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Dysglycaemias among Patients with Chronic Kidney Disease in Tanzania

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Abstract

Background

Chronic Kidney Disease (CKD) contributes to significant morbidity and mortality around the globe and especially so in the sub-Saharan Africa region. CKD influences the control of blood glucose levels resulting in glycemic dysregulation (causing either hypoglycemia or hyperglycemia) through various proposed pathways. In this study we investigated on prevalence, patterns and factors associated with dysglycaemias among patients with CKD attended at the tertiary Muhimbili National Hospital, Dar es Salaam, Tanzania.

Materials and Methods

We carried out a hospital based cross-sectional study between July 2017 and January 2018. Employing a systematic sampling method, we enrolled a total of 328 patients with CKD who were attended at the Renal Unit of the Muhimbili National Hospital in Dar es Salaam, Tanzania. We performed Oral Glucose Tolerance Test (OGTT) to selected patients and recorded their respective glycemic levels. We used SPSS version 20.0 for data analysis.

Results

Of the 328 selected patients; 128 (39%) were patients with known (established) diabetes mellitus, 7 (2.1%) were (newly) diagnosed to have diabetes mellitus and 17 (5.2%) were found to have impaired glucose tolerance by OGTT during this study. Furthermore, of the 128 patients with established diabetes mellitus; 7(5.5%) were found to have hypoglycemia and 20 (15.6%) had developed “burnt-out” diabetes mellitus, respectively. On multivariate analysis; age 50 years or more (OR 2.92, 95% C.I. (1.71 - 4.99)), having co-existent hypertension (OR 2.96 (1.71 - 4.99)) and having a positive family history of diabetes mellitus (OR 7.8 (3.74 – 17.02)) were found to be independent factors associated with presence of dysglycaemias.

Conclusion

Diabetes mellitus, impaired glucose tolerance, hypoglycemia and “burnt out” diabetes mellitus are all prevalent among patients with CKD attended at the Renal Unit of Muhimbili National Hospital, Dar es Salaam, Tanzania. Having age 50 years or older, family history of diabetes and co-existent hypertension are independent predictors of dysglycaemias among these patients.

Keywords: *Chronic Kidney Disease, Hypoglycemia, Diabetes mellitus, Hyperglycemia, Burnt-out diabetes, Tanzania.*

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Introduction

Chronic Kidney Disease (CKD) is a common contributor of significant morbidity and mortality worldwide and increasingly so in the WHO sub-Saharan African region (1). Once the kidney function is reduced below a critical level, CKD tends to progress relentlessly towards end-stage renal disease (ESRD) rendering patients dependent on renal replacement therapy for survival (2). However, studies have shown that effective control of blood glucose is important in slowing down the progression of kidney disease towards ESRD (2).

Diabetes mellitus (DM) is one of the common risk factors for CKD (3). The CKDAFRIKA study done in Moshi (Northern Tanzania) showed the overall prevalence of CKD to be 7% of the population, of which 7.0% was attributed to DM alone whilst 14.0% had both diabetes mellitus and hypertension as underlying causes of CKD (4). Diabetes alone accounts for 12–55% of the underlying causes of ESRD (5). Through different physiological mechanisms, progressive chronic kidney disease is independently associated with reduced peripheral insulin sensitivity (6), reduced insulin secretion and changes in the levels of various substances such as leptin (7)(8), cytokines, and uremic states all of which render these patients susceptible to develop both hyperglycemia (9) and hypoglycemia (10).

Patients with ESRD undergoing renal replacement therapy (RRT) have increased tendencies for developing altered glycemic control, new-onset diabetes after dialysis (NODAD) and new-onset diabetes after transplant (NODAT), all of which are associated with worse clinical outcomes and increased morbidity and mortality compared to controls (11)(112)(13)(14). Furthermore, chronic uremia resulting from progressive CKD is associated with increased insulin resistance and altered glucose metabolism (13). Paradoxically, progressive decline of renal function is often associated with spontaneous improvement of serum glucose control in most of patients with ESRD (15).This phenomenon referred to as “burnt-out” diabetes, is partly due to reduced renal and hepatic insulin clearance, decline in renal gluconeogenesis, deficient catecholamine release, anorexia and reduced food intake among CKD patients as well as the hypoglycemic effects that accompany hemodialysis therapy for patients undergoing therapy)(17).

The scaling up of renal services in Tanzania has resulted into more and more patients with CKD accessing specialized renal care and renal replacement therapies (both hemodialysis and kidney transplantation programs are now available in the country). This current study investigates on the patterns, prevalence and factors associated with dysglycaemias among patients with CKD in Dar es Salaam, Tanzania.

Materials and Methods

We conducted a hospital based cross sectional study to determine patterns, prevalence and factors associated with dysglycaemias among patients with CKD attended at the Renal Unit of the Muhimbili National Hospital, Dar es Salaam, Tanzania. This tertiary hospital provides specialized renal services including outpatient renal services, hemodialysis and recently, kidney transplantation. The hospital provides pre-, peri-, and post- kidney transplantation services organized around the Renal Unit.

Employing a statistical approach for determining the sample size in a finite population (18), we recruited a total of 328 (we picked every alternate patient from a sampling frame of about 40 patients per day until the sample size was reached) patients with CKD (defined as having estimated glomerular filtration rate of less than 60ml/min/1.73m^2 using the Modification of Diet for Renal Disease (MDRD) equation (19) into the study. We recorded patients' biodata (age, gender, height, weight, Body Mass Index (BMI), demographic data (domicile, occupation, education etc.), clinical data (blood pressure measurements) and laboratory data (serum creatinine, urea, oral glucose tolerance test etc.). After excluding patients with known diabetes mellitus (i.e. 128 patients), we used standard Oral Glucose Tolerance Test (OGTT) to classify the remaining (i.e. 200 patients) with CKD as having; normal glucose tolerance, impaired glucose tolerance or overt (previously unknown) diabetes mellitus.

Parametric continuous variables were reported as Mean ± Standard Deviation and statistical association between variables were explored using student t-test. For parametric categorical variables; frequencies, medians±interquartile ranges were used to report on distribution and the Chi-square test was used to determine the statistical association. On further analysis, univariate and multivariate logistic regression analysis model were used to determine predictors of dysglycaemia and two tailed p-values <0.05 were considered as a cut-off for determining statistical significance.

Results

Patients Characteristics

We recruited 328 patients (mean Age±SD; 51.2±15.7 years, 61.3% were male, 79.3% were living with their partners, 50.6% had attained primary education whilst 55.2% were engaged in formal employment) into the study. Over half (51.8%) had had CKD for 6 months or more, all were in advanced renal insufficiency (eGFR<60ml/min) with over three-quarters (75.9 %) being already in End Stage Renal Disease (i.e. eGFR< 15ml/min). Treatment-wise; 105 (31.7%) were on maintenance hemodialysis, 25 (7.6%) had received a kidney allograft

whereas 196 (59.8%) were yet to be on any form of renal replacement therapy (pre-RRT). Being hypertensive was reported among 283 (86.3%) patients, 128 (39.0%) patients reported as having established DM and being overweight and/or obese (BMI ≥ 25kg/m^2) was found among 134 (40.9%) patients. The median kidney function (calculated eGFR) was 8mls/min/1.73m^2. Anti-hypertensive medications were the most (86.3%) commonly used medications followed by proton pump inhibitors (30.8%). For the glucose lowering agents, over a quarter (27.4%) reported to be on oral hypoglycemic agents (OHAs) whilst 10.7% were on injectable insulin therapy. Further, with regards to supplemental therapies; 23.2% were on injectable erythropoietin therapy, 18.0% were on oral vitamin D supplements, 31.7% were on oral calcium supplements and 28.7% were on oral ferrous sulfate. The proportion of patients using immunosuppression therapies were as follows; Tacrolimus (7.0%), Prednisolone (6.4%), Mycophenolate Mofetil (MMF) (4.9%) and Azathioprine (0.3%) (Table 1).

Table 1: Sociodemographic and Clinical Characteristics of Patients with CKD (N=328)

Demographic & Clinical Variables	Mean±SD, n (%)		Supplements & Medications	Mean±SD, n (%)
Age (Mean±SD),years	51.2 ± (15.7)		Erythropoietin	76 (23.2)
Male	201 (61.3)		Vitamin D supplements	59(18.0)
Living with a Partner	260 (79.3)		Proton Pump Inhibitors	101(30.8)
Primary Education	166 (50.6)		Calcium Supplements	104(31.7)
Formal Employment	181(55.2)		Oral Hematinic	94(28.7)
Having CKD≥6 Months	170 (51.8)		Diuretics	96(29.3)
Established ESRD	249 (75.9)		Anti-Hypertensives	283(86.3)
Hypertensive	283 (86.3)		Oral Hypoglycemic	90(27.4)
HIV Infected	20 (6.1)		Insulin Therapy	35(10.7)
Diabetes Mellitus	128 (39)		Tacrolimus	23(7.0)
Hypercholesterolemia	28 (8.5)		Prednisolone	21(6.4)
Overweight or Obese	134(40.9)		MMF or Azathioprine	17(5.2)

Glycemic Control

Of the 328 study participants, 200 (61.0%) denied history of being diabetic before whilst 128 (39.0%) were previously known (established) diabetes mellitus patients. (See flow diagram below) (Figure 1).

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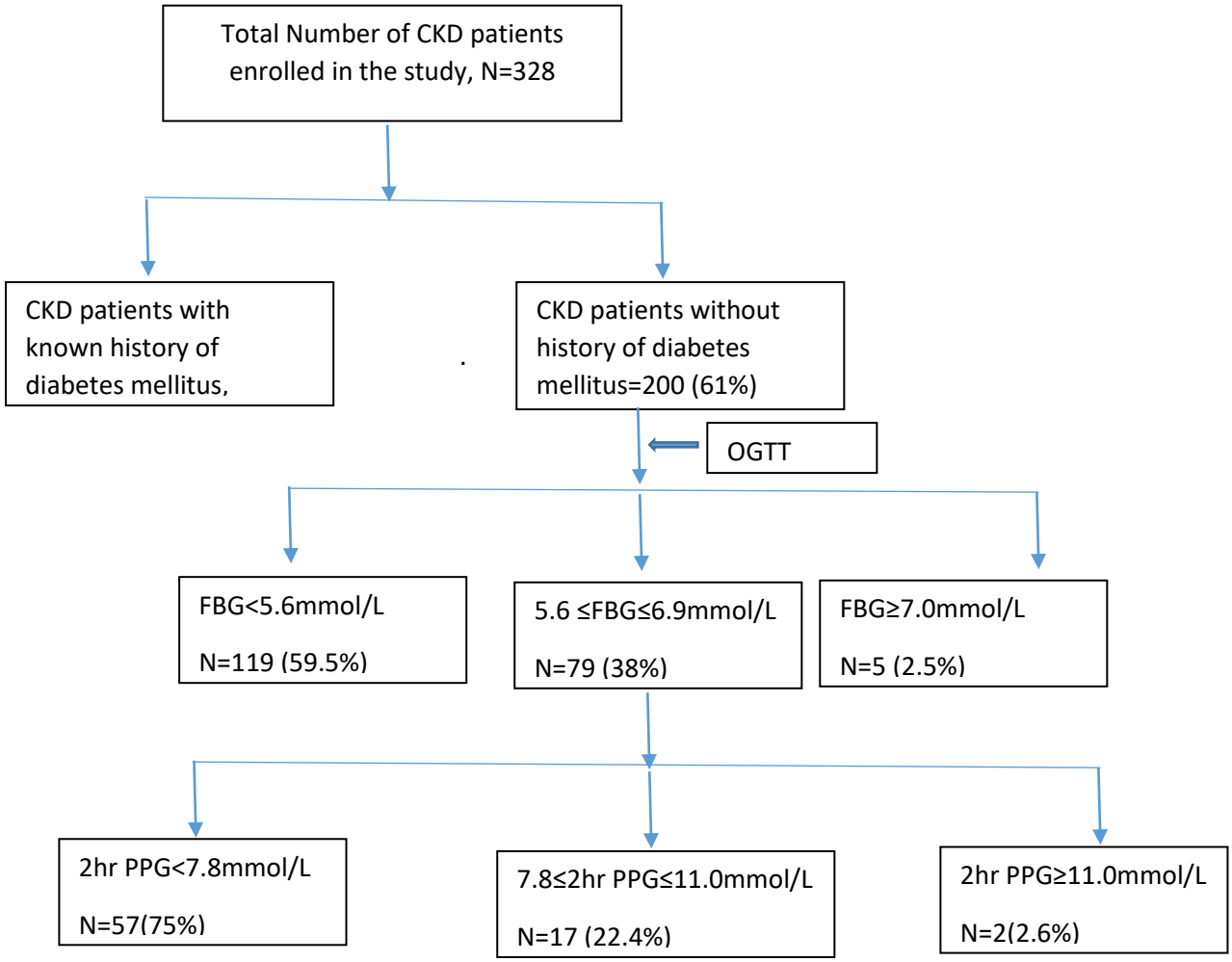

Reading	Result	Interpretation
FBG	<5.6 mmol/L	Normal
FBG	5.6 mmol/L - <7.0 mmol/L	Impaired Fasting Glucose (IFG)
FBG	≥7.0 mmol/L	Diabetic
2HR PPG	<7.8 mmol/L	Normal
2HR PPG	7.8 mmol/L - <11.0 mmol/L	Impaired Glucose Tolerance (IGT)
2HR PPG	≥11.0 mmol/L	Diabetic

Figure 1. Flow chart for showing recruitment and a table depicting categorization of CKD patients by OGTT

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Further analysis revealed that of the 128 patients with established diabetic mellitus: 7 (2.1%) had hypoglycemia while 20 (15.6%) reported having consistently normal blood glucose levels despite being off medication (oral hypoglycemic/injectable insulin) for some time. This paradoxical phenomenon is recognized as "burnt-out" diabetes. Conversely, of 200 patients (who had no history of having diabetes mellitus, 7(3.5%) were found to have diabetes mellitus at the time we conducted this study (Fig 2). These "newly" diagnosed diabetics were immediately counseled on their condition and were duly referred to the MNH Diabetes Clinic diabetes clinic to commence on standard management and follow up as per our local guidelines (Table 2).

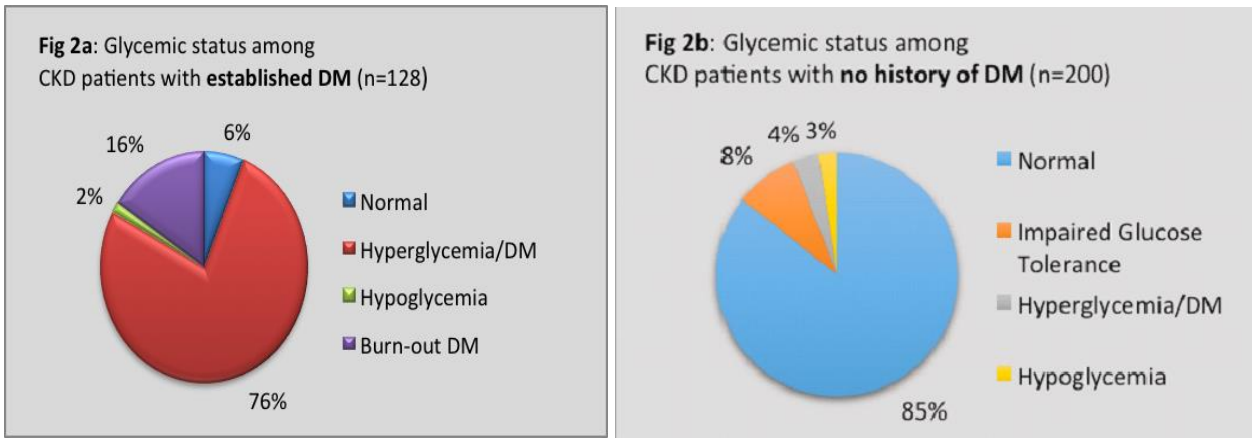

Figure 2. Glycemic status among patients with CKD with (a) and without (b) history of DM (N=328)

Univariate and Multivariate Analysis on Factors Associated with Dysglycaemias

In univariate analysis having; advanced age, male gender, high BMI, hypertension, family history of diabetes mellitus and being on Vitamin D supplementation were all associated with an increased risk for developing dysglycaemias. However, upon multivariate analysis; being old (50 years or more) (OR 2.92(1.71 - 4.99)), having hypertension (OR 2.96 (1.25 – 7.02)) as well as having a positive family history of diabetes (OR 7.98(3.74 – 17.02)) remained as strong independent factors associated with high odds for developing dysglycaemias (Table 2).

Table 2: Univariate and Multivariate Analysis for Factors Associated with Dysglycaemias (N=328)

Predicator	Status	n (%)	Crude OR (95% C.I)	Adjusted OR (95% C.I)
Age	≤50 years	44 (29.5)	1.00 (ref)	
	>50 years	105 (70.5)	3.72 (2.34-5.90)	**2.92 (1.71-4.99)**
Gender	Male	101 (5.02)	1.66 (1.06 – 2.62)	1.2 (0.69 – 2.10)
	Female	48 (37.8)	1.00 (ref)	
Body Mass Index	<25 Kg	68 (45.6)	Ref	
	≥25 Kg	81 (54.4)	1.73 (1.12 – 2.68)	1.54 (0.91 – 2.60)
Hypertension	No	10 (6.7)	1.00 (ref)	
	Yes	139 (93.3)	3.38 (1.61-7.08)	**2.96 (1.25-7.02)**
Family history of diabetes mellitus	No	94 (63.1)	1.00 (ref)	
	Yes	55 (36.9)	7.47 (3.88-14.39)	**7.98 (3.74-17.02)**
Vitamin D supplementation	Yes	35 (23.5)	1.98 (1.12 – 3.52)	1.96 (0.85 – 4.53)
	No	114 (76.5)	1.00 (ref)	

Discussion

In this study, we report that at recruitment, over half of our study participants had had CKD (eGFR<60ml/min) for over 6 months or more of whom more than three-quarters (75.9 %) were already in End Stage Renal Disease (i.e. eGFR< 15ml/min). We found that hypertension was the most prevalent comorbidity and that about half of the patients presented with dysglycaemias including those with “burnt-out” diabetes mellitus. Having advanced age, hypertension and a positive family history of diabetes mellitus were independently associated with developing dysglycaemias.

We found that about two-fifth of patients in this cohort had established (known) diabetes mellitus and from the remaining three-fifth without known history of diabetes mellitus, we diagnosed a small proportion (3.5%) of newly (i.e. previously unknown) diabetes mellitus patients. Comparatively, this proportion is lower than 20.7% reported in a similar study in the USA by Platinga et al (20). The discrepancy observed between our finding and the prevalence from western countries might be stemming from the fact that diabetes mellitus is the most common underlying cause of CKD in the western world whereas hypertension is the most common underlying cause of CKD in sub-Saharan Africa (21).

Further, we found that 5.5% of the participants with known diabetes mellitus had hypoglycemia. This incidence is almost half of that reported from a similar study in USA in which the incidence rate of hypoglycemia among patients with CKD with DM was reported to

be 10.72 per 100 patient months (22). Tendency of developing hypoglycemia among patients with CKD is largely due to reduced renal and hepatic insulin clearance, decline in renal gluconeogenesis, deficient catecholamine release, reduced food intake, and glucose clearance following dialysis treatment (23). Several physiological studies have shown that hypoglycemia is associated with acute and transient decline in GFR and renal plasma flow (24) and this could possibly worsen an already pre-existing renal dysfunction.

In this study, we found 15.6% of the participants to have “burnt out diabetes”. Our finding is comparable to a burnt out diabetes prevalence of 18.6% among adult patients in hemodialysis reported by Abe *et al* in Japan (25). Burnt out diabetes refers to the normalization of the glucose levels in diabetic patients with CKD resulting in cessation of hyperglycemia. This occurs following decreased insulin clearance by the failing kidneys and especially so, among ESRD patient undergoing hemodialysis therapy as, due to increased glucose clearance during the dialysis process. When not identified early enough, burnt-out diabetes could possibly increase the risk of hypoglycemic episodes among diabetic patients with CKD.

We found that age above 50 years (regardless of gender), a positive family history of diabetes and having hypertension were independent factors associated with poor glycemic control. Age is an already established risk factor for both diabetes and CKD (26). A previous study has reported advanced age to be associated with glucose intolerance in both gender (27). In this study, we further found that a positive family history of diabetes has been reported to be significantly associated with poor glucose control which mirrors what another study has reported earlier (28). In addition to increasing the risk of diabetes, a previous study has reported a 25% increased risk of impaired glucose tolerance among patients with CKD with a positive family history compared to those without (29).

In this study, we found that having hypertension is independently associated with poor glycemic control. Hypertension has been shown to have a substantial overlap with diabetes and the two conditions frequently occur together (30). Gress et al. found that the risk of developing Type 2 DM was about 28% higher among hypertensive patients on beta blockers (31). The Hong Kong Cardiovascular Risk Factor Prevalence Study reported 44% of patients with hypertension had poor glycemic control (32). In the USA, hypertension was found to occur in 30% and 50-80% among patients with Type 1 DM and Type 2 DM, respectively (33).

The strengths of this study are several folds. Firstly, the systematic sampling method employed in obtaining the sample size was robust enough and truly represents the cross-

sectional population of patients with CKD that we attend to in our routine clinics. Secondly, the impaired glucose tolerance was tested using the OGTT, which is a standard test for the determination of serum glucose intolerance.

Notwithstanding the strengths above, we acknowledge the limitation that this study was conducted in a specialized center at a tertiary hospital, a setting that offers specialized care to kidney disease and diabetes mellitus patients and therefore might not truly represent the set-ups across the country (as specialized care is still scarce elsewhere). Further, we did not do a subgroup analysis to cater for the differences observed within our different CKD groups which could have shed more insight into CKD stage-specific observations.

In conclusion, this study has revealed that dysglycaemias are prevalent in patients with CKD in Tanzania among patients aged 50 years and above, patients with positive family history of diabetes as well as those with hypertension.

Declarations

Ethics approval

Ethical clearance was obtained from the Institutional Review Board of Muhimbili University of Health and Allied Sciences (MUHAS). Permission was obtained from the Muhimbili National Hospital (MNH) to have access to her patients and premises to conduct this study.

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Competing interests

The authors declare no competing interests

Author contributions

NS, RP, JL, FF and MJ conceptualized the study and the study design, data collection, statistical analyses, data interpretation, and writing this manuscript.

EM was involved in the edition of the manuscript, CP and KA contributed with proofreading of the manuscript and overall supervision of the work.

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