Original Article

The Prevalence of Microalbuminuria and Associated Factors among Patients with Type 2 Diabetes Mellitus in Botswana

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Abstract

Background: Microalbuminuria (MA) has been established as an early marker of both diabetic nephropathy and vascular disease in patients with diabetes mellitus (DM). **Aims:** This study was conducted to determine the prevalence of MA and associated factors among patients with type 2 DM in Botswana. **Settings and Design:** Outpatient tertiary clinic. **Materials and Methods:** A cross-sectional descriptive study involving 289 patients with type 2DM was conducted from January 2013 to June 2013 in Block 6 Reference Clinic, a tertiary clinic in Gaborone, Botswana. A random spot urine sample was collected from each patient with MA defined as urine albumin-to-creatinine ratio (ACR) between 3.0 and 30.0 mg/mmol. **Statistical Analysis Used:** Data analysis was done using STATA version 12 (College Station, TX, USA). Unpaired Student's *t*-test was used for compairing means and Chi-squared test was used for comparison of proportions between groups. A *P* value of <0.05 was considered statistically significant. **Results:** The majority of recruited patients (191, 66.1%) were females, and the median age (interquartile range) of the patients was 52 (42–53) years. The mean glycosylated hemoglobin (HbA1c) for the study population was 8.43% with 70.6% of the population having HbA1c over 7%. MA was found in 129 (44.6%) of study participants. The duration of diabetes of 6–10 years, estimated glomerular filtration rate, HbA1c, and higher serum trigerycides levels were significantly associated with presence of MA. **Conclusion:** High prevalence of MA raises an urgent need for changes in the management of patients with type 2 DM in Botswana, with emphasis on prevention and reduction of MA to avoid development of overt diabetic nephropathy and ensuing cardiovascular morbidity and mortality.

Keywords: *Botswana, microalbuminuria, risk factors*

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Introduction

Type 2 diabetes mellitus (DM) has emerged as the new pandemic of the 21st century and it is estimated that 80% of people with diabetes live in low- and middle-income countries. It is also estimated that there were 415 million people with DM worldwide in the year 2015 and this number is expected to increase to 640 million people by 2040.[1] In Africa, the number of people with DM is expected to increase by 162.5% by the year 2045.[1] The World Health Organization (WHO) estimated that 25,000 people were living with diabetes in Botswana in the year 2000 with this figure projected to increase to 45, 000 by the year 2030.[2] However, these projections of the number of patients with DM by 2030 were already exceeded in 2015 when there were about 52,000 documented patients in Botswana.[1]

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide and renal failure has been proven to be the major cause of death in patients with type 2 DM.[3,4] Progression to established diabetic

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nephropathy occurs through several stages including hyperfiltration, microalbuminuria (MA), and frank proteinuria (macroalbuminuria).[5] MA is one of the early markers not only of diabetic nephropathy but also of cardiovascular disease morbidity and mortality in patients with diabetes.[6,7] Studies have shown that 20% to 40% of patients with type 2 DM ultimately develop nephropathy.[8,9] MA is defined as urinary albumin excretion (UAE) rate of 30–300 mg/day in a 24-h collection or albumin-to-creatinine ratio (ACR) of 3.0–30.0 mg/mmol in a spot collection.[10] Measurement of UAE in a 24-h collection is the gold standard method to determine the presence of MA because UAE follows a circadian rhythm. This, however, has been found to be cumbersome, expensive, and time-consuming, hence more practical alternatives; measurement of urinary albumin concentration (UAC) or ACR has been used. These can be done on a first morning void or a spot (random) urine sample. In a systematic review and meta-analysis of studies comparing ACR on a random urine specimen to albumin excretion rate from an overnight or 24-h timed sample, Ewald and Attia found that ACR on a random specimen had a sensitivity of 90% and a specificity of 84%, and they suggested that ACR on a random urine specimen be used routinely as the initial test in screening diabetics for MA.[11] Incerti *et al.* also observed that UAC and urinary ACR measured in a random urine specimen were accurate screening tests for MA.[12] Interestingly, random ACR is even a better alternative to 24-h urine collection as a predictor of cardiovascular morbidity and mortality if the specimen is of the first morning void urine.[13]

The prevalence and severity of diabetic nephropathy have consistently been shown to be higher in Blacks compared to other races.[14] In sub-Saharan Africa, the prevalence of MA ranges from 10.7% in Tanzania to 58% in Nigeria.[15-17] The presence of MA in patients with diabetes is associated with several factors including hyperglycemia, dyslipidemia, hypertension, smoking, long duration of diabetes, and genetic susceptibility.[15,16,18] There is good evidence that early treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease[19-21] and at the same time reduces cardiovascular morbidity and mortality.[22] In spite of the continuous increase in the number of cases of diabetes and of its renal complications in Botswana, no local data are available on the prevalence of MA among patients with type 2 DM. This study was conducted to determine the prevalence of MA among patients with type 2 DM in Botswana. We also aimed at determining factors that predict the presence of MA.

Materials and Method

A cross-sectional study was conducted at Block 6 Reference Clinic in Gaborone, Botswana. The clinic is a tertiary center catering for most patients in the capital city and the surrounding villages. Though tertiary, the Clinic serves also at the capacity of primary and secondary levels. More than 3000 patients attend it for services including consultation, eye care, and dietician appointments. About 50–60 patients are attended for physician consultations on each of the weekdays. Patients age either 21 years or above, with 21 years being a legal age for consenting in Botswana, who had a confirmed and/or documented diagnosis of type 2 DM formed the study population. Data were collected from January 2013 to June 2013. Patients known to have chronic kidney disease (CKD) or in end-stage renal disease, congestive cardiac failure, women 20 or more weeks pregnant, critically ill patients requiring admission, those with signs of urinary tract infection on urine dipstick (i.e., presence of urinary nitrites and leucocytes of at least 1+), overt proteinuria of more than 300 mg/day, and those with body temperature above 37.5°C were excluded from the study.

The minimum required sample size of 276 patients with type 2 DM was calculated according to the formula for sample size calculations in cross-sectional studies.[23,24] Patients' enrollment followed a simple systematic random sampling pattern whereby each fifth eligible patient was included if consenting to participate in the study; otherwise, the next fifth patient on the list was approached. A semi-structured questionnaire was used to interview patients to collect sociodemographic data and record clinical variables. Weight in kilograms (kg) was measured with a calibrated weighing scale with the patient on light clothing. Height in metres (m) to the nearest two decimal points was measured by standard scale, with the patient standing barefoot. Body mass index (BMI) was then calculated using the formula weight in kg/height in m^2. BMI was interpreted as per WHO reference values as follows: underweight <18.5, normal 18.5–24.99, overweight 25.0–29.99, and obesity >30 kg/m^2. Body temperature in degrees Celsius (°C) was obtained from the axilla. Blood pressure was measured with a mercury sphygmomanometer from the right arm in sitting position after at least 10 min rest. Two blood pressure measurements were taken 10 min apart and the average of the two readings was used as the patient's final blood pressure for the study. Patients were classified as hypertensive if they were known to be hypertensive and on antihypertensive therapy, or had systolic blood pressure of > 140 mmHg or diastolic pressure

of >90 mmHg.[25] All the measurements throughout the study were performed by a single trained research nurse.

Venesection was performed under aseptic technique to obtain about 5 mL of blood which was analyzed for serum creatinine, glycosylated hemoglobin (HbA1c), and lipid parameters. Glomerular filtration rate (GFR) was calculated using the 2009 CKD-EPI equation as recommended by clinical practice guidelines on the management of CKD.[10] The choice of CKD-EPI equation over MDRD equation was based on the fact that the former has been shown to improve accuracy of GRF estimates compared to MDRD equation especially for GFR above 60 mL/min/1.73 m^2.[26]

Laboratory assays

A random urine specimen was collected for urine dipstick, UAC, and urinary creatinine. Urine dipstick assessed the urine for the presence of protein, glucose, nitrites, red blood cells, and leucocytes among others and this was done using Combur[10] urine chemistry dipstick test. Albuminuria was measured using CLINITEK semi-quantitative ACR test. The test uses dye-binding and catalytic assays for albumin and creatinine, respectively, on a CLINITEK microalbumin 2 strip, which is then read by CLINITEK Status analyzer. The ACR is automatically calculated. The results of ACR are corrected for varying urine concentrations when used on CLINITEK Status family of analyzers, replacing the need for 24-h urine collection and measurement.[27] The CLINITEK microalbumin 2 strip test has a sensitivity of 90% and specificity of 91%[28] and has been recommended by the American Diabetes Association for screening of albuminuria among patients with DM.[27] Urinary albumin was interpreted as per KDIGO 2013 Clinical Practice Guideline for the evaluation and management of CKD[10] as follows: <3.0 mg/mmol, 3.0–30.0 mg/mmol, and >30 mg/mmol for normoalbuminuria (NA), MA, and macroalbuminuria, respectively.

Statistical analysis

Data were entered in Microsoft Office Excel in duplicate by two different persons and the two files were compared and non-matching entries corrected. Data analysis was done using STATA version 12 (College Station, TX, USA). Proportions in percentages were used for categorical variables, whereas for numeric variables the median and interquartile range (IQR) were used. Unpaired Student' *t*-test was used for compairing means in different subgroups and Chi-squared test was used for comparison of proportions between groups. A *P* value of <0.05 was considered statistically significant.

Ethical consideration

Ethical clearance to conduct this study was obtained from the University of Botswana Institutional Review Board, Princess Marina Hospital Institutional Review Board and the Ministry of Health Human and Research Development Committee. All the study participants signed a written informed consent.

Results

Sociodemographic and clinical characteristics

In all, 289 Black Africans participated in the study from January 2013 to June 2013. The majority of the

Table 1: Sociodemographic characteristics of participants (*N*=289)

Variable	*n* (%)
Age* (years)	
21-34	16 (5.5)
35-54	158 (54.7)
≥55	115 (39.8)
Gender	
Male	98 (33.9)
Female	191 (66.1)
Marital status	
Married	148 (51.2)
Single	108 (37.4)
Divorced	12 (4.2)
Widowed	21 (7.3)
Education level	
Primary	112 (38.8)
Junior secondary	71 (24.6)
Senior secondary	35 (12.1)
Tertiary	71 (24.6)
Cigarrate smoking	
Yes	12 (4.2)
No	277 (95.8)
Alcohol intake	
Yes	34 (11.8)
No	255 (88.2)
Hypertension	
Yes	177 (61.2)
No	112 (38.8)
Body mass index	
Underweight (<18.5)	2 (0.7)
Normal (18.5-24.9)	57 (19.7)
Overweight (25-29.9)	96 (33.2)
Obese (>30)	134 (46.3)
Duration of DM	
≤5	153 (52.9)
6-10	63 (21.8)
>10	73 (25.3)
HbA1c (mean (SD); 8.43 (2.23)	
<7%	85 (29.4)
≥7%	204 (70.6)

Contd...

Table 1:Contd..

Variable	*n* (%)
Estimated GFR	
>90	222 (76.8)
60-89	61 (21.1)
30-59	6 (2.1)
Treatment modality	
Insulin alone	10 (3.5)
Insulin + OHAs	79 (27.3)
OHAs alone	200 (69.2)

DM=Diabetes mellitus; HbA1c=Glycosylated hemoglobin; SD=Standard deviation; IQR=Interquartile range. *Median (IQR); 52 (42-58); Oral hypoglycemic agents (OHAs)

Table 2: Prevalence of microalbuminuria among study participants

Albuminuria status	Frequency (%)	*P*
Normoalbuminuria	160 (55.4%)	0.07
Microalbuminuria	129 (44.6%)	

patients (191, 66.1%) were female. The median age of study participants was 52 years (IQR = 42–58 years). Over a third of patients, 112 of 289 (38.8%), were educated to the level of primary school with the rest more educated. Over half of the patients, 153 of 289 (52.9%), had been diagnosed to have DM within the past 5 years. The mean HbA1c was 8.43 [standard deviation (SD) 2.23]. The majority of study participants, 204 of 289 (70.6%), had HbA1c above 7%. Almost half (46%) of the participants had a BMI in the obese range and over a third (33%) were overweight. Sociodemographic and clinical characteristics of study participants are summarized in Table 1.

Prevalence of microalbuminuria and associated factors

Of the 289 patients studied, 129 (44.6%) had ACR in the microalbuminuric range [Table 2]. We did not find any significant association between gender, BMI,

Table 3: Bivariate analysis to show association between categorical variables and albuminuria status (*N*=289)

	Normoalbuminuria *n* (%)	Microalbuminuria *n* (%)	*P*
Age (years)			
21-34	5 (3.1)	11 (8.5)	0.09
35-54	93 (58.1)	65 (50.4)	
≥55	62 (38.8)	53 (41.1)	
Gender			
Female	103 (64.4)	88 (68.2)	0.49
Male	57 (35.6)	41 (31.8)	
Cigarette smoking			
Yes	6 (3.8)	6 (4.7)	0.70
No	154 (96.2)	123 (95.3)	
Alcohol consumption			
Yes	16 (10.0)	18 (14.0)	0.30
No	144 (90.0)	111 (86.0)	
Hypertension			
Yes	99 (61.9)	78 (60.5)	0.81
No	61 (38.1)	51 (39.5)	
Duration of DM			
≤5	89 (55.6)	64 (49.6)	0.01
6-10	25 (15.6)	38 (29.5)	
>10	46 (28.8)	27 (20.9)	
Body mass index			
Normal (≤24.99)	30 (18.8)	29 (22.5)	0.56
Overweight (25-29.9)	57 (35.6)	39 (30.2)	
Obese (>30)	73 (45.6)	61 (47.3)	
Estimated GFR			
>90	130 (81.3)	92 (71.3)	0.04
60-89	29 (18.1)	32 (24.8)	
30-59	1 (0.6)	5 (3.9)	
DM treatment			
Insulin only	4 (2.5)	6 (4.7)	0.61
Insulin + OHA	44 (27.5)	35 (27.1)	
OHA only	112 (70.0)	88 (68.2)	

DM=Diabetes mellitus; GFR=Glomerular filtration rate

Table 4: Bivariate analysis to show association between numerical variables and albuminuria status (*N*=289)

Characteristic	Mean (95% CI)		*P*
	NA	MA	
Age (years)	50.9 (49.5±52.3)	50.3 (48.6±52.0)	0.59
Duration of DM (years)	6.98 (5.96-8.00)	6.67 (5.66-7.68)	0.67
Systolic BP (mmHg)	135.5 (133.0-138.0)	136.0 (132.7-139.3)	0.81
Diastolic BP (mmHg)	82.48 (80.85-84.11)	82.12 (80.05-84.39)	0.85
BMI (kg/m^2)	30.22 (29.22-31.22)	30.14 (29.01-31.27)	0.92
GFR (mL/min/1.73 m^2)	117.01 (114.4-119.6)	114.5 (110.9-118.2)	0.26
HbA1c (%)	7.99 (7.66-8.32)	9.01 (8.63-9.39)	0.0001
HDL (mmol/L)	1.14 (1.08-1.20)	1.14 (1.09-1.19)	0.99
LDL (mmol/L)	2.92 (2.79-3.05)	5.00 (1.04-8.97)	0.25
Total cholesterol (mmol/L)	4.55 (4.37-4.73)	4.64 (4.42-4.86)	0.52
Triglycerides (mmol/L)	1.87 (1.65-2.09)	2.17 (1.91-2.43)	0.02

NA=Normoalbuminuria; MA=Microalbuminuria; CI=Confidence interval; DM=Diabetes mellitus; BP=Blood pressure; BMI=Body mass index; GFR=Glomerular filtration rate; HbA1c=Glycosylated hemoglobin; HDL=High-density lipoprotein; LDL=Low-density lipoprotein

history of cigarette smoking, alcohol intake, history of hypertension or treatment modality, and the presence of MA. Analysis involving different age groups versus presence of MA revealed no statistically significant association (P = 0.09). We found that there was significant difference with regard to duration of DM at 6–10 years with microalbuminuric group having a prevalence of 29.5% compared to prevalence of 15.6% in normoalbuminuric group (P = 0.01). Renal function assessed as estimated GFR was found to be significantly associated with presence of macroalbumuria with prevalence of MA increasing as renal functions deteriorated (P = 0.04) [Table 3].

The mean age [95% confidence interval (CI)] of normoalbuminuric patients and those with MA was 50.9 (49.5–52.3) years and 50.5 (48.6–52.0) years, respectively (P = 0.59) indicating that presence of MA was not significantly associated with mean age. The mean HbA1c of patients with NA was 7.99 (CI 7.66–8.32) and that of microalbuminuric patients was 9.01 (CI 8.63–9.39). The difference between the two groups was statistically significant (P = 0.0001). The mean serum triglycerides was found to be significantly higher in microalbuminuric group compared to the normoalbuminuric group (P = 0.02). The means of duration of DM, BMI, systolic blood pressure, diastolic blood pressure, estimated GFR, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol did not differ between the two groups [Table 4].

Discussion

We found a prevalence of MA of 44.6% among patients with type 2 DM attending in a tertiary clinic in Botswana. This was fairly high and comparable to previous studies done in sub-Saharan Africa.The highest rate of MA in our study may be attributed to factors such as genetics which have not been studied; on the other hand, differences in MA across population have been explained by several factors including methods of measurement for MA, definitions for MA, different stages of the disease, and difference in ethnicity susceptibility to development of MA and overt nephropathy.[29-31]

Several studies have demonstrated numerous demographic and clinical variables such as age, gender, long duration of DM, high BMI, poor glycemic control, low estimated GFR, elevated systolic and diastolic blood pressure, and dyslipidemia (especially elevated triglycerides/LDL) to be predictors of MA among patients with DM.[15,16,18,32-36] Older age has been associated with MA almost certainly because of longer duration of diabetes. Our study did not show any association between age and presence of MA. This is similar to other previous studies.[37,38] Our data revealed that patients at 6–10 years duration of DM were more likely to have MA with a statistical significant association. The association seems to disappear for patients with more than 10 years duration of diabetes. Possible explanations for this finding include the fact than few patients had longer duration of diabetes of more than 10 years, accounting for 25.3% in this study. On the other hand, older patients are likely to be more symptomatic due multiple diabetes complications, hence tend to be more adherent to antidiabetic medications[39] with the latter likely to improve glycemic control and cause regression of MA. With regard to gender, our study revealed no association between gender and presence of MA; this is similar to another previous study.[37] In contrast to other studies which showed that obesity is associated with MA, we found no association between BMI and MA; this is most likely because majority of our patients in both arms were either overweight or obese. Nonetheless, the lack of association between MA

and BMI has been found elsewhere.[40-42] On the other hand, like previous studies[43] we did not find association between hypertension and presence of MA.

Even though some previous studies have shown association between smoking and MA among patients with both type 1 and 2 DM,[32,34,44] our study findings revealing no association of the presence of MA to smoking are similar to the results of other studies.[45] Possible explanations include the fact that only a minority of our patients were cigarette smokers (4%); on the other hand, we did not quantify the association between smoking pack-years and MA. Previous studies have demonstrated association between alcohol intake and MA.[46] We did not find such an association most likely due to the fact that we did not quantify the extent of alcohol intake among study participants. Low levels of estimated GFR imply progression of renal disease, hence patients with low GFR are more likely to have MA compared to those with high GFR.[37] Our study revealed similar findings whereby prevalence of MA increased as the estimated GFR declined. Our data show an association between poor glycemic control and MA; this is similar to previous studies. Clinical practice guidelines on the management of DM recommend HbA1c below 7% as a target for acceptable glycemic control to reduce diabetic vascular complications.[47-49] In this study, the mean HbA1c was higher than the recommended target at 8.43% (SD 2.23%) with only 29.4% of the study population having HbA1c below 7%. These findings call for a more aggressive approach to emphasize measures to optimize glycemic control. Of all the lipid profile parameters studied, high triglyceride levels were the only other factor independently associated with MA; this is similar to studies done elsewhere.[50,51] The lack of association between other lipid parameters, namely, total cholesterol, HDL, and LDL, may be attributed by the fact that their levels were within normal range for both microalbuminuric and normoalbuminuric groups, possibly due to predominant use of statins in our setting. Statins are known to be less effective in lowering serum triglycerides.[52] We did not collect data on the use of statins, hence future studies on this area are warranted.

The findings of this study need to be interpreted on the background of several limitations. Even though the determination of MA through a single random urine sample is highly sensitive and specific, a better option would have been to get at least two urine specimens taken 3 months apart. Second, the fact that our study participants were only patients with type 2 DM poses a limitation because it is always difficult to determine the actual duration of disease and patients tend to present after long duration of disease with complications. Third, this being a cross-sectional study, it is difficult to determine causality between MA and associated risk factors. Finally, our study site being a tertiary clinic may contribute to the possibility of referral bias making the generalization of our findings difficult. Despite the limitation as alluded earlier, the study site though tertiary serves as both primary and secondary centers and attends to both urban and rural villages of Botswana; this increases the strength of our findings.

In conclusion, the prevalence of MA in our study was higher and comparable to other studies performed in sub-Saharan Africa. The duration of DM, reduced renal function, elevated serum HbA1c, and hypertriglyceridemia are associated with the development of MA in patients with type 2 diabetes in Botswana. Due to clear evidence from both randomized control trials and epidemiological studies that strict glycemic control, blood pressure control, and low levels of serum cholesterol and triglycerides are associated with prevention and regression of MA among patients with type 2DM, we recommend aggressive glycemic control coupled with management of high triglycerides. We further recommend that screening of MA at diagnosis and annually be adopted as standard of care among patients with type 2 DM in Botswana; this will help in optimizing care and reducing the burden of overt diabetic nephropathy in the future.

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Conflicts of interest

There are no conflicts of interest.

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