Prevalence of chronic kidney disease using estimated glomerular filtration rate among diabetes patients attending a tertiary clinic in Botswana

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ABSTRACT

Background and aims: Diabetes mellitus (DM) is one of the most common contributors of chronic kidney disease (CKD). The epidemiology of CKD, a concern among patients with DM, has not been studied in Botswana. The aim of this study was to estimate its prevalence among these patients to provide future guidance to both government personnel and physicians. *Methods:* Observational cross-sectional study in a leading clinic in Botswana. Demographic and clinical data were obtained from patients through interviews and from their notes using a standard questionnaire. The study was conducted from July to October 2015. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet for Renal Disease equation. CKD was defined as an eGFR < 60 ml/min/1.73m2. Multivariable logistic regression analyses were performed to assess the associations between CKD and potential factors. *Results:* Mean age and duration of diabetes mellitus among study participants were of 54.67 years (range 21-92 years) and 5.0 years respectively. Over half, i.e. 213/370 (57.6%) and 232/370 (62.7%), had an average blood pressure greater than 140/90mmHg and poor glycemic control (HbA1c >7%) respectively. 31/370 patients (8.4%) had CKD. However, only 18/370 (4.9%) had a diagnosis of CKD documented in their charts. Age, level of education, and duration of diabetes were independently associated with CKD. *Conclusion:* The prevalence of CKD by estimated eGFR was low compared to most previous studies. However, half of patients with CKD are not documented resulting in potential prescription errors and drug toxicity. A substantial number of patients had uncontrolled hypertension and poor glycemic control. Older age, low level of education and longer duration of DM were associated with CKD. There is a need to carry

out prospective studies to determine the association and role of glycemic and blood pressure control in CKD causation among patients with DM in Botswana.

1. INTRODUCTION

Diabetes mellitus (DM) is of major public health importance as it poses a considerable threat with its growing prevalence and implications on morbidity, mortality, and costs, due to both microvascular and macrovascular complications if not adequately addressed [1-5]. DM also appreciably impacts on the quality of life of patients [6-8]. Approximately 415 million people worldwide had DM in 2015, with the number expected to appreciably increase to approximately 640 million by 2040 [9,10]. There is currently a global disproportionate burden of DM, with the highest rates now found in Africa and Asia [10]. Sub-Saharan Africa presents a higher rate of DM burden with the number of people with diabetes expected to increase by more than 161% from 8 million in 2000 to 18 million by 2030 [10], with others suggesting the prevalence of diabetes in Africa is already 16 million [11].

Complications of DM appear more prevalent in Africa compared to developed countries due to a myriad of factors. These include late presentation, poor glycemic control, lack of diagnostics to screen for complications at early stages, and failure to treat complications at early stages [3, 12].

Chronic kidney disease (CKD) is one of the complications of diabetes [13]. Progression of CKD with lower estimated glomerular filtration rates also leads to constraints in the overall management of DM with oral hypoglycemic agents (OHA). Optimal glycemic control is not easy to achieve due to limited options of suitable OHAs in CKD patients outside of newer therapies such as the dipeptidyl peptidase-4 (DPP-4) inhibitors [14,15]; consequently, the tendency is to prescribe insulin as CKD progresses towards end-stage renal disease (ESRD) [16, 17]. Despite the fact that insulin is metabolized by the kidney, with a resulting decline in renal function being a risk for hypoglycemia, it is still safe to use insulin in Type 2 DM patients as titration to lower doses is possible unlike the use of oral hypoglycemic agents, which are usually only available in fixed dose combinations.

CKD is increasingly becoming a global epidemic. According to World Health Organization (WHO), there were approximately 220 million people globally with CKD in 2012 [18]; the majority of which are attributed to DM followed by hypertension [18-20]. DM and kidney disease are independent risk factors for cardiovascular events. When the two occur together, the risk for cardiovascular morbidity and mortality is increased by more than if these events were to occur separately [16, 18]. In a study undertaken in the USA, there was an increase of 19-40% of cardiovascular events as glomerular filtration rate declined from normal ranges to below 45m L/min/1.73m^2 [21].

According to the 2012 Kidney Diseases Improving Global Outcomes (KDIGO) guidelines, CKD is defined as abnormalities of kidney structure or function that persist for over three months. In the same regard, abnormal function is defined as estimated GFR < 60 ml/min/1.73m^2, whereas markers of kidney damage include albuminuria, renal tubular disorders, abnormal urinary sediments, biopsy findings, and structural abnormalities on imaging [22]. Early diagnosis of CKD is of paramount importance due to the fact that appropriate management can be instituted to prevent deterioration to ESRD, which requires renal replacement therapy which is very expensive [23-26] and ultimately associated with poor quality of life. CKD itself is also associated with reduced health-related quality of life [27,28].

Previous studies have linked several sociodemographic and clinical variables to the occurrence of CKD in DM. Specifically factors that have consistently been associated with higher rates of CKD include older age, male sex, African-American ethnicity, obesity, family history of CKD, diabetes mellitus and hypertension [29, 30]. Despite the high burden of DM and its complications in Africa, there is currently limited literature on the complications of DM including CKD in this continent. Consequently, this study was conducted to determine the prevalence of CKD using estimated glomerular filtration rate (e GFR) in a leading clinic setting in Botswana, as well as elicit possible factors associated with CKD, to provide future guidance not only to better manage DM patients in Botswana to reduce CKD but also potentially wider.

2. MATERIALS AND METHODS

2.1 Study design, setting, population:

This was a descriptive observational cross-sectional study undertaken in a tertiary clinic in Gaborone, the capital city of Botswana. However, this clinic also operates as a primary care centre because almost all the patients with DM in Gaborone are treated at this clinic. Consequently, the clinic can provide a representational sample of the DM patients within Botswana.

A cohort of 380 patients was randomly selected and interviewed between July 2015 and September 2015. Clinical and laboratory data were obtained from patients' charts and Integrated Patients Management system (IPMS). Details of the study design including the number of patients enrolled, the setting, population and a description of the sociodemographic and clinical characteristics of these patients have been described in previous publications [6, 8,]. For the purpose of this study, the most recent laboratory results of serum creatinine that was within six (6) months of patients' recruitment was recorded for the purpose of calculating patients' renal function in the form of estimated glomerular filtration rate (e GFR).

The study was approved by Ethical Review Boards of University of Botswana, Princess Marina Hospital and Ministry of Health Botswana.

2.2 Data collection

From the cohort of 380 patients recruited in the primary study [8], 10 patients were excluded as they had missing serum creatinine in IPMS; consequently, 370 patients were included in the final analysis. In 2015, serum creatinine was measured using Beckman Coulter AU680 clinical chemistry machine (CA, United States) calibrated by modified Jaffe method. Frequency of calibration is daily and is accomplished by the use of chemistry calibrator (Cat $# DR0070), which is traceable to an isotope dilution mass spectrometry (IDMS) reference method using the National Institutes of Standards and Technology (NIST) Standard Reference Material 967 [31].

Using serum creatinine levels, the estimated glomerular filtration rate for each patient was computed according to the equation of modification of diet in renal disease (MDRD): eGFR = 186 × (serum creatinine × 0.0113)–1.154 × (age)–0.203 × (0.742 if female) [32], where eGFR is measured in ml/min per 1.73m^2, creatinine is in µmol/L, and age in years. Patients were then categorized to have CKD if eGFR was < 60 ml/min per 1.73m2 and not to have CKD if eGFR was ≥ 60 ml/min per 1.73m^2 [22]. MDRD equation has not been validated for use in Botswana, however it was chosen because it is recommended by National Kidney Foundation [33]; as well its use in this study provides room for comparisons with other studies that used similar equation [34-36]

2.3 Measurements

The processes and criteria used to select and categorize different sociodemographic and clinical variables used in this this study has been described in detail previously [6, 8]. We chose the following variables to determine the association with CKD: age, gender, level of education, marital status, body mass index, type of DM, duration of diabetes, modality of treatment for DM, glycemic control, blood pressure control and HIV status. HIV status is important in sub-Saharan countries such as Botswana given its high prevalence rate as well as high prevalence of patients with both HIV and DM [6]. Consequently, potentially a very different population to Western countries.

2.3 Data analysis

The analysis was performed by SPSS version 22 statistical software. We obtained proportions for the study participants' sociodemographic and clinical characteristics and CKD – related status. Subsequently, we computed factors associated with CKD in previous studies using unadjusted logistic regression, with significant factors run in a separate multivariable adjusted regression to determine their independent association to CKD. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1 Sociodemographic and Clinical characteristics

Baseline sociodemographic and clinical characteristics of studied patients have been described in detail elsewhere [6,8]. Of importance to this study as regards to patients' characteristics is that the mean age of study participants was 56.47 years. Close to half of them had been diagnosed less than 5 years prior to recruitment, with a mean duration of diabetes of 5 years. 60.1% had poor glycemic control and 57.4% had uncontrolled hypertension [6,8]. On the other hand, 18/370 (4.9%) of our patients had documented evidence of kidney disease in their charts.

3.2 CKD prevalence

Among the study population, 31/370 (8.4%) had CKD categorized as eGFR < 60 mL/min/1.73m^2. Of note is the fact that, eGFR of > 90, 60-89, 30-59 (CKD stage 3) and 15-29 (CKD stage 4) mL/min/1.73m^2 accounted for 74.1%, 17.6%, 7.0% and 1.4% respectively. There was no recruited patient with end-stage renal disease (Table 1).

Table 1: Prevalence of chronic kidney disease among study participants

CKD status	Number (n)	Percent (%)
GFR < 60	31	8.4
GFR ≥ 60	339	91.6
Total	370	100
GFR ≥ 90	274	74.1
GFR 60-89	65	17.6
GFR 30-59	26	7.0
GFR 15-29	5	1.4
Total	370	100

3.3 Pattern of antidiabetic medication by stage of CKD

Metformin and glibenclamide were the most commonly prescribed oral hypoglycemic agents (OHAs) used by 309/370 (83.6%) of all patients, with only 4 patients using pioglitazone in addition to common OHAs. Use of insulin alone accounted for 51/370 of all patients. There was a high likelihood of patients being on insulin alone in CKD stage 4 (80%) compared to CKD 3 (26.9%) and estimated GFR of 60-89 and ≥ 90 where insulin alone was used by 7.7% and 12.8% respectively. This association was statistically significant (p value = 0.000) (Table 2).

Table 2: Pattern of antidiabetic medication prescription by stage of CKD

	Modality of diabetes mellitus treatment					
CKD status	Diet	Oral hypoglycemic agent (OHA)	Insulin	Both OHA and Insulin	Total	p-value
GFR ≥ 90	2	174	35	63	274	
GFR 60-89	1	37	5	22	65	
GFR 30-59 (Stage 3)	1	5	7	13	26	<0.0001
GFR 15-29 (Stage 4)	0	1	4	0	5	
Total	4	217	51	98	370	

Using the study definition of CKD, the association was also found to be statistically significant with either OHAs or OHAs/Insulin more likely to be used in patients without CKD (p value = 0.001) (Table 3).

Table 3: Association between sociodemographic and clinical characteristics to CKD

Variables	Without CKD (GFR ≥ 60) n (%)	With CKD (GFR<60) n(%)	Crude OR (95% CI)	p-value
Age			**0.297 (0.164-0.540)**	**< 0.0001**
21-35	30 (100%)	0 (0%)		
36-50	75 (97.4%)	2 (2.6%)		
51-65	152 (93.8%)	10 (6.2%)		
>65	82 (81.2%)	19 (18.8%)		
Gender			0.797 (0.345-1.841)	0.595
Male	103 (92.8%)	8 (7.2%)		
Female	236 (91.1%)	23 (8.9%)		
Level of education			**1.584 (1.157-2.172)**	**0.003**
No formal education	57 (82.6%)	12 (17.4%)		
Less than primary	70 (90.9%)	7 (9.1%)		
Primary school completed	94 (92.2%)	8 (7.8%)		
Secondary school completed	74 (98.7%)	1 (1.3%)		
College/ University	38 (92.7%)	3 (7.3%)		
Postgraduate completed	6 (100%)	0 (0%)		
Marital status			0.930 (0.753-1.144)	0.493
Never married	93 (94.9%)	5 (5.1%)		
Currently married	138 (90.2%)	15 (9.8%)		
Separated	2 (100%)	0 (0%)		
Divorced	13 (100%)	0 (0%)		
Widowed	65 (86.7%)	10 (13.3%)		
Cohabiting	28 (96.6%)	1 (3.4%)		
Body Mass Index (BMI)			0.993 (0.626-1.575)	0.975
Underweight	5 (100%)	0 (0%)		
Normal weight	57 (87.7%)	8 (12.3%)		
Overweight	89 (94.7%)	5 (5.3%)		
Obese	148 (90.2%)	16 (9.8%)		
Type of Diabetes			0.480 (0.063-3.689)	0.481
Type 1	22 (95.7%)	1 (4.3%)		
Type 2	317 (91.4%)	30 (8.6%)		
Duration of Diabetes (years)			**0.514 (0.324-0.816)**	**0.005**
<5	168 (96.0%)	7 (4.0%)		
5-10	77 (90.6%)	8 (9.4%)		
>10	80 (86.0%)	13 (14.0%)		
Modality of treatment			**0.516 (0.345-0.772)**	**0.001**
Diet	3 (75.0%)	1 (25.0%)		
Oral hypoglycemic agents (OHA)	211 (97.2%)	6 (2.8%)		
Insulin	40 (78.4%)	11 (21.6%)		
Both OHA and Insulin	85 (86.7%)	13 (13.3%)		

Glycemic control			0.952 (0.416-2.175)	0.907
Good	106 (92.2%)	9 (7.8%)		
Poor	213 (91.8%)	19 (8.2%)		
Blood Pressure			0.444 (0.193-1.020)	0.056
Controlled (< 140/90 mmHg)	149 (94.9%)	8 (5.1%)		
Uncontrolled ≥ 140/90mmHg)	190 (89.2%)	23 (10.8%)		
HIV status			0.642 (0.341-1.206)	0.168
Positive	36 (94.7%)	2 (5.3%)		
Negative	210 (92.5%)	17 (7.5%)		
Unknown	93 (88.6%)	12 (11.4%)		

3.4 Factors associated with CKD

Older age (OR=0.297, p=0.000), lower levels of education (OR=1.584, p=0.003), and a longer duration of diabetes (OR=0.516, p=0.001) were associated with CKD in bivariate analysis. The remaining studied factors including gender, marital status, body mass index, type of DM, glycemic control and HIV status were not associated with CKD (Table 3). The relationship between CKD and glycemic control was not significant even when CKD stages 3 and 4 were analyzed separately (p=0.963) (Table 4).

Table 4: Glycemic control of study participants by CKD stages

	Glycemic control			p-value
CKD stages	Good control	Poor control	Total	
GFR ≥ 90	84	172	256	
GFR 60-89	22	41	63	
GFR 30-59 (Stage 3)	7	16	23	0.963
GFR 15-29 (Stage 4)	2	3	5	
Total	115	232	347	

The significant variables in the bivariate analysis were subsequently subjected to a separate multivariable logistic regression model, whereby all three variables (age, education level and duration of diabetes) remained statistically significant (Table 5).

Table 5: Multivariate logistic regression for factors associated with CKD

Variable	AOR	Rat 95% CI	P value
Age	3.52	1.565 – 7.928	**0.002**
Level of education	3.60	1.23-10.55	**0.02**
Duration of diabetes	3.90	1.498 – 10.15	**0.005**

4. DISCUSSION

We found the prevalence of CKD to be 8.4% as defined by an estimated glomerular filtration rate (eGFR) <60 ml/ min/1.73 m^2. These findings are almost similar to those observed elsewhere in primary care settings [37, 38], with our tertiary clinic typically operating as a primary care clinic for DM patients in Gaborone. On the other hand, the prevalence of CKD in this study appeared low compared to most other studies, which revealed a prevalence based on estimated glomerular filtration rate of (eGFR) <60 ml/ min/1.73 m^2 in the range of 18-24.7% [34,35,39,40]. The low prevalence in this study may well partly be attributed to the fact that we included type 1 DM patients in our analysis. Type 1 DM patients have a natural history of developing CKD after many years following diagnosis, whilst patients with type 2 DM are

likely to present with complications after only a few years due to late diagnosis. The other possibility is that our patients were mostly diagnosed less than 5 years prior to entering this study; the lower prevalence may be according to the natural history of the disease. The contribution of genetics to the prevalence of CKD among DM patients in terms of contributing to the rate of renal impairment in Botswana is unknown and this may require further research in the future.

The importance of strict glycemic control (HbA1c < 7%) and blood pressure control in preventing and slowing the progression of CKD has been well documented [41-44]. Our study revealed that 60.1% and 57.4% of study participants had poor glycemic control and uncontrolled blood pressure respectively. This is concern since if situation is not adequately addressed; there is a high likelihood of an increasing incidence of CKD in these patients. Consequently, we now recommend strict glycemic control and a more aggressive approach to controlling hypertension in this population, and we will be following this up in future research.

Glycemic control was not associated with the stages of CKD in our study. There was overall poor glycemic control across all stages, which can be interpreted that even patients with estimated GFR > 60 ml/min/ 1.73m^2 are at increased risk of CKD. Previous studies have shown that as CKD patients progress to end stage kidney disease (ESRD), their glycemic control tends to significantly improve due to factors such as HbA1c underestimating their control as well as associated loss of weight/poor appetite and more access to care leading to stressing the importance of glycemic control [45]. We did not recruit patients with ESRD in our study since most patients who are on dialysis attend the nephrology clinic in Botswana where they also receive care for their DM. We can speculate that most of them had better glycemic control; consequently, reducing the need for attending multiple clinics.

Blood pressure control is a key component of preventing and slowing progression of CKD; consequently, most guidelines emphasize the importance of reaching therapeutic goals such as < 140/80 mmHg [46, 47]. Despite the fact that we used a less strict goal of < 140/90 mmHg during our analysis, the majority of our patients still had uncontrolled blood pressure. We did not find any significant association between the level of blood pressure control and CKD. This is in contrast to other studies which showed CKD to be more associated with uncontrolled hypertension [34,39]. One possible explanation is the higher numbers of uncontrolled blood pressure among both patients with and without CKD in our study. The other reason could be that our study was not powered enough to show the effect of blood pressure on CKD.

Several sociodemographic factors and clinical variables were analyzed in our study to find any association with CKD. While there have been contradictory findings on the effect of gender on CKD, it has been shown in some studies that women tend to have a higher rate of severe kidney injury with albuminuria compared to men [48]. The other explanation being that male patients tend to be associated with a higher rate of CKD with higher mortality, whilst women have a survival benefit and appear to have higher CKD prevalence rates [48, 49]. Other studies though have shown that males tend to have a higher prevalence of CKD compared to women [50, 51]. In our study, there was no association between gender and the presence of CKD, which is similar to findings in other previous studies [40, 49, 52].

Chronic kidney disease was found to be significantly associated with older age. This is expected due to the fact that people tend to lose glomeruli with aging, and an association of age with CKD has been documented in several studies [34, 40, 53]. On the other hand, it has been established that CKD prevalence is associated with longer duration of DM [34, 54, 55]. Similarly, we found a significant association between CKD and the duration of DM.

On the other hand, we found that higher level of education was associated with less prevalence of CKD. This is in contrast to other previous studies that have shown education is not associated with CKD [40, 56]. Our results could possibly be explained by difference in other lifestyle factors such as dietary intake, smoking and alcohol use which were not assessed in this study. We are also aware that issues such as educational status and knowledge about the disease can impact on medicine adherence rates in practice in patients with chronic diseases in Africa; although this is not universal [6, 57-60]. Consequently, there is a need for further research to explore the contribution of these modifiable factors.

Previous studies have consistently shown that CKD is associated with increased body mass index (BMI) [61,62]. This is because overweight and obese people are also likely to have poor glycemic control, uncontrolled hypertension and other cardiovascular cormobidities which can contribute to CKD progression. It should be noted however that body mass index was not found to be associated to CKD in our study. This will also be explored further.

CKD has been found to be independently associated with HIV positive status, and this is due to a number of factors. These may include the fact that HIV positive patients live longer; consequently, get exposed to other traditional risk factors for CKD, effect of co-infections like Hepatitis B, CD4 less than 200/mm^3 , high viral loads and the side-effects of some antiretroviral medications [63, 64]. We expected that HIV positive status on top of DM in our study participants may play an additive role making this subgroup more at risk of CKD; however, there was no association between HIV status and CKD in our study. Possible reasons for a lack of association include a small sample size of HIV positive patients in this study (n=38). On the other hand, while a previous case matched study in Botswana [65] showed HIV positive status to be associated with CKD, which was significant for those with lower CD4 less than 200umol/l, in the current study HIV positive patients had higher CD4 levels (mean of 641.58umol/l) [8] and this could explain the difference. In addition, HIV status did not impact on adherence rates in patients with DM, perhaps because they were followed up more [8]. We have seen this situation in other African countries [58].

Understanding of the estimated glomerular filtration rate for individual patients helps in renal adjustment dosages of medications including oral hypoglycemic agents (OHA) to avoid complications such as hypoglycemia and lactic acidosis [40]. Our study showed that patients were more significantly prescribed insulin as estimated GFR declined, making them at least less likely to suffer complications of OHAs. It should be noted that, out of 8.4% with CKD, only 4.9% of them had diagnosis of kidney disease documented in their charts. These patients with undocumented CKD disease are potentially at high risk of toxicities of several medications due to lack of renal dosage adjustment.

There is growing evidence that heat stress coupled with inadequate hydration is associated with CKD that is different from that caused by traditional risk factors [66-68]. We did not study the role of heat stress on CKD among DM patients; however it should be noted that this study involved using serum creatinine results that were within 6 months of study duration (January to September 2015) with temperatures averaging between 25^0 C in January and 21^0 C in September. Botswana experiences a winter season between May to end of August, where mean temperature ranges from 13-16 ^{0} C [69]. There is a need for future prospective studies involving different seasons of the year to elicit the role of heat stress on CKD among the DM population, and this will be the subject of future research in Botswana.

The findings of this study provide data for the prevalence and associated factors for CKD in Botswana, providing a baseline for future local studies to enhance our understanding and better management of DM patients with CKD. However, the results of this study need to be interpreted with some limitations to put the findings into perspective. Firstly, this study being an observational cross-sectional design does not provide information on causal relationships and possible factors such as cardiovascular events that might have caused a rapid deterioration of renal function. Secondly, the use of a single serum creatinine results to calculate estimated glomerular filtration rates instead of at least two serum levels performed three months apart is another limitation. We also recruited ambulatory patients in our outpatient clinic who had no acute illnesses that may have predisposed them to acute kidney injuries; consequently, we believe that singe serum creatinine used here represent the stable state of our patients. Thirdly, we used estimated GFR by MDRD equation; this has not been validated against gold standard GFR in Botswana. Despite these limitations, we believe that this study provides insights into several key areas which call for future research and changes in management in Botswana.

5. CONCLUSIONS

The prevalence of CKD by estimated eGFR was low compared to most previous studies. However, half of patients with CKD are not documented resulting in potential of prescription errors and drug toxicity. A substantial number of our patients had uncontrolled hypertension and poor glycemic control. Older age, low level of education and longer duration of DM were associated with CKD. There is a need to carry out

prospective studies to determine the association and role of glycemic and blood pressure control in CKD causation among patients with DM in Botswana.

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Author contributions
GMR, OJM-B, AM, MS, YPR and TAO develop the concept for the paper and undertook data collection and analysis. GMR drafted the first paper for subsequent review. BBG, AM and DH helped with the analysis, interpretation and manuscript writing. All authors approved the final initial and revised paper.

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