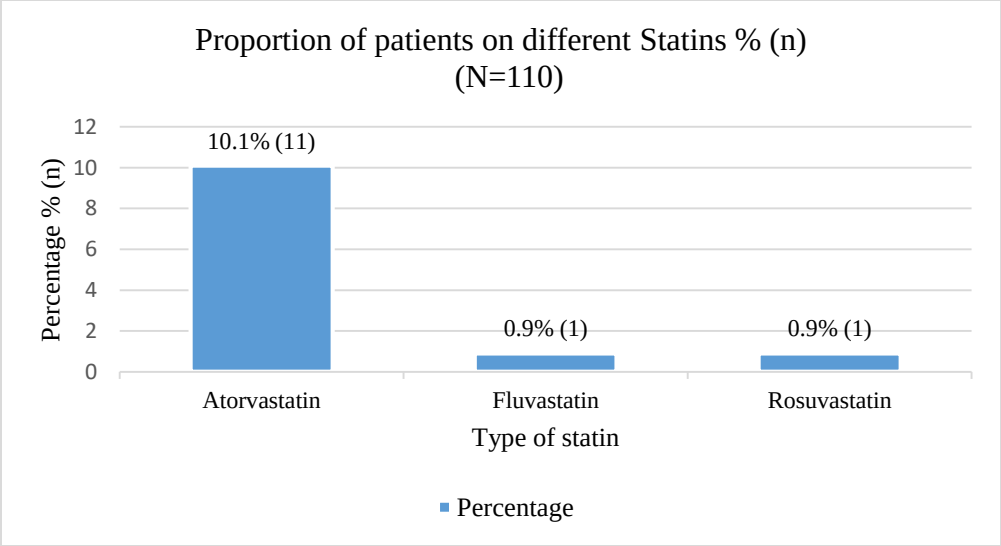

Figure 4. 6 Serum lipids lowering drugs use among participants

4.3 Dyslipidaemias

4.3.1Frequency of checking serum lipids levels

Sixty-eight (61.8%) participants had at least one measure of lipids in the last one year prior to and including the clinic date.

Among the 68 participants, forty-five (66%) had their serum lipid levels checked once in the last one year whereas 17 (25.0%) had theirs checked every 4 to 6 months. Only a few of these participants (6, 8.8%) had their lipid levels checked every 3 months.

4.3.2 Types and prevalence of dyslipidaemias among the participants

Among the 68 participants who had a measure of lipids within the last year prior to the clinic date, forty-nine (72%) had a form of dyslipidaemia. Thus, the overall prevalence of dyslipidaemia of any type among participants with a measure of lipids was 72%.

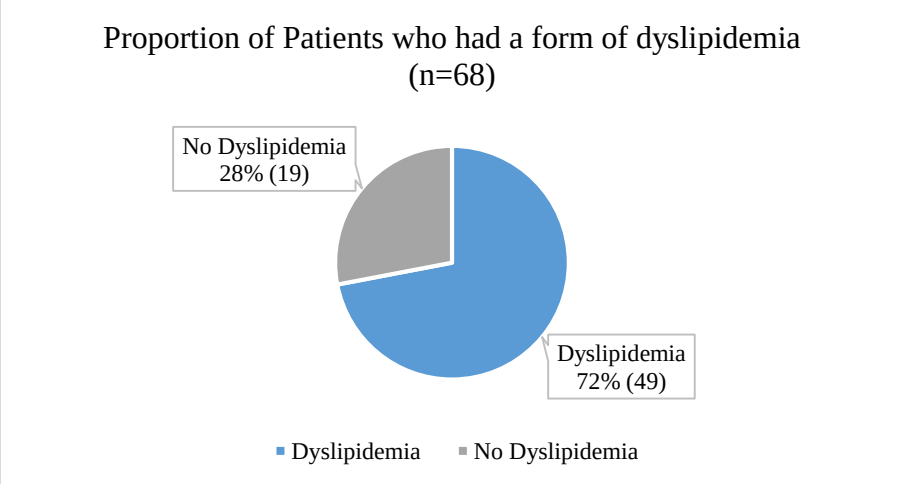

Figure 4. 7 Proportion of patients with dyslipidaemia

Types of dyslipidaemia were classified into 7 categories (**Figure 4.8**) The most common types of dyslipidaemias were raised LDL-C(30,44.1%) and raised non-HDL-C (30,44.1%) followed by raised total cholesterol, hypertriglyceridemia, Low HDL-C, raised triglycerides: HDL ratio, and raised LDL-C: HDL-C ratio which had the lowest prevalence.

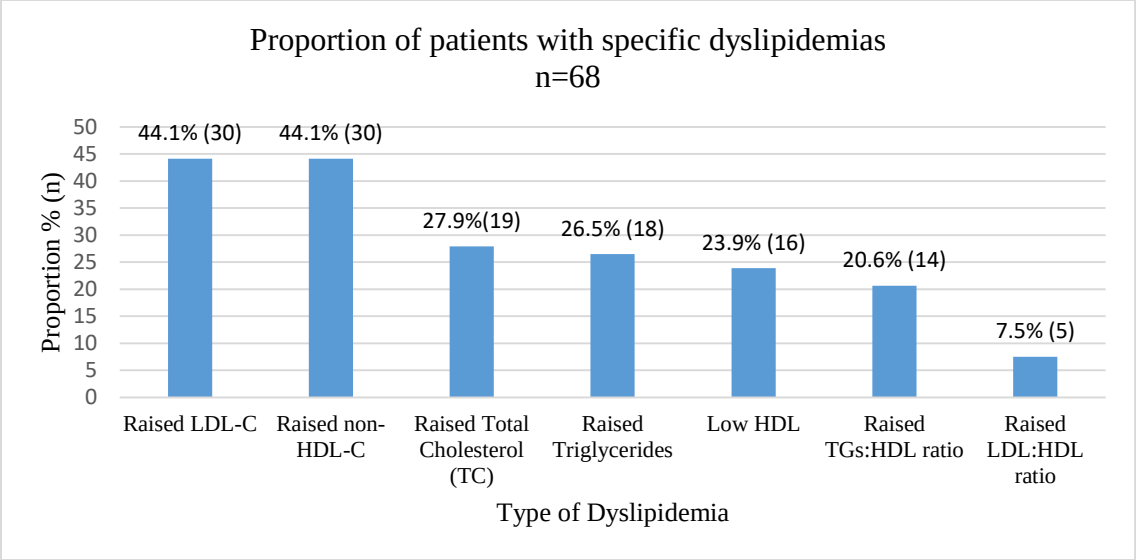

Figure 4. 8 Prevalence of different types of dyslipidaemias

Key: *LDL-C=Low density Lipoprotein cholesterol, HDL-C=High density lipoprotein cholesterol, TC= Total cholesterol TGs=Triglycerides*

In addition, some forms of dyslipidaemia including raised TC, raised LDL-C and hypertriglyceridemia were further classified into different categories (**Figure 4.9**).

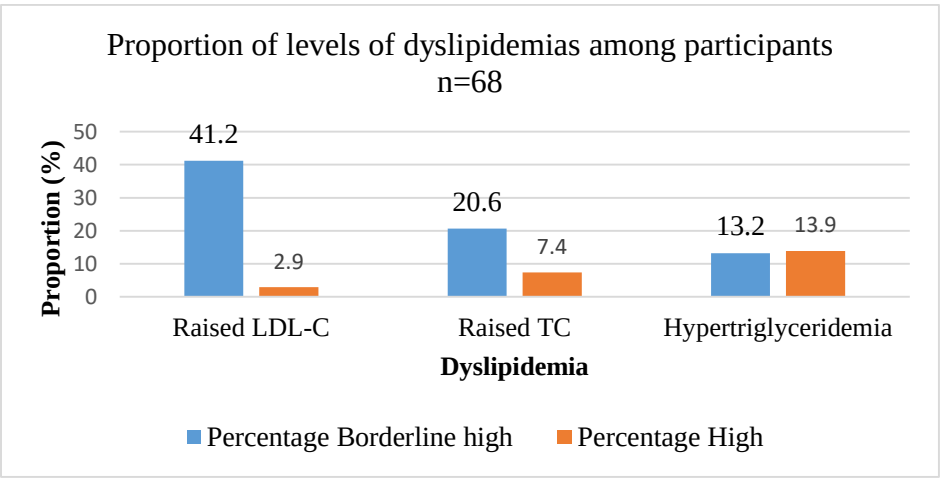

Figure 4. 9 Proportion of participants with different levels of dyslipidaemias

Key: *LDL-C=Low density Lipoprotein cholesterol, TC= Total cholesterol TGs=Triglycerides*

Nine (13.2%) participants had high levels of triglycerides whereas five (7.4%) had high levels of total cholesterol (**Figure 4.9**). Two (2.9%) participants had high levels of LDL-

C. Mean levels of most of the serum lipid parameters were close to the cutoff point for dyslipidaemia (**Table 4.3**)

Table 4. 3 Mean levels of Serum lipid levels

Variable	Mean (mg/dL) ± SD (mg/dL)	Minimum(mg/dL)	Maximum(mg/dL)
TC	175.5± 44.7	88.9	290
LDL-C	97.7± 40.0	27.1	297.8
HDL-C	54.2±24.7	19.3	208.1
TGs	128.2±71.4	11.6	363.2
Non-HDL-C	123.7±41.3	57.6	232

Key: *LDL-C=Low density Lipoprotein cholesterol, HDL-C=High density lipoprotein cholesterol, TC= Total cholesterol TGs=Triglycerides*

4.4 Complications associated with dyslipidaemias in RTRs

Thirteen (12.0%) participants had a complication that may be associated with dyslipidaemias. (**Figure 4.10**) Chronic Allograft failure had the highest prevalence of eight (7.4%) followed by angina (4, 3.7%). Transient Ischaemic attack (TIA) was the least prevalent.

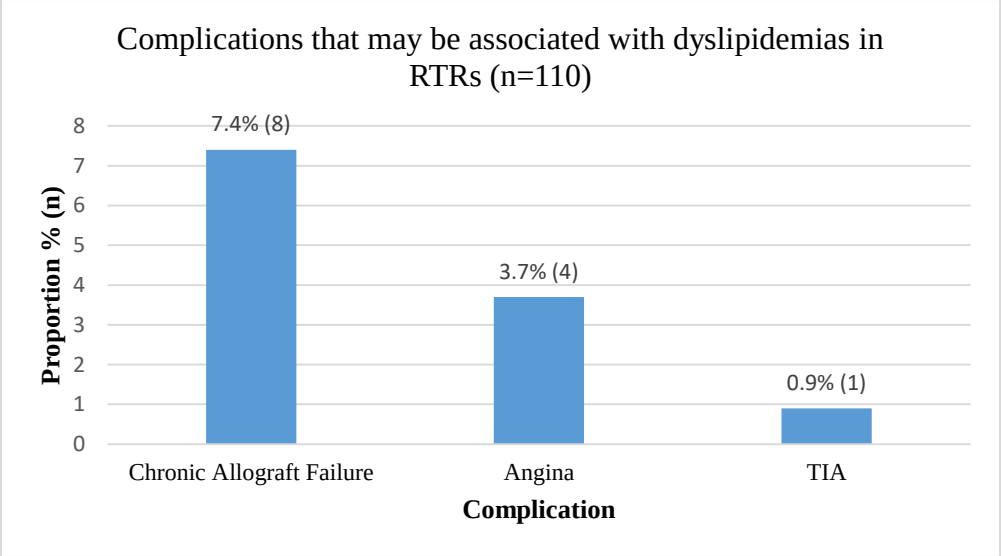

Figure 4. 10 Complications that may be associated with dyslipidaemias in RTRs

Key: TIA=*Transient Ischaemic Attack*

Thirty-five (32.1%) participants had serum creatinine levels that were higher than normal while twenty-four (22.0%) had proteinuria.

4.5 Lifestyle Modification Strategies

The study participants were using different lifestyle modification strategies (**Figure 4.11**) One hundred and nine (99%) out of 110 who responded on smoking and alcohol intake admitted to abstaining from both smoking and alcohol intake. Sixty (57.7%) participants reported that they were regularly watching their weight and sixty-nine (66.4%) participants reported that they were engaged in physical activity.

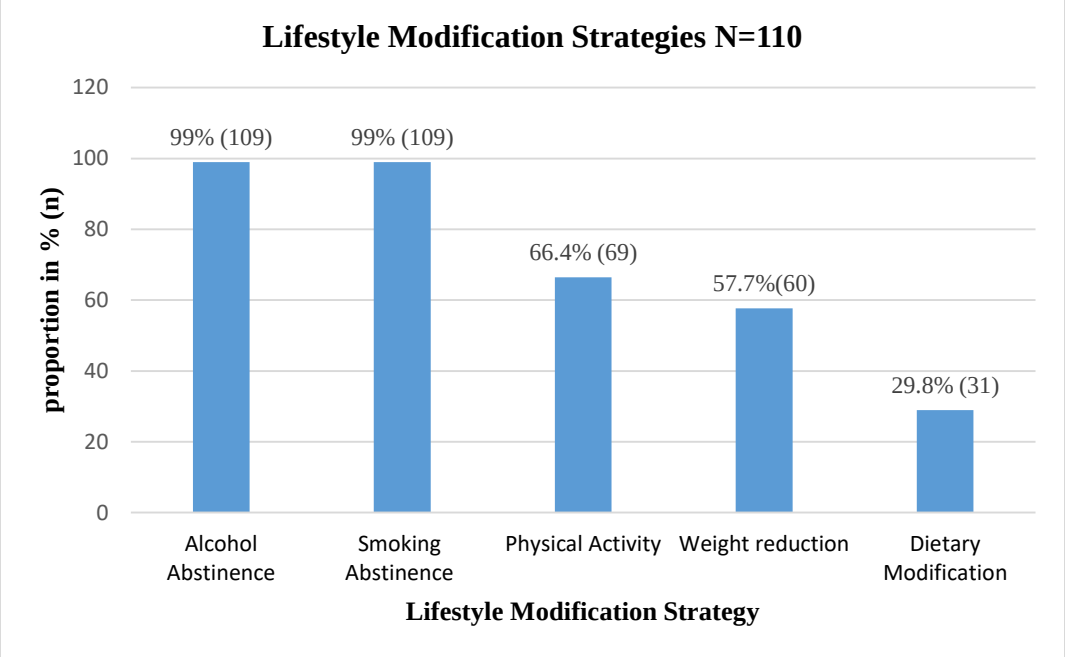

Figure 4. 11 Lifestyle modification strategies among RTRs who participated in the study

Only 31 (29.8%) participants adhered to dietary modification daily (**Figure 4.13**). The most common form of physical activity among the RTRs was walking for more than 2 kilometres (km), 98 (94.2%) followed by digging, 2 (1.9%) and exercise in a gym, 1 (0.9%)

Only 11 (10.6%) RTRs who participated in the study had an exercise plan different from their daily activity (**Figure 4.12**) and twenty-seven (26.0%) had an exercise plan with their physician (**Figure 4.12**). Interestingly, a partly twenty-nine (31.5%) participants adhered to whatever exercise plan they had. Fifty (48.5%) would engage in a physical activity lasting at least 20 minutes at least 4 times every week (**Figure 4.12**)

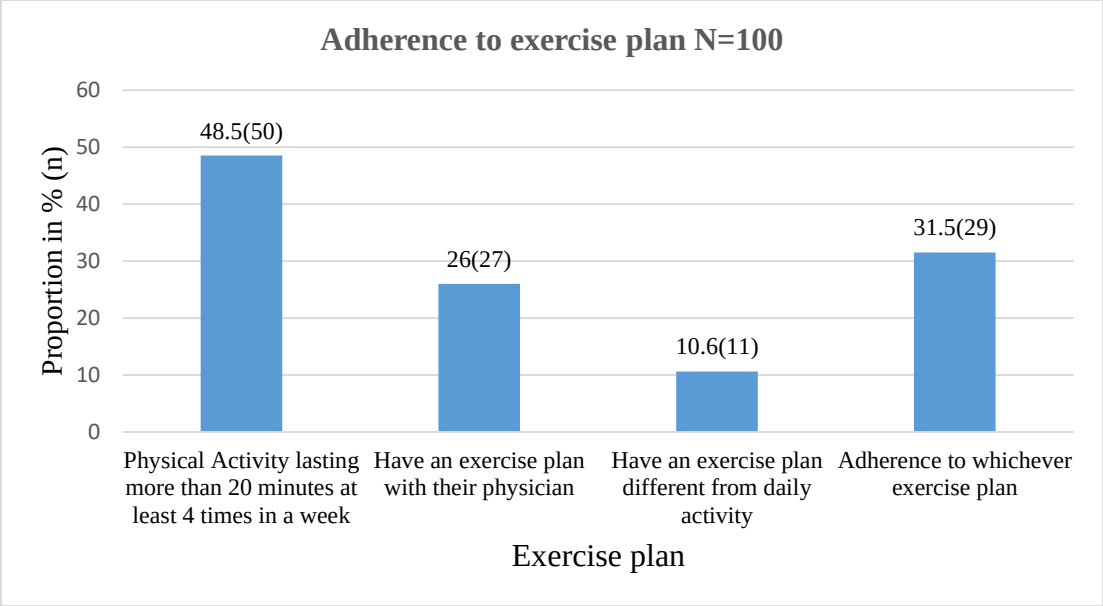

Figure 4. 12 Adherence to exercise plan

Most (56, 53.1%) participants admitted that they would only adhere to reduced saturated fats intake at times while 60 (57.7%) used increased fibre intake intermittently (**Figure 4.13**).

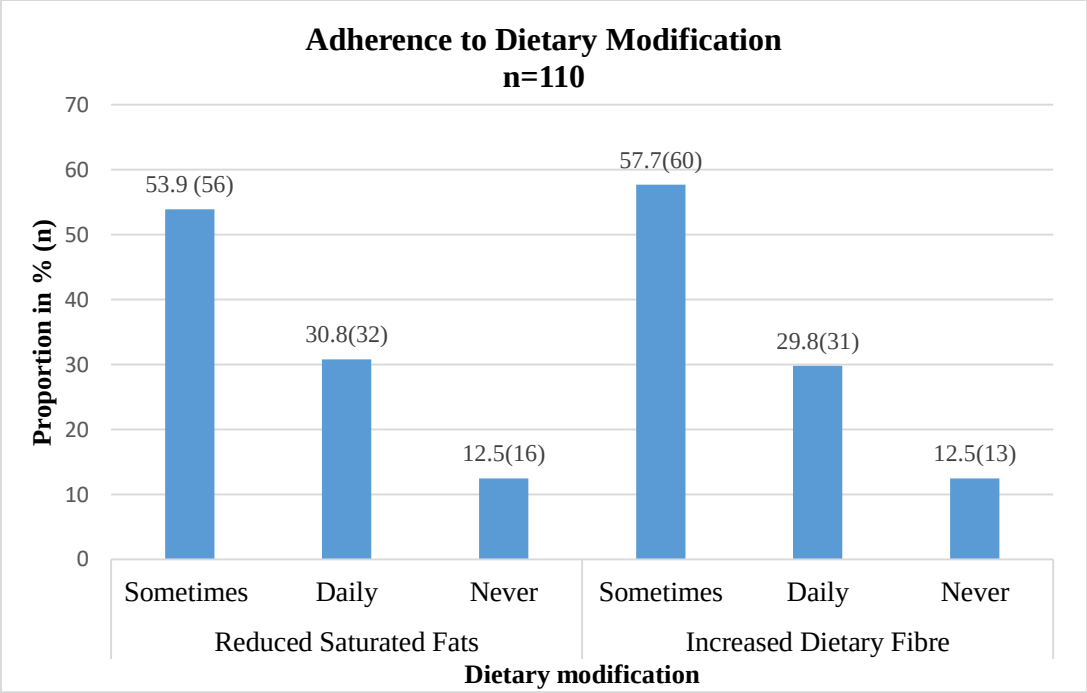

Figure 4. 13 Adherence to specific dietary modification strategies

4.6 Association between Participants' characteristics and dyslipidaemia

4.6.1 Association between sociodemographic characteristics and dyslipidaemia

Association between dyslipidaemia and sociodemographic characteristics was assessed using Fischer's exact test. None of the sociodemographic characteristics had a significant association with dyslipidaemia. However, Gender, BMI and time on dialysis before transplant had the lowest p-values; 0.103, 0.308 and 0.181 respectively. The findings are as shown in **Table 4.4**

Table 4. 4 Association between sociodemographic characteristics and dyslipidaemia

Variable	Category	Dyslipidaemia present	P-Value	
		No	**Yes**	
Gender	Male	8 (42.1%)	32 (65.3%)	0.103
	Female	11 (57.9%)	17 (34.7%)	
Age (years)	18 - 34	5 (26.3%)	15 (30.6%)	0.859
	35 - 54	9 (47.4%)	17 (34.7%)	
	55 - 64	4 (21.0)	13 (26.5%)	
	65 and above	1 (5.3%)	5 (8.2%)	
BMI	Below 18.5	1 (5.6%)	1 (2.0%)	0.308
	18.5 – 24	12 (66.7%)	24 (49.0%)	
	24 – 29	3 (16.7%)	10 (20.4%)	
	30 and Above	2 (11.1%)	14 (28.6%)	
Marital status	Single	4 (22.2%)	12 (24.5%)	1.000
	Married	14 (77.8%)	37 (75.5%)	
Employment status	Unemployed	4 (79.0%)	10 (20.4%)	1.000
	Employed	15 (21.0%)	39 (79.6%)	
Education status	Primary	1 (5.6%)	6 (12.2%)	0.853
	Secondary	6 (33.3%)	17 (34.7%)	
	Tertiary	11 (61.1%)	26 (55.2%)	
Transplant done	KNH	8 (42.1%)	22 (44.9%)	1.000
	Other*	11 (57.9%)	27 (55.1%)	
Kidney transplant	Once	18 (100.0%)	48 (98.0%)	1.000
	More than Once	0 (0%)	1 (2.0%)	
Time on Dialysis before transplant	1-6 Months	0 (0.0%)	6 (9.0%)	0.181
	More than 6 Months	18 (100.0%)	43 (91.0%)	

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More males had dyslipidaemia as compared to females although this observed difference was not statistically significant (P=0.103). Age and BMI categories of participants did not have a statistically significant influence on the occurrence of dyslipidaemia (P=0.854 and 0.308 respectively). Similarly, the highest education level attained and time on dialysis before the transplant didn't significantly influence the presence of dyslipidaemia (p=0.853 and 0.181 respectively). There was no association between marital status, employment status, venue of transplantation, number of transplant and dyslipidaemia (p=1.000)

4.6.2 Association between Clinical characteristics and dyslipidaemia

4.6.2.1 Association between Comorbidities and dyslipidaemia

There was a statistically significant association between weight gain and dyslipidaemia (P=0.001). Obesity, diabetes and the presence of proteinuria did not have a significant influence on dyslipidaemia (P=0.126, 0.786 and 0.551 respectively)

Table 4. 5 Association between Comorbidities and dyslipidaemia

Variable	Category	Dyslipidaemia present		P-Value
		No (n (%)	Yes (n (%)	
Diabetes	NO	12 (63.2)	28 (57.1)	0.786
	YES	7 (36.8)	21 (42.1)	
Obese	NO	16 (88.9)	34 (69.4)	0.126
	YES	2 (11.1)	15 (30.6)	
Proteinuria	NO	15 (79.0)	33 (68.8)	0.551
	YES	4 (21.0)	15 (31.2)	
Weight Gain	NO	17 (94.4)	21 (42.9)	**0.001***
	YES	1 (5.6)	28 (57.1)	

Key: * statistically significant

4.6.2.2 Association between drugs and dyslipidaemia

The participants were using different classes of drugs. None of the drugs had a significant association with dyslipidaemia as illustrated in **Table 4.6**. Using a calcium channel blocker was associated with dyslipidaemia even though this association was not statistically significant (P=0.090). The influence of using a Biguanide (metformin), a peripheral arterial dilator (hydralazine), α_2 agonist or a selective β-blocker on dyslipidaemia was not significant (P=0.175, 0.241, 0.353 and 0.421 respectively). Use of Tacrolimus, MMA, MMF or cyclosporine did not have a significant association with the occurrence of

dyslipidaemia (P=0.761, 0.581, 0.371 and 0.761 respectively). There was no association between use of Thiazide diuretic or Azathioprine and dyslipidaemia (P=1.000 in each)

Table 4. 6 Association between drugs and dyslipidaemia

Variable	Category	Dyslipidaemia present		P-Value
		No (n (%)	Yes (n (%)	
α 2 agonist (methyldopa and clonidine)	NO	13 (68.4)	39 (79.6)	0.353
	YES	6 (31.6)	10 (20.4)	
Calcium channel blocker	No	10 (52.6)	14 (28.6)	0.090
	Yes	9 (47.4)	35 (71.4)	
Selective β-Blocker	NO	8 (42.1)	27 (55.1)	0.421
	YES	11 (57.9)	22 (44.9)	
Peripheral arterial dilator (hydralazine)	NO	10 (55.6)	34 (72.3)	0.241
	YES	8 (44.4)	13 (27.7)	
Loop diuretic	NO	18 (94.7)	48 (98.0)	0.484
	YES	1 (5.3)	1 (2.0)	
Thiazide diuretic	NO	17 (94.4)	47 (95.90	1.000
	YES	1 (5.6)	2 (4.1)	
Insulin	NO	14 (73.7)	32 (65.3)	0.575
	YES	5 (26.3)	17 (34.7)	
Biguanide (metformin)	NO	19 (100.0)	43 (87.8)	0.175
	YES	0 (0.0)	6 (12.2)	
Tacrolimus	NO	4 (21.0)	13 (26.5)	0.761
	YES	15 (79.0)	36 (73.5)	
Cyclosporine	NO	15 (79.0)	36 (73.5)	0.761
	YES	4 (21.0)	13 (26.5)	
Mycophenolic Acid	NO	9 (47.4)	18 (36.7)	0.581
	YES	10 (52.6)	31 (63.3)	
Mycophenolate Mofetil	NO	12 (63.2)	37 (75.5)	0.371
	YES	7 (36.8)	12 (24.5)	
Azathioprine	NO	17 (89.5)	43 (87.8)	1.000
	YES	2 (10.5)	6 (12.2)	

4.6.3 Association between lifestyle modification strategies and dyslipidaemia

There was a higher number of participants with dyslipidaemia among those who did not use dietary modification strategy compared with those who used and the difference was significant (P=0.001). Engaging in physical activity, reduced intake of saturated fats and increased consumption of dietary fibre also had a significant association with

dyslipidaemia (P=0.037, <0.001 and 0.001 respectively). Additionally, adherence to exercise plan had a significant influence on dyslipidaemia (p<0.001) as was the case with physical activity for more than 20 minutes at least 4 times every week (P=0.002).

Even though weight reduction strategy (p=0.166), Type of physical activity (p=0.573), having an exercise plan different from daily activity (P=0.199) and having an exercise plan with a physician (P=0.543) had an influence on dyslipidaemia, the observed association was not significant.

Table 4. 7 Association between lifestyle modification strategies and dyslipidaemia

Variable	Category	Dyslipidaemia present		P-Value
		No (n (%)	Yes (n (%)	
Dietary modification	NO	6 (33.3)	43 (89.6)	**0.001***
	YES	12 (66.7)	5 (10.4)	
Weight reduction	NO	6 (33.3)	27 (56.3)	0.166
	YES	12 (67.7)	21 (43.7)	
Physical Activity	NO	2 (11.1)	19 (39.6)	**0.037***
	YES	16 (88.9)	29 (60.4)	
Adherence to diet	NO	5 (27.8)	42 (87.5)	**<0.001***
	YES	13 (72.2)	6 (12.5)	
Reduced intake of saturated fats	YES	13 (72.2)	6 (12.5)	**<0.001***
	NO	2 (11.1)	11 (22.9)	
	Sometimes	3 (16.7)	31 (64.6)	
Increased consumption of dietary fibre	Yes	11 (61.1)	7 (14.6)	**0.001***
	No	2 (11.1)	8 (16.7)	
	Sometimes	5 (27.8)	33 (68.70	
Type of Activity	Digging	1 (5.6)	1 (2.1)	0.573
	Walking	16 (88.9)	45 (13.8)	
	None	1 (5.6)	2 (4.2)	
Exercise plan different from daily Activity	NO	14 (77.8)	44 (91.7)	0.199
	YES	4 (22.2)	4 (8.3)	
Have exercise Plan with Doctor	NO	12 (66.7)	36 (75.0)	0.543
	YES	6 (33.3)	12 (25.0)	
Adherence to any exercise plan	NO	5 (33.3)	36 (87.8)	**<0.001***
	YES	10 (66.7)	5 (12.2)	
Physical For at least 20min at least 4 times a week	NO	4 (22.2)	32 (68.1)	**0.002***
	YES	14 (77.8)	15 (31.9)	

4.7 Independent Predictors of dyslipidaemias in RTRs

4.7.1 Predictors of the overall dyslipidaemia

Bivariate and multivariate logistic regression analysis was performed to determine the independent predictors of the presence of any type of dyslipidaemia in RTRs and the results are as summarized in **Table 4.8**. In the bivariable model, the characteristics that were found to be predictors were weight gain (COR=22.67, CI=2.79-184.11; P=0.003) and those who recorded a gain in weight were 22.67 times likely to have dyslipidaemia compared to those who didn't record gain in weight. Dyslipidaemia was less prevalent in RTRs who engaged in physical activity (COR=0.19, CI=0.04-0.93; P=0.040) where those who engaged in physical activity were 0.19 likely to have dyslipidaemia compared to those who didn't. Dietary modification (COR=0.06, CI=0.02-0.22; P<0.001) was a strong predictor where RTRs who modified their diet were 0.06 times likely to have dyslipidaemia compared to those who didn't. However, gender, BMI, proteinuria, use of a Calcium channel blocker, use of hydralazine and use of mycophenolate mofetil were not significantly associated with dyslipidaemia. Multivariable logistic regression analysis established that only one variable was statistically significant as an independent predictor for dyslipidaemia in RTRs where those who modified their diet had 0.03 times (AOR=0.03, CI=0.003-0.32; P=0.004) the odds of developing dyslipidaemia compared to those didn't.

Table 4. 8 Independent Risk factors for dyslipidaemia in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
Gender	0.39 (0.13-1.14)	0.086	0.15 (0.01-1.70)	0.126
BMI	1.85 (0.91-3.74)	0.089	0.19 (0.02-1.86)	0.155
Weight gain	22.67 (2.79-184.11)	**0.003***	171.44 (0.96-30440.68)	0.052
Proteinuria	2.67 (0.67-10.51)	0.161	10.01 (0.53-189.82)	0.125
Alpha$_2$- Agonist	0.56 (0.17-1.83)	0.333	1.35 (0.11-16.56)	0.813
CCB	2.78 (0.93-8.29)	0.067	3.54 (0.24-53.11)	0.361
Hydralazine	0.48 (0.15-1.48)	0.200	0.53 (0.04-6.62)	0.624
MMF	0.56 (0.02-0.22)	0.312	0.36 (0.03-4.50)	0.428
Dietary modification	0.06 (0.02-0.22)	**< 0.001***	0.03 (0.003-0.32)	**0.004***
Physical Activity	0.19 (0.04-0.93)	**0.040***	0.13 (0.006-2.79)	0.190

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index, CCB=Calcium Channel Blocker, MMF=Mycophenolate Mofetil

4.7.2 Predictors of high LDL-C levels in RTRs

In the Bivariable logistic analysis, the factors that were found to be predictors of elevated LDL-C (**Table 4.9**)were BMI (COR=2.05, CI=1.14-3.70; P=0.017) where those with a higher BMI had about 2 times the odds of having elevated LDL-C compared to those who didn't. Those who recorded a gain in weight had a higher prevalence of dyslipidaemia compared to those who didn't (COR=6.22, CI=2.14-18.10; P=001) where those who gained weight were 6.2 times likely to have elevated LDL-C compared to those who didn't. The odds of having elevated LDL-C in obese RTRs was 4.27 times compared with none obese ones. (COR=4.27, CI=1.29-14.06; P=0.017) whereas those who engaged in physical activity were 0.005 times likely to have elevated LDL-C compared with those who didn't. Weight reduction (COR=0.16, CI= 0.05-0.47; P=0.001) was a strong predictor where those who reduced their weight we 0.16 times likely to have elevated LDL-C compared to those who didn't. In addition, RTRs who modified their diet were 0.04 times likely to have elevated LDL-C Compared to those who didn't (COR=0.04, CI=0.005-0.35; P=0.003). However, other factors such as DM, Proteinuria, use of cyclosporine and methyldopa were not significantly associated with elevated LDL-C.

Table 4. 9 Independent risk factors for Increased LDL-C levels in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
DM	1.17 (0.44-3.10)	0.748	1.58 9 (0.29-8.60)	0.596
BMI	2.05 (1.14-3.70)	**0.017***	0.19 (0.02-2.00)	0.166
Weight gain	6.22 (2.14-18.10)	**0.001***	1.21 (0.17-8.45)	0.849
Proteinuria	1.26 (0.43-3.67)	0.671	1.32 (0.23-7.58)	0.754
Cyclosporine	3.09 (0.98-9.71)	0.054	6.52 (0.84-50.80)	0.074
Methyldopa	0.20 (0.04-1.00)	0.05	0.07 (0.004-1.12)	0.060
Obese	4.27 (1.29-14.06)	**0.017***	19.91 (0.33-1206.03)	0.153
Weight Reduction	0.16 (0.05-0.47)	**0.001***	0.03 (0.002-0.40)	**0.009***
Dietary modification	0.04 (0.005-0.35)	**0.003**	0.01 (0.0006-0.30)	**0.006***
Physical Activity	0.20 (0.06-0.62)	**0.005**	0.29 (0.05-1.72)	0.173

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index, CCB=Calcium Channel Blocker, MMF=Mycophenolate Mofetil, DM=Diabetes Mellitus**, *statistically significant**

After multivariable logistic regression analysis was conducted, only two variables retained significance including weight reduction (AOR=0.03, CI=0.002-0.40; P=0.00) and dietary modification (AOR=0.01, CI=0.0006-0.30; P=0.006)

4.7.3 Predictors of high Total cholesterol levels in RTRs

In bivariate logistic regression analysis, weight gain was found to be a significant predictor of elevated total cholesterol levels (**Table 4.10**) where those who recorded an increase in weight (COR=4.33, CI=1.39-13.53; P=0.012) had about 4 times the odds of having elevated total cholesterol compared to those who didn't. Similarly Employed RTRs (CI=3.5, CI=1.02-11.96; P=0.046) had 3.5 times the odds of having dyslipidaemia compared to the unemployed RTRs. The prevalence of dyslipidaemia was higher in those who didn't exercise regularly where those who didn't exercise (COR=6.19, CI=1.58-24.28; P=0.009)were 6.19 times likely to have elevated total cholesterol compared to those who did not exercise and this significance was sustained even after multivariable regression analysis (AOR=6.19, CI=1.24-30.75). There was no other predictor that sustained significance after multivariable regression analysis was conducted.

Table 4. 10 Predictors of elevated total cholesterol in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
BMI	1.30 (0.72-2.37)	0.387	0.42 (0.15-1.18	0.099
Weight gain	4.33 (1.39-13.53)	**0.012***	5.15 (0.93-28.54)	0.060
Education	0.50 (0.23-1.08)	0.078	0.59 (0.20-1.77)	0.351
Employment	3.5 (1.02-11.96)	**0.046***	2.65 (0.51-13.79)	0.244
Cyclosporine	2.28 (0.71-7.28)	0.166	2.22 (0.49-10.02)	0.298
Thiazide	5.53 (0.47-64.96)	0.174	19.82 (0.62-635.12)	0.091
Lack of Exercise	6.19 (1.58-24.28)	**0.009***	6.19 (1.24-30.75)	**0.026***

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index**,*statistically significant**

4.7.4 Predictors of hypertriglyceridemia in RTRs

Bivariate logistic regression analysis of predictors of hypertriglyceridemia identified only 2 characteristics that had a significant association with hypertriglyceridemia (**Table 4.11**). Time on dialysis before transplantation was a significant predictor (COR=0.15, CI=0.02-

0.90; P=0.038) where those who had been on dialysis for less than 6months before transplantation were 0.15 times likely to have hypertriglyceridemia after transplantation compared to those who had been on dialysis for longer. This significance was not sustained when the multivariable logistic regression was conducted. The participants who engaged in physical activity for more than 20 minutes at least 4 times in a week (COR=0.10, CI=0.02-0.50; P=0.005) were 0.1 times likely to have hypertriglyceridemia compared with those who didn't. The significance of this association was sustained even after multivariable logistic regression was conducted (AOR=0.15, CI=0.02-0.96; P=0.045). No other characteristic sustained significance after multivariate logistic regression was done.

Table 4. 11 Predictors of Hypertriglyceridemia in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
Time on dialysis before transplant	0.15 (0.02-0.90)	**0.038***	0.11 (0.01-1.16)	0.067
DM	2.22 (0.74-6.64)	0.153	1.08 (0.08-15.61)	0.952
Weight gain	2.71 (0.89-8.22)	0.079	1.57 (0.33-7.43)	0.573
Obese	2.48 (0.77-8.04)	0.129	0.64 (0.12-3.53)	0.610
Insulin	2.85 (0.92-8.72)	0.067	2.34 (0.15-35.69)	0.540
Dietary modification	0.13 (0.02-1.06)	0.057	0.26 (0.02-2.84)	0.268
Physical Activity lasting at least 20 minutes for at least 4 times in a week	0.10 (0.02-0.50)	**0.005***	0.15 (0.02-0.96)	**0.045***

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index, DM=Diabetes Mellitus**, *statistically significant**

4.7.5 Predictors of low HDL-C levels in RTRs

Bivariable model for low HDL-C revealed only 3 characteristics which were found to be significant predictors of low HDL-C levels in RTRs (**Table 4.12**). Use of hydralazine (COR=0.47, CI=0.25-0.88; P=0.019) was a strong predictor where RTRs using hydralazine had 0.019 times the odds of having low HDL-C compared to those who didn't. Those who did not consume dietary fibre regularly (COR=3.60, CI=1.27-10.19; P=0.016) were 3.6 times likely to have low HDL-C compared to those who did as was the case with RTRs who did not reduce their intake of saturated fats (COR=2.79, CI=1.18-6.63; P=0.020) who

had 2.8 times the odds of having low HDL-C compared to those who did. Multivariable logistic regression analysis revealed that none of the characteristics was a significant independent predictor of Low HDL-C

Table 4. 12 Predictors of Low HDL-C in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
Gender	0.38 (0.11-1.32)	0.127	0.28 (0.06-1.27)	0.098
Obese	0.33 (0.07-1.65)	0.178	0.72 (0.11-4.92)	0.738
Tacrolimus	6.86 (0.83-56.50)	0.074	8.52 (0.79-91.71)	0.077
Hydralazine	0.47 (0.25-0.88)	**0.019***	0.32 (0.05-2.08)	0.234
Increased intake of dietary Fibre	3.60 (1.27-10.19)	**0.016***	2.73 (0.41-18.03)	0.297
Reduced intake of saturated fats	2.79 (1.18-6.63)	**0.020***	1.64 (0.36-7.38)	0.520
Physical Activity lasting at least 20 minutes for at least 4 times in a week	0.35 (0.10-1.25)	0.105	0.51 (0.11-2.44)	0.398

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index**, *statistically significant**

4.7.6 Predictors of high non-HDL-C levels in RTRs

Adherence to dietary plan (COR=0.15, CI=0.04-0.59, P=0.007) and engaging in physical activity for a minimum of 20 minutes at least 4 times in a week (COR=0.27, CI=0.10-0.78; P=0.015)were the only characteristics that were significant predictors of elevated non-HDL-C in RTRs identified by the bivariable model (**Table 4.13**). Renal transplant recipients who adhered to their dietary plan were 0.15 times likely to have elevated non-HDL-C compared to those who didn't. Similarly, those who engaged in physical activity for a minimum of 20 minutes on most days of the week had 0.27 times the odds of having elevated non-HDL-C compared to those who didn't. Multivariable regression analysis revealed only one characteristic as a significant predictor of elevated non-HDL-C where those who adhered to their dietary plan (COR=0.14, CI=0.03-0.80, P=0.027) were 0.14 times likely to have elevated non-HDL-C compared to those who didn't.

Table 4. 13 Predictors of elevated non-HDL-C in RTRs

Variable	Bivariate Analysis		Multivariate analysis	
	COR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
Cyclosporine	1.61 (0.53-4.85)	0.399	5.24 (0.89-31.01)	0.068
Hydralazine	0.50 (0.17-1.48)	0.210	0.35 (0.08-1.59)	0.172
Atenolol	0.22 (0.02-2.00)	0.179	0.16 (0.01-1.90)	0.145
Proteinuria	0.63 (0.21-1.89)	0.413	0.47 (0.11-2.03)	0.315
Weight gain	2.11 (0.79-5.65)	0.137	2.17 (0.59-8.00)	0.243
Adherence to dietary plan	0.15 (0.04-0.59)	**0.007***	0.14 (0.03-0.80)	**0.027***
Physical Activity lasting at least 20 minutes for at least 4 times in a week	0.27 (0.10-0.78)	**0.015***	0.77 (0.20-2.97)	0.703

COR=Crude Odds Ratio, AOR=Adjusted Odds Ratio, CI=confidence interval, BMI=Body mass Index**, *statistically significant**

CHAPTER FIVE: DISCUSSION, SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses key findings of the study within the context of existing research literature. Conclusions and recommendations for policy, practice and further research have been highlighted based on key findings from the research study

5.2 Discussion

Findings from this study showed a male predominance with the mean age of participants being 43.4 years with most being employed and these findings were similar to those of a study done in the same setting and elsewhere around the world (48,62–65). Studies done in different settings globally including the US have revealed that women have a lower chance of accessing haemodialysis and transplantation compared to their male counterparts as result of lower income/ socioeconomic status, gender bias, lack of social support systems as well as different health-seeking behaviours (66,67).In contrast, a study in France found the mean age to be higher at 58 years because the inclusion criteria involved only patients who were 50 years or older (68) while another study in Korea had a female gender predominance (60). The predominant age group was between 35 and 54 years and this may be explained by the onset of hypertension and diabetes which are the leading causes of chronic kidney disease and subsequently renal failure (69). Hypertension was the most prevalent comorbidity affecting almost all the participants followed by diabetes and this tallies with other studies done in the same setting and in other centres around the globe (7,48,68,70,71). Both hypertension and diabetes are known to be the leading causes of renal failure.

A sizeable proportion of the patients (38%) did not have a measure of lipids within the last one year prior to the study contrary to recommendations by KDIGO guidelines which recommend at least one measure every year and even more frequent measurement for RTRs at higher risk for dyslipidaemia for example those with diabetes (55). The reason for this discrepancy was beyond the scope of this study although it could be attributable to the extra cost of doing the lipids measure given that most RTRs on follow up have to pay out of pocket for their care. The overall prevalence of dyslipidaemia among those RTRs with a

measure of lipids was 72% and this is similar to reported prevalence of dyslipidaemia among RTRs in other closely related studies done locally and internationally which vary remarkably from between 16% and 90% with most reporting a prevalence of greater than 50% (10,68,72–75). The variations in prevalence may be explained by variations in patient background, genetic factors, differences in immunosuppressive and antihypertensive regimens used by various transplant centres in addition to differences in diagnostic criteria for example amongst Japanese population elevation in total cholesterol is not considered a dyslipidaemia because it is not associated with increased CVD risk (72). Seven types of dyslipidaemia that have clinical utility were identified among participants in this study and this is in line with evidence from related studies. Elevated LDL-C and non-HDL-C had the highest prevalence at 44.1% each and these findings were similar to research done in France(13) and others done in the US (7,8,76). However other studies found a higher prevalence of LDL-C among RTRs (77,78). The prevalence of hypertriglyceridemia was relatively low at 27% contrary to higher reported prevalence in other studies which ranged from 43% to 86.6% (13,76,77,79). However, one study in Sweden reported a similar prevalence (78). Elevated total cholesterol had a prevalence of 28% in contrast to between 40% and 60% that has been reported by studies done in Europe and Asia (13,76,78). This prevalence was similar to the findings from a study done India (79). About 24% of the study participants had low HDL-C which tallies with the results of a study done in France (13). Lipids levels change with the time period from the day transplantation is done and hence because the evaluation of levels is done at a different time frame from the day of transplantation in different studies, this may further explain the variability in prevalence in addition to other factors outlined earlier that affect overall dyslipidaemia (72).

Univariate analysis of predictors of overall dyslipidaemia showed that there was a significant association between dyslipidaemia and weight gain (P=0.003), Dietary modification (P=<0.001) and Physical activity (P=0.040). However, multivariable analysis revealed dietary modification as the only significant independent predictor of overall dyslipidaemia in RTRs. These results are in accord with published studies that have shown that dietary indiscretion, lack of exercise and weight gain are significantly associated with dyslipidaemia after renal transplant (79–82). Reduced dietary total and saturated fat intake

has been shown to reduce weight significantly and also improve serum lipid profile with reduction in TC and LDL-C (81). In contrast, other studies have demonstrated that cumulative dose of prednisolone, male gender, use of β-blockers, blood levels of cyclosporine ($Cmin_{ss,}$ AUC, and C2), use of diuretics, Obesity, BMI, proteinuria, pretransplant dyslipidaemia to be significant risk factors of dyslipidaemia after renal transplantation (10,28,36,72,76,83). In this study, the cumulative dose of prednisolone, cyclosporine serum levels, and pretransplant dyslipidaemia were not evaluated and this may partially explain the discrepancy in results. Additionally, the relatively small sample size may have played a role because there were very few patients on cyclosporine and diuretics. In the Univariate model, BMI, weight gain, obesity, dietary modification, physical activity and weight reduction were all found to be significant predictors of elevated levels of LDL-C (>100mg/dl). Only weight reduction and dietary modification were found to be significant predictors of elevated LDL-C in the multivariable model. These findings are in line with published results from similar studies (36,80). Weight gain and obesity are known to induce insulin resistance which interferes with the metabolism of serum lipids including LDL-C. Other studies have shown a statistically significant association between cyclosporine, β-blockers, age, female gender and elevated LDL-C contrary to the findings in this study (69,83,84). Although an association between cyclosporine and elevated LDL-C levels was found, it was not statistically significant (P=0.054) and this could be explained by the very few participants on the cyclosporine-based regimen. The study did not also use cyclosporine levels which were mostly used by other studies that found a significant association. The only independent predictor of elevated total cholesterol (>200mg/dl) was lack of exercise. However, in the bivariable model, weight gain, employment status and lack of exercise had a significant association with elevated total cholesterol. Other studies have found elevated total cholesterol to be significantly and independently associated with age, gender, diuretic use, proteinuria cyclosporine use (69,84–86). Participants who were employed had a significantly higher odds of having elevated TC and even though the reasons for the observation were beyond this study, it could be that those who were employed were more likely to be on an indiscriminate diet with a higher intake of fats. Time on dialysis before transplantation and physical activity lasting for 20 minutes or more at least 4 times a week were significantly

associated with hypertriglyceridemia in the bivariate model. Studies done elsewhere around the world have shown several characteristics as significant predictors of hypertriglyceridemia including increasing body weight, cumulative prednisolone dose, use of cyclosporine, diuretic therapy, β-blocker therapy, duration since transplantation, plasma creatinine concentration and pre-transplant serum TG levels (76,84–87). Bivariate logistic regression analysis identified the use of hydralazine, increased dietary fibre intake and reduced consumption of saturated fats as significant predictors of HDL-C levels. They were all associated with reduced odds of having low HDL-C. Use of hydralazine has previously been shown to increase HDL-C levels (88) while another study demonstrated that reducing consumption of saturated fats led to a rise in the mean HDL-C concentration among the participants (80). None of the characteristics had significant association with low HDL-C levels in the multivariable analysis contrary to the published results that have reported BMI, gender and plasma creatinine to be independent risk factors for low HDL-C in RTRs (10,84). Absolute levels of serum creatinine were not assessed in this study. Significant predictors of elevated non-HDL-C (>130mg/dl) in the bivariable model were adherence to dietary plan and physical activity lasting for 20minutes or more at least 4 times a week. Only adherence to the dietary plan was a significant predictor in the multivariable model. One trial demonstrated cyclosporine to be associated with a significant increase in non-HDL-C in RTRs (89).

Use of statins among the participants was low (12%) despite the prevalence of dyslipidaemia being high. However, this study was not powered to explain the reasons for the low uptake of statins among RTRs who participated in this study. These findings are in contrast to findings in published research which has shown a higher percentage of RTRs (20-50%) on statins in different centres and this has been steadily increasing over the last 3 decades (90,91). Statins are safe in RTRs and several studies have demonstrated their efficacy in improving lipid profile and reducing major adverse cardiovascular events (MACE) (92–94).

Dietary modification, physical activity, weight reduction, smoking cessation or abstinence and limitation/ abstinence from alcohol intake were the lifestyle modification strategies that were used among the participants. Prevalence of active smoking and alcohol intake

was low (less than 1% each) in contrast to published results that have reported higher prevalences of about 20-25% active smokers among RTRs (24,94). This could be explained by population differences and also some participants may have been unwilling to admit to taking alcohol or being active smokers. Most participants reported that they did not have a dietary plan and hence adhered to dietary modification intermittently. The low uptake of some of the lifestyle modification strategies including diet modification, physical activity and weight reduction may have been as a result of lack of routine formal counselling on such during regular clinic visits.

5.3 Summary and Conclusions

The results of this study revealed that there is a huge burden of dyslipidaemia among RTRs attending Nephrology clinic at KNH. Seven types of dyslipidaemias among the participants were identified and the most prevalent were elevated LDL-C and elevated non-HDL-C levels. The usage of statins among those patients was low. Other lipid lowering drugs such as ezetimibe, bile acid sequestrants, niacin and fibrates were not used at all in the study participants. Several predictive factors for different types of dyslipidaemias were identified including dietary modification, weight gain, weight reduction, BMI, obesity, lack of exercise, time on dialysis before transplantation, employment status, use of hydralazine and physical activity. Apart from smoking cessation/ abstinence and limitation of alcohol intake which were almost universal, other lifestyle modification strategies including dietary modification, physical activity and weight reduction were less commonly used by RTRs who participated in the study.

5.4 Study Strengths and Weaknesses

Renal transplantation is gaining momentum as the treatment of choice for ESRD in Kenya and Sub-Saharan region as a whole. There is very limited available literature on cardiovascular disease among RTRs in the Sub-Saharan region and more so on dyslipidaemia in that cohort of patients. This study highlighted the huge burden of dyslipidaemias in the largest transplant centre in East and Central Africa. Additionally, the study evaluated predictors/ risk factors of dyslipidaemias in RTRs. Most available published literature has focused on drugs and socio-demographic characteristics as predictors of dyslipidaemia with little consideration for lifestyle modification strategies as

predictors of dyslipidaemias in RTRs. This study in addition to other factors evaluated the association of dyslipidaemia with lifestyle modification factors. The study also highlighted the low uptake of statins among RTRs despite the significantly increased risk of ACVD in these patients. The study design was a cross-sectional study and hence it was prone to reporting bias in that the participants may have given information that would please the PI. For example, active smokers and those participants who took alcohol were more likely to conceal that information from the PI. The study was also prone to measurement bias/ investigator bias because the PI relied on lipid levels, creatinine levels and urinalysis that had been done in different laboratories and at different times. Some serum lipid parameters like triglycerides are affected by fasting status. It was not possible to analyse the lipid levels at standard timeframes from the time of transplantation because of the study design. A significant number of participants did not have a measure of lipids and this may have affected the P-value of some associations between dyslipidaemia and its predictors.

5.5 Recommendations

5.5.1 Recommendations for Policy and Practice

1. We recommend that evaluation and counselling on lifestyle modification strategies including modification of diet, physical activity and weight reduction should be included as part of routine procedures during every follow-up visit of the renal transplant patients.
2. More RTRs in whom Statins and other lipid lowering drugs are indicated should be identified and therapy with statins commenced as this has a proven benefit especially in reducing MACE. This is especially so for RTRs with elevated TC, LDL-C, triglycerides and low HDL-C.
3. We also recommend that all RTRs on follow up at the Nephrology clinic in KNH should have at least one measure of lipids every year. Additionally, modifiable risk factors for dyslipidaemia should be adequately managed.

5.5.2 Recommendations for Further Research

1. Further studies are necessary to establish the relationship between different dyslipidaemias and serum levels of cyclosporine, tacrolimus and everolimus, cumulative dose of prednisolone and time after transplantation.
2. Further prospective research is necessary to assess the short-term and long-term complications of dyslipidaemia among RTRs

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APPENDICES

APPENDIX 1: ELIGIBILITY SCREENING FORM

Renal Transplant Outpatient Clinic (RTOC)

Unique Identifier:_____

RTOC Number:_____

Criteria	**Remark**	
Adult aged ≥18 years	YES ☐	NO ☐
Received Transplant ≥ 3 months	YES ☐	NO ☐
On follow up at KNH RTOC	YES ☐	NO ☐
Not Pregnant	YES ☐	NO ☐
Not on dialysis	YES ☐	NO ☐
Not psychosocially challenged	YES ☐	NO ☐
Given Consent	YES ☐	NO ☐
If all **YES** please proceed to the study Questionnaire		

APPENDIX 2A: PARTICIPANT INFORMATION FORM

Study Title

PREVALENCE AND DETERMINANTS OF DYSLIPIDEMIAS AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

Principal Investigator

Dr Esbon Wambugu Njau- Master of Pharmacy (Clinical Pharmacy) Second-year student at the University of Nairobi (UoN)

Co-Investigators Dr S. Opanga (PhD)-Lecturer, UoN; Dr P.N. Karimi (PhD) – Lecturer, UoN

Introduction

I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: i) Your decision to participate is entirely voluntary; ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal, and iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? **YES** ☐ **NO** ☐

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No.: _____

WHAT IS THIS STUDY ABOUT?

The researchers listed above are interviewing individuals who received a kidney transplant at least 3 months before recruitment into the study. The purpose of the interview is to find out whether your blood lipids are within the normal range, whether you have any complications of abnormal blood lipid levels, to find out which drugs the patient is using and if there any interactions and identify things the patient is doing (or not doing) that may be affecting serum lipid levels. You will be asked questions about the management of your condition. There will be approximately 113 participants in this study. 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, you will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 25 minutes. The interview will cover topics such as your medication history, biodata, and lifestyle choices. 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. We may need to contact you to clarify your responses when necessary.

ARE THERE ANY RISKS, HARMS OR DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Although any medical research has the potential to introduce psychological, social, emotional and physical risks, efforts will be made to minimize the risks. One potential risk of being in the study is the loss of privacy. However, we will safeguard your privacy by keeping everything you tell us as confidential as possible and also by interviewing you in a private room. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out that you were in this study and could access information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

It may be embarrassing for you to have these diseases. We will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these interviews. In case of an injury, illness or complications related to this study, contact the study staff right away using the number provided at the end of this document. The study staff will treat you for minor conditions or refer you when necessary.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Participants in this study will benefit from free counselling on ways to control their blood lipids levels. We will refer you to your primary care physician or nutritionist for additional care and support where necessary. The findings of this research will provide more scientific information for practice as well as build on the existing body of knowledge on human health and science.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

This study will cost you about twenty-five minutes of your time.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

This study will not cost you money.

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 the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant, you may contact the Principal Investigator on Email: wambuguesbon@gmail.com, and Telephone: **0729330867** OR my supervisor Dr. Sylvia Opanga (PhD) (Lecturer, UoN) on Email: Sylvia.adisa@gmail.com and Telephone 0721296448 OR the Secretary/Chairperson

Professor Chindia /Professor Guantai, 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 without injustice or loss of any benefits.

APPENDIX 2B: CONSENT DECLARATION FORM

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 a study counsellor. 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 anytime. 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. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: **YES** ☐ **NO** ☐

I agree to provide contact information for follow-up: **YES** ☐ **NO** ☐

Participant printed name: _____

Participant signature / Thumb Print _____

Date _____

Witness_____Date_____

Researcher's statement

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

Researcher's Name: _____ **Signature** _____

Date: _____

Role in the study: _____

For more information contact _____ at _____ from _____ to _____

APPENDIX 3A: MAELEZO KUHUSU KUSHIRIKI KATIKA UTAFITI

Kichwa cha Utafiti

KUCHUNGUZA UDHIBITI NA MADHARA YA VIWANGO VYA JUU VYA MAFUTA NA KOLESTEROLI KWENYE DAMU KATIKA WAGONJWA AMBAO WAMEPANDIKIZWA FIGO NA WANAHUDHURIA KLINIKI YA FIGO YA KNH.

Mtafiti Mkuu

Dkt. Esbon Wambugu Njau-Mwanafunzi wa Mwaka wa pili (Mwanafamasia) Chuo Kikuu cha Nairobi

Watafiti Wengine

Dkt. Sylvia Opanga (PhD)-Mhadhiri, Chuo Kikuu cha Nairobi, Dkt. P.N. Karimi (PhD) Mhadhiri, Chuo Kikuu cha Nairobi

Utangulizi:

Ningependa kuzungumza nawe kuhusu utafiti huu utakaofanywa na waliotajwa hapo juu. Umuhimu wa mazungumzo haya ni kukufahamisha zaidi ili ufanye uamuzi wa busara kushiriki au kutoshiriki katika utafiti huu. Kuwa huru kuuliza maswali yoyote kuhusu kitakachofanyika utakapokubali kushiriki, madhara yanayoweza kutokea, manufaa ya utafiti huu, haki zako kama mshiriki na maswali yoyote kuhusu lolote ambalo hulielewi. Tutakapo jibu maswali yako yote, basi utaamua kushiriki au la. Utakapokubali, nitakuuliza tafadhali utie sahihi na majina yako kwa ukurasa hapa chini.

Unafaa uelewe kwa ujumla nguzo muhimu ambazo zinalinda washiriki katiaka ufatiti wa sayansi ya afya: i) Kushiriki kwako ni kwa hiari; ii) Unaweza kujiondoa wakati wowote bila kushurutishwa kutoa maelezo ya kufanya hivyo; na iii) Kutoshiriki kwako katika utafiti huu hakutaathiri huduma unazopaswa kuzipata kwa hosipitali hii. Tutakupa nakala yako ili ujiwekee kwa manufaa yako binafsi.

Ninaweza kuendelea? **NDIO** ☐ **LA** ☐

Utafiti huu umeidhiniswha na kitengo cha maadili na utafiti cha hospitali kuu ya Kenyatta na chuo kikuu cha Nairobi nambari: _____

UTAFITI HUU UNAHUSU NINI?

Watafiti waliondikwa hapo juu wanawahoji washiriki ambao wamepandikizwa figo. Mahojiano haya yana madhumuni ya kuchunguza mambo yanayohusika na udhibiti wa

viwango vya juu vya mafuta na kolesteroli kwenye damu. Washiriki wataulizwa maswali kuhusu matibabu yao na pia magonjwa mengine ambayo inawaadhiri na inahusiano na uwepo wa viwango vya juu vya mafuta na kolesteroli kwenye damu. Kutakuwa na washiriki 113 ambao wamechaguliwa kwa njia ya kisayansi ya bahati na sibu. Tunaomba idhini yako uwe mshiriki kwa utafiti huu.

NINI KITAKACHOFANYIKA UKIKUBALI KUSHIRIKI?

Yafuatayo yatafanyika: Utahojiwa na mtafiti aliyehitimu kwa sehemu ya tulivu na ya kisiri ambapo utakuwa huru kwa muda wa dakita ishirini na tano hivi. Mahojiano yatahusu historia ya ugonjwa wako, matibabu yako na pia magonjwa mengine ambayo inawaadhiri na inahusiano na uwepo wa viwango vya juu vya mafuta na kolesteroli kwenye damu. Tutahitaji nambari yako ya simu ambayo tutawasiliano nawe kwa maswala yanayohusika na utafiti huu pekee. Nambari yako ya simu haitapewa watu wengine wasiohusika na utafiti huu. Tukikupigia simu, itakuwa ni kufafanua majibu ya maswali ulioulizwa.

UTAFITI HUU UNA MADHARA YOYOTE?

Ijapokuwa utafiti wa kiafya una madhara yake kama ya kisaikolojia, tutajitahidi kabisa kupunguza madhara yoyote kwako. Kwa mfano, dhara moja ni uwezekano wa kupoteza usiri wako. Hata hivyo, mambo yote utatueleza tutayaweka kwa siri. Tutakupa nambari ya siri kwa compyuta ambayo imelindwa. Stakabadhi zote zitawekwa kwenye kabati itakayofungwa kwa kufuli. Lakini, kama unavyojua, bado kunao uwezekano wa kuvunjwa kabati na kuiba stakabadhi zako za siri.

Pia kuyajibu maswali katika mahojiano huenda kusikuridhishe. Kama kutakuwa na maswali ambayo hungetaka kuyajibu, utaruhusiwa kutoyajibu. Uko na haki ya kutojibu swali lolote katika mahojiano. Unaweza kuwa na aibu kwa kugonjeka magonjwa haya. Tutajaribu kuhakikisha mahojiano yamefanyika kwa njia ya siri. Pia, watafiti wetu wote wamehitimu kufanya mahojiano haya. Kama kutakuwa na kuumia, ugonjwa au shida zingine zozote kwa ajili ya utafiti huu, tafadhali wasiliana nasi kupitia nambari iliyo chini ya kurasa hizi. Watafiti wetu wanaweza kutibu magonjwa kidogo na pia wanao uwezo wa kukuelekeza ifaavyo kwa usaidizi zaidi.

UFATITI HUU UNA MANUFAA YOYOTE?

Utafaidika kwa kupata wosia mwafaka kuhusu kudhibiti ugonjwa wako kwa njia mbalimbali. Tunaweza kukuhimiza kutembelea kituo maalum cha afya kadiri inavyofaa. Aidha, utafiti huu utatuwezesha kuelewa magonjwa haya zaidi and jinsi ya kukabiliano nayo. Pia, tutaongeza ufahamu zaidi kwa sayansi ya afya na binadamu.

KUNA GHARAMA YA KUSHIRIKI?

Utafiti huu utahitaji dakika kidogo tu za muda wako.

UTAREJESHEWA PESA ZAKO?

Utafiti huu hautakugharimu pesa.

NA KAMA UTAKUWA NA MASWALI BAADAYE?

Kama una maswali zaidi au lolote ambalo hulielewi kuhusu utafiti huu, tafadhali usisite kuwasiliana nasi kupitia nambari ambazo zimeandikwa hapa chini.

Kwa maelezo zaidi kuhusu haki za mshiriki katika utafiti, wasiliana na Mtafiti Mkuu Tovuti: wambuguesbon@gmail.com Simu: **0729330867** au Dkt. Sylvia Opanga (PhD)-Mhadhiri, Chuo Kikuu cha Nairobi au Katibu/Mwenyekiti Profesa Guantai Simu.: **2726300** ongezo: **44102** Tovuti: *uonknh_erc@uonbi.ac.ke.* Utarudishiwa ada ya mazungumzo kupitia laini hizi kama mazungumzo yenyewe yanahusu utafiti huu.

KUNA CHAGUO LINGINE?

Kushiriki kwa utafiti huu ni kwa hiari yako. Una uhuru wa kutoshiriki au kujiondoa wakati wowote bila kupoteza haki yako ya kupata huduma zozote.

APPENDIX 3B: RIDHAA (KUKUBALI KUSHIRIKI)

Taarifa ya Mshiriki

Nimesoma au nimesomewa nakala hili. Nimepata kuzungumza kuhusu utafiti huu na mtafiti mwenyewe. Maswali yangu yamejibiwa kwa lugha ninayoielewa vizuri. Madhara na manufaa yameelezwa wazi. Ninaelewa kushiriki kwangu ni kwa hiari na kwamba ninao uhuru wa kutoshiriki wakati wowote. Ninakubali bila kushurutishwa kushiriki katika utafiti huu. Ninaelewa kwamba bidii itatiwa kuhakikisha habari zangu zimewekwa siri. Kwa kutia sahihi kwa daftari hili, sijapeana haki zangu za kisheria ambazo ninazo kama mshiriki katika utafiti huu.

Nimekubali kushiriki katika utafiti huu: NDIO ☐ **LA** ☐

Nimekubali kupeana nambari ya mawasilianao baadaye: **NDIO** ☐ **LA** ☐

Jina la Mshiriki: _____

Sahihi / Kidole _____

Tarehe _____

Taarifa ya Mtafiti

Mimi, ninayetia sahihi hapo chini, nimeelezea maswala muhimu ya utafiti huu kwa mshiriki aliyetaja hapo juu na ninaamini ya kwamba ameyaelewa vilivyo na kwamba ameamua bila kushurutishwa kukubali kushiriki.

Jina la Mtafiti: _____ **Sahihi** _____

Tarehe: _____

Kazi yangu kwa utafiti huu: _____

Kwa maelezo zaidi wasiliana na _____kwa_____

Saa_____ hadi _____

APPENDIX 4: QUESTIONNAIRE

STUDY TITLE: Prevalence and determinants of dyslipidaemias among renal transplant recipients attending the nephrology clinic at Kenyatta National Hospital

Serial Number ☐

Date…. /…. /….

Patient's Study Number

PART A: SOCIO-DEMOGRAPHIC CHARACTERISTICS

1. Gender ☐

1. Male 2. Female

2. Age…… years

3. Weight……. KGs

4. Height……...M

5. BMI

BMI KG/M^2	CODE
< 18	1
18-25	2
25-30	3
30-35	4
> 35	5

6. Marital Status: ☐

   1. Single 2. Married 3. Divorced 4. Widowed 5. Separated

7. Employment status ☐

   1. Employed 2. Unemployed

8. Level of education ☐

   1. None 2. Primary 3. Secondary 4. Tertiary

PART B: DYSLIPIDEMIAS

9. Is your blood lipid profile checked regularly? ....

   1. Yes 2. No

10. If yes in 10 above, how often? …….

1. Every clinic visit 2. Every 6 months 3. Yearly 4. Other (Specify)…….

11. If the answer to question 11 above is yes, how often? ☐

    1. Monthly 2. Every 2 months 3. Every 3 months 4. Every 4-6 months

12. Dyslipidaemia present or not? 1. Yes 2. No …….

Dyslipidaemia	Status (1. Present 2. Absent)	
	Present	Absent
Elevated LDL-C		
Elevated Total Cholesterol		
Hypertriglyceridemia		
Low HDL-C		
Elevated Non-HDL-C		
Elevated LDL-C: HDL-C ratio		
Elevated TG: HDL-C ratio		

PART C: RISK FACTORS AND COMPLICATIONS OF DYSLIPIDEMIA

13. Any of the following risk factors present?

Drugs Associated with dyslipidaemia

Drug class	Specific drug	Status	
Immunosuppressant		1.Yes	2.No
	Tacrolimus		
	Prednisolone		
	Sirolimus		
	Everolimus		
	Cyclosporine		
	Other? Specify		
β - Blockers	Propranolol		
	Nadolol		
	Sotalol		
	Timolol		

	Other? Specify ……		
Diuretics	Furosemide		
	Torsemide		
	Hydrochlorothiazide		
	Metolazone		
	Indapamide		
	Chlorthalidone		
	Other? Specify …….		

Other Factors associated with dyslipidaemia in renal transplant recipients

Factor	Status	
	1. Yes	2. No
Diabetes		
Obesity		
Alcohol consumption		
Proteinuria		
Weight gain		
Lack of Exercise/ physical activity		
Hormone replacement		
Pre-transplant dyslipidaemia		

14. Any complication associated with dyslipidaemias present? ….. 1. Yes 2. No

Complications Associated with dyslipidemia

Complication	Status	
	1.Yes	2.No
History of ischaemic stroke		
History of TIA		
History of MI		
History of peripheral vascular disease		
History of Angina or has a history of use of sublingual nitroglycerin or on isosorbide mononitrate or isosorbide dinitrate		
Chronic Allograft failure		

PART D: TYPES OF DRUGS AND LIFESTYLE MODIFICATIONS USED IN MANAGEMENT OF DYSLIPIDAEMIAS

15. Are you on any lipid-lowering drug? …. 1. Yes 2. No

Types of Drugs used in the management of dyslipidaemias

Drug class	Specific Drug	Status	
		1. Yes	2. No
Statins	Atorvastatin		
	Fluvastatin		
	Simvastatin		
	Rosuvastatin		
	Other? Specify		
Fibrates	Gemfibrozil		
	Fenofibrate		
	Other?		
Cholesterol Absorption inhibitor	Ezetimibe		
Bile acid sequestrants	Cholestyramine		
	Colestipol		
	Colesevelam		
Nicotinic Acid	Nicotinic acid		

16. Are you on any lifestyle modification Strategy? ..... 1. Yes 2. No

Lifestyle Modification Strategies

Lifestyle Modification Strategy	Status	
	1. Yes	2. No
Dietary Modification		
Weight reduction		
Physical Activity		
Smoking (If a smoker)		
Abstinence or limitation of Alcohol intake to one drink per (beer) per day		

Dietary Modification

17. If you indicated that you have a dietary plan with your Doctor in 16 above, do you always adhere? …. 1. Yes 2. No 3. Sometimes

18. What type of Dietary plan? ……..

a) Reduced saturated Fats (Fatty foods, Cheese, Fast foods, butter, fried foods, red meat, egg yolk, poultry skin …)…… 1. Yes 2. No 3. Sometimes

b) Increased dietary fibre intake ….. 1. Yes 2. No 3. sometimes

Other type of dietary plan?

Specify…

Physical Activity

19. Which of the following activity/ activities do you undertake? …… 1. Riding a bicycle 2. Digging 3. Walking for > 2km 4. None 4. Other Activity? Specify……

20. Do you exercise at the Gym? …….. 1. Yes 2. No

If No to question (20) above, do you have an exercise plan that is not part of your daily activity? 1. Yes 2. No

21. Do you have an exercise plan with your Doctor? ……. 1. Yes 2. No.

If yes to 21 above do you adhere to the plan? ..... 1. Yes 2. No 3. At times

How many times per week do you exercise for 20 minutes or more? .....

1. Less than 4 times 2. More than 4 times

Other forms of exercise? …….

Habits

Smoking

22. Do you smoke cigarettes? ..... 1. Yes 2. No

If yes to 22 above, how many packs of cigarettes per day? .....

1. Less than Half 2. Half 3.Greater than half

Alcohol Consumption

23. Do you take Alcohol? …… 1. Yes 2. No

a) If yes to 23 above, how often? ……. 1. Daily 2. Weekly 3. Once a year 4. Other (specify)……..

b) Which type do you take? ..... 1. Beer 2. Wine 3. Spirits 4. Local brew 5. Other (specify)……

c) Approximately how much do you consume in one sitting?

(1) Bottle…… (300ml, 500ml) Glasses…… (200ml, 500ml) Other (specify) …….

Weight Reduction

24. Do you regularly weigh yourself and check your BMI? ....

1. Yes 2.No

If yes to 53 above, have you been advised by your primary

PART E: OTHER DISEASE RELATED CHARACTERISTICS

25. How long were you on dialysis before receiving a kidney transplant? …..

1. < 1 Month 2. 1-6 Months 3. > 6 Months

26. How long ago did you receive a kidney transplant? ……..

1. 3 Months- 1 yr. 2. 1- < 3yrs 3. 3yrs and above

27. How many times have you received a Kidney Transplant? ……

1. Once 2. More than Once

28. Do you attend Kidney transplant clinic regularly? …….

1.Yes, 2. No

If the answer to question 28 above is yes, how often? ……

1. Monthly 2. Every 2 months 3. Every 3 months 4. Every 4-6 months

29. Do you have any other chronic disease conditions? …..

1. Yes, 2. No

30. If yes to question (13) above, which one(s) ……

1. Diabetes 2. Hypertension 3. Heart Failure 4. Other (Specify)…….

31. Are the levels of your immunosuppressive drugs checked regularly? …...

1. Yes 2. No

32. If your answer to question (23) above is **YES**, how often? ……..

1. Every clinic Visit 2.Every 6 Months 3. Yearly 4. Other (Specify)…….

33. Which other drug (s) are you on APART from all the others listed in sections above

Drug Name	Indication	Dose/Frequency /Duration	Prescribed in this clinic?	
			1. Yes	2. No

34. Are you on any Herbal/ Alternative medication? ……. 1. Yes 2. No If yes please specify……..

35. Any interaction present? ……. 1. Yes 2. No

APPENDIX 5: DATA ABSTRACTION FORMAT

Section (a) Serum Lipids Profile

Last 3 Fasting lipid profiles

	Reading one		**Reading two**		**Reading Three**	
	Mg/dl/ Date	1. Normal 2. Borderline high 3. High or Low for HDL 4. Very High	Mg/dl Date	1. Normal 2. Borderline high 3. High or Low for HDL 4. Very High	Mg/dl Date	1. Normal 2. Borderline high 3. High or Low for HDL 4. Very High
TC						
LDL						
TG						
HDL						
Non-HDL						

Formulae for calculating LDL-C and non-HDL-C

$$\boldsymbol{Non\text{-}HDL = TC - HDL\text{-}C}$$

$$\boldsymbol{LDL = TC - HDL - (TGs \div 5)\ in \frac{mg}{dL}} \quad \textbf{OR}$$

$$\boldsymbol{LDL = TC - HDL - (TGs \div 2.19)\ in \frac{mmol}{L}}$$

To convert mg/dL to mmol/L, multiply triglycerides by 0.001129, and cholesterol by 0.02586

Last 3 Lipid level Ratios

Ratio	Reading one		Reading two		Reading three	
	Value Date	1 Normal 2 Raised	Value Date	1 Normal 2 Raised	Value Date	1 Normal 2 Raised
LDL-C: HDL-C						
TG: HDL-C						

For LDL-C: HDL-C ratio; consider elevated if > 3.3 in males and > 2.9 in females

For TG: HDL-C ratio; consider elevated if > 4 in both males and females

Section (c) Medications prescribed and Laboratory tests

36. Urinalysis done in the last 3 visits? …… 1. Yes 2. No

37. If yes in 56 above proteinuria present? 1. Yes 2. No

Urinalysis measure	Proteinuria present
1	
2	
3	

38. UECs done in the last 3 visits? ……. 1. Yes 2. No

39. If yes in 58 above, serum Creatinine normal or elevated? 1. Normal 2. Elevated

Last 3 UECs measures	Serum Creatinine Normal or elevated
1	
2	
3	

APPENDIX 6: REFERENCE RANGES FOR LIPID PROFILES AND OTHER CHEMISTRIES

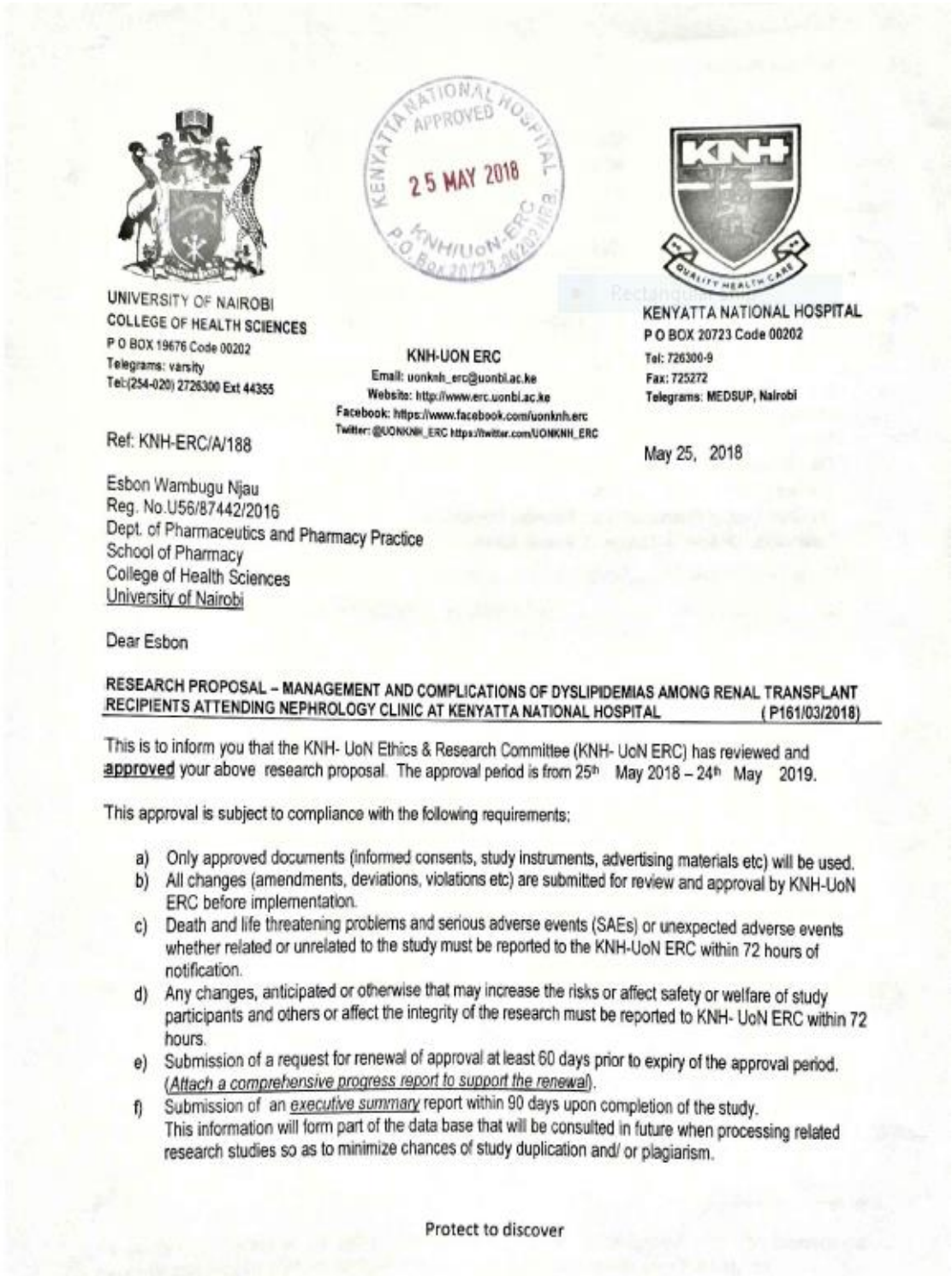
Serum Lipids

Lipid profile In mg/dL	**Normal**	**Borderline High**	**High or Low for HDL-C**	**Very High**
Total Cholesterol	< 200	200-249	≥ 240	-
LDL-C	< 100	100-159	160-189	≥ 160
TGs	< 150	150-199	200-499	≥ 500
Non-HDL-C	<130	-	>130	-
HDL-C	>40	-	<40	-

Serum Urea, Electrolytes, Creatinine and other blood biochemical parameters

Parameter	Units	Reference range
Sodium	Mmol/L	135-145
Potassium	Mmol/L	3.5-5.0
Chloride	Mmol/L	98-106
Urea	Mmol/L	2.5-6.7
Creatinine	Mmol/L (mg/dL) Male	0.05-0.12 (0.6-1.2)
	Mmol/L (mg/dL)Female	0.05-0.1(0.5-1.1)
Phosphate	Mmol/L	0.7-1.25
Calcium	Mmol/L	2.12-2.65
Albumin	g/L	35-50
Creatinine Clearance	ml/minute/1.73m2BSA (male)	75-190
	Ml/minute/1.73m2 BSA (female)	85-160
Blood sugar	Fasting blood sugar mg/dL (mmol/L)	70-99 (3.9-5.5)
	Random blood sugar mg/dL (mmol/L)	79-160 (4.4-7.8)

APPENDIX 7: APPROVALS FROM KNH-UoN EETHICS AND RESEARCH COMMITTEE AND KNH RESEARCH DEPARTMENT.



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Ref: KNH-ERC/A/188

May 25, 2018

Esbon Wambugu Njau
Reg. No.U56/87442/2016
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Esbon

RESEARCH PROPOSAL – MANAGEMENT AND COMPLICATIONS OF DYSLIPIDEMIAS AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL (P161/03/2018)

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 from 25th May 2018 – 24th May 2019.

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) 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*).
f) 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.

Protect to discover

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 Deputy Director, CS, KNH
The Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice,UoN
Supervisors: Dr. Sylvia A. Opanga, Dr. Peter N. Karimi

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Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   Dr. Esbon Wambugu Njau
2. Email address: wambuguesbon@gmail.com Tel No. 0729 330867
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   Management and complications of dyslipidaemias among Renal Transplant Recipients attending Nephrology clinic at Kenyatta National Hospital
6. Department where the study will be conducted Renal Unit
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: [illegible] Signature ..... Date 29/5/18
9. KNH UoN Ethics Research Committee approved study number P161/03/2018
   (Please attach copy of ERC approval)
10. I Esbon Wambugu Njau commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature ..... Date 29/05/2018
11. Study Registration number (Dept/Number/Year) Renal Unit /148/2018
    (To be completed by Research and Programs Department)
12. Research and Program Stamp _____

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

DYSLIPIDEMIAS AMONG RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

13%	10%	10%	2%
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PRIMARY SOURCES

1	bmcresnotes.biomedcentral.com Internet Source	1%
2	www.tandfonline.com Internet Source	<1%
3	Chauhan, Veeraish, and Megha Vaid. "Dyslipidemia in Chronic Kidney Disease: Managing a High-Risk Combination", Postgraduate Medicine, 2009. Publication	<1%
4	kdigo.org Internet Source	<1%
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