CARDIOVASCULAR RISK FACTORS IN RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI, KENYA

A dissertation submitted in part fulfillment for the degree of Master of Medicine in Internal Medicine, University of Nairobi

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DECLARATION

I hereby certify that this dissertation is my original work and has not been presented for a degree in any other university.

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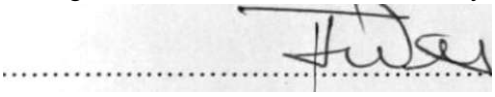

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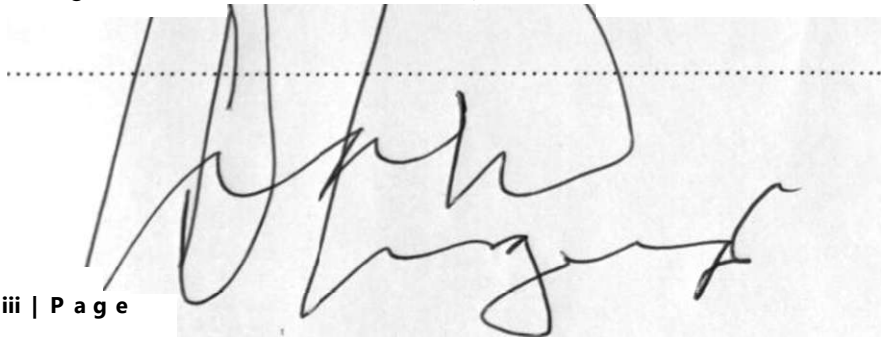

DEDICATION

I dedicate this book to my family members and especially to the memory of my father, the late John Olweny Wagude.

You all have been very supportive and will always remain a great inspiration to me.

ACKNOWLEDGMENT

I thank God Almighty ibr His boundless grace and blessing that renew me daily.

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ARB	Angiotensin II Receptor Blockers
AZA	Azathioprine
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRI	Chronic Renal Insuffiency
CRP	C-Reactive Protein
CSA	Cyclosporine
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ESRD	End-stage Renal Disease
EVE	Everolimus
GFR	Glomerular Filtration Rate
HD	Haemodialysis
HDL	High-Density Lipoprotein
HR	Hazard Ratio
IFG	Impaired Fasting Glucose
IHD	Ischemic Heart Disease
ISH	International Society of Hypertension

LDL	Low-Density Lipoprotein
LVH	Left Ventricular Hypertrophy
KNH	Kenyatta National Hospital
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate Mofetil
NCEP	National Cholesterol Education Program
NKF	National Kidney Foundation
NODAT	New-onset Diabetes After Transplantation
PD	Peritoneal dialysis
PPPM	Per Person Per Month
PVD	Peripheral Vascular Disease
RR	Relative Risk
RRT	Renal Replacement Therapy
RTR	Renal Transplant Recipients
SD	Standard Deviation
SPSS	Statistical Package for Social Scientists
TAC	Tacrolimus
TG	Triglyceride
USRDS	United States Renal Data System
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organization

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ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is recognized as the leading cause of morbidity and mortality amongst patients with chronic kidney disease (CKD). Currently, 50-60% of deaths in renal transplant recipients are directly attributable to CVD. No data existed on the prevalence of cardiovascular risk factors in renal transplant recipients (RTR) in Kenya.

OBJECTIVE: The aim of the study was to determine the prevalence of established cardiovascular risk factors and to analyze for associations of these risk factors with age, gender, duration of dialysis pre-transplant, medications including immunosuppressant use, cause of CKD, pre-existent diabetes or hypertension, and type and number of renal allograft in RTR in Nairobi, Kenya.

SETTING: The Renal Unit Transplant Clinic at Kenyatta National Hospital (KNH) and nephrology clinics at KNH Doctors Plaza, Nairobi Hospital Doctors Plaza and Parklands Nephrology Centre.

STUDY POPULATION: Renal allograft recipients attending nephrology clinics in Nairobi

METHODS: This study was conducted as a cross-sectional prevalence design. 91 renal allograft recipients underwent consecutive sampling and were evaluated for selected CVD risk factors including hypertension, obesity, decreased GFR, cigarette smoking, hypertension, diabetes mellitus, impaired glucose tolerance, anemia, dyslipidemia and proteinuria.

DATA COLLECTION AND ANALYSIS: Continuous variables were expressed as means and standard deviations, prevalence expressed as percentages with 95% Confidence Intervals and associations between CVD risk factors and patient variables or immunosuppressant drugs evaluated by Chi-square test. A *P* value less than or equal to 0.05 was considered statistically significant.

RESULTS: In the study, 91 renal transplant recipients were enrolled between 1st August 2011 and 1st February 2012 with a male to female ratio of 2.1 to 1 and mean age of 44.2 years (SD 12.44). Hypertension, dyslipidemia and abdominal obesity by waist-hip ratio were the most prevalent risk factors among the study population at 95.6%, 73.6% and 68.1% respectively. Statistically significant associations were found between the presence of a second renal allograft and NODAT ($P = 0.011$) as well as history of pre-transplant diabetes mellitus and use of insulin with impaired graft function ($P = 0.026$ and $P = 0.004$ respectively). Most allograft recipients were on Prednisolone, Cyclosporine and Mycophenolate mofetil combination therapy with those on Azathioprine having the longest duration of exposure (142.0 months) while those on Everolimus had the shortest duration (7.5 months). No statistically significant associations were found between any of the immunosuppressant agents and the cardiovascular risk factors.

LIMITATIONS: Recall bias in past medical history. Misclassification bias in use of a single occasion blood pressure reading for hypertension and single urine sample for microalbuminuria. Overestimation bias in use of estimated GFR equation. Misclassification bias in use of Caucasian cutoffs values for BMI_i and waist circumference in Africans.

CONCLUSIONS: There is a high magnitude of cardiovascular risk factors in the renal transplant population especially hypertension, abdominal obesity and hyperlipidemia. Statistically significant associations were described between presence of a second renal allograft and development of NODAT as well as between both history of pre-transplant diabetes mellitus and the use of insulin by renal transplant recipients with impaired graft function. The most common immunosuppressants used by the transplant recipients were Prednisolone. Mycophenolate mofetil and Cyclosporine with no statistically significant associations were found between immunosuppressant agents and the cardiovascular risk factors.

RECOMMENDATIONS: Renal transplant recipients should be prioritized as a population at high risk for cardiovascular mortality in health policy formulation for interventional measures with local adaptation and implementation of guidelines on cardiovascular risk factors. Long term prospective studies should be carried out to characterize post-transplantation anemia, control of diabetes mellitus and associations between immunosuppressive agents, drug dosages and duration of use in renal transplant recipients with cardiovascular risk factors using larger sample sizes.

1. LITERATURE REVIEW

1.1 INTRODUCTION

Patients with CKD are known to be at greatly increased risk of cardiovascular morbidity and mortality, with the prevalence of coronary artery disease and left ventricular hypertrophy as high as 40 and 75%, respectively, in dialysis patients in the United States. Patients with ESRD are at high risk of developing premature vascular disease ['']. Although the prevalence of CVD and cardiac risk factors such as dyslipidemia. hypertension and diabetes mellitus among dialysis patients is well described, less is known about renal transplant recipients.

Transplantation of the human kidney remains the treatment of choice for end-stage renal disease (ESRD) patients and is now performed within Kenya. The mortality associated with renal transplantation decreased significantly in the 1960s to 1980s due to a reduction in the incidence of infection-related deaths [""]. At the same time, however, there was an increase in the proportion of cardiovascular disease-related deaths. Presently, 50-60% of deaths are directly attributable to cardiovascular disease, with an incidcnce of ischemic heart disease approximately one per 100 person years at risk [J]. Death from cardiovascular disease is now the most common cause of graft loss [4].

Traditional risk factors for cardiovascular disease, such as smoking, diabetes mellitus and dyslipidemia. are well known to increase the risk of cardiovascular disease in otherwise healthy individuals, and studies now show that these factors also increase the risk of ischaemic heart disease (IHD) in renal transplant recipients. Transplant recipients have been shown to have increases in a number of traditional risk factors with studies showing that these risk factors can predict the incidence of ischaemic heart disease [5 6]. A retrospective study of renal transplant recipients showed that older age. diabetes mellitus, male gender, anemia and hypertension were dominant risk factors in the development of congestive heart failure and ischaemic heart disease [*]. An analysis of registry data in the USA showed that older age and comorbidities such as diabetes mellitus. angina or peripheral vascular disease were important risk factors for post-transplant myocardial infarction

1.2 REVIEW OF CARDIOVASCULAR DISEASE IN RENAL TRANSPLANT RECIPIENTS

Cardiovascular mortality rates among renal transplant recipients (RTR) are significantly higher than among those in the general population; even when adjustments are made for age. gender and diabetic status. Renal transplant recipients are at increased risk of CVD, compared with the same risk factors in the general population including older age, heredity, obesity, smoking, hypertension, diabetes mellitus and dyslipidemia [10].

The prevalence of both IHD and cardiac failure is approximately 50% among patients starting renal replacement therapy in the United States while approximately 80% of patients start dialysis therapy with LVH, left ventricular dilatation or systolic dysfunction [''']. The prevalence, incidence and prognosis of clinically manifested CVD are not known with precision in CKD patients but are highly likely to exceed those found in the general population. Left ventricular enlargement is common in CKD. with an inverse relationship between the prevalence of LVH and kidney function ['].

1.3 PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE

Left ventricular remodeling in CKD patients is a complex process whose sensor and effector mechanisms are not yet well understood. The high risk for CVD in patients with CKD results from the additive effect of multiple factors, including hemodynamic overload and several genetic, metabolic and endocrine abnormalities.

CVD includes disorders of the cardiac structure and function (LVH. cardiomyopathy) and disorders of the vascular system (atherosclerosis, arteriosclerosis) [""]. These two disorders are frequently associated and can exacerbate each other. Cardiomyopathy of overload and IHD are the two principal causes of heart failure and the most frequent causes of cardiac death. Cross-sectional studies have shown that LVH is the most frequent cardiac alteration in ESRD and is caused by volume or pressure overload [").

1.4 STAGES OF RENAL DISEASE

CKD is defined by the National Kidney Foundation (NKF) as either kidney damage for >3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR), or GFR< 60 mL/min per 1.73 m^2 for 3 months (with or without kidney damage). Kidney damage is ascertained by either kidney biopsy or markers of kidney damage, such as proteinuria, abnormal urinary sediment, or abnormalities on imaging studies ["].

Kidney failure is defined as GFR <15 mL/min per 1.73m^2 or treatment by dialysis. Approximately 98% of patients beginning dialysis for CKD in the United States have an estimated GFR of <15 mL/min per 1.73 m^2. Among individuals with CKD, the stage of severity is based on the level of GFR (Table 1).

TABLE 1. Stages of Chronic Kidney Disease [16]

Stage (*)	Description	GFR, mL/min per 1.73m^2	US prevalence, %
1	Kidney damage with normal or increased GFR	>90	3.3
2	Kidney damage with mildly decreased GFR	60-89	3.0
3	Moderately decreased GFR	30-59	4.3
4	Severely decreased GFR	15-29	0.2
5	Kidney failure	<15 or dialysis	0.1

More recently, attempts have been made to classify the stages of renal disease in the kidney transplant recipient population and correlate these stages with clinical features as per the Kidney Disease Outcomes Qudity Initiative (KDOQI) guidelines (Table 2). Sarnak and Levey reclassified the stages of renal disease to emphasize the emphasize the population at risk, number of patients affected, clinical outcomes, and cost of treatment while focusing on the risks of CVD and progression of renal disease [17]. Their staging formed a basis for exploring the parallels between the progression of CVD and CKD; and proved also useful in the area of risk reduction strategies for CVD in renal transplant recipients.

TABLE 2. Stages and Clinical Features of Diseases in the Kidney Transplant Recipient [16]

Stage Description	Clinical Features			
	Rejection	Drug Toxicity	Recurrent Disease	Transplant Glomerular Disease
At Increased Risk	All	Treatment with cydosporine or tacrolimus	Glomerular disease in native kidneys	Proteinuria, High blood pressure
1T-2T Kidney Damage	High blood pressure	High blood pressure	Proteinuria	Proteinuria, High blood pressure
3T-4T Decreased GFR	High blood pressure, Complications	High blood pressure, Complications	High blood pressure, Complications	High blood pressure, Complications
5T Kidney Failure	Uremia, CVD	Uremia, CVD	Uremia, CVD	Uremia, CVD

*T suffix used to describe stage in renal transplant recipients

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1.5 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

1.5.1 Epidemiology of CKD

Kenya with a population of 38.6 million is estimated to have a prevalence of ESRD of 15.6 per million population [18- "]. No data exists on the prevalence or incidence of CKD patients in the larger East African community. Data for ESRD from North Africa (Morocco, Algeria, Tunisia, Libya and Egypt) estimated an annual incidence ranging between 34 - 200 per million population and prevalence of 30 - 430 per million population [20].

The estimated prevalence of ESRD in Sub-Saharan Africa (SSA) and India is less than 100 per million population compared to about 400 per million population in Latin America, higher than 2000 per million population in Japan, about 1500 per million population in the United States, and about 800 per million population in the European Union [21]. The epidemiology of CKD in SSA is strikingly different from those observed in other regions. Although middle-aged and elderly populations are predominantly affected in developed countries, in SSA, CKD mainly affects young adults in their economically productive years; with hypertension and infection-related chronic glomerulonephritis as the common causes. Despite the relatively high mortality, the prevalence of ESRD is increasing in SSA. Without an equivalent increase in transplant activity, it is estimated that the dialysis pools would not reach a steady state before accommodating eight times the new patient load [20],

Renal transplant activity as a means of renal replacement therapy is on the increase in the African continent though reliable data is hard to come by. Kenya has pioneered in the renal transplant program within the East African region with about 20 patients undergoing transplantation annually while 300 ESRD patients undergo dialysis at KNH alone [22]. In South Africa, the South African Dialysis and Transplant Registry in 1994 noted 299 renal transplants were performed in the same year with a total of 1,578 functioning grafts at year end and a transplant rate of 8.7 patients per million population [23].

1.5.2 Cardiovascular Disease in End-Stage Renal Disease

The presence of cardiovascular disease, defined as coronary disease, cerebrovascular disease and peripheral vascular disease (PVD). is an important predictor of mortality in patients with ESRD, as it accounts for almost 50% of deaths [ ]. Of these, approximately 20% can be attributed to the consequcnces of CAD. CVD is the leading cause of morbidity and mortality in patients at every stage of CK.D. Coronary disease often presents in atypical fashion in dialysis patients thus the presence of CHD is frequently overlooked due to the absence of classic symptoms and/or signs of heart disease. Overall, the incidence is much higher than that observed in the general population. 40% of incident dialysis patients have ischemic heart disease [38J, with an annual rate of myocardial infarction and/or angina of 10%.

The most common cause of death is attributed to arrhythmic mechanisms or sudden cardiac arrest, accounting for approximately 60% of all cardiac deaths [2"J. CVD mortality is 10 to 30 times higher in patients treated by dialysis than in patients in the general population, despite stratification for sex, race, and the presence of diabetes (Table 3). After stratification for age, CVD mortality remains 5-fold higher in dialysis patients than in the general population, even at the extremes of age. The high mortality rate is likely due to both a high prevalence of CVD and a high case fatality rate after acute myocardial infarction and in patients with heart failure.

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TABLE 3. Comparison of CVD Mortality in the US General and ESRD Population by Gender, Race and Diabetes (Annual Mortality %) [17]

Population	All	Men	Women	White	Black	Diabetic	Non-diabetic
General population	0.28	0.28	0.27	0.29	0.23	0.80	0.26
Haemodialysis	9.12	9.38	8.83	11.18	6.68	11.09	7.78
Peritoneal dialysis	9.24	10.27	8.14	10.76	6.07	13.22	7.09
Renal transplant recipient	0.54	0.59	0.43	0.53	0.56	1.11	0.39

Note: CVD mortality is defined as death due to arrlythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease and pulmcinary oedema.

1.5.3 Cardiovascular Disease in Renal Transplant Recipients

CVD accounts for 35% to 50% of all-cause mortality in kidney transplant recipients [26], and CVD mortality rates are at least twice as high as in an age-stratified sample of the general population but significantly lower than an age-stratified dialysis population. The most likely explanations for the reduced risk in kidney transplant recipients compared with dialysis patients are selection bias for those undergoing transplantation and removal of the hemodynamic and uremic abnormalities associated with dialysis. The prevalence of IHD after renal transplantation is between 6 - 14.6% in Europe versus 12.6 - 15.1% in the USA [27].

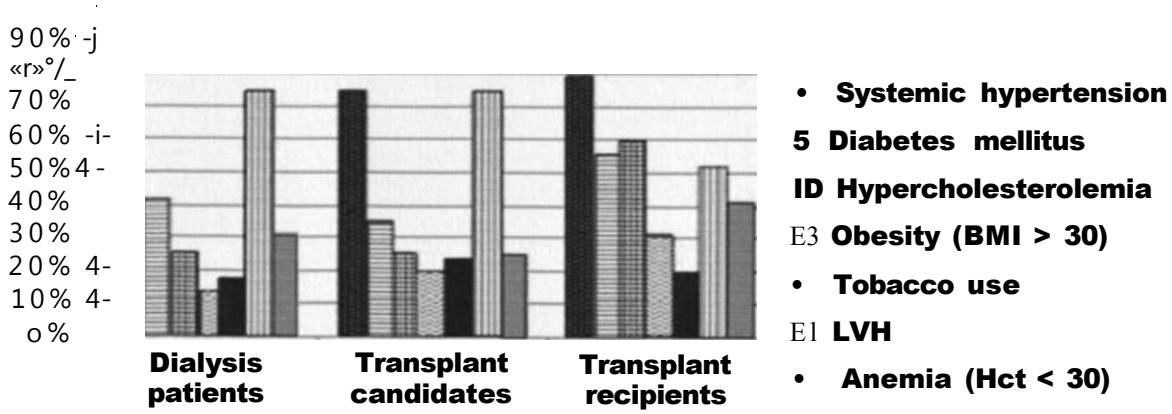
CVD morbidity is also higher in transplant recipients than in the general population. In RTR, the prevalence of coronary artery disease is 15%, and of LVH is 50% to 70%. The incidence of CVD in RTR is at least 3 to 5 times that of the general population [8]. It has been demonstrated that although the Framingham risk equation predicts ischemic heart disease after kidney transplantation, it tends to underestimate the risks [7], The latter effect is probably due to more severe diabetic vascular disease in patients with diabetic kidney disease. Estimates show that the annual rate of fatal or nonfatal cardiovascular events is 3.5-5.0% among kidney transplant recipients, 50-fold greater than in the population at large [3].

1.6 CARDIOVASCULAR DISEASE RISK FACTORS IN RENAL TRANSPLANT RECIPIENTS

Risk factors for CVD in kidney transplant recipients are multiple and are divided into traditional and non-traditional risk factors. Traditional CVD risk factors are defined as those risk factors in the Framingham Heart Study that have been used to estimate the risk of developing symptomatic ischemic heart disease such as older age, diabetes, hypertension, male gender, family history of coronary disease, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein cholesterol, history of smoking, physical inactivity, menopause and psychosocial stress. Some of these traditional CVD risks, such as hypertension, diabetes, hyperlipidemia, LVH, age, gender and obesity are highly prevalent in renal transplant patients with evidence from studies showing a positive correlation between the risk factor and CVD progression (Figure 1).

Non-traditional CVD risk factors can be defined as other CVD risk factors that increase in prevalence or severity as renal function or GFR deteriorates. These include among others, albuminuria or proteinuria, extracellular fluid volume overload, hypertriglyceridemia, elevated lipoprotein (a), hyperhomocysteinemia, genetic polymorphisms, microinflammation or infection markers (for example C-reactive protein [CRP]), increased oxidant stress, anemia, thrombogenic markers, or factors unique to transplantation itself, including the direct effects of immunosuppression, hyperparathyroidism or rejection.

FIGURE 1.Prevalence of CVD risk factors in ESRD and Renal Transplant Recipients [3]



Several non-traditional factors, such as hyperhomocysteincmia. oxidant stress, dyslipidemia. and elevated inflammatory markers, are associated with atherosclerosis and oxidant stress and inflammation may be the primary mediators of the tremendous burden of CVD in CKD. Other factors such as anemia are associated with cardiomyopathy, whereas abnormal calcium and phosphorus metabolism is associated with vascular remodeling and development of noncompliant vessels.

After accounting for pre-transplant vascular disease, multivariate analysis revealed that the following risk factors were independently associated with post-transplant atherosclerotic cardiovascular disease: increasing patient age, diabetes mellitus, male sex, cigarette smoking, hypertension and elevated serum cholesterol [""]. The Assessment of Lescol in Renal Transplantation (ALERT) study after multivariate analysis found independent risk factors for myocardial infarction, cardiac death, and non-cardiac death included preexisting coronary heart disease (hazard ratio, 3.69), total cholesterol level (HR. 1.55 per 50 mg/dL), and prior acute rejection (HR, 1.58). Age, diabetes. ST-T changes, and elevated serum creatinine levels were independent risk factors for cardiac death [32].

Some factors contribut-ng to the risk of CVD may improve after renal transplantation, such as volume overload, hypertension, anemia, and abnormalities in calcium and phosphate metabolism. Usually, risk factors such as hypertension and lipid abnormalities can persist, in part because of immunosuppressive drugs such as steroids, calcineurin inhibitors, or newer agents. Kasiske et al reported that age. smoking history, male sex. and lipid abnormalities were independent risk factors for ischemic heart disease after renal transplantation while diabetes carried a relative risk of 2 for ischemic heart disease [7],

1.6.1 Traditional Risk Factors

A. **Hypertension**

Hypertension is common in RTR despite normalization of renal function and resolution of chronic volume overload. There are several pharmacologic causes of hypertension in RTR. Cyclosporine increases blood pressure even in healthy volunteers and non-transplant patients. Tacrolimus also causes hypertension, although with less systemic vasoconstriction than cyclosporine. Use of calcineurin inhibitors and steroids for immunosuppression plays a significant role in post-transplant hypertension, but other factors, such as impaired renal graft function, stenosis of the renal transplant artery, donor kidney disease, weight gain, and presence of native kidneys, may also contribute ['"].

Souza et al found the prevalence of hypertension in RTR was 86% [']. While hypertension has been shown to increase CVD risk both in the general population and in RTR, optimum levels of blood pressure are being more clearly defined Studies correlating hypertension with CV risk have used blood pressure levels of lower than 140/90 mm Hg as a reference point, but there may be an additional benefit with tighter blood pressure control. Hypertension has been linked to chronic allograft nephropathy and has been shown to be an independent factor in graft failure; lower goals for blood pressure control may be helpful in preserving renal graft function as extrapolated from studies evaluating control of blood pressure in diabetic nephropathy. Control of hypertension decreases the risk of CVD and reduces proteinuria and the rate of decline of kidney function in patients with CKD. The NKF KDOQI published clinical practice guidelines for the care of RTR indicating a goal blood pressure of <130/80 mm Hg [36].

B. Hyperlipidemia

Hyperlipidemia is a frequent finding among RTR with increases in total cholesterol and LDL levels most common; >70% prevalence of dvslipidemia was reported by Diaz et al ["] and several studies have associated hyperlipidemia with CVD post-transplantation [,s|. There may also be an association with graft dysfunction secondary to chronic rejection.

Contributing factors to lipid abnormalities in renal transplant patients include renal insufficiency, obesity, chronic liver disease, diabetes, drug therapy for hypertension, and immunosuppressive drugs (steroids and calcincurin inhibitors). Non-selective and beta-1-selective beta blockers lead to approximately 10% fall in HDL-cholesterol and a 20 - 44% rise in triglyceridcs[39J. Cyclosporin leads to 15 - 20% elevations in total and LDL cholesterol levels directly and indirectly through hyperuricemia while steroids may act by leading sequentially to peripheral insulin resistance, hyperinsulinemia, and increased hepatic VLDL synthesis [40].

Epidemiologic studies have provided evidence that treatment of elevated LDL cholesterol significantly decreased the risk of CVD mortality in high-risk individuals in the general population but similar studies demonstrating reduction of risk with treatment of hyperlipidemia in RTR are not available. However, extrapolation from general population studies and some data in kidney transplant patients supports the view that the assessment and treatment of dyslipidemia should be part of routine post-renal-transplant care. Since immunosuppressive medications often cause secondary dyslipidemia. medication regimens should be individualized to minimize the competing risks of rejection and cardiovascular disease.

C. **Diabetes Mellitus**

Both pre-existent diabetes and New-onset diabetes after transplantation (NODAT) contribute to the increased cardiovascular risk profile. The total prevalence of diabetes mellitus in renal transplant recipients was reported at 55% while NODAT was noted to affect 25% of renal transplant recipients by Ojo et al[J].

NODAT is characterized by decreased insulin secretion and increased insulin resistance secondary to the effects of immunosuppression. Although impaired P cell function appears to be the primary mechanism of calcineurin inhibitor-induced new-onset diabetes, impaired peripheral glucose utilization also appears to contribute to insulin resistance and abnormal glucose metabolism. Reported rates of NODAT after transplantation were as high as 46% in early studies of steroid-treated transplant recipients and are now as low as the 14.4% prevalence reported by Diaz et al [37]. The major factor for the variability in reported rates of NODAT was the lack of a uniform definition of hyperglycemia and diabetes in post-transplant studies.

Many of the same risk factors that predispose non-transplant patients to diabetes mellilus have been identified as risk factors for its development after transplantation such as increased age especially older than 43 to 45 years, race particularly African-Americans and Hispanics, obesity and family history of diabetes. In addition, unique factors, such as specific agents used for immunosuppression (calcineurin inhibitors, glucocorticoids and Sirolimus), HLA mismatch, donor gender, and type of underlying renal disease, may also enhance the risk of NODAT[''].

The development of NODAT correlates with increased cardiovascular mortality, which is the most prevalent cause of poor long-term survival with NODAT. The increased relative risk for death from cardiovascular disease ranges from 1.5 to 3 among those who develop NODAT versus those without diabetes. Some of the excess risk is associated with coexistence of other cardiovascular risk factors, particularly increased age and dyslipidemia [',2].

D. Obesity

The epidemic of obesity in the United States has not spared kidney transplant candidates. Obesity trends in transplant recipients tend to mimic the general population. 65% of whom are now defined as overweight (body mass index [BMI] 25 to 29.9 kg/m2). In one study from the United Network for Organ Sharing, approximately one-half of patients who underwent kidney transplantation between 1997 and 1999 were obese (BMI 30 to 35) [''']. Weight gain is a common complication of kidney transplant, increasing the frequency of obesity-related transplant complications and making re-transplant difficult after a transplant is lost.

Obesity in the general population increases the risk of cardiovascular disease. Among kidney transplant recipients, the presence of obesity, particularly within the context of the metabolic syndrome, also appears to be associated with an increased number of adverse cardiovascular events. Obesity also increases the risk of heart failure and atrial fibrillation. Many important risk factors for CVD and transplant loss have a higher incidence in obese patients, including hypertension, hyperlipidemia. and NODAT. Abdominal obesity which is a risk factor for ESRD may contribute to elevated CRP levels. Both truncal fat mass and waist circumference correlate significantly with CRP levels in pre-dialysis patients and RTR. respectively. Cofan found the prevalence of obesity and overweight was 16% and 38% respectively in RTR in Spain [''].

E. Smoking

Cigarette smoking has adverse effects on humans, causing cardiovascular disease, chronic obstructive lung disease, liver disease, and cancer. It may also have adverse effects on renal function. Cigarette smoking itself is the main cause of cardiovascular mortality increment in RTR. Smoking increases the mean arterial pressure and heart rate via activation of catecholamines and beta-adrenergic mechanisms. Chronic cigarette smoking increases proteinuria, reduces renal plasma flow, probably increases synthesis of vasoconstrictor endothelin, and reduces generation of the vasodilator endothelial nitric oxide [1>].

A study in renal transplant recipients found that cigarette smoking was associated with decreased patient survival and an increased graft failure rate, largely due to the increased mortality. A study by Yavuz et al found cigarette smoking prevalence in RTR of 12% with male gender, marriage, pre-transplant smoking habitus, and alcohol intake related to post-transplant cigarette smoking [J6]. Other studies also found that smoking increases the risk of cardiovascular disease. The relative risk of death ranges from 1.56 in recipients with cumulative smoking history of 11-25 pack years to a RR of 2.14 for recipients with 25 pack years but with smoking cessation, the increased risk dissipates after 5 years [47]. Therefore, smoking cessation is recommended for all renal transplant recipients, with the adoption of measures to encourage smoking cessation.

1.6.2 Non-Traditional Risk Factors

A. **Anemia**

Anemia in the context of CKD is a well recognized phenomenon associated with worsening renal function. Anemia in this setting usually is a result of erythropoietin (EPO) deficiency, resistance to EPO, iron deficiency (either absolute or functional), and/or blood loss. Anemia is a risk factor both for the development of de novo and recurrent CHF, as well as for CVD mortality, and is also one of the important risk factors for the development of LVH [14].

The development of post-transplantation anemia can occur either early (in the first 6 months) or late (after the first 6 months) post-transplantation with the causation being usually multifactorial. Some causes are shared with patients with CKD who did not undergo transplantation (e.g., impaired kidney function, iron and nutrient deficiency, infection, inflammation, blood loss, and medications [e.g., angiotensin-converting enzyme (ACE) inhibitors]), whereas others are unique to transplant recipients (e.g., rejection episodes, immunosuppressive drugs, antivirals. antibiotics and malignancy). There are also potentially rare causes for profound anemia, including infection with parvovirus B19. and thrombotic microangiopathy secondary to calcineurin-inhibitor. Tacrolimus or Sirolimus therapy [4IS|. Risk factors for anemia include recipient sex. race, renal function, iron depletion, cytomegalovirus status and prophylaxis, donor age. immunosuppressive regimen, and use of ACE inhibitors or angiotensin **II** receptor blockers (ARBs) among others.

The prevalence of anemia depends critically on its definition which is surprisingly diverse in the literature. The WHO defines anemia as a hemoglobin level <13 g/dL in men and < 12 g/dL in women compared to the National Kidney Foundation KDOQI criteria using hemoglobin level <13.5 g/dL for adult men and < 12 g/dL for adult women [49 50]. Using the WHO definition, the Transplant European Study on Anemia Management (TRESAM) Study reported a prevalence of anemia of 38.6% in RTR compared to 30 - 35% noted by Varirenterghem using the KDOQI guidelines [M '2], A retrospective study found that 1 -g/dL (10-g/L) decrease in hemoglobin level carries an independent relative risk (RR) for de novo cardiac failure of 1.36 (/^<0.001) in the post-transplantation setting, but well-designed prospective trials are required to support the current opinion that presence of low hemoglobin levels correlates with poorer cardiovascular outcomes in RTR [53].

B. **Immunosuppressive Drugs**

Immunosuppressive drugs have been associated with the occurrence and/or persistence of CVD risk factors in RTR, including hypertension, PTDM and lipid abnormalities. Recent attention has been directed at examining differences in the association of adverse effects with specific drugs and the possible role of drug conversion in reducing CVD risk profile.

The onset of diabetes after transplantation is partially attributable to immunosuppressants, in particular steroids and calcineurin inhibitors. Insulin resistance and increased body weight represent the main mechanisms of steroid-induced diabetes. Immunosuppressive agents, such as Cyclosporine (CSA), Tacrolimus (TAC) and steroids, are known to contribute to the onset of hypertension following transplantation, in contrast to Azathioprine (AZA). Mycophenolate Mofetil (MMF), and the proliferative signal inhibitors: Sirolimus (SRL) and Everolimus. The prevalence of lipid disorders among RTR has been reported to be up to 80% in those treated with SRL and 40% to 60% in those treated with CSA or TAC [54].

C. **Inflammation**

The potential mechanisms of atherosclerosis, a chronic inflammatory disease, include responses to oxidative stress and/or infection. The great number of inflammatory stimuli among transplant patients can accelerate atherosclerosis. Systemic inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, have been correlated with CVD. CRP is a marker of low-grade systemic chronic inflammation and in the ALERT clinical trial of fluvastatin in RTR. high-sensitivity C-reactive protein levels were independently associated with mortality and major cardiovascular events ["].

Possible proatherogenic effects of CRP include activation of the complement system, binding to LDL and VLDL cholesterol and stimulation of tissue factor. Ducloux et al observed an association between raised CRP levels and cardiac events among kidney transplant patients [42].

I). Renal dysfunction

Chronic kidney disease is an independent risk factor for cardiovascular disease. In a study by Meier-Kriesche et al, the serum creatinine level at 1 year in RTR was strongly associated with the incidence of cardwascular death [56]. CKD of stage 3 or greater (GFR <60 ml/min/1.73m2) is present in more than 60% of RTR which remained stable through follow-up [57].

Proteinuria is considered to be an independent risk factor for CVD mortality, as it reflects a generalized endothelial dysfunction which is a pathogenic mechanism of atherosclerosis. Microalbuminuria identifies subjects with insulin resistance which predisposes to diabetes, but also to a greater risk for CVD [58]. Prevalent in up to 40% of RTR, proteinuria is associated with an increase in 10-year risk of CVD from 20.9 to 39.4%. With proteinuria defined as protein greater than 300mg/day. the prevalence of proteinuria was 34.3% in a study by Ibis et al [79].

1.6.3 KDIGO Clinical Practice Guideline

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative formed to '"improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." To this end, a KDIGO work group has recently published a new comprehensive set of recommendations for the care of RTR with a chapter on CVD risk reduction ["b]. To have practical applicability, the various recommendations and suggestions need adaptation to suit individual countries. Because CVD is the most common cause of patient death in RTRs. a concerted effort at minimizing risk factors for heart disease likely will have a greater impact on optimizing patient and graft outcomes than the discovery of new anti-rejection therapies.

CVD risk reduction strategies should include regular screening for new-onset diabetes (using ADA-based definitions) in the post-transplant period in previously non-diabetic patients, good glvcemic regulation for diabetic patients according to current ADA guidelines, and lipid management and blood pressure control according to current KDOQI recommendations. In addition, promotion of a healthy lifestyle through weight control, exercise, and smoking cessation should be a central part of post-transplant counseling and care J"36n60].

2. JUSTIFICATION OF THE STUDY

ESRD and its complications including cardiovascular disease today constitute a major and expanding health challenge in Kenya. The ever increasing numbers of diabetic and hypertensive patients portends a future rise in the population of ESRD and ultimately RTR. More patients with ESRD are now accessing renal transplantation services at KNH with at least 20 patients undergoing transplantation annually. As the major cause of mortality in this population is cardiovascular related disease, it is essential to identify risk factors in order to effectively manage these patients.

There is no local data on the prevalence of co-existing cardiovascular risk factors amongst renal transplant recipients. There is also paucity of data from within the African continent. Subsequently, most data currently available emanates from developed countries which may not accurately reflect our situation due to socio-cultural, economic and environmental differences.

This study proposed to determine the prevalence of certain known risk factors established to be of major importance in the genesis and progression of CVD post-renal transplantation.

The data generated from this study would be useful in:

a) Assessing the burden of established major CVD risk factors in renal transplant patients attending nephrology clinics in Nairobi, Kenya
b) Planning and conducting further detailed studies on CVD morbidity and mortality within this population
c) Planning strategies for comprehensive CVD management and risk factor prevention and/or reduction within this population

5. MATERIALS AM) METHODS

5.1 STUDY DESIGN

5.1.1 Study Setting

This was a cross-sectional descriptive study. The designated study sites were the Renal Unit Transplant Clinic at KNH and nephrology clinics at KNH Doctors Plaza, Nairobi Hospital Doctors Plaza and Parklands Nephrology Centre. Renal transplant patients attend clinics at the Renal Unit at KNH on Tuesday morning and specialist nephrology clinics on daily basis in Nairobi.

5.1.2 Study Population

The study population consisted of consenting adult patients post renal allograft transplantation attending nephrology ciinics in Nairobi.

5.2 PATIENT SELECTION

5.2.1 Inclusion Criteria

1. Written informed consent
2. Age above 18 years of age

5.2.2 Exclusion Criteria

1. Patients on haemodialysis for any cause
2. Patients with acute kidney failure and/or acute liver failure

5.3 SAMPLE METHOD

5.3.1 **Sample Size Calculation**

The sample size for this study was estimated using Fischer's formula for one - sample situation for prevalence studies [61] as shown below:

$$N = \frac{Z\backslash._{a/2}P(1 - p)}{d^2}$$

Where:

- N is the required minimum sample size
- Z is the confidence interval at 95% (standard value of 1.96)
- P is the estimated prevalence of other studies in renal transplant recipients
- d is the margin of error at 10% (0.10)

The prevalence of the risk factors to be investigated in this study was indicated in Table 4 below.

TABLE 4. Minimum Sample Size required for the Study Variables (d = 0.10)

Study Variable	Prevalence (other studies)	Estimated sample size
Hypertension	86% [34]	46
Hyperlipidemia	70% [37]	81
Diabetes	23% [34]	68
Obesity	18% [34]	57
Smoking	12% [46]	41
Anemia	35% ["]	87
Proteinuria	34.3% [59]	87

Thus, the minimum sample size calculated for the study was 87 patients.

5.3.2 Sampling Technique

All files of transplant recipients on follow-up at the KNH Renal Unit and specialist nephrology clinics were screened. All those patients who fulfilled the inclusion criteria and gave informed consent were enrolled into the study through consecutive sampling technique.

5.3.3 Study Feasibility

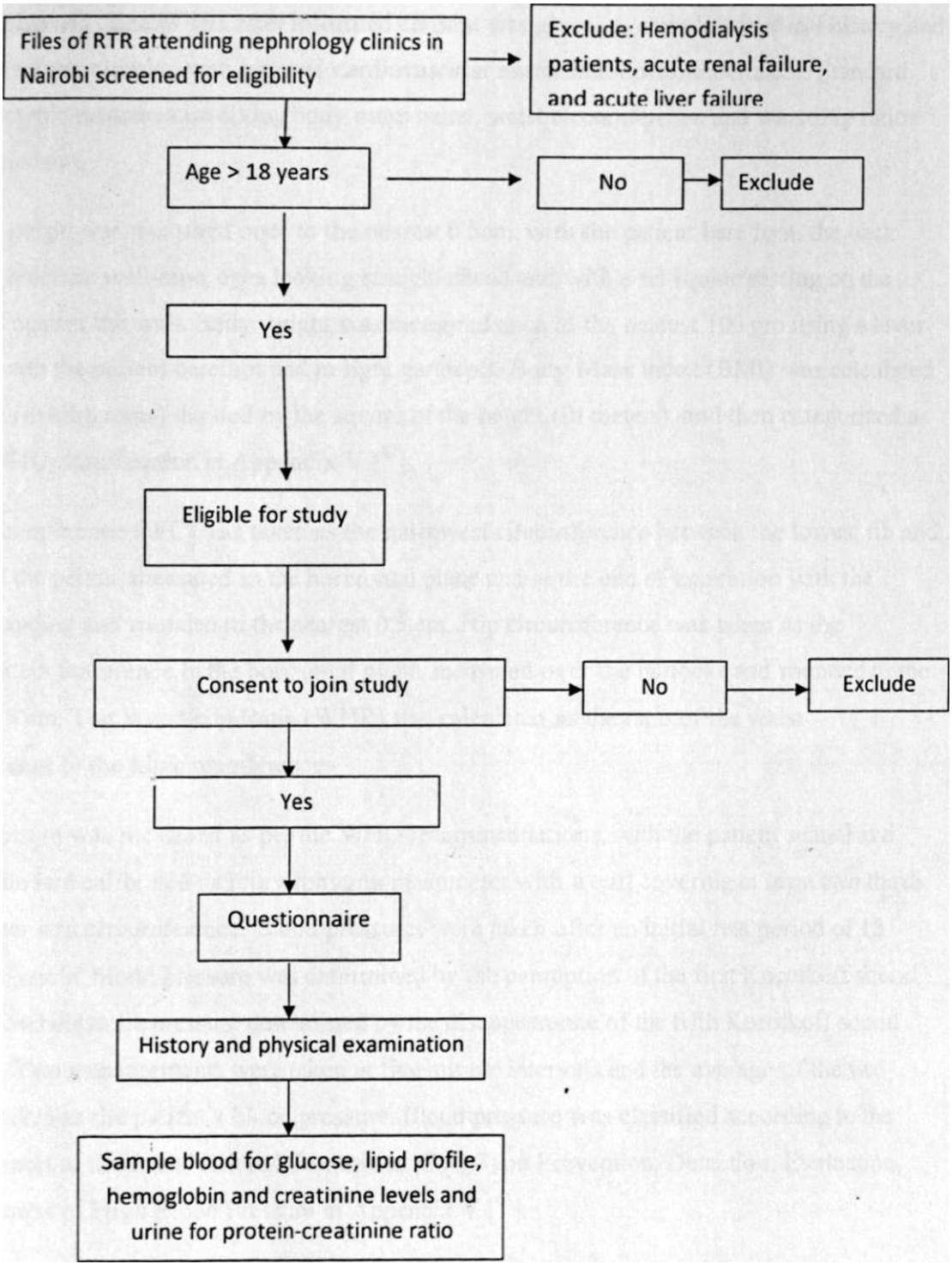
There were **124** renal transplant recipients on regular monthly follow-up at the KNH Renal Unit and the nephrology clinics in Nairobi. The patient files were located in nephrology clinics and were available to the investigator before the clinical visits with history, pre-transplant work-up studies and contact information inside each file. Approximately **10** patient files were screened each week for eligibility and the patient contacted for enrolment if satisfying the inclusion and exclusion criteria.

5.4 PATIENT EVALUATION

5.4.1 Screening and Recruitment

The files of patients who had undergone renal transplantation due for a visit on any clinic day were scrutinized for eligibility. Patients who did not meet the exclusion criteria and satisfied the inclusion criteria were then contacted and informed about the study. Those recipients who agreed to participate were then requested to fill the informed consent form before recruitment. The recruited patients were given a special appointment to be seen by the principal investigator for assessment and data collection and also advised to come having fasted for at least 10 hours for blood sample collection.

FIGURE 2.Flow chart of protocol screening and recruitment



5.4.2 Clinical Methods

The investigator administered questionnaire as outlined in Appendix I was used to collect demographic and clinical data after informed conscnt was given. A complete medical history and full physical examination with targeted cardiovascular examination was undertaken. Standard anthropometric measures involving body mass index, waist circumference and waist-hip ratios were carried out.

Standing height was measured once to the nearest 0.5cm. with the patient bare foot, the back square against the wall-tape, eyes looking straight ahead and with a set square resting on the scalp and against the wall. Body weight was measured once to the nearest 100 gm using a lever balance, with the patient barefoot and in light garments. Body Mass Index (BMI) was calculated as weight (in kilograms) divided by the square of the height (in meters), and then categorized as per the WHO classification in Appendix V f[62]].

Waist circumference (WC) was taken as the narrowest circumference between the lowest rib and the top of the pelvis, measured in the horizontal plane and at the end of expiration with the subject standing and rounded to the nearest 0.5 cm. Hip circumference was taken as the maximum circumference in the horizontal plane, measured over the buttocks and rounded to the nearest 0.5 cm. The Waist-Hip Ratio (WI1R) was calculated as the ratio of the waist circumference to the hip circumference.

Blood pressure was measured as per the WHO recommendations, with the patient seated and using a standard calibrated mercury sphygmomanometer with a cuff covering at least two thirds of the upper arm circumference. Blood pressures were taken after an initial rest period of 15 minutes. Systolic blooH pressure was determined by the perception of the first Korotkoff sound (phase 1) and diastolic pressure determined by the disappearance of the fifth Korotkoff sound (phase 5). Two measurements were taken at five minute intervals and the average of the two readings taken as the patient's blood pressure. Blood pressure was classified according to the seventh report of the Joint National Committee (JNC 7) on Prevention. Detection. Evaluation, and Treatment of High Blood Pressure in Appendix V [[63]].

5.4.3 Laboratory Methods

Following 10 hours of overnight fasting, 8 ml of venous blood was drawn from the cubital vein. 5 ml of blood was placed in a sterile plain vacutainer for the measurement of fasting lipid profile, blood glucose and creatinine levels and 3ml was put in an EDTA (ethylene diamine tetra acetic acid) vacutainer for hemoglobin determination. 5ml of spot urine samples were taken for albumin-creatinine ratio determination to assess for proteinuria. All laboratory tests were undertaken at Lancet laboratory.

Lipid profiles were analyzed using the Integra 400 Plus® chemistry analyzer machine. Triglycerides were ascertained after enzymatic splitting with lipoprotein lipase to free fatty acids and glycerol. The glycerol, after phosphorylation by adenosine triphosphate with glycerol kinase produced glycerol-3-phosphate and adenosine disphosphate, the former of which was further oxidized by glycerol phosphate oxidase to yield dihydroxyacetone phosphate and hydrogen peroxide. Hydrogen peroxide then catalyzed a reaction involving 4-aminoantipyrine and 4-chlorophenol to produce a red color dye, the absorbance of which was proportional to the concentration of triglycerides in the sample.

Plasma total cholesterol levels were determined after enzymatic hydrolysis of cholesterol esters and oxidation to produce hydrogen peroxide, which then combined with hydroxybenzoic acid to form a chromophore which was quantified at 500nm. HDL-cholesterol was determined using the precipitation process where chylomicrons, VLDL and LDL were precipitated by adding phosphotungstic acid and magnesium chloride. After centrifugation, the supernatant fluid containing the HDH fraction was then assayed. LDL-cholesterol was calculated from the total cholesterol, HDL-cholesterol and triglycerides levels through the Friedman formula [64].

Fasting blood glucose was determined by the Integra 400 Plus machine by reflectance photometry technique. Hemoglobin was determined by use of the Sysmex 2000 coulter counter machine. Urine albumin-creatinine ratio was measured using the Integra 4000 Plus® machine. Urine protein amount was assayed by a turbidimetric. Proteins present in the urine were denatured by benzethonium chloride resulting in the formation of a fine suspension which was quantitated turbidimetrically at 405 nm. Serum and urine creatinine were assayed using a photometric colorimetric test. The color intensity of the complex was directly proportional to the creatinine concentration and assayed at 492 nm.

5.5 DEFINITION OF STUDY VARIABLES

5.5.1 Patient variables

Patient variables included demographic characteristics of age and gender and clinical characteristics including pre-transplant dialysis duration, cause of CKD if known, current medications including immunosuppressant drugs, number and type of renal allograft, and pre-existent diabetes and hypertension.

5.5.2 Hypertension

Hypertension was defined as use of antihypertensive therapy or systolic blood pressure of >140 mm Hg and diastolic blood pressure of >90 mm Hg in patients not receiving antihypertensive therapy. It was classified as controlled or uncontrolled based on target blood pressure <130/80 mm Hg for RTR as per current KDOQI recommendations [63].

5.5.3 Decreased Glomerular Filtration Rate

The GFR was estimated with the creatinine clearance (CrCl) value derived from the Cockcroft - Gault equation shown below [65]:

- GFR = (140 - age) * (body weight in kg)/72 * serum creatinine (mg/dL) [for women, results were multiplied by 0.85]

Normal graft function was considered as CrCl values above 60mL/min while impaired graft function was defined as CrCl values below 60mL/min [34].

5.5.4 Dysglycemia

Dysglycemia was defined as presence of diabetes mellitus or impaired fasting glucose. The latter were based on the American Diabetic Association definitions with fasting defined as no caloric intake for at least 8 hours f[66]:

- **Diabetes mellitus** - fasting blood glucose > 7.0mmol/l or the use of antidiabetic therapy
- **Impaired fasting glucose** - fasting blood glucose 5.6 - 6.9 mmol/l while not receiving antidiabetic medication

Diabetes was further classified into pre-existent diabetes, impaired fasting glucose and NODAT.

5.5.5 Obesity

Body mass index **(BMI)** was classified as per the WHO classification into underweight, normal, overweight or obesity (Appendix V). Abdominal obesity was evaluated by use of the waist circumference and considered abnormal if>94.0 cm in males and >80.0 cm in females. Waist-hip ratio DO.90 in men and DO.85 in women was considered to be a high-risk factor for cardiovascular events [$^{67,6\$}$].

5.5.6 Dyslipidemia

Dyslipidemia was defined as use of lipid lowering agents or the presence of any of the following; total cholesterol >5.2 mmol/L, triglycerides >1.69 mmol/L, LDL-cholesterol >3.3 mmol/L or HDL-cholesterol <1.0 mmol/L. Lipid profiles were classified below as per the National Cholesterol Education Program (NCEP) Adult Treatment Panel **III** guidelines [ ]:

Total cholesterol:

- Normal <5.2 mmol/L
- Borderline High 5.2 - 6.1 mmol/L
- High >6.2 mmol/L

Triglycerides:

- Normal <1.69 mmol/L
- Borderline Higli 1.69 - 2.25 mmol/L
- High >2.26 mmol/L

LDL-cholesterol:

- Normal <3.3 mmol/L
- Borderline High 3.3 -4.Ommol/L
- High 4.1 -4.8mmol/L
- Very High >4.9mmol/L

HDL-cholesterol:

- Low <1.0mmol/L or Normal >1.0 mmol/L

5.5.7 **Anemia**

The diagnosis of anemia in RTR was the same as for patients with CKD and diagnosed at the following hemoglobin levels as per the National Kidney Foundation KDOQI criteria [M.J:

- hemoglobin level < 13.5 g/dL for adult men
- hemoglobin level < 12 g/dL for adult women

5.5.8 Proteinuria

Proteinuria was defined as presence of either microalbuminuria or albuminuria. Proteinuria was diagnosed based on a single spot urine albumin-creatinine ratio using thresholds established for the general population since there are no uniquely defined thresholds for proteinuria in the kidney transplant population [70]. The urine albumin-creatinine ratio was obtained by dividing the urinary albumin concentration by the urine creatinine concentration. Proteinuria was further classified as shown below:

- Microalbuminuria - Spot urine albumin-creatinine ratio 3.5 - 33.90mg/mmol (equivalent to 30 - 300mg/24hours)
- Albuminuria - Spot urine protein-creatinine ratio >33.90mg/mmol (equivalent to 300mg/24hours)

5.5.9 Cigarette Smoking

Cunent cigarette smoking status was defined as the smoking of cigarettes, pipes or cigars in the last 12 months [47].

Cigarette smoking was quantified as the number of pack years smoked. Pack years were calculated as follows:

- Number of pack years = (number of cigarettes smoked per day x number of years smoked)/20

6. QUALITY ASSURANCE

The recommended procedure for specimen collection, proper labeling and storage was adhered at all times to minimize pre-analytical sources of errors. To ensure quality control, the tests were run in the same laboratory at Lancet and results only accepted if the machines were properly calibrated using standard calibration methods and materials and tests assayed against controls. Lancet laboratory performed both internal and external quality controls.

7. DATA MANAGEMENT AND ANALYSIS

A questionnaire was used to collect information about RTR demographic and clinical information. All data collected on the study proforma was entered into a password-protected computer data base using Microsoft Excel computer software and statistical analysis was done using SPSS version 17.0 after cleaning and verification.

Continuous variables such as age, blood pressure, BMI, or blood glucose were described using means, medians and standard deviations and presented in the form of tables.

Categorical data such as gender were described as proportions and presented in the form of tables, graphs or pie charts.

Prevalence was expresjed as a percentage of the study population with 95% Confidence Intervals.

The recipient variables of age. gender, duration of dialysis pre-transplant, cause of CKD. pre-existent diabetes or hypertension, drugs including immunosuppressant agents, and type and number of renal allografts were expressed as proportions and then evaluated for associations with the cardiovascular risk factors using the Chi-square test.

Correlations were deemed to be of statistical significance when the *P* value was less than 0.05.

8. ETHICAL CONSIDERATIONS

The study was undertaken after ethical approval by the Department of Internal Medicine, University of Nairobi and the KNH Scientific and Ethical Review committee. Patients eligible to participate in the study were included only after providing consent/assent as outlined in the following process:

1. The patients were informed that the project involved local research.

2. Full explanation of the purpose of the research and the procedures involved in the study was given to the patients as well as full details of all the tests would be done.

3. The patients were assured that participation was voluntary and no medical attention would be denied should they decline to participate. They were informed of the medical benefits and of any physical and psychological harm to their satisfaction prior to being included in the study.

4. The patients were assured of full and free access to their results and that therapeutic interventions would be recommended where need arises, according to the accepted standards of practice.

5. Confidentiality was strictly maintained and all data were securely stored and only revealed upon a need-to-know basis. All costs in this study were borne by the principal investigator.

Following the full explanation, the patient was requested to sign the consent form.

9. STUDY DURATION

1. Proposal presentation - February 2011

2. Ethics approval - April 2011 to July 2011

3. Data collection -August 2011 to February 2012

4. Data analysis -March 2012

5. Results presentation April 2012

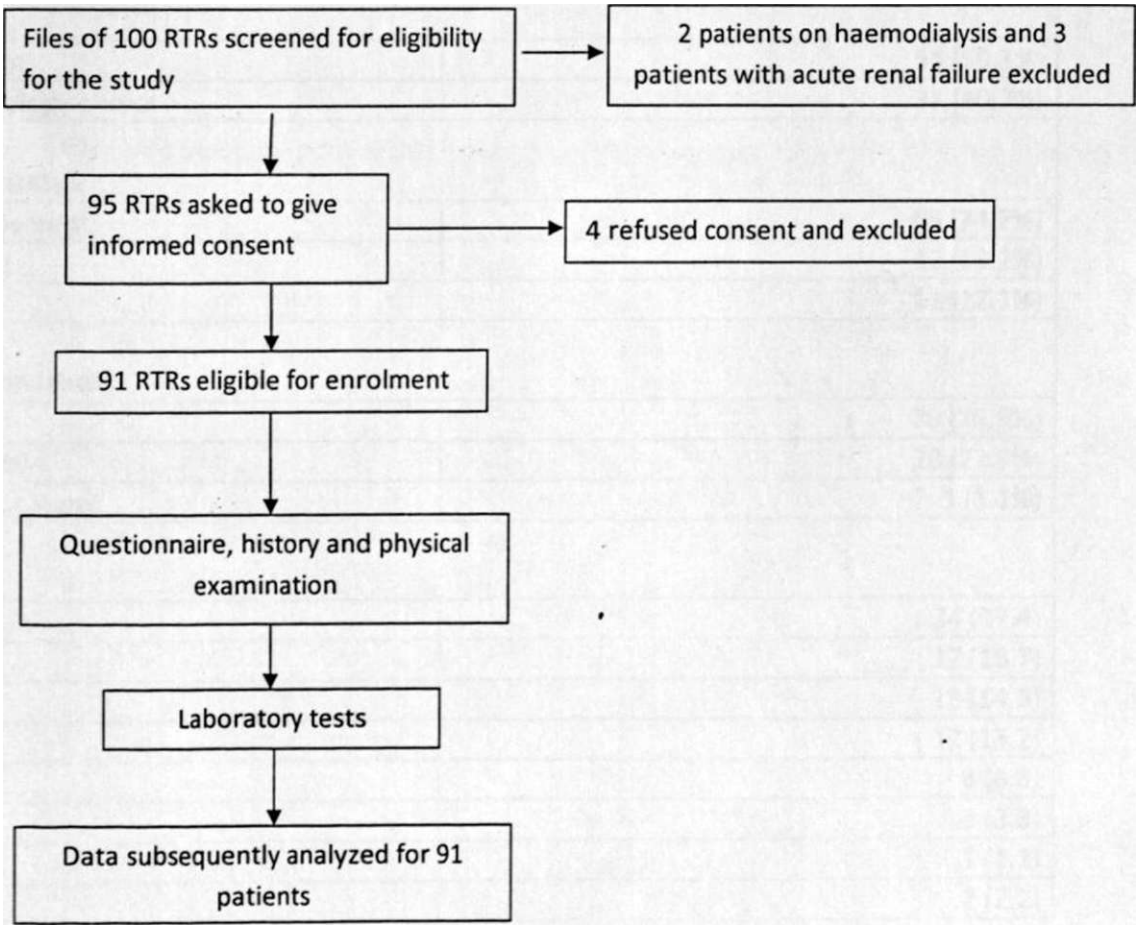
10. RESULTS

Files of 100 renal allograft recipients from nephrology clinics in Nairobi, Kenya were screened for enrolment in the six month period between 1st August 2011 and 1st February 2012. Of these patients screened, 91 patients satisfied the eligibility criteria and were enrolled while 9 patients were excluded for the following reasons:

- 2 recipients were undergoing haemodialysis after graft failure
- 3 recipients were found to have acute renal failure
- 4 recipients refused consent for the study voluntarily citing lack of time to undergo the laboratory and clinical examinations

Data for 91 patients was then analyzed as shown by the recruitment flow chart in Figure 3.

FIGURE 3. Flow chart of renal transplant recipient screening and recruitment



10.1 TRANSPLANT RECIPIENT CHARACTERISTICS

The socio-demographic characteristics of the study participants are summarized in Table 5 **below.**

TABLE 5. Socio-demographic Characteristics of Renal Transplant Recipients

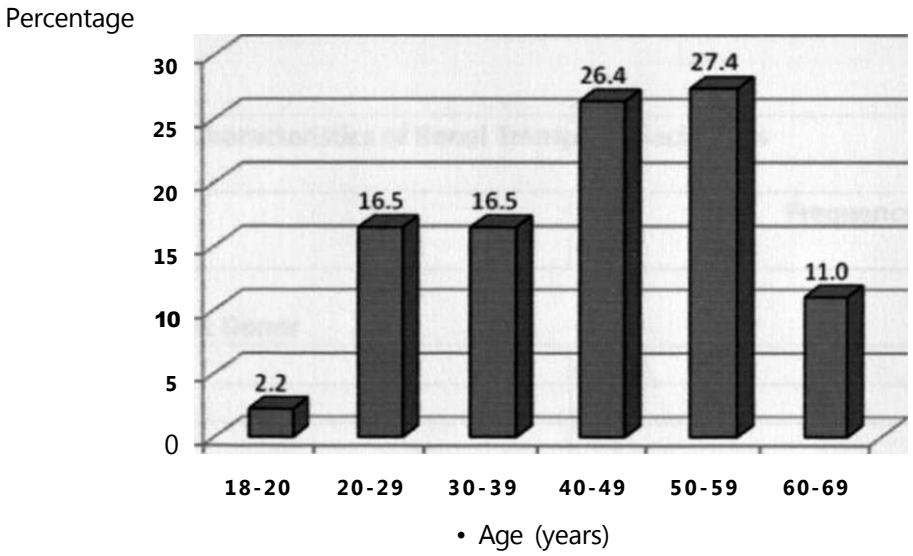
Variable	Frequency (Percentage), N=91
Sex	
Male •	62(68.1)
Female	29 (31.9)
Marital status	
Married	69 (75.8%)
Single	19 (20.9%)
Widowed	3 (3.3%)
Site of clinic	
KNH Renal Unit	54 (59.3%)
Private nephrology clinics	37 (40.7%)
Employment status	
Gainful employment	68 (74.7%)
Not employed	12 (13.2%)
Retired	11 (12.1%)
Peak education level	
Tertiary level	70 (76.9%)
Secondary level	20 (22.0%)
No formal education	1 (1.1%)
Residence	
Central	34 (37.4)
Rift Valley	17(18.7)
Nairobi	13(14.3)
Eastern	12(13.2)
Nyanza	8 (8.8)
Western	3 (3.3)
Coast	1(1.1)
East Africa	2(2.2)

There were 62 male patients and 29 female patients giving a male to female ratio being 2.1 to 1.

Most of the transplant recipients (59.3%) were enrolled from K.NH Renal Unit while the rest (40.7%) attend private nephrology clinics. Majority of the patients were gainfully employed (74.7%) and were married (75.8%). Most of the RTRs (76.9%) had attained a tertiary level of education.

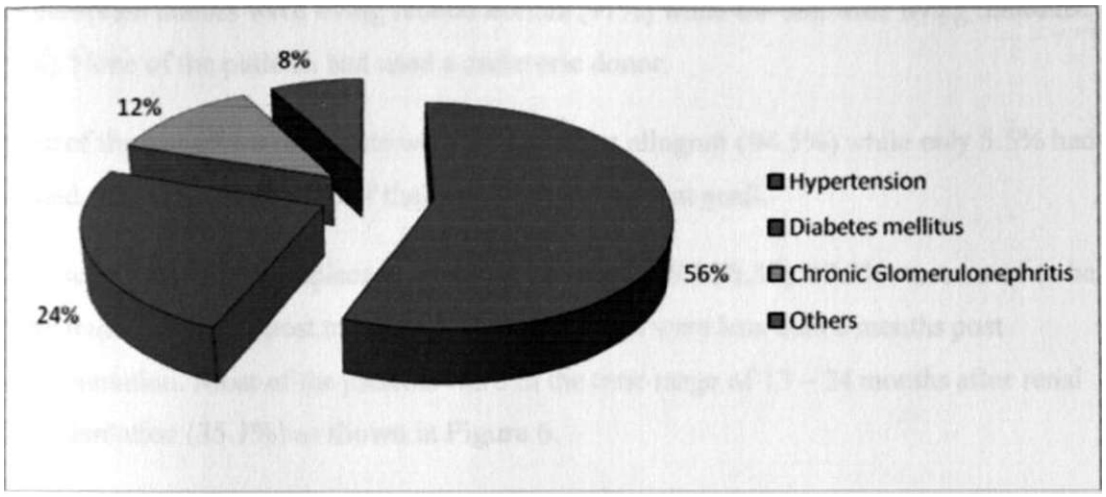
Majority of the transplant recipients were from provinces in or around Nairobi with Central province having the highest number of patients (37.4%). There were 2 patients who were non-Kenyans and resided in Burundi and Southern Sudan.

FIGURE 4.Age distribution of Renal Transplant Recipients



The mean age of the entire patient population was 44.2 years (SD 12.44), median age was 46 years and the range was 18 - 65 years. The peak age group was 50 - 59 years who constituted 27.4% of the study population (Figure 4).

FIGURE 5.Presumed cause of CKD in Renal Transplant Recipients



The presumed causes of CKD in the transplant recipients included hypertension (56%), diabetes mellitus (24%) and chronic glomerulonephritis (12%) as shown in Figure 5. Other causes of CKD included lupus nephritis, drug toxicity, obstructive uropathy, polycystic kidney disease and pyelonephritis.

TABLE 6. Clinical Characteristics of Renal Transplant Recipients

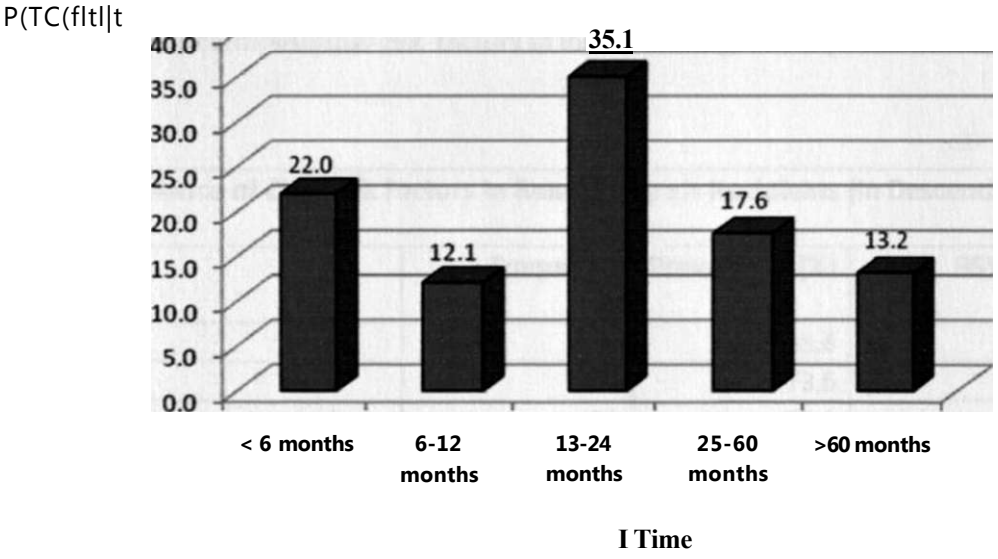
Variable	**Frequency (Percentage), N=91**
Type of Transplant Donor	
Living related	**83 (91.2%)**
Living unrelated	8 (8.8%)
Cadaveric	0
Number of kidney grafts	
I First	**86 (94.5%)**
Second	5 (5.5%)
Immunosuppressant Drugs	
Prednisolone	**89 (97.8%)**
Mycophenolate Mofetil	81 (89.0%)
Cyclosporine	57 (62.6%)
Tacrolimus	26 (28.6%)
Azathioprine	6 (6.6%)
Everolimus	2 (2.2%)

The clinical characteristics of the renal allograft recipients are summarized in Table 6. Majority of transplant donors were living related donors (91%) while the rest were living unrelated donors (9%). None of the patients had used a cadaveric donor.

Most of the transplant recipients were on their first allograft (94.5%) while only 5.5% had a second allograft after failure of their first renal transplant graft.

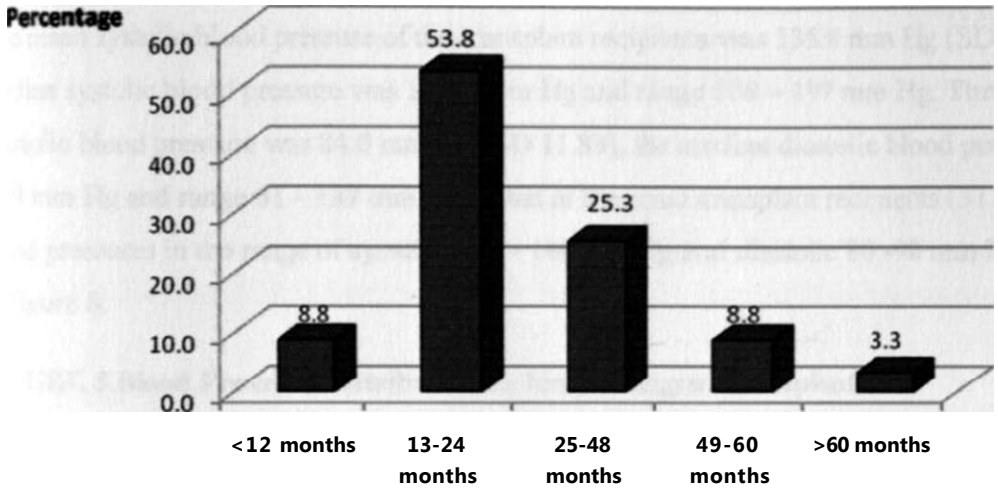
The mean time after transplantation was 29.9 months (SD 38.38). 13.2% were noted to be at more than 60 months post transplantation while 22% were less than 6 months post transplantation. Most of the patients were in the time range of 13 - 24 months after renal transplantation (35.1%) as shown in Figure 6.

FIGURE 6.Duration of time after Renal Allograft Transplant



Most patients (53.8%) had undergone 13-24 months on haemodialysis before transplantation compared to 3.3% who had a prolonged duration on haemodialysis of more than 5 years before transplantation (Figure 7). None of the transplant recipients had undergone peritoneal dialysis before transplantation.

FIGURE 7.Duration of time on Haemodialysis before Renal Allograft Transplant



The prevalence of cardiovascular risk factors in the renal allograft recipients is summarized in Table 7 below.

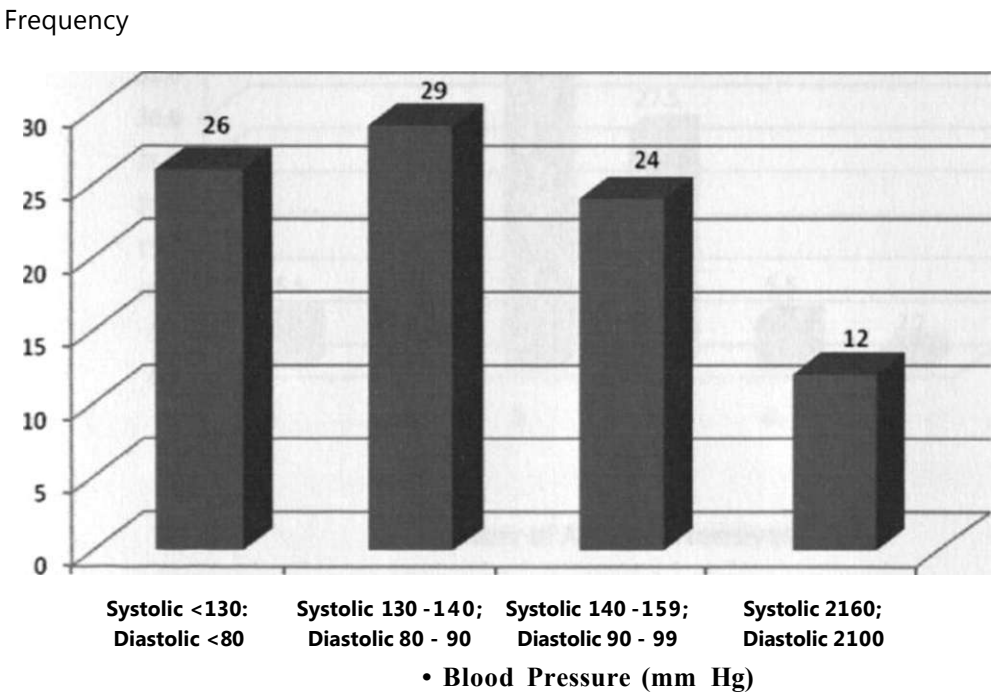
TABLE 7. Prevalence of CVD Risk Factors in Renal Allograft Recipients (In Descending Order)

Variable	Frequency	Prevalence (%)	95% Confidence Interval
, Hypertension	87	95.6	88.5-98.6
Dyslipidemia	67	73.6	63.2-82.1
Abdominal obesity — elevated waist-hip ratio	62	68.1	57.4-77.3
Abdominal obesity - elevated waist circumference	48	52.7	42.1-63.2
Dysglycemia	45	49.5	38.9-60.1
Overweight/obesity (BMI £25.0)	44	48.4	37.8-59.0
Proteinuria	41	45.1	34.7-55.8
Anemia	20	22.0	14.2-32.1
Impaired graft function (CrCI <60 mL/min)	15	16.5	9.8-26.1
[^moking_	3	3.3	0.9-10.0

10.2 HYPERTENSION

The mean systolic blood pressure of the transplant recipients was 135.8 mm Hg (SD 19.08), the median systolic blood pressure was 130.0 mm Hg and range 108-197 mm Hg. The mean diastolic blood pressure was 84.0 mm Hg (SD 11.89), the median diastolic blood pressure was 82.0 mm Hg and range 61-137 mm Hg. Most of the renal transplant recipients (31.9%) had blood pressures in the range of systolic 130-140 mm Hg and diastolic 80 -90 mm Hg as shown in Figure 8.

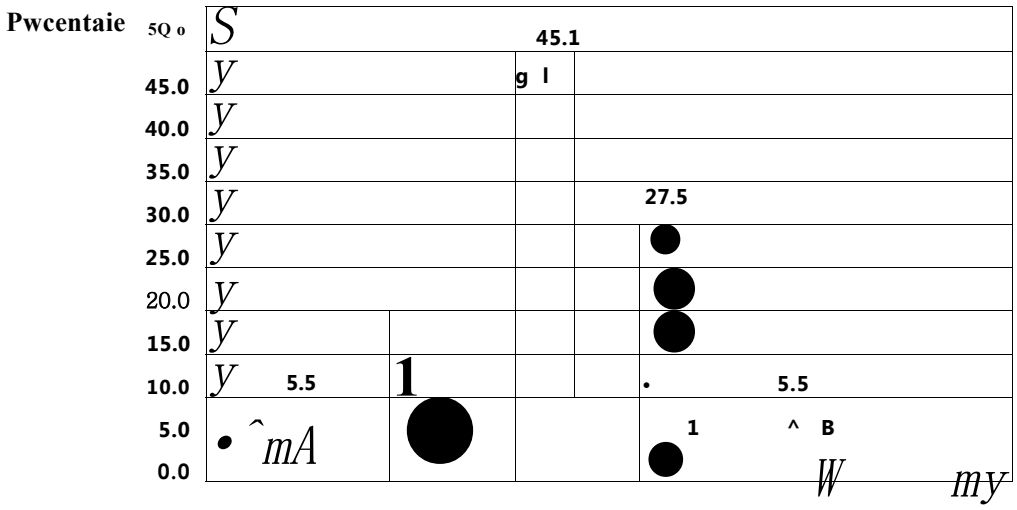
FIGURE 8.Blood Pressure Distribution in Renal Allograft Recipients



The recommended target blood pressure of less than 130/80 mm Hg was achieved by 26 patients (28.6%) while 36 patients (39.6%) had blood pressures above 140/90 mm Hg. Overall, 85 patients had blood pressures over 140/90 mm Hg or were on antihypertensive medications giving a prevalence of 95.6% (95% **CI** 88.5 - 98.6). Majority of patients (95.6%) had history of pre-transplant hypertension.

Majority of the transplant recipients were on antihypertensive medications with only 5 patients (5.5%) not on medications; out of these 4 patients had normal blood pressures while one had stage 1 hypertension. Majority of the patients (80.2%) were on 2 or more antihypertensive drugs as shown in Figure 9 with the mean number of antihypertensive medications used per patient at 2.2 drugs.

FIGURE 9.Number of Antihypertensive Drugs used by Renal Allograft Recipients



10.3 DYSGLYCEMIA

The mean fasting glucose of renal transplant recipients was 5.8 mmol/L (SD 2.55), the median fasting glucose was 5.1 mmol/L and the range was 2.5 - 17.9 mmol/L.

Diabetes mellitus was present in 30 of the patients giving a prevalence of 33.0% (95% CI 23.7 - 43.7). Impaired fasting glucose was present in 15 transplant recipients with a prevalence of 16.5% (95% CI 9.8 - 26.1). NODAT was present in 8 of the patients (8.8%) while 22 patients had history of pre-transplant diabetes mellitus.

The prevalence of dysglycemia in renal transplant recipients which defined as presence of diabetes mellitus or impaired fasting glucose was 49.5% (95% CI 38.9 - 60.1).

18 patients (19.8%) were on insulin medication while 13 patients (14.3%) were on oral hypoglycemic agents for treatment of diabetes mellitus. Overall, 29 patients were on anti-diabetic medication with 16 patients (17.6%) on insulin alone, 11 patients (12.1%) on oral hypoglycemic agents alone and 2 patients (2.2%) on combined insulin and oral hypoglycemic agents.

10.4 DYSLIPIDEMIA

The mean total cholesterol level of the renal transplant recipients was 5.2 mmol/L (SD 1.19) with a median of 5.1 mmol/L and range of 2.7 - 9.4 mmol/L. Most of the transplant recipients (52.7%) had normal total cholesterol levels with 25 patients (27.55) having borderline high total cholesterol and 18 patients (19.8%) having high total cholesterol levels.

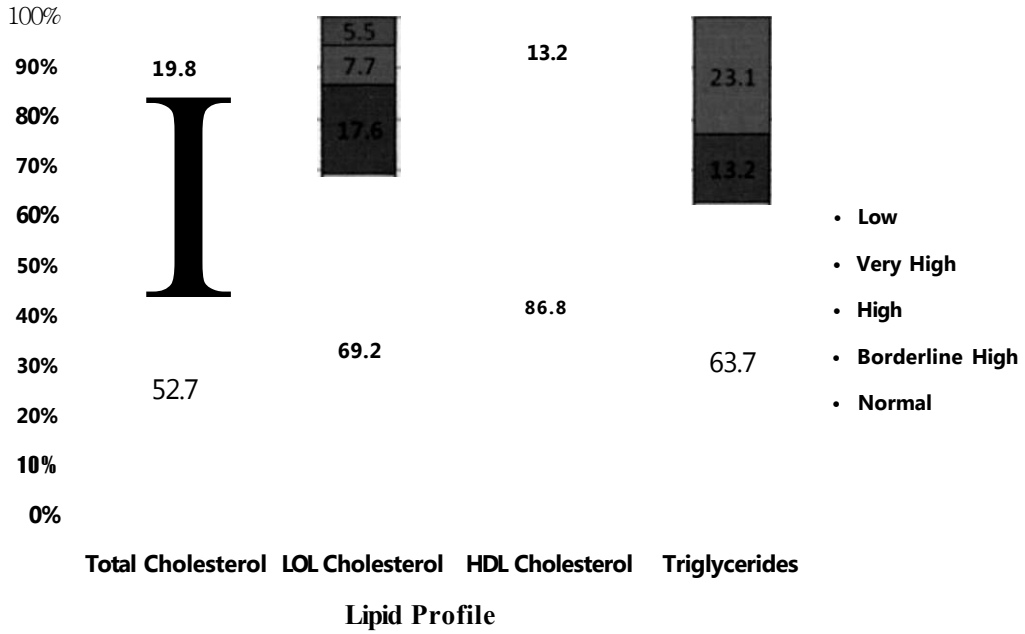
The mean triglyceride level of the renal transplant recipient population was 1.71 mmol/L (SD 0.845) with a median cf 1.50 and a range of 0.49 - 4.73 mmol/L. Majority of the transplant recipients (63.7%) had normal triglyceride levels with 12 patients (13.2%) having borderline high triglyceride and 21 patients (23.1%) having high triglyceride levels.

The mean LDL-cholesterol level of the renal transplant recipients was 2.9 mmol/L (SD 0.96) with a median of 2.8 mmol/L and range of 1.1 - 5.3 mmol/L. Majority of the transplant recipients (69.2%) had normal LDL-cholesterol levels with 16 patients (17.6%) having borderline high LDL-cholesterol, 7 patients (7.7%) having high LDL-cholesterol and 5 patients (5.5%) having very high LDL-cholesterol levels.

The mean HDL-cholesterol level of the renal transplant recipients was 1.5 mmol/L (SD 0.50) with a median of 1.4 mmol/L and range of 0.4 - 3.1 mmol/L. Majority of the patients (86.8%) had normal HDL-cholesterol levels while only 12 patients (13.2%) had low HDL-cholesterol levels.

The lipid profiles of the renal allograft recipients for total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are shown in Figure 10. In the study population, 43 patients (47.3%) had high total cholesterol levels, 33 patients (36.3%) had high triglyceride levels, 28 patients (30.8%) had high LDL-cholesterol levels and 12 patients (13.2%) had low HDL-cholesterol levels.

FIGURE lO.Characterization of Lipid Profiles in Renal Allograft Recipients

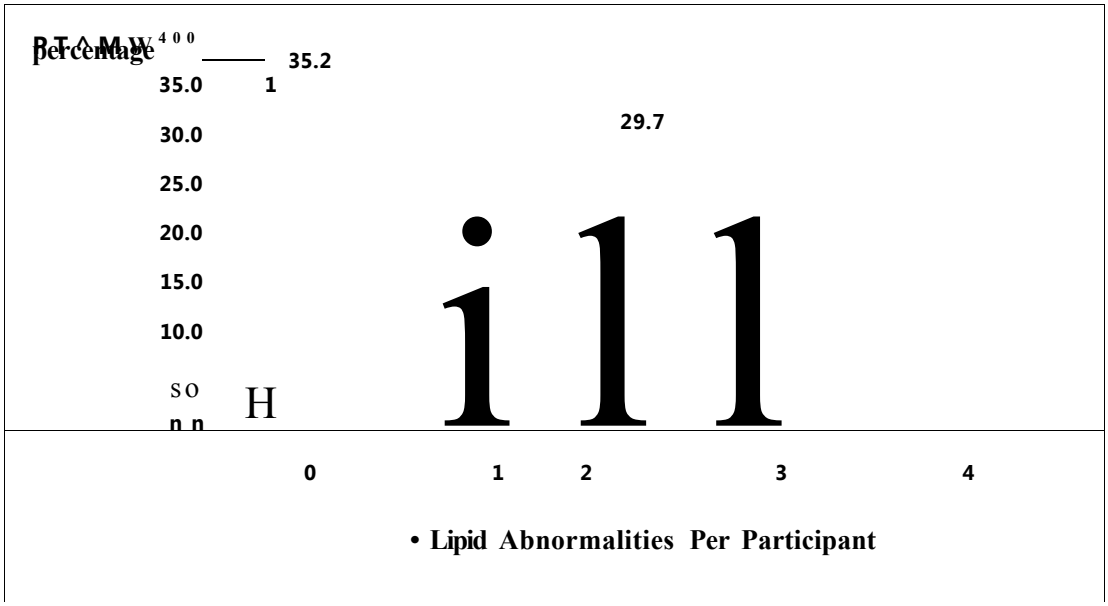


The total number of transplant recipients on lipid lowering agents or with of any of the following abnormalities; total cholesterol >5.2 mmol/L, triglycerides >1.69 mmol/L, LDL-cholesterol >3.3 mmol/L or HDL-cholesterol <1.0 mmol/L was 67 patients. This gave an overall prevalence of dyslipidemia of 73.6% (95% CI 63.2 - 82.1).

Only 16 of the renal transplant recipients (17.6%) were on lipid lowering drugs.

In the transplant recipient population, 32 patients (35.2%) had a normal lipid profile while 59 patients (64.8%) had 1 or more lipid profile abnormalities as shown in Figure 11.

FIGURE ll. Number of Lipid Abnormalities in Renal Allograft Recipients

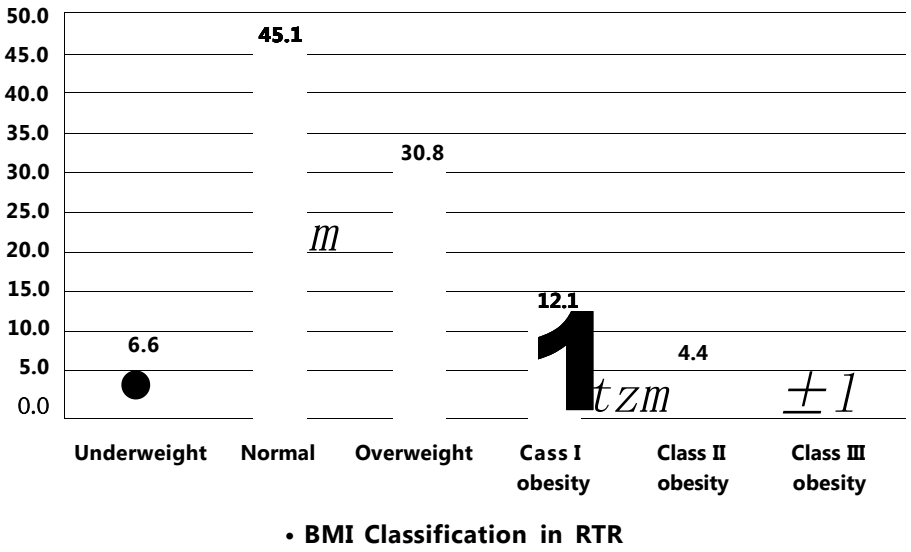


10.5 OBESITY

The mean BMI of the transplant recipient population was 25.7 kg/m^2 (SD 5.74) with a median of 24.6 kg/m^2 and range of 16.2 - 54.7 kg/m^2. The mean waist circumference was 91.0 cm (SD 13.38) with a median of 90.5 cm and range of 63 - 122 cm. The mean waist-hip ratio was 0.92 (SD 0.075) with a median of 0.93 and range of 0.71 - 1.14.

Most of the renal allograft recipients had a normal BMI range with 41 patients (45.1%) having a BMI of 18.5-24.9 (Figure 12).

FIGURE **12.BMI** Classification in Renal Allograft Recipients



• **BMI Classification in RTR**

In the renal transplant population, 16 patients were classified as obese (17.6%) while 28 patients were classified as overweight or pre-obese (30.8%). In overall, 44 renal transplant recipients had BMI >25.0 kg/m^2 giving a prevalence of 48.4% (95% CI 37.8 - 59.0).

Based on waist-hip ratio for sex, 62 patients had a high waist-hip ratio giving a prevalence of 68.1% (95% CI 57.4 - 77.3). Using waist circumference for sex, 48 transplant recipients had a high waist circumference giving a prevalence of 52.7% (95% CI 42.1 - 63.2).

10.6 ANEMIA

The mean hemoglobin level in the renal transplant recipients was 14.3 g/dL (SD 2.33) with a median of 14.3 g/dL and range of 8.4 - 20.5 g/dL. Out of the patients with anemia, 14 were male and 6 were female giving a male to female ratio of 1:0.43.

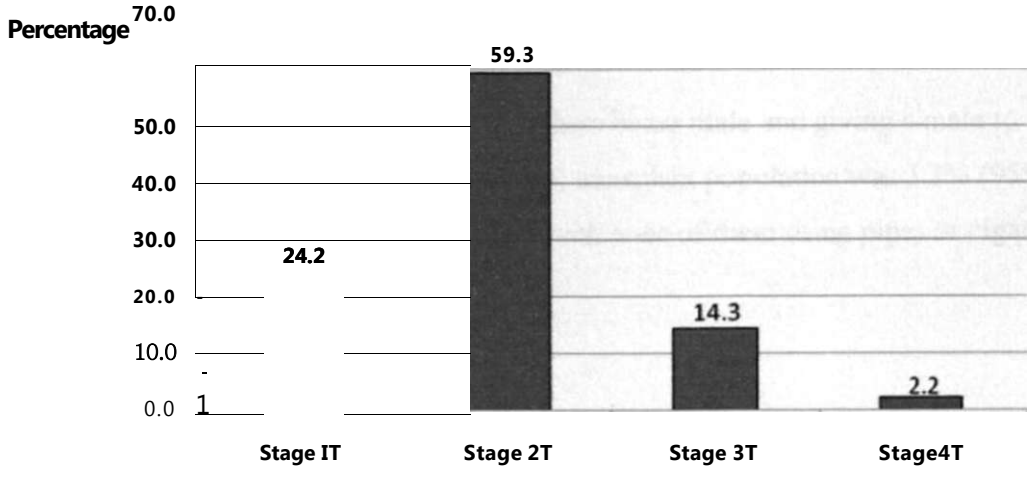
Using the National Kidney Foundation KDOQI criteria based on sex, 20 renal allograft recipients were classified as having anemia with a prevalence of 22.0% (95% CI 14.2 - 32.1).

None of the patients was on any erythropoietin stimulating agent or haematinic drugs.

10.7 DECREASED GLOMERULAR FILTRATION RATE

The mean creatinine level of the renal transplant recipients was 113.2 umol/L (SD 51.87) with a median of 99.0 umol/L and range of 60 - 431 umol/L. The mean creatinine clearance of the patients was 78.6 mL/min (SD 23.11) with a median of 79.3 mL/min and range of 23.4 - 158.5 mL/min. Majority of renal transplant recipients (59.3%) were classified in stage 2T based on their creatinine clearance level (Figure 13).

FIGURE 13.Chronic Kidney Disease Classification in Renal Allograft Recipients



In the renal transplant population. 15 patients had impaired renal graft function as defined by creatinine clearance below 60 mL/min with a prevalence of 16.5% (95% CI 9.8 - 26.1).

10.8 PROTEINURIA

The mean urinary albumin/creatinine ratio was 10.84 mg/mmol (SD 19.700) with a median of 2.63 mg/mmol and range of 0.14 - 114.05 mg/mmol.

In the renal transplant population, 31 patients had microalbuminuria with a prevalence of 34.1% (95% CI 24.7 - 44.8) while 10 patients had macroalbuminuria with a prevalence of 11.0% (95% CI 5.7 - 19.7). Majority of the patients (54.9%) had normal protein levels in urine. In overall. 41 transplant recipients had proteinuria defined as presence of either microalbuminuria or nacroalbuminuria with a prevalence of 45.1% (95% CI 34.7 - 55.8).

10.9 SMOKING

The mean number of cigarette sticks smoked daily by the renal allograft recipients was 5.7 sticks (SD 1.70) with a median of 5 sticks smoked daily and range of 4 - 8 sticks smoked daily.

The mean number of years smoked by the renal allograft recipients was 28.3 years (SD 19.29) with a median of 20 years smoked and range of 10 - 55 years smoked.

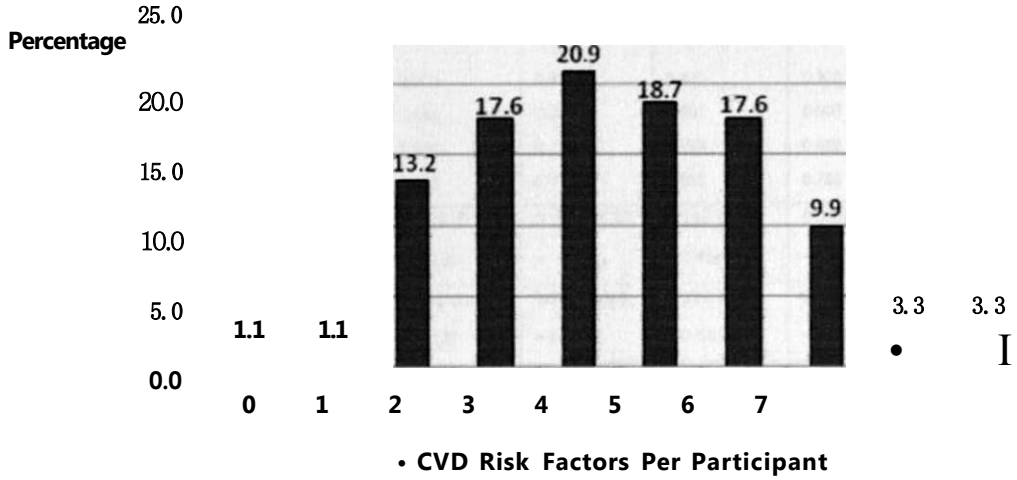
The mean number of pack years smoked by the renal allograft recipients was 6.7 pack years (SD 3.09) with a median of 5 pack years smoked and range of 4 - 11 pack years smoked.

Only 3 patients were currently smokers with 2 of them being male and giving a male to female ratio of 2:1. The prevalence of smoking in the renal transplant population was 3.3% (95% CI 0.9 -10.0). All of the 3 smokers preferred cigarettes with none of them using pipes or cigars.

The number of cardiovascular risk factors per transplant recipient was assessed by the number of the following risk factors present in each patient; hypertension, dyslipidemia, overweight or obesity by BMI, abdominal obesity, dysglycemia, proteinuria, anemia, impaired graft function and smoking.

The mean number of cardiovascular risk factors per patient was 4.8. Majority of the transplant recipients (97.8%) of participants had two or more cardiovascular risk factors while only one patient had none of the risk factors mentioned (Figure 14).

FIGURE 14.Number of CVD risk factors in Renal Allograft Recipients



10.10 ASSOCIATIONS BETWEEN PATIENT VARIABLES AND RISK FACTORS

Associations between recipient age, gender, duration of dialysis pre-transplant. medications used, cause of CKD, pre-existent diabetes or hypertension, and type and number of renal allografts and the cardiovascular risk factors are summarized in Table 8.

TABLE 8. Correlation of Transplant Recipient Characteristics and CVD Risk Factors

Variable *	P value (95% Confidence Interval)							
	Hypertension	Dyslipidemia	Dysglycemia	NOOAT	Anemia	Proteinuria	Obesity	Impaired graft function
	0.363 (0.64 -0.71)	0.942 (0.04 -0.28)	0.198(1.08 -1.56)	0.213 (0.89 -1.00)	0.660 (0.09 -0.39)	0.696 (0.29 -0.72)	0.454 (1.99 -2.01)	0.652 (0.33 -0.88)
j Gender	0.426 (0.18 -0.64)	0.490(0.72 -1.14)	0.546(1.61 -1.99)	0.720(1.23 -1.58)	0.839(1.73 -2.03)	0.976 (0.21 -0.53)	0.243 (0.88 -1.22)	0.894 (1.90 -2.36)
Dialysis duration pre-transplant:								
< 2 months*	1.230	1.150	1.070	0.990	0.870	0.920	0.970	1.020
2« - 48 months	1.213	1.133	1.053	0.973	0.853	0.903	0.953	1.003
H - 60 months	0.996	0.916	0.836	0.756	0636	0.686	0.736	0.786
> 60 months	1.013	0.933	0.8S3	0.773	0.653	0.703	0.753	0.803
'resumed cause of CKD	0.959 (1.42 -1.88)	0.139(1.64 - 2.02)	0.569 (0.06 -0.32)	0.941 (-1.47 --1.96)	0.192 (0.12 **-0.45)**	0.336(1.26 -1.55)	0.568(1.09 -0.57)	0.358 (0.23 -0.95)
Presence of 2 -enal graft**	0.622 (0.86 -1.35)	0.739 (0.59 -1.08)	0.160 (0.67 -1.16)	0.011(1.24 - 63.88)	0.222(0.17 -0.56)	0.815(2.14 **- 2.48)**	0.312(3.19 -3.54)	0.307 (0.74 -1.23)
Jvig unrelated graft donor	0.525 (0.50 -0.98)	0.455 (0.72 -1.21)	0.479 (0.96 -1.45)	0.698(2.37 -2.77)	0.267 (5.08 -5.34)	0.768 (2.64 - 2.69)	0.601 (0.15 -0.50)	0.497 (3.34 -3.53)
®re-transplant tabetes mellitus	0.217 (0.51 -0.84)	0.912 (2.23 - 2.39)	0.583(2 49 -2.97)	0.955 (4.29 -4.38)	0.491 (1.95 -1.44)	0.654 (0.74 - 1.19)	0.847 (0.25 -0.70)	0.026 (1.11 -10.36)
Pre-transplant ••vpertension	0.159 (0.34 -0.80)	0.949 (0.93 -1.03)	0.296 (0.09 -0.40)	0.525 (0.11 -0.43)	0.166(1.72 **-2**.16)	0.839 (2.08 - 2.50)	0.222 (0.59 -1.07)	0.363 (1.65 -2.10)
insulin use	0.121(0.31 -0.75)	0.880 (8.08 -8.27)	0.635(1.37 -1.83)	0.698(1.05 - 1.53)	0.194(2.52 -2.91)	0.557(2.79 -2.95)	0.917 (0.87 -1.22)	0.004 (0.06 -0.64)
1 Oral lypogiycemic Sruguse	0.404 (0.11 -0.44)	0.698 (10.28- 10.44)	0.732(1.16 -1.64)	0.880(4.26 **-4.22)**	0.918 (IJ.72 -1.21)	0.491 (1.67 -2.11)	0.105 (0.92 -1.36)	0.489 (-0.66 —0.14)
ljp<d lowering 9tug use	0.345 (0.03 **-0.24)**	0.891 (7.23 -7.44)	0.615(1.51 -1.97)	0.564(2.20 **-2.52)**	0.731 (0.09 -0.39)	0.908(1.02 **-1.50)**	0.488 (-0.09 **-0.34)**	**0.080** (-1.34 **- 0.43)**
Cotmoxacde use	0.798 (0.01 -0.07)	0.219 (2.26 - 2.95)	0.081(0 40 **-0.44)**	**0.241(0.98** -1.23	0.237 (-0.11 -0.51)	0.461 (1.56 -2.36)	**0.204(0.19** -0.38)	**0.323 (-0.24** -1.38)

The presence of a second renal allograft in transplant recipients was significantly associated with development of NODAT with a p-value of 0.011 and an Odds Ratio of 8.89 (95% CI of 1.237 - 63.881). Patients with a second renal allograft were eight times more likely to develop NODAT than those with only one kidney graft. However, this association was not significant on further multivariate analysis (p-value of 0.856 with 95% CI 0.02 - 1.44) indicating it was not an independent association.

The history of pre-transplant diabetes mellitus in renal allograft recipients was significantly associated with development of impaired renal graft function with a p-value of 0.026 and an Odds Ratio of 3.56 (95% CI of 1.114 - 10.363). Patients with pre-transplant diabetes were three times more likely to have impaired graft function than those without impaired graft function. This association was not significant on further multivariate analysis (p-value of 0.432 with 95% CI of 0.11 - 0.98) which indicated it was not an independent association.

The use of insulin by renal transplant recipients was significantly associated with development of impaired renal graft function with a p-value of 0.004 and an Odds Ratio of 0.19 (95% CI of 0.058 - 0.641). This association was may not be clinically significant with likelihood of developing impaired graft function in patients on insulin being very small. On multivariate analysis, the association did not reach significant values (p-value of 0.588 with 95% CI 0.24 - 0.71) and therefore did not prove to be independent.

Associations between recipient age, gender, duration of dialysis pre-transplant, medications used, cause of CKD, pre-existent diabetes or hypertension, and type and number of renal allografts did not show significant associations with hypertension, dyslipidemia, dysglycemia, anemia, proteinuria and obesity in transplant patients. Multivariate analysis in the correlation of recipient variables and the cardiovascular risk factors did not yield any significant associations.

The prevalence of smoking in the renal transplant population was very low and therefore not used to analyze for associations with recipient variables in the transplant patients.

10.11 IMMUNOSUPPRESSANT DRUG USE

Renal allograft recipients were on 6 types of immunosuppressant drugs; namely Prednisolone, Mycophenolate mofetil, Cyclosporine, Tacrolimus, Azathioprine and Everolimus. Majority of the patients were taking Prednisolone with 89 transplant recipients on the drug (97.8%). 81 recipients (89.0%) were taking Mycophenolate mofetil, 57 subjects (62.6%) were using Cyclosporine, 26 recipients (28.6%) were on Tacrolimus, 6 subjects (6.6%) were using .Azathioprine (6.6%) and only 2 patients (2.2%) were taking Everolimus. The renal transplant recipients in the study were on different combinations of immunosuppressant drugs as shown in Table 9. The most common combination of immunosuppressant drugs was Cyclosporine, Mycophenolate mofetil and Prednisolone which was used by 52 transplant recipients (57.1%).

TABLE 9. Types of Immunosuppressant Drug Combinations in Renal Allograft Recipients

Type of Combination	Frequency (Percentage), N=91
CSA+ MMF + Prednisolone	52 (57.1%)
MMF + TAC + Prednisolone	23 (25.2%)
MMF + Prednisolone	4 (4.4%)
AZA + Prednisolone	3 (3.3%)
CSA + Prednisolone	2 (2.2%)
Other combinations*	7 (7.8%)

[4] Other combinations include: Prednisolone + TAC + EVE; CSA + MMF + AZA; MMF + EVE + Prednisolone; TAC + Prednisolone; CSA + AZA + Prednisolone; TAC + AZA + Prednisolone; and CSA only.

The duration of exposrre of renal recipients to immunosuppressant drugs varied widely with a range of 1 month - 216 months. Allograft recipients on Azathioprine had the longest mean duration of exposure at 142.0 months (SD 45.65) with range of 60 - 216 months. Transplant recipients on Everolimus had the shortest mean duration of exposure at 7.5 months (SD 4.50) with range of 3 - 12 months. The duration of exposure of allograft recipients to the immunosuppressant agents is shown in Table 10.

TABLE 10. Duration of Exposure of Renal Allograft Recipients to Immunosuppressant Drugs

Drug	Mean Duration in Months (SD)	Range (Months)
Azathioprine	142.0 (45.65)	60-216
Prednisolone	29.3 (37.21)	1-216
Cyclosporine	26.1(32.44)	1-144
Tacrolimus	23.7(17.42)	3-72
Mycophenolate mofetil	22.7 (25.55)	1-144
Everolimus	7.5 (4.50)	3-12

I

10.10 ASSOCIATIONS BETWEEN IMMUNOSUPPRESSANT DRUGS AND RISK FACTORS

There were no statistically significant associations between any of the immunosuppressant agents used by renal transplant recipients and the cardiovascular risk factors on bivariate (Table 11) or multivariate analysis. However, use of Prednisolone and NODAT (P of 0.067 with 95% CI 0.01 - 0.06), use of Cyclosporine and dysglycemia (P of 0.070 with 95% CI 0.01 - 0.14) and use of Tacrolimus and development of anemia {P of 0.066 with 95% CI 0.04 - 0.10) all approached but did not reach significant levels.

TABLE **11.** Correlation of Immunosuppressant Drugs and Cardiovascular Risk Factors

Risk Factor	**P Value (95% Confidence Interval)**					
	Prednisolone	**MMF**	**Cyclosporine**	**Tacrolimus**	**Azathioprine**	**Everolimus**
Hypertension	**0.759(2.73-3.57)**	**0.359 (0.36-0.76)**	**0.601(1.17-1.84)**	**0.872 (6.33-7.30)**	**0.587(1.10-1.75)**	**0.759 (2.73-3.57)**
Dyslipidemia	**0.443 (0.45 - 1.14)**	**0.300 (0.20-0.66)**	**0.317 (0.22-0.71)**	**0.259 (0.15-0.55)**	**0.689(1.69-2.75)**	**0.443 (0.45 - 1.14)**
Dysglycemia	**0.148 (0.04-0.31)**	**0.479 (0.48 - 1.36)**	0.070 (0.01 – 0.14)	**0.320 (0.18-0.76)**	**0.383 (0.27-0.97)**	**0.148 (0.04-0.31)**
NODAT	0.067 (0.01 – 0.06)	**0.185 (0.10-0.35)**	**0.439 (0.49 - 1.08)**	**0.558'(0.89-1.63)**	**0.481 (0.61 - 1.25)**	**0.657(1.48-2.35)**
Anemia	**0.448 (0.59 - 1.04)**	**0.873 (6.44 - 7.31)**	**0.605(1.23-1.83)**	0.066 (0.04– 0.10)	**0.745 (2.55 - 3.29)**	**0.333 (0.33 - 0.67)**
Proteinuria	**0.114 (0.03 - 0.22)**	**0.093 (0.03 - 0.18)**	**0.109 (0.03-0.21)**	**0.286 (0.16-0.64)**	**0.271(0.15-0.60)**	**0.114 (0.03-0.22)**
impaired **graft** function	**0.525 (0.76-1.45)**	**0.136 (-0.07-0.39)**	**0.415 (0.47-0.95)**	**0.284(0.20-0.60)**	**0.260 (-0.18-0.88)**	**0.525 (0.76 - 1.45)**
Obesity	**0.343 (0.39-0.66)**	**0.224 (-0.15 - 0.72)**	**0.105 (0.05-0.18)**	**0.190 (-0.06-0.53)**	**0.275 (0.03 - 0.73)**	**0.360 (0.43 - 0.70)**

11. DISCI SSION

CVD related morbidity and mortality are the main cause of graft loss in the renal allograft recipient population. Studies done in mainly Caucasian population have shown high burden of CVD risk factors in this population and preventive measures need to be implemented in countries with a renal transplant population. This study was done to fill the gap in knowledge about the burden of CVD risk factors in our local Kenyan population of renal allograft recipients.

There was a male predominance of patients with most patients aged between 40 - 60 years. Most of the patients are married with a tertiary level of education and in gainful employment. Most of the kidney allografts were from living related donors in contrast with more developed countries which have a robust cadaveric donation system. Souza et al found that the sources of 192 donor kidneys in Brazil were living related, living unrelated, or cadaveric in 58.8%, 11.5%, and 29.7%, respectively [34]. The mean time from transplantation in our study was about 2 years, reflecting a shorter duration of time from transplantation in contrast to other studies. The mean time since transplantation was 63.0 months (SD 44.5) as found by Cofan et al in 2,793 Spanish allograft recipients RTR and 92.4 months (SD 70.7) as described by Souza et al in Brazil [34,44].

Hypertension is a well-known risk factor for CVD morbidity and mortality in the general population: this cardiovascular risk is more prevalent in the transplant population. Hypertension was present in majority of renal transplant recipients in our study, being the most prevalent CVD risk factor. Most of the patients have a short post transplantation time and are still currently on antihypertensive medications. The magnitude of hypertension may reflect the high prevalence of hypertension pre-transplantation, the effects of immunosuppressive medication and dietary indiscretion as a result of relaxation of restrictions present during haemodialysis.

There is a high level of poor blood pressure control in the renal transplant population with majority of patients not achieving the target blood pressure of <130/80 mm Hg recommended for RTR by KDOQ1. The level of blood pressure control in renal transplant patients shows slight improvement compared to CKD patients with a study done by Rajula showing 16.6% of 90 CKD patients at the KNH Renal Unit had achieved target blood pressure of <130/80 mm Hg [']. Lower rates of hypertension have been reported in other renal transplant studies with 86% by Souza et al in Brazil and 75% by Cofan et al in Spain ['

The high prevalence of hypertension and in particular poor blood pressure control in renal transplant recipients may result in decreased graft survival and increased cardiovascular morbidity unless countering measures are initiated both at policy and clinic levels. Renal transplant recipients need to be categorized as a high risk group in terms of national public health policy for hypertension and measures need to be implemented to counter the high prevalence of hypertension. Interventions may include local adaptation of KDOQI recommendations for treatment of hypertension, intensified screening for and control of hypertension in renal transplant recipients and future studies to identify ideal antihypertensive drug combinations.

There was a high prevalence of dyslipidemia in the renal transplant population, especially in terms of elevated total cholesterol, hyper-triglyceridemia and elevated LDL-cholesterol, with a minority of patients on lipid lowering drugs. This may be explained by the high prevalence of abdominal obesity in the patients and the use of both immunosuppressant drugs (especially corticosteroids and calcineurin inhibitors) and antihypertensive medications such as beta blockers f[41,42].

The elevated total cholesterol, triglyceride and LDL-cholesterol levels predispose the renal transplant recipients to atherosclerotic disease and cardiovascular mortality if not addressed. In the KDOQI Dyslipidemia Guidelines, all adult KTRs are at high risk for ischemic heart disease, and therefore should be treated to maintain LDL-Cholesterol <2.59 mmol/L in absence of severe hypertriglyceridemia. The renal transplant population as such should be identified as a high risk group for ischemic heart disease in national public health policies and should be closely monitored by surveillance and interventions done with lifestyle changes and lipid lowering agents. Local adaptation of KDOQI guidelines and patient education are interventional measures which may play a role in control of dyslipidemia in renal transplant recipients.

High levels of dyslipidemia were noted in other studies with Suleiman et al observing that 62.8% of 78 renal allograft recipients in Sudan (post transplant duration mean 45.3 months SD 35.5) had hyperlipidemia with the main abnormality being hypertriglyceridemia at 47.7% [72]. Souza et al studying Brazilian recipients found elevated total cholesterol, elevated triglyceride, elevated LDL-cholesterol and low HDL-cholesterol levels at 60%, 59%, 50% and 30% respectively [34].

"Pie prevalence of obesity was high in the renal transplant population with most of the patients having abdominal obesity and almost half of the patients having elevated BMI above 25 kg/nr. This may be attributable to the role of steroid use in fat redistribution and dietary indiscretion post-transplantation. Bivll > 25 kg/m2 has been associated with a 2-fold to 3-fold increased risk of CVD and a 2-fold increased risk for graft loss and death [10]. Sheikh found obesity to be at 32.5% in 83 CRI patients at KNH, which may indicate that the problem with obesity starts before transplantation and may need to be addressed at this stage [73]. Cofan ct al observed that 38% of 2,691 Spanish RTR were overweight and 16% were obese [4]. Urgent interventions need to be undertaken at policy level and at the clinics to educate renal transplant recipients on lifestyle changes and the need to avoid post-transplant weight gain.

Dysglycemia defined as diabetes mellitus or impaired fasting glucose was present in almost 50% of the transplant recipients with only a minority developing NODAT. The progression to NODAT may be due to the frequent use of steroids and cyclosporine, as well as the high prevalence of obesity (which is associated with increased insulin resistance) in the transplant recipients. The fact that almost half of our transplant recipient population has dysglycemia increases the overall risk of cardiovascular mortality thus making transplant recipients with diabetes a high risk group for ischemic heart disease. Interventions should include local adaptation of KDOQI diabetes screening and treatment guidelines as well as future research to assess levels of diabeti: control in renal transplant recipients.

Souza at al found similar metabolic derangements in renal allograft recipients with prevalence of diabetes mellitus and IFG of 23% and 23% respectively in Brazil while Bora et al found a higher NODAT prevalence of 16.7% in 78 RTR in India (time post-transplantation 12 months) [34,74]. The lower prevalence of NODAT may be due to the fact that Tacrolimus use in our study was less compared to Bora et al at 80.8%.

Renal transplant recipients with a second graft were significantly more likely to develop NODAT in our study which may be due to prolonged duration of exposure to immunosuppressant agents. Second graft donors also tend to have higher chances of HLA mismatch which has also been associated with development of NODAT most likely through selection of calcineurin inhibitors as immunosuppressant agents. However, this association was not an independent association on further multivariate analysis.

Less than half of the renal transplant recipients had proteinuria with majority of these having microalbuminuria. Studies have shown that proteinuria is associated with an increased risk of allograft dysfunction, reduced patient survival and increased cardiovascular mortality [75]. Transplant recipients with proteinuria should thus be considered a high risk group for graft loss and cardiovascular disease. Proteinuria may be related to pre-transplant lesions caused by hypertension or diabetes, chronic allograft nephropathy or recurrent glomerulonephritis. Local policies should be formulated for screening and treatment of proteinuria since a reduction in the incidence of proteinuria is associated with improved graft survival. Future studies can also

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evaluate if the level of proteinuria in renal transplant recipients is associated with renal graft dysfunction by performing renal biopsies.

Ibis et al in a study of 130 allograft recipients in Turkey (mean time post transplantation 24 months) found a higher prevalence of macroalbuminuria at 34.8% which may be due to the more frequent use of cadaveric donor allografts in the Turkish study (19.3%) [59]. However, future studies need to explore potential differences in HLA mismatch and donor age with proteinuria.

The prevalence of impaired graft function was low in our renal transplant population compared to Souza et al with a higher prevalence of impaired graft function of 49.5% in Brazilian recipients. However, this may be explained by the longer mean time post-transplantation of 92.4 months (SD 70.7) and the use of cadaveric donor allografts in the Brazilian study (29.7%) compared to our study [34]. Patients who develop impaired graft function need to be considered a high risk population for cardiovascular mortality. National policies should target formulation of local guidelines to screen for and prevent progression of impaired graft function through lifestyle and therapeutic interventions. Further studies should also explore which factors may be associated with rapid progression to impaired graft function in our transplant recipient population.

History of pre-transplant diabetes mellitus in renal allograft recipients was significantly associated with impaired graft function, which may be caused by on-going exposure of the graft to the hyperglycaemia mediated cell damage that lead to the initial kidney with consequent hypertension and proteinuria. Diabetes mellitus also causes premature atherosclerosis in the allograft and predisposes to graft loss. However, this did not prove to be an independent association on further multivariate analysis.

•Pic use of insulin by renal transplant recipients was significantly associated with impaired renal graft function but this may be confounded by the fact that insulin use occurred only in diabetic patients. On multivariate analysis, the association was not significant and thus was not an independent association. No mechanisms have been described to link insulin to impaired renal function and no similar-associations have been reported in other studies on renal transplant recipients.

A small proportion of the renal allograft recipient population had post-transplantation anemia but no patients were on haematinic drugs or erythropoietin stimulating agents or hematinic drugs. The causes of post-transplantation anemia may include impaired renal function with suppressed production of erythropoietin, chronic inflammation or immunosuppressant drug use. Anemia is a risk factor for left congestive cardiac failure and cardiovascular mortality and should be screened for in all transplant recipients regularly. Local guidelines should be developed to treatment of post-transplantation anemia with both physician and patient education on the importance of treating anemia. Future studies can also further characterize and type the anemia and define ideal therapies in local renal allograft patients.

In comparison with ESRD patients, Gitari found the prevalence of anemia using similar definition as per KDOQI criteria in 165 ESRD patients at KNH Renal Unit to be 98.2%. This shows that marked improvement in hemoglobin levels occurs after transplantation from a mean hemoglobin of 7.9 gm/dL (SD 1.9) in ESRD patients in the study by Gitari to 14.3 gm/dL (SD 2.3) in our study; suggesting a restored synthesis of erythropoietin [22]. A European multi-center study by Vanrenterghem et al of 4,263 renal allograft recipients with a mean post transplantation time of 30 months (SD156) found a prevalence of 38.6% and a mean hemoglobin of 13.2 gm/dL(SD 1.9): however the study employed anemia definition cutoffs of <13 g/dL for males and <12 g/dL for females [51],

There was a low prevalence of smoking in the renal transplant recipients in this study with majority of the cigarette smokers being male. Cigarette smoking in renal transplant recipients contributes to cardiovascular mortality and intervention measures are needed to address this risk. Local adaptation of KDOQI guidelines should be done and smoking patients when identified through screening should be offered intensive counseling and pharmacotherapy if available to assist them quit smoking.

The prevalence of smoking in renal transplant recipients is lower than that of CRI patients at KNH by Sheikh which was 19.3% [7 'J. 'This may indicate that screening and intervention for CKD patients is successful during the initial preparation process for kidney transplantation. Long-term follow-up and counseling of the patients who stop smoking is necessary because of the likelihood of relapse after transplantation. Similar trends were seen in a study of 226 RTR in Turkey with mean time post transplantation 57 months (SI) 54) by Yavuz et al which showed a reduction in the smoking prevalence from 42% in the ESRD population to 12% in the renal transplant population [46].

The most common immunosuppressant agents used by the transplant recipients were Prednisolone, Mycophcnolate mofetil and Cyclosporine with most of the patients on a combination therapy of the three drugs. Prednisolone was used by almost all the renal transplant recipients, exposing them to side effects such as obesity, glucose intolerance and hypertension and contributing to making the patients a high risk group for cardiovascular mortality. Cyclosporine use in most of the patients also may expose them to long term side effects such as hyperlipidemia. hypertension and NODAT. thus increasing their cardiovascular risk burden.

Studies in other renal transplant recipients also show similar level of Prednisolone use for immunosuppression but higher preference for Cyclosporine in comparison to Mycophenolate mofetil. Souza et al found that 99.0% of 192 RTR in Brazil were on Prednisolone. 49.0% on Cyclosporin and 47.9% on Mycophenolate mofetil [34]. In Europe, Vanrenterghem et al showed that the most often used combination therapy was Prednisolone. Cyclosporine and Mycophenolate mofetil at 30.7% while 84.5% of 4.263 RTR were on Prednisolone. 66.6% were on Cyclosporine and 50.2% on Mycophenolate mofetil f1].

No statistically significant associations were found between any immunosuppressant agent and the cardiovascular risk factors. Steroids and calcineurin inhibitors have been associated with impaired glucose tolerance while calcineurin inhibitors have been linked to hyperlipidemia and anemia in renal transplant recipients. This study did not show such associations but small sample sizes, different immunosuppressant drug formulations, the powering of the study for prevalence and use of differing drug dosages may have been limiting factors. Further prospective studies with larger sample sizes may be useful to explore possible associations in detail.

12. CONCLUSION

There is a high magnitude of cardiovascular risk factors in the renal transplant population. Hjpertension, abdominal obesity and hyperlipidemia were the most common cardiovascular risk factors with poor blood pressure control in particular present in most patients. Impaired graft function and smoking were the least common cardiovascular risk factors in the renal allograft recipients evaluated in this study. Policy should be guided towards implementing guidelines and protocols to lessen the burden of cardiovascular risk factors through appropriate risk factor screening, treatment and control in renal allograft recipients.

Statistically significant associations were found between presence of a second renal allograft and development of NODAT as well as between both history of pre-transplant diabetes mellitus and the use of insulin by renal transplant recipients with impaired graft function.

The most common immunosuppressants used by the renal allograft population were Prednisolone, Mycophenolate mofetil and Cyclosporine with most of the patients on a combination of these three drugs.

No statistically significant associations were found between any of the immunosuppressant agents used by the renal transplant recipients and the cardiovascular risk factors. This may have been caused by small sample sizes, powering of the study for prevalence and use of different immunosuppressant drug formulations and drug dosages.

13. STUDY LIMITATIONS

1. Recall bias in collection of past medical data from renal transplant recipients such as cause of CKD or duration of time and amount of cigarettes smoked could not always be corroborated by medical chart review and can thus lead to misclassification bias in either direction with either underestimation or overestimation of variables.

2. Two blood pressure measurements done on one occasion has potential of misclassification bias in either direction giving underestimation or overestimation of hypertension ard cannot be a substitute of long-term blood pressure control assessment.

3. Single spot reading of urine for microalbuminuria without repeat value for confirmation has potential for misclassification bias in either direction giving underestimation or overestimation of prevalence. Single spot urine measurements can however be used in research studies to give an interpretation of microalbuminuria levels.

4. All the equations for deriving estimated GFR using calculated creatinine clearance value including Cockcroft - Gault equation show a tendency toward GFR over-estimation compared to di;ect plasma clearance measurements and thus giving underestimation of impaired graft function prevalence. These equations have however been validated for renal transplant recipients despite this drawback.

5. The use of Western norms as cut-offs for BMI and waist circumference for Africans with different body habits though recommended may cause misclassification bias in either direction. No validated BMI cut-offs have been designed for the African population with studies set in African making reference to the Western cut-offs for the present time.

6. The definition of dyslipidemia based on use of lipid lo.wering agents may be confounded by the use of some of these agents in reduction of cardiovascular risk and not necessarily because of elevated lipid levels thus causing an overestimation of dyslipidemia prevalence.

14. RECOMMENDATIONS

1. The renal transplant recipients should be considered as a priority population at high risk for cardiovascular mortality and morbidity in health policy formulation for interventional measures in non-communicable disease.

2. Local adaptation and implementation of KDOQ1 renal transplant recipient guidelines on the prevention, screening, treatment and control of specific cardiovascular risk factors such as hypertension, dyslipidemia, obesity and dysglycemia should be carried out. Specifically, measures to improve control of blood pressure in hypertensive renal transplant recipient population need to be adapted locally and disseminated to both physicians and the renal transplant patient population.

3. Follow-up long term prospective studies to characterize the type and causes of post-transplantation anemia and the control of diabetes mellitus in renal allograft recipients should be carried out using larger sample sizes.

4. Long term prospective studies should be carried out to determine any associations between immunosuppressive agents, drug dosages and duration of use in renal transplant recipients with cardiovascular risk factors should be carried out using larger sample sizes.

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16. APPENDICES

16.1 APPENDIX I: STATEMENT OF INFORMATION FORM

Cardiovascular risk factors in renal transplant recipients attending Nephrology clinics in Nairobi.

STATEMENT OF INFORMATION FOR PATIENTS PARTICIPATING IN THE STUDY

Purpose of the study:

I, DR. JAMES WAGUDE, a post-graduate student in Internal Medicine at the University of Nairobi, would like to introduce you to a study I will be undertaking entitled Cardiovascular risk factors in renal transplant recipients attending nephrology clinics in Nairobi, Kenya.

This study involves investigating the prevalence of cardiovascular risk factors such as age, sex, cigarette smoking, hypertension, anemia, proteinuria, high glucose and lipid levels and renal disease in renal transplant recipients. The presence with these risk factors in post-transplant recipients is associated with increased risk of heart disease and death. Therefore, early detection of these risks can help reduce this risk and improve patient outcomes and quality of life. The study is being conducted at the KNH renal unit and specialist nephrology clinics with cooperation from the staff and permission from the hospital administration.

Procedures:

You are being asked to participate in a survey that will take 45 to 60 minutes. If you agree to participate, it will involve checking of your medical records before I ask you questions and note your responses in writing in a questionnaire. I will then take your weight, height, waist and hip measurements and blood pressure. Afterwards, I will examine you thoroughly before drawing about 8 ml of venous blood for lab analysis to assess your renal function, haemoglobin, fasting lipid profile and fasting blood sugar. The blood tests will involve asking you to remain without eating for 10 hours the previous night before your blood is taken. I will also take a random urine sample for urine albumin-creatinine ratio assay. All the information you provide and the results will remain confidential but a copy of the lab results will be placed in your file for continued care. The purpose of the consent form is to ask you permission to do so. If you agree to participate, I shall ask you to sign the consent form before you start. Your individual responses will be seen only by the researcher and will be stored in a locked place under my control.

The risk to you as a participant in this study includes:

t Pain in the cubital region on your arm upon blood sample removal.

- Swelling at the venepuncture site may appear due to collection of blood under the skin (haematoma).
- NB: should any of the above happen to you; please feel free to contact Dr. James Wagude for examination and management on 0721413773.

The benefit to you as a participant includes:

- Free evaluation of your serum creatinine, fasting blood sugar, fasting lipid profile, haemoglobin and urine albumin-creatinine ratio.
- Free copy of your results will be availed to you on request or placed inside your file.
- The findings of this study will assist in patient care as far as the management of cardiovascular risk factors in renal transplant patients is concerned.

Right to refuse or withdraw:

Your participation in this research is voluntary. You do not have to participate. If you choose to participate, but prefer not to answer certain question, you are free to do so. You are also free to withdraw from the study at any time and this will not affect your care or treatment in any way. You are free to ask questions before signing the consent form. If you agree to participate in the study, please sign the consent form.

Thank you for your cooperation.

Sincerely,

Dr James Wagude

16.2 APPENDIX II: INFORMED CONSENT FORM

INFORMED CONSENT FORM

Names

Age

Number

I, the above named have been requested to take part in a study concerning prevalence and associations of cardiovascular risk factors in renal transplant recipients seen in nephrology [1] dinics in Nairobi, Kenya. This will involve taking a full history, general examination including blood pressure, weight, height, waist and hip measurements. It will also involve taking of 8ml of my blood for assessment of lipid levels, blood sugar and renal function. Costs for laboratory expenses will be met by the investigator. All the results obtained will remain confidential.

I also understand that this consent is voluntary and that I can withdraw from the study at any time without any penalties.

i therefore consent to be recruited into the study.

Signature of patient:

Date:

If you have any question during the course of the study, you may contact the following:

DR JAMES WAGUDE on Mobile: 0721 413773

Investigator's statement:

I the investigator have educated the research participant on the purpose and implication of this study.

Signed:. . . . . .Date:

16.3 APPENDIX III: STUDY PROFORMA

STUDY QUESTIONNAIRE

CARDIOVASCULAR RISK FACTORS IN RENAL TRANSPLANT RECIPIENTS IN NEPHROLOGY CLINICS IN NAIROBI, KENYA

Study No. . . . . **Date**

(A)HISTORY

1. SOCIO-DEMOGRAPHIC DATA

Name_____Hospital No._____;

Birth Date_____Sex

1 = Male CD 2 = Female •

Usual Occupation_____Current Employment Status

1 = employed • 2= self employed • 3 = retired • 4 = Other ^

Residence (province)_

Marital Status • S i n g l e • Married I I Divorced HZ) Widowed

Education attainment

1= No formal Education • 2 = Primary • 3 = High School •

4 = College/University • 5 = Other (specify) •

2. PRESUMED CAUSE OF CHRONIC KIDNEY DISEASE

CD Chronic GN • Polycystic

CD Pyelonephritis • Diabetes

CO Hypertension • Other (specify)

3. DATE OF DIAGNOSIS OF RENAL DYSFUNCTION

4. DATE OF COMMENCEMENT OF HEMODIALYSIS

5. NO. OF HEMODIALYSIS SESSIONS PER WEEK

6. TRANSPLANT

"ransplant Date_

Donor Relationship f I Living related I I Cadaveric [ZD Other

Graft **No.** *C3* First I I Second dD More (specify)

5. **CURRENT MEDICATION**

Class	**Drug**	Date of commencement	Dose
Immunosuppressant			
Antihypertensive			
Antidiabetic			
Prophylaxis			
Haematinics			
Others **k.**			

6. HISTORY OF PRE-TRANSPLANT DIABETES

1 = Yes CD 2 = No IZD

7. HISTORY OF PRE-TRANSPLANT HYPERTENSION

1 = Yes • 2 = No 1 I

8. SMOKING STATUS

Non-smoker I I

Current smoker I I

No of sticks/day_____No of years

9. PAST MEDICAL HISTORY

• Coronary heart disease • Heart attack

I I Coronary surgery/angioplasty !! • Stroke/TIA

10. FAMILY HISTORY

I I Hypertension CZI Sudden death

I I Diabetes • Kidney disease

CD Coronary heart disease • Stroke

(B) PHYSICAL EXAMINATION

1. Anthropometric data

height (kg)

Height (cm)

Waist circumference (rm)

Hip circumference (cm)

BMI_____Waist-Hip Ratio

2. Vital signs

SBP(mmHg) First reading_____Second reading _____ Average

DBP(mmHg) First reading_____Second reading _____ Average

PR 'min RR_____/min Temperature

3. Systemic examination

System i	Abnormality Yes = 1; No $=2$	Description of abnormality
Cardiovascular		
Abdomen		
Respiratory-		
Central Nervous System		
Musculoskeletal		

Interviewer's Name

Signature

16.4 APPENDIX IV: LABORATORY DATA FORM

LABORATORY DATA FORM

Study No._____Name_____

LAB TEST	RESULTS	DATE
Creatinine		
Creatinine clearance	.	
Fasting blood sugar		
Total cholesterol		
HDL-cholesterol		
LDL-cholesterol		
Triglyceride		
Albumin-creatinine ratio		
Hemoglobin level		

COMMENTS

16.5 APPENDIX V: CLASSIFICATION OF HYPERTENSION AND OBESITY

16.5.1 Classification of Hypertension

TABLE 12. JNC 7 Classification of Blood Pressure]*[3]!

Class	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140 -159	or 90-99
Stage 2 hypertension	>160	or>100
Isolated systolic hypertension	>140	and <90

16.5.2 Classification of Obesity

TABLE 15. WHO Classification of Obesity Based on BMI [[6]-J	
Classification	BMI (kg/m^2)
Underweight	<18.5
Norma' range	18.5-24.9
Overweight Pre-obese Obese class 1 Obese class II Obese class III	>25.0 25.0-29.9 30.0-34.9 35.0-39.9 >40.0