

**DYSGLYCEMIA AMONG KIDNEY TRANSPLANT RECIPIENTS AT
KENYATTA NATIONAL HOSPITAL**

A DISSERTATION SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF
MASTER OF MEDICINE (M MED) IN INTERNAL MEDICINE

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DEDICATION

I dedicate this work to all my family members who have tirelessly stood up with me, supported me and always praying for my success.

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LIST OF ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risks in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease
AZA	Azathioprine
BMI	Body Mass Index
CMV	Cytomegalovirus
cm	Centimeters
CNI	Calcineurin Inhibitors
CsA	Cyclosporine A
DCCT	Diabetes Control and Complications Trial
DKA	Diabetes Kidney Disease
DM	Diabetes Mellitus
DPP IV	Dipeptidyl peptidase IV
EC-MPS	Enteric coated mycophenolate Sodium
ELITE	Efficacy limiting Toxicity Eliminating
ESKD	End Stage Kidney Disease
F BGL	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin A1c glycated
HR	Hazard ratio
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose tolerance
KDIGO	Kidney Disease Improving Global Outcome
KNH	Kenyatta National Hospital
KTRs	Kidney Transplant Recipients
MMF	Mycophenolate mofetil
mTOR	Mammalian Target Of Rapamycin
mo	Month
NGSP	National Glycohemoglobin Standardization Program

NODAT	New Onset Diabetes After Transplantation
NPV	Negative Predictive Value
OGTT	Oral Glucose tolerance test
OR	Odds Ratio
OPTN/UNOS	Organ Procurement and Transplant Network/United Network for Organ Sharing
PTDM	Post transplantation Diabetes mellitus
RBS	Random blood sugar
SPSS	Statistical Package for Social Sciences
Tac	Tacrolimus
T2DM	Type 2 Diabetes Mellitus
USRDS	United States Renal Data System
UTI	Urinary Tract Infection
WHO	World Health Organisation
Yr	Year

Abstract

Background

Diabetes mellitus (DM) is the commonest cause of end stage renal disease worldwide. There is an increased incidence of DM in the third world countries, Kenya being one of them. Evidence has shown that kidney transplantation is the best treatment for end stage kidney disease (ESKD). It improves health related quality of life and prevents complications of kidney failure. Higher incidence of dysglycemia among kidney transplant recipients (KTRs) has been documented. This makes them more susceptible to fatal cardiovascular events. Preventing, detecting and treating the dysglycemia early in KTR have beneficial effects.

Objectives of the study:

The primary objective of our study was to determine the prevalence of dysglycemia {pre transplant DM, new onset diabetes after transplantation (NODAT), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)} among KTRs at Kenyatta National Hospital (KNH). Secondary objectives were to determine quality of glycemic control in the known diabetic patients and to describe the clinical characteristics of the KTRs with dysglycemia.

Methods

We did a cross-sectional, descriptive hospital based study at the transplant clinic at the renal unit of KNH. All adults (aged 18 and above) KTRs, who agreed to participate were included with a minimum targeted sample of 103. Study questionnaire was filled after a signed written consent was obtained. Patients' weight, height and waist circumference were later measured by principal investigator (PI) and later blood samples were taken for glycated hemoglobin c (HbA1c) percent for the diabetic patients, and fasting blood sugar (FBS) and oral glucose tolerance test (OGTT) for the rest to determine presence of dysglycemia. Data was managed in Microsoft Access 2013 database. Study population was described using their socio demographic and clinical characteristics. Statistical package for social sciences (SPSS) version 21.0 software was used for statistical analysis. The prevalence of dysglycemia was analyzed and presented as a percentage of all KTRs and a 95% confidence interval (CI) of the prevalence was presented. T test method was used to compare continuous data and chi-square test for categorical data. Univariate and

multivariate analyses were performed to investigate associations between patient characteristics and dysglycemia.

Results

Between September 2016 and May 2017, 105 kidney transplant recipients were recruited in the study and we found a prevalence of 13.3% for new onset diabetes after transplantation (NODAT), 14.29% for impaired glucose tolerance (IGT) and 6.67% for impaired fasting glucose (IFG). The prevalence of pre transplant DM was 23.81%. Important risk factors noted at univariate analysis were female gender, longer duration post transplantation, BMI more than 25kg/m^2 , higher waist hip ratios and family history of diabetes. There were no independent associations found at multivariate analysis. More than half of the diabetes KTRs had poor glycemic control (56%) with a mean HbA1c of 8.4 ± 2.1 percent.

Conclusion

We found a high prevalence of dysglycemia in our set up and also poor glycemic control in KTRs with diabetes mellitus. This calls for improved screening programs on KTRs who previously were non diabetic and intensive risk stratification to optimize graft survival.

1.0 INTRODUCTION

Dysglycemic states encompass overt diabetes, impaired fasting glucose (IFG) and abnormal glucose tolerance. Dysglycemia is a common phenomenon in renal transplant recipients. There is a variability in the natural history of IFG and oral glucose tolerance (OGT) but approximately 25% develop diabetes in three to five years (1).

Diabetes mellitus (DM) is the commonest cause of end stage renal disease (ESRD) worldwide and third after chronic glomerulonephritis and hypertension in Kenya (2). Kidney transplantation has been proven to improve the health related quality of life and also reduce cardiovascular disease effect (3). On the other hand, there is an increased risk of cardiovascular events in the group of patients with dysglycemia compared with other kidney transplant recipients (4).

Renal transplantation science has been developing with improved survival rates due to enhancement in treatment with immunosuppressive or antirejection drugs. In Kenya, there has been an accelerated program: *interlife*® which is a private public partnership between KNH and Novartis pharma from the year 2010. This has made the numbers of KTRs increase exponentially.

Diabetes mellitus is an important risk after renal transplantation and it has been implicated to be a cause of increased mortality due to cardiovascular events (5), deleterious effects on allograft survival (6) and high incidence of infection rates (7). The diagnosis of DM in KTRs is per the International consensus guidelines meeting which is in line with the WHO/ADA guidelines (8).

Several factors have been associated with the impairment of glucose metabolism, for example, the use of certain immunosuppressive medications. Glucocorticoids are the backbone drugs in many immunosuppressive regimens but causes DM by increasing insulin resistance (9).

Calcineurin inhibitors (tacrolimus and cyclosporine), commonly used in many regimens induce DM by affecting insulin secretion process (10). Other risks factors include increasing age, family history of DM, pre transplant impaired glucose, overweight and obesity, ethnicity and lifestyle changes such as smoking and alcohol intake (11).

Early identification and intensive treatment of the abnormal sugar levels have beneficial outcomes on overall patients' survival (12). Adjustment of antirejection (13), lifestyle changes

(14) and intensive early treatment (15) are some of the management plans of new onset diabetes after transplantation (NODAT). The usual anti-diabetic medications are used with a stepwise approach with an aim of achieving good glycemic targets, reduced side effects and favorable costs.

2.0 LITERATURE REVIEW

2.1 DEFINITIONS:

Diabetes is a term that describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or absolute impairment of insulin secretion, together with differing degrees of peripheral resistance to the actions of insulin.

According to the American diabetes association (ADA), diagnosis of diabetes is based on one of four abnormalities as shown in table 1 (8).

Impaired glucose tolerance (IGT) is defined as during an oral glucose tolerance test (OGTT), subjects have blood sugar values between those in normal subjects and those in patients with overt diabetes (140 to 199mg/dl{ 7.8 to 11mmol/l} (8).

Impaired fasting glucose (IFG) is defined as a fasting blood sugar of 100 to 125mg/dl (5.6 to 7 mmol/l) (8).

Impaired glycated hemoglobin c (HbA1c) is defined as HbA1c of 5.7 to 6.4 percent (39 to 46 mmol/mol) as per ADA, or (6.0 to 6.4 percent [42 to 46 mmol/mol] in the International Expert Committee report (16).

Categories of increased risk of diabetes include IFG, IGT and impaired HbA1c. These together with DM are occasionally also termed as dysglycemic states.

New onset diabetes after transplantation (NODAT) also known as post transplantation diabetes mellitus (PTDM) after the International consensus meeting guidelines (17), is the diabetes defined by World Health Organization (WHO) and American Diabetes Association (ADA) that develops for the first time after transplantation. The diagnosis is as per the WHO/ADA criteria (see table 1: any of the four categories) of diabetes mellitus. HbA1c is not recommended for

diagnosis until after 3 months post transplantation, to allow new hemoglobin to be synthesized and glycosylated for appropriate period in the diabetogenic post transplantation setting (18).

Table 1 ADA criteria for the diagnosis of diabetes (8)

1	A1c \geq 6.5 %. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
2	FBS \geq 126mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least eight hours
3	Two-hour plasma glucose \geq 200mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). (after a 75g load of anhydrous glucose)
4	Classic symptoms of hyperglycemia or hyperglycemic crisis and a random plasma glucose \geq 200mg/dl(11.1mmol/l)

2.2 EPIDEMIOLOGY

There has been a significant growth of incidence and prevalence of diabetes mellitus throughout the world. According to the WHO, in 2014 the global prevalence of diabetes was estimated to be 9% among adult age 18 years and above (19). In 2012, an estimated 1.5 million deaths were directly caused by diabetes and more than 80% of the diabetes deaths occur in middle and low income countries (20).

The increase in the number of people developing diabetes has had a major impact on the development of diabetes kidney disease (DKD). To note, diabetes is the leading cause of end stage renal disease (ESRD), accounting for approximately 50% of cases in the developed world. Sheikh et al. (2) did a study on prevalence of cardiovascular risks among patient with renal failure and found diabetes as a cause of CKD had a prevalence of 28.9%. Among the KTRs studied by Maina et al. (21) in 2014, 20% of them had diabetes as a cause of ESRD. Wagude et al. in their study on cardiovascular risks factor among KTRs attending nephrology clinics in Nairobi found a prevalence of 49.5% for dysglycemic states (22).

Early dysglycemia is common such that it should always be taken seriously as majority of these patients are at risks of developing NODAT. It had been shown that day 7 fasting plasma glucose may be predictive at year one (23). A study which was done recently (24) measured continuous

capillary blood sugar levels for the first 4 days post-transplant in 43 patients. There was an increased level of hyperglycemia and 43% of patients spent more than 12 hours per day with blood sugar levels above 7.7mmol/l. After a mean follow up of 72 months, NODAT was frequently seen. Moreover, a normal OGTT within the first week has been shown to have a high negative predictive value of 97.6% for future development of NODAT (25). Early hyperglycemia does not necessarily predict future permanent dysglycemic states. There is variability in impairment of glucose metabolism and considerable degree of transiency. A Chinese study done in 428 patients who were not diabetic before surgery found an incidence of 20.32% for NODAT after a mean follow up of 5.65 years in patients who survived more than one year post transplantation. Among these 65.5 % developed NODAT within 1 year and 17.2% had transient NODAT (26).

Studies done using current WHO/ADA diagnostic criteria suggest that up to one third of non-diabetic KTRs develop persistent dysglycemia by six month post transplantation. This includes a study done in Norway, by Valderhaug et al. (27) where they found an incidence of NODAT to be 14-17%. A retrospective South African study on 221 KTRs showed an incidence of 22.6% for NODAT (28). These and other studies on dysglycemia on KTRs done in Africa and rest of the world are summarized in table 2. Of note, whilst there is consensus regarding cut off blood glucose levels, it's not clear which tests should be used and which time post-transplant (29). Some studies had witnessed remission of some patients with dysglycemia (though not commonly documented) to normoglycemia post-transplant (30), further complicates analysis of rates of new onset post-transplant abnormalities in glucose metabolism.

Table 2 Selection of studies that reported rates of abnormalities in glucose metabolism post renal transplantation which were done locally, Africa and rest of the world

References	Study Design	Criteria	Sample size	Rates
Valderhaug et al. (27) (Norway)	Cross sectional	OGTT	1410	17% NODAT at 10weeks 47.8% other dysglycemia
Vincenti et al.	Prospective	OGTT	682	30% at 6 month

(10) (USA)	randomised			dysglycemia
Cosio et al. (31) (USA)	Retrospective	Use of medication, FBS	490	13% at 1yr. 33% dysglycemia
Bapoo et al. (28) (South Africa)	Retrospective	Patient records documentation	221	22.6 with NODAT
Cole et al. (6) (Canada)	Prospective pilot study	Use of medication, FBS, OGTT	49	4% at 6 mo
Wagude et al. (22) (Kenya)	Cross sectional	FBS and self-reporting	91	49.5%

2.3 RISK FACTORS

2.3.1 Immunosuppressive therapy

The medications that contribute to dysglycemia include glucocorticoids, calcineurin inhibitors (CNI) and mammalian target of rapamycin (mTOR) inhibitors. These are potentially modifiable risk and are transplant related. The antimetabolites including mycophenolate mofetil (MMF) and azathioprine are not diabetogenic.

2.3.2.1 Glucocorticoids

Systemic (oral) glucocorticoids are the backbone drugs for many antirejection regimen therapies. Its effect on impairment of glucose metabolism has been well documented and this is mainly by cumulative exposure. Several data show different incidence rates (ranges 1-22%) over 1-5 year period post transplantation when analyzing glucocorticoid withdrawal, glucocorticoids free and rapid tapering which compares with rates of 15%-35% in regimens without glucocorticoids maintenance (29).

Not all studies analyzed found benefit from glucocorticoids withdrawal. A meta-analysis of high quality trials in which glucocorticoids withdrawal was done on day 14 post transplantation while treating them with CNI/MMF did not find a reduction in NODAT (32), though insulin therapy was not required in the arm of patients with early withdrawal of glucocorticoids i.e. at day 7, and there was no difference in the rate of NODAT. This was from the largest randomized placebo-

controlled trial (33). Nevertheless, many other studies found an advantage to glucocorticoid avoidance. United States renal data system (USRDS) found that patients discharged on glucocorticoid containing regimen had an odd ratio (OR) of 1.42 for NODAT compared to those on a glucocorticoid free regimen (34). Another one, a pilot study (n=49) of thymoglobulin induction, MMF, low dose cyclosporine (CsA) and rapid glucocorticoid reduction in low immunological risks patients found that 42 out of 49 patients were normoglycemic at 6 months (30). Questions to glucocorticoids effect may be answered in an ongoing multicenter study evaluating Steroid-free immunosuppressive protocol, based on ATG Induction and a LOw tacrolimus dose, Reduces the incidence of new onset diabetes after transplantation (SAILOR). The study compares a steroid free, CNI/MMF maintenance with thymoglobulin induction and another arm on basiliximab induction and ongoing steroid exposure (35). Frequent acute rejection episodes necessitating pulsing with glucocorticoid have been attributed to an increased risk of developing NODAT (36).

2.3.2.2 Calcineurin inhibitors

The calcineurin inhibitors (CNI) include cyclosporine (CsA) and tacrolimus (Tac). Their usage and especially Tac, have been associated with less acute rejection and improved graft function but at the expense of an increased incidence in abnormalities of glucose metabolism especially NODAT (33). In a large international randomized trial comparing glucose metabolism disorders and outcomes with cyclosporine versus tacrolimus, the investigators found 6-mo cumulative incidence of NODAT of 33.6% in Tac treated KTRs and 26% in CsA treated KTRs. More patients in the Tac group required hypoglycemic agents and more in the CsA treated group who were not treated with hypoglycemic agents had an improvement in their glycemic state at 6-mo (10). There is also evidence that the impairment of glucose metabolism is also associated with the degree of CNI exposure. Chan et al. (37) found that NODAT was significantly less frequent in the low dose Tac (17% versus 31%). This was a 6-month prospective open label, multicenter study, de novo KTRs were randomized (1:1) to low dose or standard dose Tac with basiliximab, enteric coated mycophenolate sodium (EC-MPS), and steroids. A larger study; Efficacy limiting toxicity eliminating (ELITE)- SYMPHONY, also suggested a dose dependent relationship. It found higher rates of NODAT in the low dose Tac group(12%), compared with low dose CsA (5%), low dose sirolimus (8%) or standard dose CsA (8%). (38)

2.3.2.3 Mammalian target of rapamycin: Sirolimus

Sirolimus is often used in conjunction with or instead of CNI. Clinical data suggest that the risk of abnormality in glucose metabolism is not low. Conversion to sirolimus from Tac or CsA has also been associated with significant worsening in insulin resistance (39). There has been some inconsistency finding on sirolimus. A study done recently (n=440) found higher doses of Tac but not high or standard dose of sirolimus contributed to NODAT (40).

2.3.2 Age

Age at time of kidney transplantation has been reported to be an independent risk factor for NODAT. Age older than 40 to 45 years is most frequently cited as the threshold level that is associated with markedly increased risk. Casio et al. found up to 2.2 times higher risks of NODAT development in KTRs older than 45 years compared with younger recipient (41). Similarly, USRDS data show a strong relationship between age of recipients and NODAT development. KTRs age 45-59 years had 1.9 times higher risk than recipients age 18-33 years and the KTRs older than 60 years the risk was double that of younger recipients(11). There is usually an important interaction between modifiable factors such as antirejection medicines and non-modifiable factors such as older age. Multivariate analysis has found that older age and higher sirolimus trough levels were associated with increased hazard for NODAT (42).

2.3.3 Overweight and Obesity

Overweight and obesity is a known modifiable risk factor for cardiovascular disease. Obesity independently correlates with development of NODAT (11). Weight gain after transplantation is common because of several factors, including increase of appetite after reversal of the uremia, relatively high doses of steroids especially in early post-transplant period and reduced physical activity (43). An analysis of 15,309 adult kidney recipients using the Organ procurement and Transplant Network/United network for Organ Sharing (OPTN/UNOS) database found that the risk of NODAT increased 1.4 fold for those with BMI of 25-30 and almost doubled for those with BMI more than 30 (44). Central obesity as measured by waist circumference has been associated with increased risk of NODAT. Using univariate analysis, Kodgire et al. (45) found

statistically significantly greater waist circumference in patient at time of transplantation later developed NODAT when followed up 12 months post transplantation.

2.3.4 Family History of DM

Family history of diabetes especially in first degree relatives has been associated with NODAT. For example, Hjelmesaeth et al. using univariate analysis revealed that family history of diabetes was associated with NODAT (46).

2.3.5 Lifestyle factors

Cigarette smoking, poor diet and physical inactivity are known risk factors for diabetes in the general population (8). Patients post transplantation have improved appetite which can lead to unhealthy eating leading to obesity which has been shown to be correlated with NODAT (11). Although not well studied, good dietary diet intake, increased physical activity and smoking cessation improve dysglycemia in KTRs.

2.4 PATHOGENESIS

The pathogenesis of dysglycemia is complex and widely assumed to be closely aligned to the pathogenesis of type 2 diabetes mellitus (T2DM). KTRs are considered to be at a chronic kidney state and therefore an ongoing impact of the end stage renal failure and dialysis on glucose homeostasis. Insulin resistance and insulin secretion changes have both been shown to be responsible for the development of abnormalities in glucose metabolism states post kidney transplantation. The changes are dynamic and occasionally transient, particularly in the early post-transplant period.

2.4.1 Insulin resistance

It refers to decreased action of insulin at the target cells, that is, a state in which a given concentration of insulin produces a less than expected biological effect. Glucocorticoids cause an increase in insulin resistance. Their effects are mediated by cytosolic glucocorticoids receptors and result from both genomic and non-genomic mechanisms that also have a role in the therapeutic effects of these agents(9). Glucocorticoids impair peripheral glucose uptake, impair hepatic glycogen synthesis and enhance gluconeogenesis. At higher doses they may induce pancreatic beta cell apoptosis (47). The diabetogenic effect has not only been associated with

high doses but also prolonged exposure even at low doses (48). The desired anti-inflammatory effects of glucocorticoids are mainly mediated via repression of genes transcription and the side effects largely from transactivation (9).

The persistent state of CKD (49) post transplantation contributes to the dynamic nature of post transplantation dysglycemia. These patients prior to being transplanted have had a considerable period of ESKD requiring dialysis with considerable amount of uremic effect to insulin resistance (49). A study comparing 27 diabetic patients and 35 non-diabetic ESKD patients to assess insulin resistance using a homeostatic assessment-insulin resistance model found increased insulin resistance in the diabetics. There was an elevated C-peptide in the non-diabetic patients with increased insulin resistance, indicating a compensatory response maintaining non diabetic state (50).

2.4.2 Insulin secretion

Several studies show decreased insulin secretion in KTRs who have developed NODAT. A study done by Nagaraja et al. (51) described insulin indices pre and followed up patient at 3 and 12 months post-transplant. Patients who developed NODAT at 12 months had improved insulin resistance but low insulin secretion. This also explains that despite reducing doses of glucocorticoids and improvement of peripheral insulin resistance the level of insulin secretion failed to be compensatory (51). Nam et al. (52) first demonstrated abnormal insulin secretion as a component of pathogenesis. They followed up 144 patients, pre and post-transplant and noted that those who developed dysglycemia at 9-12 months post-transplant had significantly lower insulin secretion despite improved insulin resistance. Another longer study (53) followed up patients up to 6 years and noted that patients who were dysglycemic at 10 weeks and became normoglycemic had improvement in insulin resistance and a non-significant impairment of insulin secretion, thus retaining a compensatory response.

Calcineurin inhibitors (CNI) are the main cause of abnormal insulin secretion post transplantation. Pancreatic beta cell function is impaired due to the inhibition of calcineurin. Calcineurin is a cytosolic phosphatase enzyme that has two targets in the beta cell: the nuclear factor of activated T cells and cyclic AMP responsive element binding protein transcription co-activator (29) .

Hyperglycemia by itself is a recognized stressor for beta cells, suppressing insulin secretion and or leading to beta cell apoptosis. Beta cell failure plays a major role in type 2 DM development (54) and is thus very likely to play a key role in the development of NODAT.

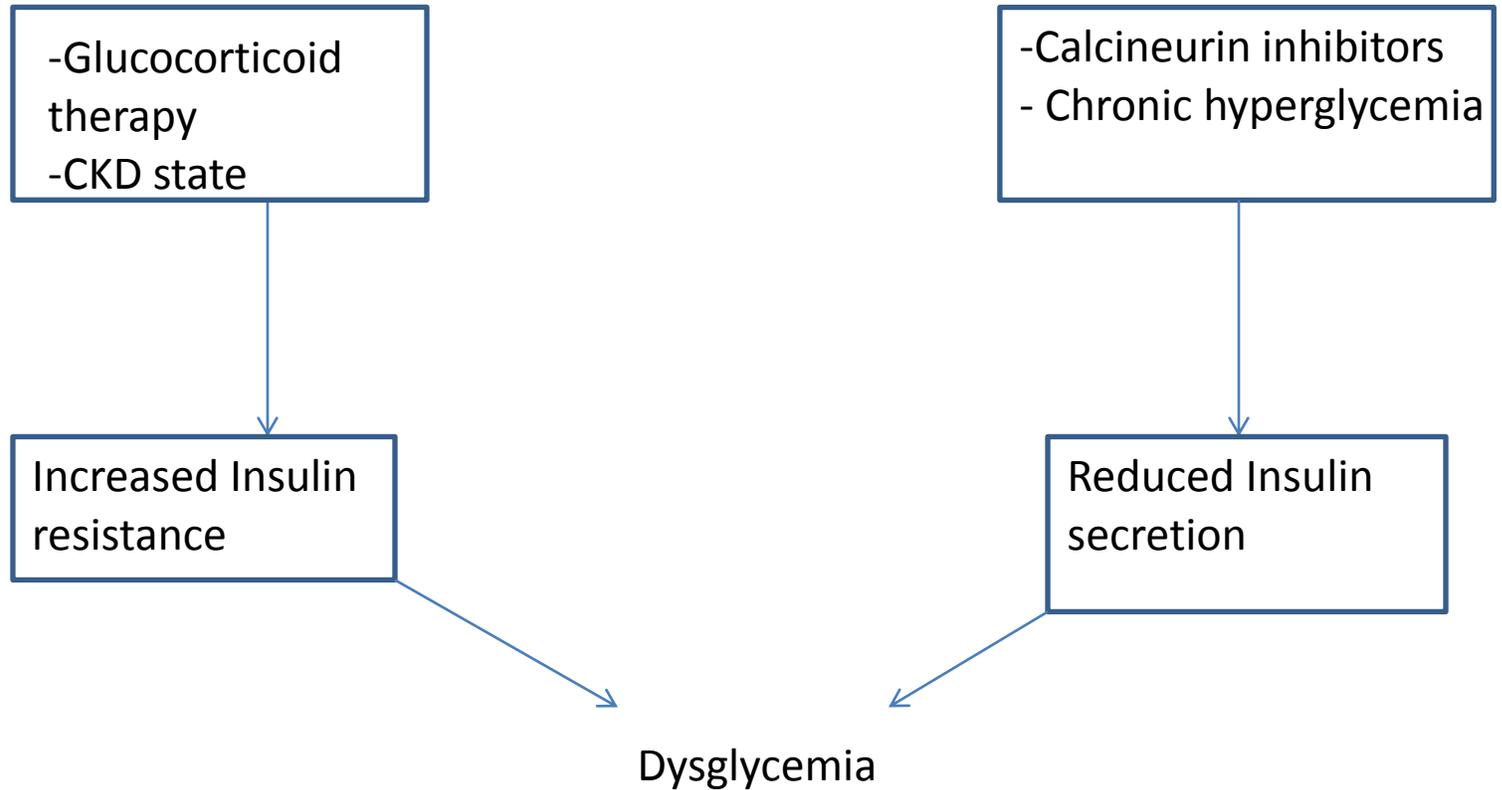


Figure 1 : Summary of pathogenesis of dysglycemia in KTRs

2.5 CLINICAL OUTCOMES

2.5.1 Patient survival

The development of dysglycemia post transplantation, especially diabetes mellitus has adverse effects on patient survival. In one study, one year survival was 83% and 98% in those KTRs with and without NODAT respectively (5). A subsequent report found that 5 year survival with NODAT was 87% versus 93% among nondiabetic patients (55). The development of NODAT correlates with increased cardiovascular mortality, which is the most prevalent cause of poor long term survival (27) (43) . Excess risk is sometimes associated with coexistence of other cardiovascular risk factors, particularly increased age and dyslipidemia (56). Though limited by the short study period of follow up; 1.5 years, the effect of pre transplant diabetes on all cause cardiovascular mortality is more than the new onset diabetes (57).

2.5.2 Allograft survival

The effect of diabetes on allograft survival is due to the increased mortality associated with it. For example, in a retrospective analysis of 27,707 KTRs, NODAT was associated with increased risk of allograft failure from any cause, but not for death-censored graft loss (or graft loss without death) (6). Acute rejection has been noted to be the most significant potentially modifiable factor in allograft survival. This shows the importance of maintaining sufficient immunosuppression to prevent rejection even at the expense of developing dysglycemia particularly diabetes (58).

2.5.3 Infections

With hyperglycemic effect on immune system, diabetes in KTRs has been associated with an increased risk of infections and sepsis (5) (7) (56). The commonly reported infections from similar studies include urinary tract infections (UTI), pneumonia and cytomegalovirus (CMV) (5) (7).

2.6 SCREENING AND DIAGNOSIS

Oral glucose tolerance test (OGTT) is the gold standard for diagnosis of dysglycemia, that is, NODAT and IGT. However, it's not an easily completed test. Although they have some limitations, simple office or laboratory tests may adequately screen KTRs especially those at high risk include fasting blood glucose (F BGL), 4 pm capillary blood glucose or HbA1c. A

study of 374 non diabetic patients found a normal F BGL in 59% of patients with abnormal OGTT over the first 12 months period (59). Any red cell abnormalities could also impact on HbA1c results such as anemia, transfusions, erythropoietin administration and hemoglobin abnormalities. A recently done study, using combined test of HbA1c \geq 6.5% and FBS \geq 7.0mmol/l, by a Norwegian group (n=1619), have demonstrated a negative predictive value (NPV) of 97.4% for NODAT, using OGTT as gold standard at 10 weeks post transplantation (60). The combination of two tests had very little additive value, and lower cut off value of HbA1c made little difference in exclusion of NODAT (\geq 5.5% NPV 97.5% compared with \geq 6.5% NPV 93%). This shows that HbA1c can be used as a screening test but not recommended to be used as a diagnostic test in transplant patients. Fasting blood glucose may underestimate dysglycemia especially in patients who take the glucocorticoids in the morning. Recently it has been shown that there is an increased afternoon or evening blood glucose for patients who take morning glucocorticoid (approximately 7-8 hours). Therefore 4 pm capillary blood glucose can be a good screening test for such patients.

2.7 MANAGEMENT

Management principles of post-transplant dysglycemia are pre transplant risk assessment, early detection, appropriate therapy to reduce the poorer outcomes in whom post-transplant dysglycemia develop and good glycemic control of pre transplant diabetes patients. The pre transplant variables mentioned as predictors for glucose impairment post transplantation include age, body mass index (BMI), fasting and random blood glucose, impaired glucose tolerance (IGT) on OGTT and metabolic syndrome (61) (62) (63). Kidney disease improving global outcome (KDIGO) recommends screening all non-diabetic KTRs with fasting plasma glucose, OGTT and or HBA1c at least weekly for 4 weeks, every 3 months for 1 year and annually thereafter (12).

2.7.1 Adjusting immunosuppression

Adjustment of immunosuppression therapy aiming at improving glucose tolerance may be considered among patients who develop NODAT. The benefit must be weighed against risk of allograft rejection. These considerations include glucocorticoid dose tapering, starting a patient on cyclosporine and maintaining a low trough level of tacrolimus. Switching of tacrolimus to cyclosporine is not recommended unless there are other Tac related side effects. This is because

the effect of Tac on glucose tolerance may be reversible without been discontinued (13). One other study reported an improved graft survival with Tac therapy despite increased in NODAT rates (64). Conversion to sirolimus is not recommended. Sirolimus may worsen insulin resistance (39). Use of belatacept, a co-stimulatory blockade agent, has been shown to improve cardiovascular and metabolic outcomes including NODAT compared with cyclosporine (BENEFIT and BENEFIT-EXT studies) (65).

2.7.2 Lifestyle changes

There are some data showing low physical activity post-transplant especially in patients whose appetite may have improved has greater cardiovascular and all-cause mortality risks. Improved diet, increased physical activity and weight loss have been shown to improve dysglycemia in KTRs.

2.7.3 Intensive and early glycemic control

In the immediate to up to 3 months post transplantation periods, KTRs are usually on high dose of diabetogenic immunosuppressive drug and a large proportion of them experience abnormalities in glucose metabolism. Concept of “resting” pancreatic beta cells has been explored. Hecking et al. TIP STUDY (Treat to Target Trial of Basal Insulin in Post-transplant Hyperglycemia) n=50, randomized patients to early basal insulin or standard therapy. By 12 months no patients in the treatment group required hypoglycemic agents compared to 8 in the control group. The majority of the patients on basal insulin did not need any hypoglycemic agent after 120 days. There were no changes in insulin resistance in both groups but better results in the group of patients whose beta cells were “rested” at time of maximal stress. The limitations of this study were a small number of patients and shorter follow up period (15) .

2.7.4 Standard hypoglycemic agents

The 2003 international consensus guideline-based stepwise approach to the management of NODAT recommends non pharmacological therapy including diet, weight reduction and exercise, followed by oral monotherapy, oral combination, insulin +/- oral agent and ultimately insulin monotherapy (66), provided metabolic decompensation had not occurred which would require earlier insulin initiation. There is limited data on use of hypoglycemic agent within KTRs. However drug selection should consider efficacy, side effects and cost.

2.7.5 Glycemic targets

Studies done in the general population for example Diabetes control and Complication Trial(DCCT) (67), United Kingdom Progressive Diabetes Study (UKPDS) (68), Action to Control Risks in Diabetes (ACCORD) (69) and ADVANCE (70) have shown a lower target of HbA1c reduces the risks of microvascular complications(includes retinopathy, nephropathy and neuropathy). In the UKPDS study, when a follow up the patients for another ten years was done, the investigators found a reduction in macrovascular complications (coronary diseases, stroke and peripheral arterial diseases). Other studies had to be stopped, for example, the Action to Control cardiovascular Risks in Diabetes(ACCORD) (69) ,because mortality was seen to be higher in the arm of patients which intensive glucose control program(target HBA1c < 6.0%). This was a study in adult with T2DM for a longer duration of time (10years). The ADVANCE (70) (target HBA1c was< 6.3%) study also failed to demonstrate more intensive glycemic control compared to standard practice had reduced CVD events. These results may not apply to CKD patients or KTRs with diabetes but show serious doubts on advisability of targeting low HbA1c. KTRs with diabetes, and especially those who diabetes was the cause of ESRD often has difficult-to-control diabetes with advanced autonomic neuropathy causing diabetes gastroparesis and hypoglycemia unaware. A randomized controlled trial (RCT) was done on KTRs comparing intensive glucose control with usual care showed a significant incidence of hypoglycemia (67). Therefore it may be difficult to achieve HbA1c <7.0 percent. ADA recommends target of less than 7% for most patients while KDIGO recommend HBA1c target to be between 7.0 to 7.5% for KTRs. Patients with IFG and IGT should be closely monitored and aggressive intervention be put in place aiming at decreasing others cardiovascular risks such as dyslipidemia and hypertension.

3.0 STUDY JUSTIFICATION

The increase in the number of people developing diabetes has had a major impact on the development of diabetes kidney disease (DKD) thereafter progressing to end stage kidney disease (ESKD) requiring renal replacement therapies (RRT). It is a well-known fact that renal transplantation is the best mode of RRT and is being increasingly being practiced in Kenya. Apart from the already known DM prior to transplantation, studies done using current WHO/ADA diagnostic criteria suggest that up to one third of non-diabetic KTRs develop persistent dysglycemic states by six month post transplantation (27) and these have been associated with adverse effects on patient's survival.

Although they achieve improvement in health status post transplantation, their demand for glycemic control increases because of additional risks of immunosuppressive therapy. Early discovery of these disease states and intervention have been shown to be beneficial in terms of general patient survival. Post transplantation data showing the status in terms of burden of dysglycemia in KTRs and the quality of glycemic control in diabetic KTRs at Kenyatta national Hospital (KNH) is unavailable. Data generated from this study will sensitize the clinicians on the magnitude of the disease thereby improving strategies for early detection and treatment thereafter prevention of complications. The patients who will be identified with dysglycemia will benefit from early treatment.

4.0 STUDY QUESTION

What is the burden of dysglycemia in terms of pre transplant diabetes mellitus (DM), new onset diabetes after transplantation (NODAT) impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) among kidney transplant recipients at Kenyatta National Hospital?

5.0 OBJECTIVES

5.1 BROAD OBJECTIVE

To determine the prevalence of dysglycemia among kidney transplant recipients at KNH

5.2 PRIMARY OBJECTIVES

1. To determine the prevalence of dysglycemic states among KTRs at KNH in terms of;
 - Diabetes mellitus (pre transplantation)
 - New onset diabetes after transplantation
 - Impaired fasting glucose
 - Impaired glucose tolerance

5.3 SECONDARY OBJECTIVE

1. To determine the quality of glycemic control among the KTRs with established diabetes using HBA1c levels
2. To describe clinical characteristics of KTRs with dysglycemia in terms of:
 - Cause of ESRD
 - Duration of dialysis before transplantation
 - Duration after transplantation
 - Body mass index
 - Waist hip ratio
 - Immunosuppressive therapy regimen

6.0 STUDY METHODOLOGY

6.1 Study design

Hospital based, descriptive cross-sectional study

6.2 Study site

The Kenyatta national Hospital (KNH), the largest referral facility in East and Central Africa is situated in Nairobi City County in Kenya. It has various specialist units, renal unit being one of them. Kidney transplantation started many years ago (1980) (71) in Kenya, though at a slow pace until 2010, when an accelerated program *Interlife*® which was a five year public private partnership (PPP) between KNH and Novartis pharma, a pharmaceutical company and Hospital Clinic de'Barcelona . The kidney transplant clinic runs every Tuesday morning at the renal unit, where 15 to 20 patients are seen. This clinic is attended by consultant physicians/nephrologists, fellows in nephrology program, resident in internal medicine and the transplant coordinator nurse.

6.3 Case definition

Kidney transplant recipients studied were adult patients aged more than 18 years who had a kidney allograft from whichever source.

6.4 Study population

All post KTRs, aged eighteen years and above, who attended the kidney transplant follow up clinic at KNH.

6.4.1 Patient selection

A) Inclusion criteria

- i. KTR aged 18years and above
- ii. Willing to participate in the study

B) Exclusion criteria

- i. Patients (KTRs) on hemodialysis

6.4 Sample size estimation

Using the Daniel's formula below, the minimal sample needed was calculated to 103 patients.

$$n = \frac{Nz^2Pq}{\{E^2(N-1) + (z^2Pq)\}}$$

Where:

n = Minimum sample size

N=Total population of kidney recipients on follow up in our transplant clinic= 140 (finite population)

Z= Normal standard deviation 95% confidence interval (Z = 1.96)

P= Prevalence of the dysglycemic states (49.5 % based on; *Wagude et al.*, Kenya 2012)

q= 1 – Prevalence

E= Margin of error (0.05)

6.5 Sampling

Consecutive sampling was done, that is, every KTR who attends the transplant clinic and fulfills the inclusion criteria was requested to participate in the study and subsequently recruited on giving consent.

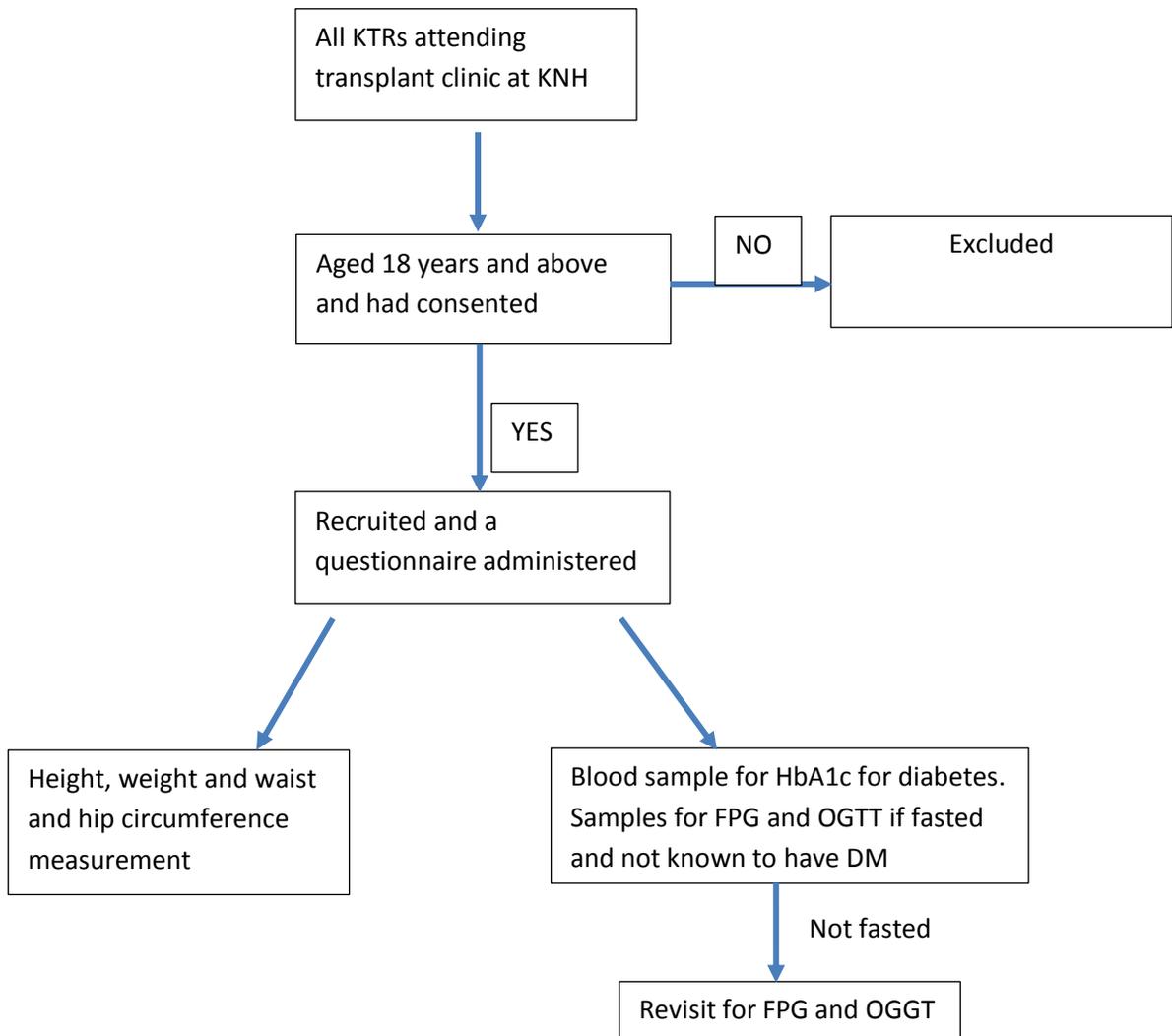
6.6 Study feasibility

There are good records of patients who had kidney transplantation. All transplanted patient medical records files are kept at the renal unit by a medical record officer in charge of the unit so easy retrieval once a patient has been recruited in the study. The transplant clinic runs once a week and approximately 15 to 20 patients are seen. Approximate 6-10 were eligible to be recruited but study was interrupted because of the national doctors' industrial action therefore it took us 9 months to achieve the desired sample size. The laboratory tests were all available in the local market with proper standardization procedures.

6.7 Recruitment

During routine follow up visits, the KTR who fit the inclusion criteria were informed about the study. Once the patient had understood the details of the study, an informed consent (appendix II) was obtained thereafter considered recruited. Patients unable to read and write were guided through the study details (appendix 11) by the principal investigator (PI) and a provision to consent by a thumb print was made.

Figure 2: Flow chart representing summary of the study



7.0 Data collection

7.1 Clinical methods

The patients' files were perused and later a study questionnaire was used to obtain demographic data and a complete medical history from the recruited patients (appendix I). The principal investigator (PI) undertook the clinical assessment using standard procedures:

Body mass index: BMI was calculated as weight (in kg) divided by height (in meters) squared and categorized as per WHO criteria (78). Height measurement was to the nearest 0.5m value. The patient was asked to stand without shoes with the back square against the wall tape, eyes looking straight ahead with a set square resting on the scalp and against the wall. Weight was measured once without shoes and in light garments using a lever balance to the nearest 100 milligrams.

Waist circumference, in centimeters, was taken at the level of umbilicus using a tape measure with the subject standing, measuring in horizontal plane at the end of gentle expiration. Hip circumference (in centimeters) was measured at the maximum circumference in the horizontal plain over the buttocks. Waist to hip ratio (WHR) was calculated as the waist circumference divided by the hip circumference measured (79).

7.2 Blood specimen collection and processing:

Three milliliters of blood were drawn from the ante cubical fossa using aseptic technique and put in the EDTA containing container, transported in a cooler box maintaining a temperature of 15-25°C to stabilize samples for a minimum of 3 days. Roche clinical chemistry analyser known as COBAS INTEGRA 400/400 PLUS/800 analyser using COBAS INTEGRA hemolysing reagent Gen.2 for the quantitative determination of HbA1c percent in whole blood was used.

Three milliliters of blood were drawn from the antecubital fossa either right or left for the fasted patients (they were advised to observe overnight fasting for approximately 8-12 hours) it was done twice, pre and post 75g of anhydrous glucose load intake diluted in 250ml of water. Samples were put in a fluoride containing container and later stored in a cooler box to maintain temperatures of 15-25°C (making it stable for 3 days) and processed using the Roche clinical chemistry analyser. Any participant with clinically significant results was contacted and referred to the transplant clinic clinicians for appropriate intervention.

7.3 Study variables

The dependent variables were the dysglycemic states, that is, presence of diabetes mellitus (pre transplant and post transplantation), impaired fasting glucose and impaired glucose tolerance.

The independent variables were age, gender, obesity, waist circumference, WHR, cigarette smoking, inactivity and current immunosuppressive therapy.

7.4 Definition of variables

Pre transplantation Diabetes was defined as any of:

- Documentation in patient's file of diabetes which started before transplantation
- Being on hypoglycemic agents before transplantation

New onset diabetes after transplantation was defined as any of:

- Documentation in patient's file of diabetes which started after transplantation
- Starting of hypoglycemic agents after transplantation
- FBS greater than 7.0mmol/l
- 2h blood sugar more than 11.1mmol.l, during OGTT
- HbA1c > 6.5%

Impaired fasting glucose was defined as fasting blood sugar between 5.6 and 6.9mmol/l

Impaired glucose tolerance was defined as 2 hour blood glucose between 7.8 and 11.0mmol/l during an OGTT

Weight gain and obesity were defined as shown in the table below

Table 3 Definition of BMI criteria

Criteria	BMI
Underweight	Less than 18.5
Normal	18.5-24.9
Overweight	25-29.5
Obesity	>30

Waist circumference of significance was defined as greater than 102 cm in men and 88cm in women

Waist hip ratio of >0.9 in men and >0.85 in women was considered significant.

Age of increased risk was taken as greater than 45 years

Family history of DM was defined as any patient's sibling, one or both parents or grandparents diagnosed to have diabetes

Quality of glycemc control using HbA1c: Good control was taken as HbA1c $< 7\%$, poor control HbA1c $> 8\%$ and 7-8% as moderately controlled.

Smoking was categorized as previous smoker, current smoker or never smoked

Physical inactivity was defined as self-reported lack of vigorous daily activity in terms of occupation status or participating in an exercising program

Immunosuppressive therapy defined as use of below agents;

- Glucocorticoids
- Tacrolimus
- Cyclosporine
- Sirolimus
- Azathioprine
- Mycophenolate mofetil or mycophenolate sodium

7.5 Quality assurance

The filling of study questionnaire was done by a trained registered clinical officer with supervision from the PI. The measurement of height, weight and waist and hip circumference were done by the PI. Standard methodology was followed for laboratory involving collection, handling and storage. Commercial reagents were used for all analysis and following manufacturer's instructions. Tests for HbA1c were done in batches with commercial controls run before each batch. Patients' samples were only run if the control materials were within acceptable limits.

8.0 Data management

Data for questionnaires was collected during visits to the transplant clinic. Additional details about kidney transplantation and patient progress were retrieved from checking the file. For adequate standardization of the laboratory results, a central laboratory was used to get these samples analyzed. Completed questionnaires were stored under lock and key by the PI, awaiting data processing.

8.1 Data Analysis and presentation

Questionnaires were coded, entered and managed in Microsoft Access 2013 database. Statistical analysis was done using SPSS version 21.0. The study population was described using their socio-demographic and clinical characteristics.

Analysis involving descriptive statistics such as mean, median and standard deviation were used for continuous data such as age and waist circumference and frequency distribution for categorical variables such as obesity, cigarette smoking, immunosuppressive drugs, inactivity, with their corresponding 95% confidence intervals. T test method was used for comparison for continuous data and chi-square test for categorical data.

Prevalence of dysglycemia was analyzed and presented as a percentage of all KTRs and a 95% confidence interval (CI) of the prevalence was presented.

$$x/n \times 100\%$$

Where x = Number of patients with dysglycemia

n = minimum sample size i.e. 103(using Daniel's formula)

Multivariate analysis was performed to investigate independent association between risk factors (socio demographics and clinical factors) and dysglycemic states. The level of statistical significance was $P \leq 0.05$

9.0 Ethical considerations

This study was carried out after a written approval had been issued by the Department of Clinical Medicine and Therapeutic, University of Nairobi (UON), and KNH/UON Ethics and Research committee based at KNH.

All patients recruited into the study consented in writing after the study details had been explained to them in the language they understood (Appendix II). The only procedure required was withdrawal of blood samples. There was freedom to withdraw from the study at any given time without the participants' usual follow up clinical care being affected.

Details of the information gathered in the study were kept by the PI. Any relevant result was thereafter explained to the KTRs participating in the study and appropriate clinical advice was given.

10.0 Role of investigator

The principal investigator's role was to train and then supervise the research assistant who was a qualified and registered clinical officer with the clinical officer's council of Kenya, when administering the questionnaire. The PI did the clinical assessments of the patients and took the measurements of weight, height, waist circumference and hip circumference. He was responsible for storage of all the raw data, data analysis with the help of a statistician and presentation of results.

11.0 RESULTS

The data collection commenced in the month of September 2016 and ended in May 2017. One hundred and seven patients were interviewed at the KNH transplant renal clinic thereafter two were excluded. One had a failed graft and hemodialysis had been started and the other one was 17 years old, one year younger of the inclusion age. Therefore, 105 KTR were recruited fulfilling the target minimum sample of 103. This is presented in the flow chart below.

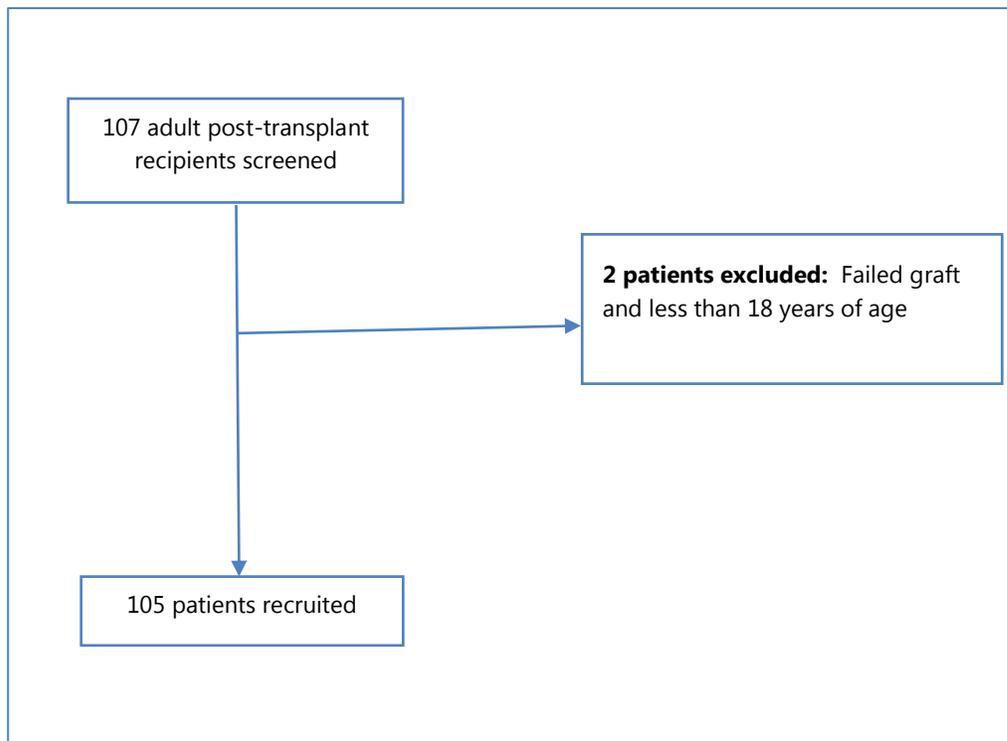


Figure 3: Flow chart showing study participants recruitment

11.1 Study participants' characteristics

The mean age of the participants was 45 ± 12.4 years with an age range of 19-69 years. Males made up almost two third of the study participants making 64.8%. Majority of the study participants had post primary education (91.4%) and employed (67.6%). Thirty seven percent of the KTRs were residents of Nairobi City County and only a patient in Coastal and North Eastern region each. Other baseline socio-demographic characteristics are summarized in table 4.

Table 4: Social and demographic characteristics of study participants

Study Variable	N=105	%
Age yr		
Mean,SD(min,max) ¹	45 ±12.4	19,69 ¹
Sex		
Male	68	64.8
Marital status		
Single	38	36.2
Married	66	62.9
Widowed	1	1.0
Level of education		
Primary	9	8.6
Secondary	38	36.2
Tertiary	58	55.2
Employment status		
Employed	71	67.6
Unemployed	24	22.9
Retired	10	9.5
Region of stay		
Coast	1	1.0
North Eastern	1	1.0
Eastern	11	10.5
Central	27	25.7
Rift Valley	18	17
Western	5	4.8
Nyanza	3	3.0
Nairobi	39	37

The three commonest causes of ESRD were chronic glomerulonephritis 56 (53.3%), Diabetes mellitus 25 (23.8%) and hypertension 15 (14.3%). Majority of patients also had hypertension irrespective of their primary cause of ESRD (68.6%). All patients recruited had undergone dialysis before transplantation with a minimum period of half a month to a maximum of 96 months (8 years) and median dialysis duration of 12 months. The maximum graft age was 25 years and the minimum was one month. Mean and median duration post transplantation were 35 months and 29 months respectively.

All grafts were from live donors and 67% of donors were male. The mean WHR was 0.901 ± 0.07 (SD) with 46 (43.8%) having higher WHR. The mean body mass index was 24.6 ± 4.13

Kg/m² with 56 (53%) having normal BMI, 4 (3.8%) being underweight, 35 (33.3%) overweight and 10 (9.5%) obese. (See table 5)

Table 5: Clinical characteristic of all study participants

Study variable	Total study participant n=105
Cause of ESRD no.(%)	
HTN	15,(14.3)
DM	25,(23.8)
CGN	56,(53.3)
PKD	3,(2.9)
OTHERS	6,(5.7)
Dialysis period months:	12
Median (IQR)	(8-24)
Duration after transplant months: Median	29
(IQR)	(10-51.5)
Graft source: Living no. (%)	105,(100)
Previous graft: None no. (%)	104,(99)
Donor sex: Male no. (%)	67,(63.8)
BMI Mean SD	24.6±4.13
min/max	(15.5/39.5)
BMI Categories no. (%)	
Underweight	4,(3.8)
Normal	56,(53.3)
Overweight	35,(33.3)
Obese	10,(9.5)
WHR Mean SD,	0.901±0.07,
min/max	0.78/1.05
Higher WHR no. (%)	46,(43.8)
Family H/O DM no. (%)	34,(32.4)

Note: SD: Standard deviation, min: minimum, max: maximum, Others: SLE, severe malaria, eclampsia, chronic NSAID use, unknown and Higher WHR= Female >0.85, male > 0.9

All the patients were on prednisone as part of their immunosuppressive regimen and 72% were using tacrolimus. The rest were on cyclosporine or neither. Majority of the participants (90.5 %) were using mycophenolate sodium or mycophenolate mofetil. With regards to social and lifestyle practices, 16.2% were ex-smokers, 3.8% had drunk alcohol, 28% were engaging in manual activities or exercise and 35.2% reported to adhere to nutritional advice.

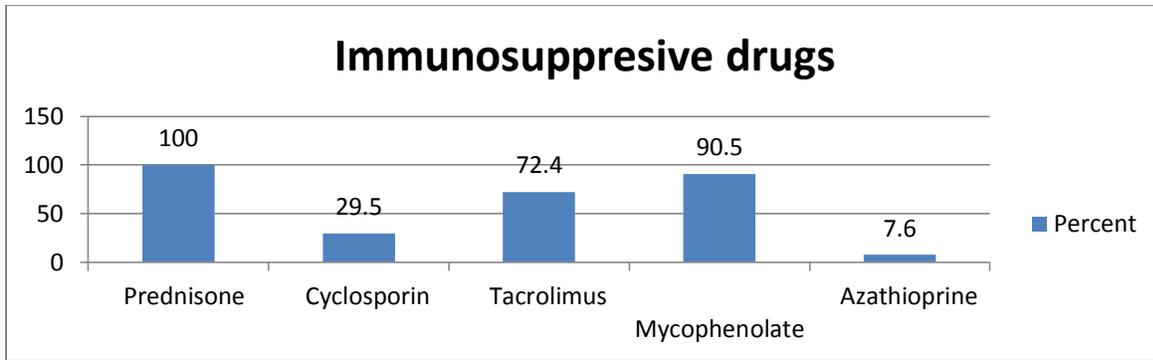


Figure 4: Immunosuppressive drugs used

11.2 Prevalence of Dysglycemia

Among the study participants, 25 (23.81%) had diabetes before transplantation, 44 (41.9%) of the participants were normoglycemic and almost one third had a form of dysglycemia post-transplant, that is, 14 (13.33%) had new onset diabetes after transplantation (NODAT), 15 (14.29%) had impaired glucose tolerance and 7 (6.67%) had impaired fasting glucose. This is represented in the pie chart below:

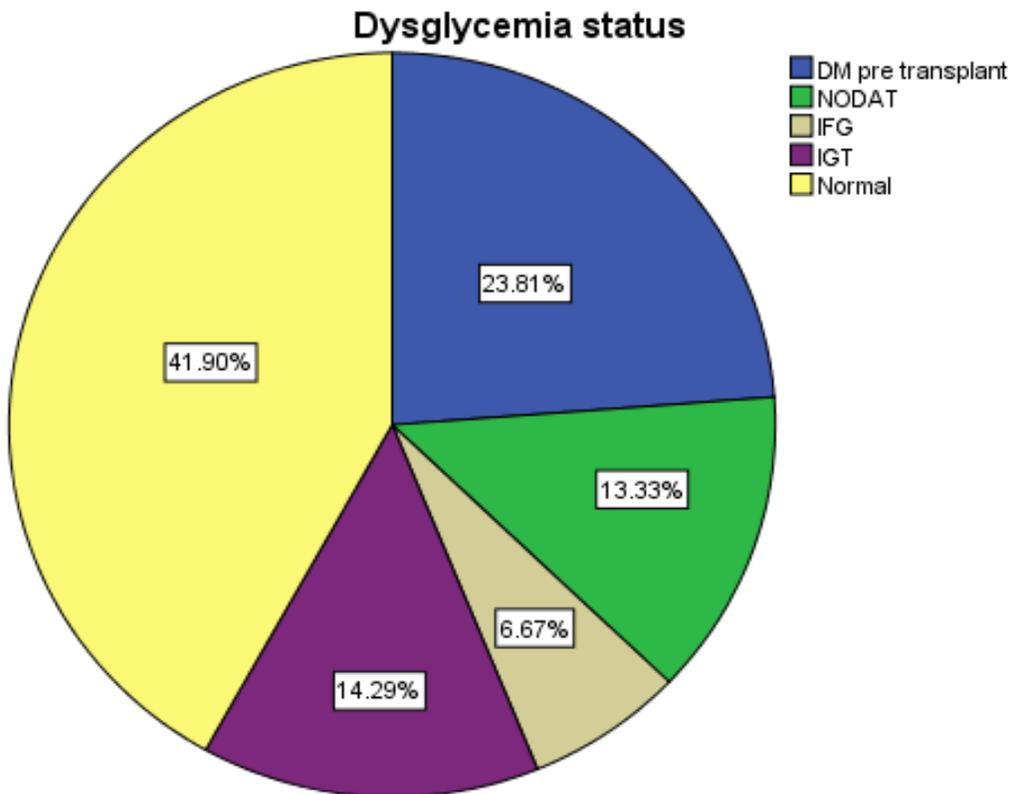


Figure 5: Pie chart of dysglycemia statuses of the study participants

The mean ages were comparable (44-46) but the sexes were different with predominantly male in the NODAT group (64%) and female sex was commoner in the IFG and IGT category, 71.4% and 60% respectively. Chronic glomerulonephritis was the commonest cause of ESRD, 10 (27.8%) in NODAT, 11 (30.6%) in IGT and 2 (5.6%) in IFG. (n=36). All these were also on antihypertensive therapy). One patient in NODAT and IFT each had SLE, and one in IFG had eclampsia as the cause of ESRD.

Apart from the IFG group which had a lower median duration of dialysis, there were no much differences in the median duration of dialysis before transplantation across the dysglycemic group(11.5 months for NODAT and 12months for IGT) and comparing with the total n=105 (12months). Majority of the participants had at least undergone dialysis for 1 year.

The patient with eight years of dialysis was in the NODAT category whereas the patient with oldest graft was in the impaired glucose tolerance group (transplanted in year 1992). All participants had received grafts from live donors and predominantly male with frequency percentages of 57.1% in NODAT, 71.4% IFG and 53.3% IGT categories. All of them were on prednisone while tacrolimus was the main calcineurin inhibitor with 85.7% usage in NODAT, 100% in IFG and 46.7% in IGT. Mycophenolate sodium or mofetil was used more than azathioprine. Half of the patient who had NODAT had at least a close family member with DM while only 28.6% and 20% in IFG and IGT statuses respectively.

The mean BMI was 24.6Kg/m² in NODAT and a range of 16.6-33.3, 27 Kg/m² in IFG a range of 23.4-28.9 and 27.23 Kg/m² a range of 21-34 in the IGT category of dysglycemia. Cigarette and alcohol usage was uncommon and none among the participants who had IFG ever involved themselves in manual activities, or exercise but do adhere to some extent to nutritional advice. Participant found to have NODAT and IGT had poor adherence to dietary advice.

Study Variable	Dysglycemia Posttransplant ,		
	NODAT N=14	IFG N= 7	IGT N=15
Age mean SD min/max¹	46±12.7 (30/67)	44.6±13 (31/60)	44±14 (21/60)
Sex Male no. (%)	9(64.3)	2(28.6)	6(40)
Cause of ESRD no.(%)			
HTN	3, (21.4)	2,(28.6)	3,(20)
DM	-	-	-
CGN	10,(71.4)	2,(28.6)	11,(73.3)
PKD	0,(0)	1,(14.3)	1,(6.7)
OTHERS²	1,(7.1)	2,(28.6)	0,(0)
Dialysis period months: Median (IQR)	11.5 (8-24)	7 (7-26)	12 (7-26)
Duration after transplant : months: Median (IQR)	17 (12.25-33.75)	10 (1-46)	53 (28-62)
Graft source: Living no. (%)	14,(100)	7,(100)	15,(100)
Previous graft: None no. (%)	13,(92.9)	7,(100)	15,(100)
Donor sex: Male no. (%)	8,(57.1)	5,(71.4)	8,(53.3)
BMI Mean SD min/max	24.6±4.8 (16.6/33)	27±2.5 (23/28.9)	27.4±4 (21/34)
BMI Categories no. (%)			
Underweight	1,(7.1)	0,(0)	0,(0)
Normal	6,(42.9)	2,(28.6)	3,(20)
Overweight	5,(35.7)	5,(71.4)	8,(53.3)
Obese	2,(14.3)	0,(0)	4,(26.7)
WHR Mean SD, min/max	0.903±0.086 0.78/1.06	0.887±0.011 0.88/0.91	0.893±0.075 0.8/1.06
Higher WHR³ no. (%)	6,(42.9)	5,(71.4)	9,(60)
Family H/O DM no. (%)	7,(50)	2,(28.6)	3,(20)
Immunosuppressant no. (%)			
Prednisone	14,(100)	7,(100)	15,(100)
Cyclosporin	2,(14.3)	0,(0)	7,(46.7)
Tacrolimus	12,(85.7)	7,(100)	7,(46.7)
Mycophenolate	12,(85.7)	7,(100)	14,(93.3)
Azathioprine	2,(14.3)	0,(0)	0,(0)
Lifestyle no. (%)			
Smoking (Ex-smokers)	3,(21.4)	0,(0)	2,(13.3)
Alcohol (Previous)	1,(2.8)	0,(0)	2,(5.6)
Exercise/manual activity	6,(16.7)	0,(0)	0,(0)
Diet advice adherence	5, (35.7)	7,(100)	3, (20)

When combining the pre DM status, that is, IFG and IGT, the odds ratios of risks factors were increased, especially female sex, BMI above normal and increased WHR and they were statistically significant(see table 7) but there was none which was independently significant on multivariate analysis using logistic regression. The odds ratio for ages more than 45 years, duration post transplantation and family history of DM were higher but they were not statistically significant. The risk factors for NODAT which were statistically significant were family history of DM and increased BMI of more than 25Kg/M².

Table 7: Dysglycemia (Pre DM) and NODAT post-transplant and some risk factors

Risk factor	Pre DM		NODAT	
	Odds ratios	P value	Odds ratios	P value
Age yr >45	1.59(0.56-4.46)	0.380	1.59(0.47-5.33)	0.454
Female Sex	5.25(1.74-15.85)	0.003	7.8(1.92-31.68)	0.437
Duration post-transplant (years) > 1year	1.38(0.45-4.25)	0.576	1.90(0.46-7.85)	0.375
Family History of DM	2.29(0.59-8.98)	0.230	7.80(1.92-31.68)	0.002
Tacrolimus usage	0.73(0.25-2.17)	0.545	2.51(0.49-12.86)	0.256
Cyclosporine usage	1.0(0.33-3.00)	1.0	0.36(0.70-1.82)	0.201
BMI >25kg/m ²	11.22(3.30-38.11)	0.0001	3.85(1.04-114.1)	0.042
WHR (>0.85 female, >0.90 male)	5.25(1.74-15.85)	0.003	2.25(0.64-7.93)	0.201
Exercise status(less active)	19.28(1.09-341.54)	0.044	0.56(0.16-1.93)	0.359
Dietary advice non adherence	0.69(0.24-1.94)	0.476	0.97(0.28-3.41)	0.965

11.3 Characteristics and Glycemic control in DM patients

Almost a quarter (23.8%) of the study participants had DM as a cause of their ESRD with males being more than females (72% versus 28%) and majority of them had hypertension (76%). Insulin usage was commoner 22 (88%) than oral hypoglycemic medication 10(40%) with 7 (28%) of them using both oral and insulin to control their diabetes. Lipid lowering agent (statin in particular) usage was low at 16%. The mean BMI was 25 Kg/m² (range of 16.45-39.5) and almost half of subjects were either overweight 7 (28%) or obese, 4 (16%). The ex-smokers and previous alcohol intake were few 4 (16%) and 1 (4%) respectively among the diabetes participants and almost half reported to engage themselves in physical activities, 11 (44%). (See table 8). Significant differences were on antidiabetic medications and means of HbA1c, when

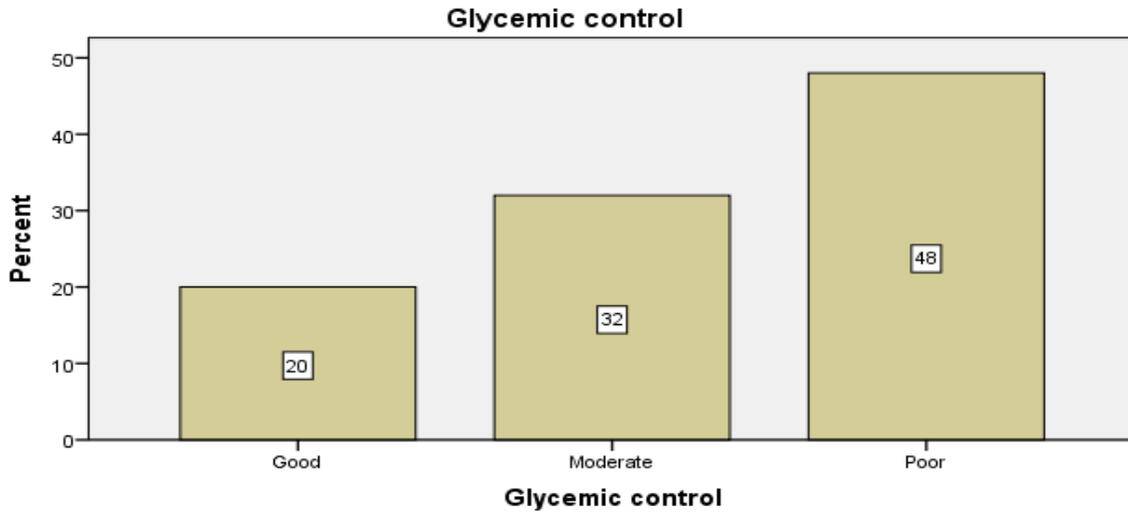
comparing good control in this case (HbA1c <7.5) and poor control. The other characteristics are fairly comparable. (Table 8)

Table 8: Social and Clinical characteristics of participant with DM pre transplantation

Variable	Diabetes KTRs n=25	Good control n=11	Poor control N=14	P value
Age Mean SD	49.2 ±13	51.9±12	47±13.6	0.356
Sex Male no. (%)	18(72)	9(81.8)	7(50)	0.100
Post Primary Education	23(92)	10(90.9)	13(92.9)	0.859
Form of Employment	18(72)	8(72.7)	10(71.4)	0.943
Duration after transplant >1yr	18(72)	9(81.8)	9(64.3)	0.332
Hypertension no. (%)	19(76)	8(72.7)	11(78.8)	0.206
Immunosuppressant no. (%)				
Prednisone	25(100)	11(100)	14(100)	-
Tacrolimus	19(76)	7(63.6)	12(85.7)	0.199
Cyclosporine	8(32)	4(36.4)	4(28.6)	0.878
Antidiabetic drugs no. (%)				
Oral	10(40)	8(72.7)	2(14.3)	0.003
Insulin	22(88)	8(72.7)	14(100)	0.037
Statin use	4(16)	3(27.3)	1(7.1)	0.173
BMI Mean, SD , (min/max)	25.0±4.8 (16.45/39.5)	24.4±2.8 (16.45/28.59)	25.55±5.53 17.44/39.5	0.551
BMI Categories no. (%)				0.149
Underweight	2(8)	1(9.1)	1(7.1)	
Normal	12(48)	5(45.5)	7(50)	
Overweight	7(28)	5(45.5)	2(14.3)	
Obese	4(16)	0(0)	4(28.6)	
WHR mean ±SD, Min/max	0.901±0.07 0.78/1.05	0.906±0.08 0.78/1.05	0.90±0.07 0.79/1.01	0.584
Higher WHR no. (%)	15(60)	7(63.6)	8(57.1)	0.742
HbA1c mean ±SD Min/max	8.4±2.1 5.5/13.9	6.76±0.66 5.5/7.5	9.62±2.03 7.6/13.90	0.0001
Lifestyle no. (%)				
Cigarette smoking(ex-smoker)	4(16)	3(27.3)	1(7.1)	0.173
Previous alcohol intake	1(4)	1(9.1)	0(0)	0.250
Exercise/physical activity	11(44)	6(54.5)	5(35.7)	0.346
Dietary advice adherence	6(24)	4(36.4)	2(14.3)	0.199

The mean HbA1c was 8.4 ± 2.1 percent and the majority of the diabetic patients were poorly controlled (48%) and moderately (32%) and only a fifth had good control (20%). This is shown in the bar chart in figure 6:

Figure 6: Bar chart illustrating quality of glyceimic control (Good HbA1c <7.0%, moderate 7%-8% and poor >8%).



The prevalence of well controlled DM was 44% when the target HbA1c $\leq 7.5\%$ was analyzed as good and above it as poor glyceimic control.

Although not statistically significant, the odds ratio of glyceimic control being poor were more in the participants who had BMI above normal, poor dietary advice adherence and lack of exercise or involvement in physical activities (table 9).

Table 9: Glycemic control and some risk factors

Risk Factor	Odds Ratio	p value
Age > 45years	0.11(0.01-2.25)	0.1521
Insulin	2.25(0.16-31.33)	0.546
Overweight	1.11(0.13-9.61)	0.924
WHR	1.0	1
>1 year Post-transplant	0.58(0.53-6.37)	0.659
Diet	3.778(0.43-33.07)	0.230
Tacrolimus	0.75(0.07-8.38)	0.815
Exercise	7.43(0.69-79.96)	0.098
Alcohol	0.2(0.01-3.91)	0.289

11.4 Anti-hypertensive drug usage

Two thirds of all the study participants were hypertensive and were on either one or multiple antihypertensive drugs. The calcium channel blocker group of antihypertensive medications was mostly used followed by adrenergic blocking agents whereas the ACE inhibitors group was the least, 42%, 28% and 9% respectively. The other groups of drugs are illustrated in the chart below:

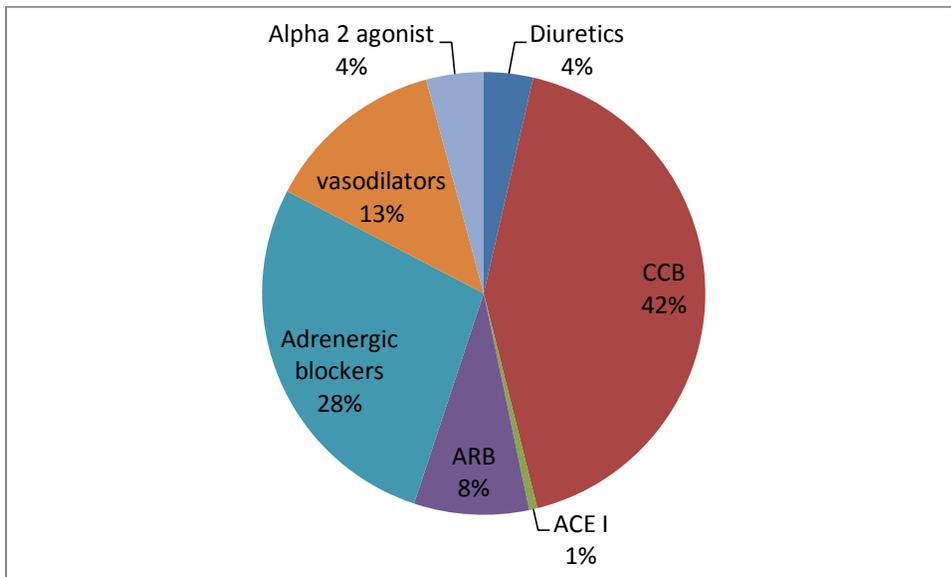


Figure 7: Pie chart illustrating antihypertensive medications

12.0 DISCUSSION

Our study was set to determine primarily the prevalence of NODAT, IFG, IGT and also pre transplantation DM. We found that a third of the KTR had a form of new onset dysglycemia and when including the pre transplant DM status (which was found to be as the second commonest cause of ESRD following CGN) a total of 58.10% was witnessed. We got a prevalence of 13.3% for NODAT with a median duration post-transplant of 29 months and a mean age of 45 ± 12.4 . Bapoo in South Africa (28) got an incidence of 17% at 36 months for NODAT only with a mean time post-transplant and age of 18 months and 41 years respectively. It is fairly comparable and the slight difference could be attributed by the different population (race), ethnicity or maybe bigger sample size with the South African study ($n=221$) while ours was 105. Cosio at Mayo Clinic and foundation, USA (31) found an incidence of 10% at 3 years and 13% at 5 years. Porrini's et al. study (72) on NODAT and prediabetes states using OGTT found a prevalence of 33% of prediabetes with IGT being the abnormality most frequently observed (25% at 1 year) and 20% of the participants had NODAT at 1 year. We found a prevalence of 14.29% for IGT and 6.67% for IFG. Several risks factors may explain the different prevalences which were not categorically analyzed. These include race, commoner in African American, infections such as hepatitis C, deceased donors and also human leucocyte (HLA) antigens mismatching.

Several factors have been studied and showed causative effect for dysglycemia.

Immunosuppressive therapies are mainly implicated. Steroids and more importantly, a prolong exposure and intermittent pulsing due to episodes of acute rejections with high doses predispose the KTRs to diabetes mellitus. Combining it with tacrolimus which is a CNI with more diabetogenic effect than cyclosporine (38) augments the risks of getting dysglycemias. The study done by Porrini et al. in Spain (72), was a multicenter, prospective study ($n=154$) and all patients studied were on tacrolimus based immunosuppressive regimen with mycophenolate and low dose steroids. This is also the case in our setup as majority of the participants were on tacrolimus (72.4%) and all were on prednisone. This is due to the effects on insulin resistance and suppression of insulin secretion (β cell toxic effects) by the steroids and tacrolimus respectively. We did not find any significant associations with any immunosuppressive drug. This was

beyond the scope of our study. SAILOR study group, an in progress multicenter study evaluating whether a steroid free immunosuppressive protocol based on ATG induction and low tacrolimus dose will reduce the incidence of NODAT may give us a clear guidance once it is completed (35).

Increasing age, higher BMI, dyslipidemia (72), duration post transplantation(41) and family history of DM (46) are other risks which have been shown to be independently associated with increased dysglycemia((41). Some of these were evident in our study as the duration post transplantation; higher BMI, higher WHR and family history of DM related to the dysglycemic status were statistically significant at univariate analysis. Cosio et al. (41) found upto 2.2 times higher risks of developing NODAT in KTRs older than 45 years compared with younger population. Despite that, we did not find any significant association though our mean age of the participants was 45 ± 12.4 . This could be explained by our study being under powered. Improved quality of life and appetite after transplantation make the KTRs gain weight and because they do minimal manual activities due to fear of the post operational pain and graft failure they tend to become obese and this keeps them at a higher risk of getting dysglycemia (11). We found a population which was less active (only 28.6%), and had poor adherence to dietician advice (35.2%). This imposes a bigger problem than imagined. Family history was significantly associated with NODAT ($p = 0.002$) in our study at univariate analysis (we did not find any significant association on multivariate analysis and this could also be due to being less powered to bring out associations. Hjelmessaeth et al. (46) found a similar association.

Despite the majority of diabetes KTRs being educated and having a form of employment, only a fifth (20%, $n=25$) of them had achieved good glycemic control whereas almost half of them had poor control ($HbA1c > 8\%$) using standard recommendation (8). KDIGO (12) recommends HbA1c target of up to 7.5% as these patient are still considered to have CKD. The large number of poorly controlled could be related to the higher frequency of BMI more than 25kg/m^2 , increased mean WHR, lack of exercise and poor adherence to dietary advice but all these were not statistically significant in our study(beyond the scope). Diabetes and NODAT are associated with increased cardiovascular complications in post-transplant patients such as both myocardial infarction and heart failure (73) and also graft failure (11). The UKPDS (74) showed that cardiovascular risk reduction in type 2 DM (such as smoking cessation, dyslipidemia and

hypertension control) reduce cardiovascular mortality. Our study showed that majority of the pre-transplant diabetes patients had hypertension and very few were on a statin. Targeted therapy of these conditions and controlling them well is paramount.

12.1 Conclusion

1. There is a high prevalence of dysglycemic states in KTRs at KNH
2. The glyceemic control of the diabetic KTRs is generally poor
3. Some of risks factors for dysglycemia noted to be highly prevalent include older age, BMI above 25kg/m², increased WHR, poor dietary advice adherence, less actively involved in manual activities or exercises and family history of DM

12.2 Implication of the study and recommendations

Our study found a prevalence of dysglycemia post kidney transplantation to be 34.29% (more importantly NODAT at 13.33%) that means for every three kidney transplanted patients one of them will have a form of dysglysemia. Routine screening of all recipients for these conditions will enable early detection and institution of appropriate measures to prevent progression of pre diabetic states to overt diabetes. This will improve health status of KTRs, reduce societal burden in terms of loss man power time and reduction in health costs. KDIGO (12) recommends screening of all non-diabetic KTRs with fasting plasma glucose, oral glucose tolerance testing and/or HbA1c at least weekly for 4 weeks initially, then every 3 months for 1 year and annually thereafter.

We also found that majority of the diabetic KTRs had poor glyceemic control. This call for measures to be put to ensure patients are put in good diabetic care programs to avoid overweight, to promote good adherence to dietary and exercise advices and optimizing different safe and cost effective antidiabetic agents either singly or in combination.

The prevalent risk factors found in our study merit further exploration in longitudinal studies to determine correlations with risks both of getting dysglycemia among KTRs and effects on glyceemic control among the diabetic KTRs.

12.3 Study limitation

1. A cross sectional study may not bring causal effects in an ongoing disease process
2. HbA1c level was used to show the quality of glycemic control but any red cell abnormalities were not ruled out.

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APPENDICES

APPENDIX 1: Study Proforma

1. Study number _____
2. Date of examination _____

Demographics

3. Date of birth mm/yy _____
4. Sex 1. Male 2. Female
5. Marital status
1. single 2. Married 3. Divorced 4. Widowed 5. Separated
6. County of residence _____ Ethnicity _____
7. Employment status
1. Employed 2. Unemployed 3. Retired
8. Level of education
1. None 2. Primary 3. Secondary 4. Tertiary 5 other

Past medical history.

9. Aetiology of ESRD
 - a. Chronic glomerulonephritis
 - b. Diabetes nephropathy
 - c. Hypertensive renal disease
 - d. Obstructive uropathy
 - e. Polycystic kidney disease
 - f. Others
10. Duration of dialysis (months) _____
11. Date of transplantation _____
12. Source of kidney
 1. Living 2. Cadaveric
13. Previous renal graft
 1. None 2. One 3. Others

14. Donor sex 1. Male 2. Female

15. Any other chronic illness Duration_____

1. DM 2. Hypertension

16. Current immunosuppressive medication/dose/ frequency

- a. Prednisolone _____/_____/_____
- b. Cyclosporine _____/_____/_____
- c. Tacrolimus _____/_____/_____
- d. Mycophenolate _____/_____/_____ -
- e. Azathioprine _____/_____/_____
- f. Sirolimus _____/_____/_____
- g. Others_____

17. Other current medications

- a. Oral hypoglycemic drug/dose_____ / _____
- b. Insulin formulation/ dose _____/_____
- c. Blood pressure drugs/dose_____ / _____
- d. Lipid lowering agents/ dose _____/_____
- e. Others_____ / _____

18. History of smoking

1. Never smoked 2. Ex-smoker 3. Current smoker

19. How many sticks/day: A. 1-15 or B. > 15

20. History of tobacco intake 1. Yes 2. No

21. Duration of tobacco intake_____

22. Do you take alcohol 1. Yes 2. No

23. How much alcohol _____ Duration_____

24. Do you usually exercise or involved in manual activities 1. Yes 2. No

25. What is the frequency

1. 15mins/day 2. 30mins/day 3. Others specify

26. Do you eat what you have been advised by the nutritionist 1. Yes 2. No

Family history

27. Family history of diabetes

1. parent 2. Parents 3. Sibling 4. Others, specify _____

Physical examination

28. Weight (kg) _____ Heights (m) BMI _____

29. Waist circumference (cm) _____

30. Hip circumference (cm)

Laboratory tests:

31. HBA1c(percent) _____

32. FPG (mmol/l) _____

33. 2h plasma glucose during OGTT(mmol/l) _____

Appendix II: Research Consent Explanation Form

My name is Dr. Faraj Amir, I am currently pursuing my Masters of Medicine degree in Internal Medicine at the University of Nairobi, Kenya. I would like to explain to you about the research I am intending to do.

Title: Dysglycemia among kidney transplant recipient at Kenyatta National Hospital

Introduction: I am inviting you to participate in this study, whose aim is to find out how common is diabetes (characterized by high blood sugar levels) or conditions with abnormal blood sugar levels that precede diabetes among patients who underwent kidney transplantation and are attending the transplant clinic at KNH.

Objectives of the study: The study aims to find out how common the above conditions are among the transplanted patients and also to show what are the common risk factors associated with these conditions are.

Benefits: The benefits are that if you are found to have any abnormalities you will be referred to the appropriate doctor for treatment. Information obtained from the study may help in coming up with recommendation to the transplant clinic. You will not receive any money for participating in this study.

Risks: Apart from the prick of a needle into your body to withdraw the blood samples no other risk are involved in this research. We will ensure high level of cleanliness is practiced when taking blood sample to avoid any infections.

Role in the study: Once you accept to participate you, will be required to answer few questions about yourself, the medication you use, we will take your weight, height, waist circumference .Blood sample will be withdrawn to check for HbA1c for patients known to have diabetes. This will show us how well the blood sugar was controlled for the last three months, and for fasting blood sugar test thereafter you will be given glucose solution to drink and after two hours another blood sample will be taken to check for blood sugar level again. This test is called oral glucose tolerance test (OGTT). It will be helpful to show if you have any sugar abnormalities. 3mls of blood will be withdrawn for any test. This will not reduce your blood level. The samples

will not be used for any other tests. They will be stored at the laboratory and discarded once the study has ended.

Costs or compensation: These tests will be done for free and you will be reimbursed your fare if you are required to come another day.

Confidentiality: All the information relates to you will be treated in strict confidence as per the legal requirement. No names will be indicated anywhere. All the clinical assessments will be done in a screened room in the presence of a chaperon if need be. .

Voluntarism: Your participation in this research is completely voluntary and refusal to participate or withdrawing at any given time will not have any bearing on any services you are currently receiving.

Contact: If you have any question about the study feel free to ask me at any given time, Dr. Faraj Amir mobile number 0722508610 or any of my below supervisors;

Prof. C F Otieno , mobile no. 0722752558

Prof . Kayima , Mobile no.0733730650

Dr. Were , mobile no. 0722711444

Dr. Ngare, mobile no. 0722881579 and

The Secretary, KNH/UON Ethics and review committee, Tel No. 2726300 Ext 44102

Maelezo kuhusu utafiti kabla ya kutoa ridhaa ya kuhusika.

Jina langu ni Daktari Faraj Amir, kutoka Chuo Kikuu cha Nairobi, ningependa kukueleza kuhusu utafiti ninayotaka kufanya.

Anwani: “Dysglycemia among kidney transplant recipient at KNH”

Utangulizi: Nataka kuchukua fursa hii kukualika kwa utafiti huu wewe kama mmoja wa wale waliopewa figo. Madhumuni ya utafiti huu ni kujua ni kiasi gani ya wagonjwa wanapata ugonjwa wa kisukari au wanapata hitilafi ya kuwa na kiwango cha juu ya sukari pindi wakipimwa damu.

Madumuni ya utafiti: utafiti huu unataka kuchunguza ni kiasi gani ya wagonjwa walipewa figo kwa upasuaji wanapata hitilafu ya kisukari na pia kujaribu kuchunguza ni nini chanzo ya shida hii.

Faida: Faida itakayopatika kwa kuhusika kwako ni ikiwa hizi ihitilafu ya kisukari uko nayo, utaelezwa na kushauriwa kuonekana na daktari muhusika wa maradhi haya ili uweze kupewa matibabu na ila ukiwa sawa, maelezo yatakayopatikana kwa utafiti huu utaweza kushauru wenye kuhusika na kliniki hii ya figo na KNH kwa jumla. Hautapewa hela zozote kama malipo ya kujiunga na utafiti huu.

Madhara: Hakuna madhara yoyote utakayo pata kwa kuhusika kwako kwa utafiti huu ila utapata maumivu kidogo ya sindano ukitolewa vipimo vya damu. Tutahakikish usafi wa hali yaa juu ili usipate madhari yoyete pindi damu inachukuliwa.

Jukumu lako: Pindi utakapo kubali utahitajika kujibu maswali kuhusu wewe mwenyewe, na historia fupi ya maradhi yako. Kisha baadaye utapimwa upana wa kiuono, mapaja na ratili au uzito wako utachukuliwa. Tutachukua damu kupima HbA1c kwa wale waojulikana kuwa na ugonjwa wakisukari. Hii itajulisha vile sukari yako ilikuwa kwa miezi mitatu iliyopita. na pia kipimo cha sukari kabla hujakula, baadaye utapewa sukari ya “glucose” katika maji ukunye kisha baada ya masaa mawili upimwe tena sukari hichi kipimo kinaitwa OGTT. Milimita tatu pekee ya damu itachukuliwa kila mara. Damu uliopeana haitapimwa ugonjwa wowote na itawekwa kwa maabara mpaka utafiti ukamilike na kisha kutupwa.

Gharama: Hutatakikana kulipa gharama yoyote ya upimaji huu wa damu na pesa za usafiri ukihijika kurudi siku nyingine utarudishiwa.

Stara: Maelezo yote kukuhusu wewe na stara yako itahifadhiwa na bila kutanjwa kwa jina lako pahali popote.

Hiari: Kuhusika kwa utafiti huu ni hiari yako nzuri na ukikataa au ukitaka kujitoa wakati wowote inawezekana na hakuna upungufu wowote wa huduma ya afya itakayopatikana.

Kwa maelezo zaidi: Kwa maswali yoyote kuhusu utafiti huu unawaeza kuwasiliana na mimi Daktari Faraj kwa simu ya mkono wakati wowote. Nambari 0722508610

Prof. C F Otieno , mobile no. 0722752558

Prof . Kayima , Mobile no.0733730650

Dr. Were , mobile no. 0722711444

Dr. Ngare, mobile no. 0722881579 and

The Secretary, KNH/UON Ethics and review committee, Tel No. 2726300 Ext 44102

Appendix III: Voluntary consent form

I _____, hereby voluntarily agree to participate in the research. This is done after the details of the study in terms of nature, purpose, potential benefits and risks have been explained to me by the principal investigator.

Signature _____

Date _____

Witness:

Name _____

Signature: _____

Date _____

Ridhaa ya kuhusika katika uafiti

Mimi _____ nimekubali kwa hiari yangu mwaaliko wa utafiti huu. Nimetoa idhini hii baada ya kuelezwa kuhusu utafiti kwa namna ya vipi nitahusika, umuhimu wake na madhara yake na daktari muhusika.

Sahihi _____

Tarehe _____

Shahidi:

Jina: _____

Sahihi _____

Tarehe _____