Evaluation of risk factors associated with nephropathy in type 2 diabetic patients in Rwanda

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Abstract—

Background: *Diabetic nephropathy is an emerging clinical and public problem and is related with poor outcomes such as heart failure, and end stage renal disease. In the Rwanda countryside there are no recent studies on renal complications.*

Objective: *To evaluate risk factors associated with nephropathy in Type 2 diabetic patients in Rwanda.*

Methods: *A case-control study was conducted from January to September 2019 in four hospitals of Republic of Rwanda. Diabetic patients were screened for nephropathy by measuring microalbuminuria. Those with microalbuminuria were the cases and those patients free of nephropathy were the controls. The study sample had 592 participants, 83 cases and 509 controls enrolled. Plasma glucose was measured by enzymatic colorimetric test. HbA_{1c} test was performed using the unique procedure of Bio -Rad Variant II. Albuminuria was measured by quantitative method using spectrophotometer. Total plasma cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, Urea and Creatinine were assayed by colorimetric methods using commercial kits. A questionnaire was used to assess other risk factors such as alcohol consumption, smoking, level of physical activity, family history of T2DM, obesity, stress, and demographic status. The data was analyzed on SPSS version 20. Statistical analysis was performed by Chi square to show association in nominal and ordinal data. Multivariate logistic regression analysis to select independent variables was performed. Odds ratio was used as measure of association.*

Results: *In this study the prevalence of Diabetic nephropathy was 14%, (microalbuminuria was 12.5% and macroalbuminuria 1.5%). The major independent risk factors associated with diabetic nephropathy were male gender, long duration of type 2 diabetes (≥16 years), elevated HbA_{1c} (> 7.5%) , poor adherence to diabetic medication, elevated creatinine (> 1.2 mg/dl), and lower level of education.*

Conclusion: *Management of those modifiable risk factors of nephropathy could reduce its incidence in diabetic patients.*

Keywords— *Type 2 Diabetes Mellitus, Nephropathy, Risk Factors, Rwanda.*

I.   INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is a syndrome characterized by persistent hyperglycemia and other abnormalities of metabolism, resulting from defective insulin secretion by the pancreas, insulin action, or sometimes both [1].

Diabetes is the single major cause of chronic kidney disease leading to the end-stage renal disease (ESRD) [2]. Diabetic nephropathy (DN) is an emerging clinical and public problem and is related with poor outcomes such as heart failure, and ESRD [3]. Deaths related to these severe complications decrease life expectancy [4] in particular in most African countries [3].

DN is the cause of about 40% of end-stage renal disease in USA and Europe. Clinically DN is characterized by albuminuria (> 300 mg/day or 200 μg/min), decreased glomerular filtration rate (GFR) [2] and hypertension. Microalbuminuria (MA) is considered to be an early marker of DN and predictor for cardiovascular disease [4].

In Africa, about 32 to 57% of type 2 diabetic patients have microalbuminuria and macroalbuminuria after 5 to 10 years of diagnosis. Albuminuria is an indicator of poor renal outcomes in type 2 diabetics [4]. In Rwanda the prevalence of T2DM is about 3.16% of the population, and mortality 2% per annum [5]. In the countryside T2DM in slim adult is higher [6]. In the Rwanda countryside there are no recent studies on renal complications. Based on studies done in Kigali University Teaching Hospital, 20.4% of the patients with renal failure requiring haemodialysis suffered from T2DM [7]. The aim of this study was to evaluate the risk factors associated with nephropathy in type 2 diabetic patients in Rwanda.

II.   METHODS

2.1   Study design

A case-control study was conducted from January 2019 to September 2019 in four hospitals of Rwanda namely: Kabgayi district hospital, Kabutare district hospital, Ruhengeri hospital and University Teaching Hospital of Butare. The patients were recruited from ongoing routine diabetes clinic attendance of the participating hospitals. They were consecutively consented to the study and informed consent obtained from the patients. Participants were screened for nephropathy by measuring microalbuminuria, Patients positive for microalbuminuria were the cases and patients free of nephropathy were controls. Of the 592 participants, 83 were cases and 509 controls.

2.2   Study population

The study population was all diabetic patients receiving healthcare at the four mentioned hospitals in Rwanda. The inclusion criteria were as follows: Have type 2 diabetes and aged 25 years and above, and with fasting plasma glucose above 7.0 mmol/l, be on regular oral antidiabetic drugs for at least 6 months, and be willing to give informed consent and able to communicate orally.

2.3   Study tool

Participants were identified through diabetic patient cards and registries. The patients were questionnaire interviewed by the investigator on medical history, socioeconomic information and physical examination performed. Results of the interview and laboratory findings were documented and collected.

2.4   Study procedure

Morning urine and blood specimens were collected and labeled accordingly. Plasma glucose was determined by spectrophotometry (Abbott kits, Germany). Glycated hemoglobin was determined by colorimetric enzyme test (Glycohemoglobin $HbA1_C$ liquicolor test kit, Human campany, Germany). Samples were measured by Humastar 80 (Human, SN 20888, 2011, Germany).

Serum urea, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured using colorimetric test kits (Human campany, German). Values were determined by measuring the increase in absorbance at a wave length of 546 nm, 510 nm, 545nm, 546 nm, 600 nm and 545 (Humastar 80 2000; Human, SN 20888, 2011Germany) respectively.

Albuminuria was determined quantitatively by spectrophotometry. For positive albuminuria tests, urinalysis, full blood count, erythrocytes sedimentation rate were performed to exclude other causes of albuminuria. Urine specimens with urinary infection were not confirmed for albuminuria. For those participants albuminuria was repeated 1 month later.

Blood pressure was determined using a digital sphygmomanometer (AMRON, MI plus, Hem- 4011C-E, China). Body Mass index (BMI) was calculated as follows: BMI= Body weight (Kg)/ Height (m^2).

2.5   Ethical consideration

The study was approved by the College of Medicine and Health Sciences, University of Rwanda (no. 288/CMHS IRB/2018.) and Kenyatta National Hospital/University of Nairobi (Ref.KNH/ERCA3), Institutional Review Boards before commencement.

2.6   Data analysis

Data was analyzed on SPSS version 20. Statistical analysis to determine interactions of risk factors was performed by Chi square (x^2). Multivariate logistic regression analysis was performed to pick independent variables. Odds ratio (OR) was used as measure of association.

III.   RESULTS

Of the 592 type 2 diabetic participants, 509 were controls and 83 cases. The mean age, for controls and cases were 56.12 years (SD ± 11.68, CI 95%) and 56.72 years (SD ±11.15 CI 95%) respectively. The minimum and maximum for age were 26 and 89 years in control group, while in case group, they ranged between 34 and 85 years. Thirty four (40.7%) of cases and 163 (32.02%) of controls were males. 49 (59.03%) of cases and 310 (60.90%) of controls lived in the rural area.

TABLE 1
AGE, GENDER, ANTHROPOMETRIC MEASURES AND DIABETIC NEPHROPATHY

Risk factor/Outcome			Diabetic Nephropathy				Total	χ^2	95%	p
			83 Cases	%	509 Controls	%				
Age		25 - 34	0	0.0	14	100	14	26.147	95%	0.000
		35 - 44	5	6.6	71	93.4	76			
		45 - 54	13	8.5	140	91.5	153			
		55 - 64	30	14.5	177	85.5	207			
		65 and above	35	**25.7**	101	74.5	136			
BMI		< 18.5	4	12.9	27	87.1	31	0.801	95%	0.849
		18.5 - 24.9	43	15.2	240	84.8	283			
		25 -29.9	26	13.5	166	86.5	192			
		30 - 34.9 and above	10	11.6	76	88.4	86			
Waist circum.		Lower risk (< 94 cm in men, < 80 cm in women)	37	13.6	236	86.4	273	0.672	95%	0.715
		Increased risk (94 – 102 cm in men, 80 -88 cm in women)	19	16.4	97	83.6	116			
		Substantially increased risk (> 102 cm in men , > 88 cm in women)	27	13.3	176	86.7	203			
			Cases		Controls		Total	OR	CI	P
Gender		Male	34		163		197	1.473	95%	0.0109
		female	49		346		395			
Waist : Hip Ratio		Lower risk	28		130		158	0.674	95%	0.118
		Increased risk	55		379		434			

Table 1 shows age, gender and anthropometric variables. In univariate analysis, advanced age of 65 and above was associated with Diabetic nephropathy (25.7 % of DN, χ^2 = 26.47, p 0.000). Male gender was 1.473 times more at risk of diabetic nephropathy (OR 1.473, p 0.0109) compared to female.

TABLE 2
MEDICAL RISK FACTORS AND NEPHROPATHY

Risk Factor/Outcome		Diabetic Nephropathy			OR	CI	P
		cases	controls	Total			
Hypertension	yes	56	256	312	2.05	95%	0.004
	no	27	253	280			
Stress	yes	44	223	267	1.45	95%	0.064
	no	39	286	325			
Alcohol consumption	yes	66	336	402	1.99	95%	0.015
	no	17	173	190			
Smoking	yes	26	110	136	1.65	95%	0.05
	no	57	399	456			
T2DM in the fam.	yes	24	140	164	1.072	95%	0.97
	no	59	369	428			
Abandonment of treatment	yes	17	60	77	1.928	95%	0.029
	no	66	449	515			
Soft drink	yes	24	175	199	0.776	95%	0.328
	no	59	334	393			
		Cases	Controls	Total	χ^2	CI	P
DurationT2DM	½ - 5	25	327	352	64.678	95%	0.000
		7.1%	92.9%				
(years)	6 - 10	23	128	151			
		15.2%	84.8%	1			
	11 - 15	20	38	58			
		34.5%	65.5%				
	≥ 16	15	16	31			
		48.4%	51.6%				

Table 2 above shows variables of medical history studied in this study. In univariate analysis hypertensive participants had 2 times the risk of developing diabetic nephropathy (OR 2.02, p 0.004) compared to non-hypertensive participants. Participants with history of alcohol consumption had 1.99 times the risk of developing diabetic nephropathy compared to participants who did not (OR 1.99, P 0.015). Participants, who smoked, had 1.65 times the risk of developing diabetic nephropathy (OR 1.65, p 0.05) compared to non-smokers. Participants who regularly did not take oral anti-diabetic drugs were 1.928 times more at risk of diabetic nephropathy (OR 1.928, p 0.029). Having T2DM in a period of 16 years and above was associated with diabetic nephropathy (48.4% of DN, χ^2 = 64.678, p 0.000).

Table 3 below shows the association between socio- demographic variables, physical activity and diabetic nephropathy. In univariate analysis, being a widow was associated with diabetic nephropathy (21.2% of DN, χ^2 = 10.787, p 0.029). Illiteracy and retirement were associated with Diabetic nephropathy (21.3% of DN in illiteracy group, χ^2 = 9.871, p 0.02, and 30.6% of DN in retired group, χ^2 = 13.992, p 0.016).

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TABLE 3
SOCIO – DEMOGRAPHIC RISK FACTORS AND NEPHROPATHY

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Risk factor/Outcome		Diabetic Nephropathy				Total	χ^2	95%	p
		cases	%	controls	%				
Marital status	single	0	0.0	17	100.0	17	**10.787**	95%	**0.029**
	married	54	12.8	367	87.2	421			
	divorced	0	0.0	8	100.0	8			
	separated	1	7.1	13	92.9	14			
	widowed	28	21.2	104	78.8	132			
Education	**none**	23	21.3	85	78.7	108	**9.871**	95%	**0.02**
	primary	45	14.3	270	85.7	315			
	secondary	15	10.0	135	90.0	150			
	university	0	0.0	19	100.0	19			
Residence	town	26	12.7	179	87.3	205	5.334	95%	0.149
	agglomeration	8	28.6	20	71,4	28			
	village	36	14,0	222	86.0	258			
	isolated	13	12.9	88	87.1	101			
Profession	cultivator	49	15.5	267	84.5	316	**13.992**	95%	**0.016**
	employed	3	6.4	44	93.6	47			
	private	13	12.4	92	87.6	105			
	retired	11	30.6	25	69.4	36			
	student	0	0.0	1	100	1			
	unemployed	7	8.0	80	92.0	87			
Transport	public	5	10.0	45	90.0	50	1.933	95%	0.586
	private	2	28.6	5	71.4	7			
	motor/bicycle	10	13.7	63	86.3	73			
	on foot	66	14.3	396	85.7	462			
		Cases		Controls		Total	OR	CI	P
History of exercise	yes	36		233		269	0.907	95%	0.684
	no	47		276		323			

Table 4 shows the association between biomarkers and diabetic nephropathy.

Hyperglycemia was associated with diabetic nephropathy (20.2% of DN, χ^2 14.143, p 0.001. $HBA_{1C} > 7.5\%$, and positive C-Reactive Protein were associated with diabetic nephropathy ($HBA_{1C} > 7.5\%$, 39.3 % of DN, χ^2 98.767, p 0.000, and in positive CRP diabetic group 24.1 % had DN, χ^2 14.344, p 0.000). High levels of plasma creatinine and serum urea were associated with DN, (in the category with high creatinine 37.5% had DN, χ^2 37.487, p 0.00, while in the category with high urea 30.3% had DN, χ^2 7.686, p 0.006).

TABLE 4
BIOMARKERS AND T2DM NEPHROPATHY

Biomarkers/ Outcomes		Diabetic Nephropathy				Total	χ^2	P
		cases	%	controls	%			
Blood glucose (mg/dl)	70 - 126 normal	34	10.2	300	89.2	334	**14.143**	**0.001**
	< 70 hypoglycemia	0	0.0	15	100.00	15		
	> 126 hyperglycemia	49	20.2	194	79.8	243		
HbA1c	< 6.5 % optimal	18	5.1	336	94.9	354	**98.767**	**0.000**
	6.5 - 7,5% fair	10	10.2	88	89.2	98		
	> 7.5% poor	55	39.3	85	60.7	140		
Creatinine: mg/dl	0.5 -1.2 normal	56	10.8	456	89.2	520	**37.487**	**0.000**
	> 1.2 high	27	37.5	46	62.5	72		
urea: mg/dl	10 -50 normal	73	13.1	486	86.9	559	**7.686**	**0.006**
	> 50 high	10	30.3	23	69.7	33		
Total cholesterol (mg/dl)	< 200 Normal	62	14.5	366	85.5	428	0.288	0.866
	200 -239 Borderline high	12	13.0	80	87.0	92		
	> 240 High	9	12.5	63	87.5	72		
HDL Cholesterol (mg/dl)	< 40 low	21	11.9	156	88.1	177	0.982	0.612
	40 - 60 normal	54	15.0	306	85.5	360		
	> 60 high	8	14.5	47	85.5	55		
LDL cholesterol (mg/dl)	< 130 normal	69	15.0	390	85.0	459	5.217	0.157
	130 – 159 borderline high	5	6.1	77	93.9	82		
	160 – 189 high	6	17.6	28	82.4	34		
	>190 very high	3	17.6	14	82.4	17		
Triglycerides (mg/dl)	40 – 160 normal	54	13.1	357	86.9	411	0.991	0.609
	>160 – 200 Borderline high	12	15.0	68	85.0	80		
	> 200 high	17	16.8	84	83.2	101		
C reactive protein	negative	51	11.1	408	88.9	459	**14.344**	**0.000**
	positive	32	24.1	101	75.9	133		

In multivariate analysis, male sex (OR: 2.442, p 0.015), advanced age (p value 0.0367), lack of good adherence to oral andiabetic drugs (OR 2.404, p 0.0201), profession (retirement) (p 0.003), long duration of type 2 diabetes (p 0.009), low education (OR 1.635, p 0.0179), uncontrolled HbA_{1C} (OR 3.195, p 0.000), elevated creatinine (OR 3.148, p 0,007) were statistically significant associated with diabetic nephropathy.

TABLE 5
MULTIVARIATE ANALYSIS (RISK FACTORS AND DIABETIC NEPHROPATHY)

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1ª	Sex	.893	.366	5.939	1	**.015**	2.442
	Age			9.425347	4	0.051304	
	Age(1)	-19.1113	8531.207	5.02E-06	1	0.998213	0.000
	Age(2)	-0.86197	0.588461	2.145584	1	0.142981	0.422
	Age(3)	-1.28317	0.435099	8.697408	1	**0.003187**	0.277
	Age(4)	-0.73273	0.350765	4.363741	1	**0.036712**	0.481
	PROFESSION	-.279	.095	8.615	1	**.003**	.757
	GhycoHB			44.195	2	**.000**	3.195
	GhycoHB(1)	-2.157	.338	40.801	1	.000	.116
	GhycoHB(2)	-1.625	.427	14.517	1	.000	.197
	CREATININ_R	1.147	.424	7.307	1	**.007**	3.148
	Urea	-.700	.598	1.371	1	.242	.496
	CRP	.530	.319	2.768	1	**.096**	1.700
	Educ_r2	.491	.365	1.808	1	**.0179**	1.635
	DURATION_R			11.686	3	**.009**	
	DURATION_R(1)	-1.695	.538	9.905	1	.002	.184
	DURATION_R(2)	-1.438	.547	6.908	1	.009	.238
	DURATION_R(3)	-.750	.575	1.700	1	.192	.472
	TTTABANDON	0.876938	0.37741	5.398974	1	**0.020149**	2.404
	M_status			4.208	3	.240	
	M_status(1)	-18.651	9.355E3	.000	1	.998	.000
	M_status(2)	-.767	.382	4.020	1	.045	.465
	M_status(3)	-.936	1.111	.711	1	.399	.392
	ALCOHOL	.117	.351	.112	1	.738	1.125
	HYPERTENSION	.353	.325	1.186	1	.276	1.424

a. Variable(s) entered on step 1: Sex, Age, Ttt Abandonment, Profession, Ghycosylated HB, Creatinine, Urea, CRP, Education,, Duration of diabetes, M_status, Alcohol, Hypertension.

IV.   DISCUSSION

In the present study the prevalence of Type 2 diabetic nephropathy was 14%, much lower than what was found in a study conducted in Botswana (44.6%, [8]). A recent study reported 30.1% prevalence of type 2 diabetic nephropathy in Pakistan [9]. The prevalence found in Rwanda is also slightly lower than that found in Tanzanian another study that reported 17% [10]. These studies were conducted in a single setting, while the current one was conducted in four hospitals and may therefore be said to be more representative of the country population.

In the present study, the univariate analyses for hypertenstion and alcohol consupmtion were associated with diabetic nephropathy compared to multivariate logistic regression analyses which were not. The lack of statistical association between hypertension and diabetic nephropathy here is similar to an earlier study conducted in Oman [11]. However previous other studies reported the independent association between hypetension and diabetic nephropathy [12;13]. This may be attributed to various factors such as the age of participants which was in the range of 40-60 years [12] and 40-74 years [13], compared to the present study where the range was 26-89 years.

The present study showed that the male gender is independently associated with diabetic nephropathy, which is similar to what previous studies found [14;15]. It is already documented that gender is an important factor influencing the use of outpatient health services in Rwanda where females are more likely to visit outpatient services compared their male counterparts [16]. As a consequence, some male diabetic patients tend to visit the hospital when complications have already

set in. The duration of type diabetes mellitus was an independent risk factor associated with diabetic nephropathy in the current study similar to a previous study [17]. In this study there was increased chance of developing diabetic nephropathy after 16 years of being diagnosed with type 2 diabetes.

This study also found that poor adherence to diabetic medication was associated with nephropathy, similar to previous studies [18; 19]. Poor adherence to medication nullifies the power and efficacy of a drug to reduce glycemia thus resulting in chronic hyperglycemia and in turn chronic hyperglycemia which consequently cause the events leading to diabetic nephropathy. The lack of schooling as an indicator of low social economic status is known to be associated with many chronic diseases. Diabetic patients with lack of education have lower utilization rates of follow-up care and associated benefits, which could result in poor outcomes such as the development of nephropathy [20; 21]. The lack of education may also contribute to poor adherence to diabetic medication. In this study, the highest percentage of diabetic nephropathy was associated with advanced age of 65 years and above, this being in an age group who had limited chances of attending school because only few were available during their childhood. Elderly patients with no schooling have less knowledge about importance of adherence to treatment in controlling diabetes.

In the present study obesity (classified as high BMI) and dyslipidemia were not associated with diabetic nephropathy. This was attributed to general population fitness, where the majority of the patients came to hospital on foot and are in general of ectomorph body constitution. Inadequate glycemic control was found to be a major risk factor for the development and progression of diabetic nephropathy. This is similar to other studies that in turn found chronic uncontrolled glycemia (indicated as high HbA1c) levels, to be associated with an increased risk for developing nephropathy [22, 23].

Elevated plasma creatinine was found to be an independent factor associated with diabetic nephropathy. In this study microalbuminuria was a major biomarker of diabetic nephropathy. This observation was similar to a previous study [24]. Another study conducted inTanzania among type 1 and type 2 diabetic patients reported similar outcomes [10]. This study found that by logistic regression analysis there was association between C- Reactive Protein and diabetic nephropathy but not in multivariate analysis. This association cannot be easily dismissed because it may emphasize the role of C – Reactive Protein in the progression of diabetic nephropathy. An important role of human CRP in Type 2 diabetic kidney disease has been reported in mice which developed progressive kidney injury, higher levels of hyperglycemia, microalbuminuria as well as renal fibrosis [25].

V.   CONCLUSION

The prevalence of diabetic nephropathy based on levels of microalbuminuria in this study was 14% in type 2 diabetic patients. The major independent risk factors associated with diabetic nephropathy were male gender, long duration of disease, elevated glycosylated hemoglobin, poor adherence to diabetic medication, elevated creatinine, lower level of education and positive C- Reactive – Protein. It is expected that the management of these modifiable risk factors of diabetic nephropathy shall help significantly reduce its incidence or delay its onset thus impacting positively the quality of life of diabetic patients.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

There are no conflicts of interest.

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