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ORIGINAL ARTICLE

Prevalence and determinants of proteinuria among type 2 diabetics in Kumasi, Ghana

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Diabetic nephropathy is the leading cause of end stage kidney disease among type 2 diabetics worldwide. Proteinuria has been noted to be the cardinal symptom of progressive loss of renal function. This study examined the impact of duration of diabetes, demography (age, gender) and metabolic factors on the frequency of proteinuria among type 2 diabetics visiting the Komfo Anokye Teaching Hospital (KATH). In this cross-sectional study, 350 type 2 diabetics aged between 28-87 years were randomly selected from January to April 2004, and parameters estimated include fasting blood glucose (FBS), body mass index (BMI), urine protein and blood pressure. Proteinuria among the study cohorts was graded no proteinuria, mild proteinuria to heavy proteinuria. The frequency of proteinuria for the varied grades in type 2 diabetics enrolled in the study ranged from 73.3% (no proteinuria), 15.2% (mild proteinuria) and 15.6% (heavy proteinuria). 1(100%) patient with heavy proteinuria presented with grade 3 hypertension; and 4(33.3%) and 11(20.8%) patients presented with grade 1 and isolated systolic hypertension respectively. Multiple logistic regression analysis showed study participants with duration of diabetes ranging from 11-15 years (OR=2.8; 95% CI=1.1-7.2; p=0.028) and 16-20 years (OR=5.6; 95% CI=1.4-22.5; p=0.016) were at an increased risk of proteinuria. The frequency of nephropathy is promoted independently by advanced age, hypertension and duration of diabetes.
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Keywords*:* Proteinuria, type 2 diabetes, obesity, hypertension

INTRODUCTION

Diabetes mellitus is a clinical syndrome associated with insulin deficiency, inefficiency or both (Harris and Zimmet, 1997). The world health organization (WHO) estimates that over 170 million people worldwide are presenting with diabetes with the number possibly rising to 370 million in the next 20 years (USRD, 2004). One of the complications of type 2 diabetes mellitus (T2DM) is nephropathy characterized by increased excretion of protein in the urine which is presently the leading attributable cause of chronic kidney disease (CKD) (USRD, 2004).

To date, there is a paucity of information on proteinuria (macroalbuminuria) among type 2 diabetics in Ghana; however, studies conducted in Nigeria and other African countries have reported highly varying prevalence rates ranging from as low as 7.0% to 82.5% (Lutale *et al.*, 2007; Balogun and Abbiyesuku, 2011).

Several studies have concluded that factors such as age, gender, diet and obesity, hypertension and proteinuria influence the progression of diabetic nephropathy (Rossing *et al.*, 2004; Leehey *et al.*, 2005; Imai *et al.*, 2008). Subsequently, glycaemic

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control and the reno-protective effect of angiotensin converting enzyme inhibitors and blockers on proteinuria have been identified as factors that influence proteinuria in T2DM (Klahr *et al.*, 1994; Peterson *et al.*, 1995; Mandal and Hiebert, 2008). The interplay of these factors in the development and progression of proteinuria and subsequent diabetes associated nephropathy among Ghanaian diabetics has not been well elucidated. This study therefore examined the impact of age, obesity, hypertension, blood glucose concentration and duration of diabetes on the frequency of proteinuria among T2DM patients.

MATERIALS AND METHODS

Study area and subjects

This randomised cross-sectional study was conducted at the Diabetic clinic of the Komfo Anokye Teaching Hospital (KATH), Kumasi, in the Ashanti region of Ghana from January to April 2004. A total of 350 subjects comprising 251 females and 99 males with ages ranging from 28-87 years were selected from the diabetic centre of the KATH. A self-structured questionnaire was administered to each participant after recruitment into the study. The participation of the respondents who were all indigenes of Ghana was voluntary and informed consent was obtained from each study participants prior to enrolment into the study. The study was approved by the School of Medical Sciences and KATH Committee on Human Research, Publication and Ethics (SMS/KATH/CHRPE).

Inclusion criteria

All type 2 diabetics with ages ranging from 28 years and who were on hypoglycaemic agents or on diet therapy, but not on insulin therapy were enrolled into the study. Confirmation of diagnosis was made from patient folders before being recruited into the study.

Exclusion criteria

Type 1 diabetics and type 2 diabetics undergoing any form of dialysis were excluded from the study. Diabetics on insulin therapy were excluded from the study.

Blood Sample collection

Two millilitres (2 ml) of venous blood was drawn from each study participant after an overnight fast (12-14 hours) and dispensed into fluoride oxalate tubes. After centrifugation at 1500 *g* for 3 minutes, the plasma was aliquoted into cryovials and stored at - 80°C until assayed.

Fasting blood sugar

This was estimated using the glucose oxidase/peroxidase method (Trinder, 1969) and the colour developed was measured with a spectrophotometer [(Spectronic-20), 820 Linden Avenue, Rochester, NY 14625, USA] at a wavelength of 500 nm.

Urine collection and estimation of urine protein

Early morning urine samples collected into clean, wide mouth and leak proof containers were obtained from the participants and preserved with boric acid (0.1 g) for every 10 ml of urine. Proteinuria (semi-quantitative) was assessed using dipstick (CYBOW™ DFI Co Ltd, Gimhae-City, Republic of Korea) and confirmed with the sulphosalicylic acid method. Proteinuria was defined as none when the dipstick test turns out negative; mild for dipstick results ranging from trace to 1+ and heavy for dipstick results ranging from 2+ to 4+.

Anthropometric variables

Height to the nearest centimetre without shoes was measured with a wall-mounted ruler and weight to the nearest 0.1 kg in light clothing was measured using a bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China). Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2).

Blood Pressure (using Krotkoff 1 and 5)

Blood pressure was measured by trained personnel using a mercury sphygmomanometer and a stethoscope. All measurements were in accordance with recommendations of the American Heart Association (Kirkendall *et al.*, 1967). Mean values of duplicate measurements were recorded as the blood pressure. Hypertension was graded as normal when the systolic blood pressure (SBP) is less than 120 mm Hg and diastolic blood pressure (DBP) is less than

80 mm Hg; pre-hypertension: SBP= 120-139 or *DBP* =80-89; Stage 1 hypertension: SBP=140-159 *or* DBP=90-99; Stage 2 hypertension: SBP >160 *or* *DBP*>100 (Chobanian *et al.*, 2003).

Calculation of Mean Arterial Pressure (MAP)

The mean arterial pressure was estimated using the formula:

$$MAP \cong DP + \frac{1}{3}(SP - DP)$$

Statistical analysis

Results are expressed as means ± SD. Unpaired *t*-test was used to compare mean values of continuous variables and χ^2test statistic was used to compare all categorical variables. For all statistical comparisons, a p-value<0.05 was considered as statistically significant. Multivariate logistic regression was used to estimate the odds ratios of risk factors of proteinuria after adjusting for age and sex. GraphPad Prism version 5.00 for windows (GraphPad software, San Diego California USA, www.graphpad.com) and SYSTAT version 12 (SYSTAT software, 239 Western Street, Suite F Fairfield, CA, USA, www.systat.com) were used for all statistical analysis.

RESULTS

Clinical characteristics of the study population

The mean duration of diabetes was significantly higher in the group with heavy proteinuria compared to the groups with mild and no proteinuria respectively. The mean age, diastolic blood pressure, and fasting glucose of the group with heavy proteinuria are significantly higher compared to the group without proteinuria. The mean arterial pressure and systolic blood pressure of the heavy proteinuria group were significantly higher compared to the mild proteinuria group (Table 1).

Frequency of proteinuria in relation to body mass index

The prevalence of proteinuria among the study respondents stratified by body mass index are as shown in Table 2. Out of the total of 16 (4.7%) underweight study participants, 62.5% (10/245) had no proteinuria, 25% (4/49) had mild proteinuria and 12.5% (2/47) had heavy proteinuria. Out of the 137 (40.2) study participants with normal weight, 73.7% (101/245) had no proteinuria, 15.3% (21/49) had mild proteinuria and 10.9% (15/47) had heavy proteinuria. For the 138 (40.0%) pre-obese study participants, 104 (75.4%) had no proteinuria, 14 (10.1%) had mild proteinuria and 20 (14.5%) had heavy proteinuria. For the 50 (14.7%) obese study participants, 60.0% (30/245) had no proteinuria with 20.0% each having mild (10/49) and heavy (10/47) proteinuria respectively.

Table 1: Demographic, clinical and biochemical characteristics of the study participants stratified by the level of proteinuria on dipstick

Variable	Total (n = 341)	None (n = 245)	Mild (n = 49)	Heavy (n = 47)
Duration of diabetes (years)	5.8 ± 4.8	5.2 ± 4.1	6.0 ± 5.7	8.5 ± 5.8*†
Age (years)	54.9 ± 11.0	53.9 ± 11.1	56.4 ± 8.7	58.9 ± 11.8*
MAP	94.6 ± 10.2	92.9 ± 7.7	97.8 ± 15.4*	100.3 ± 12.1*
SBP (mm Hg)	130.3 ± 14.9	127.7 ± 13.0	134.6 ± 14.6*	139.3 ± 19.5*
DBP (mm Hg)	76.4 ± 7.0	75.5 ± 6.1	77.2 ± 7.5	80.3 ± 9.1*
BMI (kg m^{-2})	25.5 ± 4.4	25.4 ± 4.1	25.0 ± 5.5	26.6 ± 4.8
Fasting blood glucose (mmol L^{-1})	9.2 ± 3.0	9.0 ± 2.8	9.4 ± 3.4	10.3 ± 3.3*

p<0.05; **p<0.01; ***p<0.001; *significantly different from group with no proteinuria; †significantly different from group with mild proteinuria; MAP = mean arterial pressure; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; None = negative; Mild = trace to 1+; Heavy = 2+ to 4+

Table 2: Prevalence of proteinuria stratified by body mass index and the level of proteinuria on dipstick

Body Mass Index	Total (n = 341)	None (n = 245)	Mild (n = 49)	Heavy (n = 47)
Underweight (<18.5)	16(4.7)	10(62.5)	4(25.0)	2(12.5)
Normal (18.5-24.9)	137(40.2)	101(73.7)	21(15.3)	15(10.9)
Pre-obese (25.0-29.9)	138(40.0)	104(75.4)	14(10.1)	20(14.5)
Obese (≥30.0)	50(14.7)	30(60.0)	10(20.0)	10(20.0)

Prevalence of proteinuria in relation to fasting blood glucose

Analyses of the frequency of proteinuria in relation to plasma fasting blood glucose concentration are as shown in Table 3. For the 43 (12.6%) study participants with normal blood glucose concentration, 74.4% (32/245) had no proteinuria, 11.6% (5/49) had mild proteinuria and 14.0% (6/47) had heavy proteinuria. For the 48 (14.1%) study participants with impaired fasting glucose, 83.3% (40/245) had no proteinuria, 12.5% (6/49) had mild proteinuria and 4.2% (2/47) had heavy proteinuria. For the 250 (73.3%) study participants with fasting blood glucose greater 7.0 mmol L^{-1}, 69.2% (173/245) had no proteinuria, 15.2% (38/49) had mild proteinuria and 15.6% (39/47) had heavy proteinuria (Table 3).

Duration of diabetes and frequency of proteinuria

Figure 1 assesses the frequency of proteinuria among the study participants in relation to the duration of diabetes. The frequency of heavy proteinuria showed a gradual increase from a frequency of 7.8% in study participants with diabetes duration of <1 year, through 8.1% (in the 2 – 5 years diabetes duration group), 14.5% (in the 6 – 10 years diabetes duration group), 33.3% (in the 11 – 15 years diabetes duration group) and 60.0% in the 16 – 20 diabetes duration group. None of the study participants with >20 years diabetes duration showed visible signs of heavy proteinuria. Mild proteinuria, from a frequency of 14.1% in participants with <1 year diabetes duration rose to 14.5% in the 2 – 5 and 6 – 10 years duration of diabetes groups respectively before gradually declining to 0.0% in the 16 – 20 and >20 year duration of diabetes respectively. Generally, the frequency of no proteinuria in the study participants decreased gradually from 78.1% in the ≤1 year duration of diabetes group through 77.4% (2 – 5 years), 70.0% (6 – 10 years), 56.7% (11 – 15 years), 40.0% (16 – 20 years) and 33.3% (>20 years).

Blood pressure categories and frequency of proteinuria

From Table 4, with the exception of 6 (8.2%) study participants with optimal blood pressure who tested positive for heavy proteinuria, none of the study participants with normal blood pressure and prehypertension tested positive for heavy proteinuria.

Table 3: Frequency of proteinuria in relation to the level fasting blood glucose as well as the level of proteinuria on dipstick

Fasting blood glucose	Total (n = 341)	None (n = 245)	Mild (n = 49)	Heavy (n = 47)
Normal (<6.1)	43(12.6)	32(74.4)	5(11.6)	6(14.0)
IFG (≥6.1 – <7.0)	48(14.1)	40(83.3)	6(12.5)	2(4.2)
DM (>7.0)	250(73.3)	173(69.2)	38(15.2)	39(15.6)

IFG = impaired fasting glucose; DM = diabetes mellitus

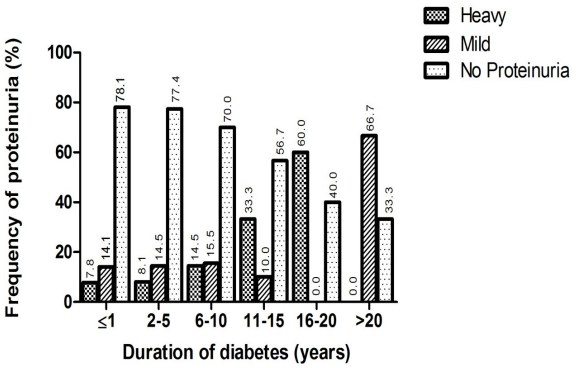

Figure 1: Relationship between frequency of proteinuria and duration of diabetes.

There was a gradual increase in the frequency of participants with mild proteinuria from 5.5% in participants with optimal blood pressure through 12.5% for participants with normal blood pressure and 37.5% for participants with pre-hypertension. For the blood pressure categories, 86.3% of the participants with optimal blood pressure had no proteinuria; 87.5% of the participants with normal blood pressure had no proteinuria and 62.5% of the participants with pre-hypertension had no proteinuria. On grading hypertension, 33.3% of the participants with grade 1 hypertension had heavy proteinuria, 16.7% had mild proteinuria and 50.0% had no proteinuria. The study participant with grade 3 hypertension had heavy proteinuria. Among the study participants with isolated systolic hypertension, 20.8% had heavy proteinuria, 22.6% had mild proteinuria and 56.6% had no proteinuria.

Table 4: Frequency of proteinuria in relation to blood pressure categories as well as the level of proteinuria on dipstick

Blood Pressure Category	Systolic	Diastolic	Total (n= 341)	None	Mild	Heavy
Optimal	<120	<80	73(21.4)	63(86.3)	4(5.5)	6(8.2)
Normal	120 – 129	80 – 84	8(2.3)	7(87.5)	1(12.5)	0(0.0)
Prehypertension	130 – 139	85 – 89	8(2.3)	5(62.5)	3(37.5)	0(0.0)
Hypertension						
Grade 1	140 – 159	90 – 99	12(3.5)	6(50.0)	2(16.7)	4(33.3)
Grade 2	160 – 179	100 – 109	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Grade 3	≥180	>110	1(0.3)	0(0.0)	0(0.0)	1(100.0)
Isolated systolic	≥140	<90	53(15.5)	30(56.6)	12(22.6)	11(20.8)

Odds analysis of some selected variables and their association with proteinuria

Multivariate logistic regression analysis of selected variables and their association with proteinuria are as shown in Table 5. Sex was not significantly associated with proteinuria. Testing positive for urine glucose was associated with approximately 2 times risk of testing positive for proteinuria (OR = 1.9; p = 0.023). On the analysis of BP, systolic (≥140 mm Hg) and diastolic (≥90 mm Hg) blood pressure were both linked with 3 times risk for proteinuria (p = 0.000 and p = 0.019 respectively). Analysis of age categories for the participants showed a marginal risk for proteinuria within the 50 – 60 year age group (OR = 4.4; p = 0.051) and the 72 – 82 year age group (OR = 5.5; p = 0.053) respectively. The 61 – 71 year age group however showed a significant association with proteinuria with a 7.2 times risk (p = 0.010). The fasting blood glucose concentration of the participants was not significantly associated with proteinuria. Stratification of the study participants by BMI showed no significant association between the classes of BMI and proteinuria (p >0.05). On analysing diabetes duration however, periods from 11 – 15 years and 16 – 20 years were linked with a significant presence of proteinuria with odds ratios of 2.8 and 5.6 respectively.

Table 5: Multivariate logistic regression of factors associated with proteinuria

Variables	OR(95% CI)	P value	SE
Gender			
Female*	1		
Male	1.2(0.7 - 1.9)	0.597	0.304
MAP	1.1(1.0 - 1.1)	0.000	0.015
Urine glucose			
Positive	1.9(1.1 - 3.2)	0.023	0.506
BP (mm Hg)			
Systolic (≥140)	3.0(1.8 - 5.2)	0.000	0.833
Diastolic (≥90)	3.0(1.2 - 7.8)	0.019	1.453
Age (years)			
28 – 38*	1		
39 – 49	3.8(0.8 - 17.6)	0.089	2.971
50 – 60	4.4(1.0 -19.6)	0.051	3.356
61 – 71	7.2(1.6 - 32.7)	0.010	5.574
72 – 82	5.5(1.0 - 31.5)	0.053	4.908
≥83	–	–	–
Fasting Glucose (mmol L^{-1})			
<6.1 *	1		
6.1 – 7.0	1.0(0.3 - 3.4)	0.976	0.623
>7.0	1.8(0.6 - 5.5)	0.330	1.024
BMI (kg m^{-2})			
Underweight*	1		
Normal	0.7(0.2 - 2.2)	0.572	0.418
Pre-obese	0.7(0.2 - 2.1)	0.486	0.388
Obese	1.3(0.4 - 4.5)	0.642	0.826
Diabetes duration (years)			
≤1*	1		
2 – 5	1.1(0.5 - 2.2)	0.839	0.401
6 – 10	1.6(0.8 - 3.3)	0.186	0.590
11 – 15	2.8(1.1 - 7.2)	0.028	1.351
16 – 20	5.6(1.4 - 22.5)	0.016	3.968
>20	7.4(0.6 - 88.0)	0.112	9.369

**** Reference variables; OR = odds ratio; CI = confidence interval; SE = standard error of the odds ratio estimates; MAP =mean arterial pressure; BP = blood pressure***

DISCUSSION

This study evaluated the effects of blood pressure, obesity, fasting blood glucose concentration, duration of diabetes and age on the frequency of proteinuria among type 2 diabetics. The degree of proteinuria increased with advancing age, blood pressure and the duration of the diabetes. Such significant association with proteinuria (appearance of protein in urine) therefore presents each of the assessed variables as independent risk factors to the development of nephropathy (kidney damage).

The observed association between heavy proteinuria and the mean duration of diabetes among study participants from this study corroborates similar observations made in numerous studies and confirms duration of diabetes as an important factor in the development of proteinuria (Klein *et al.*, 1995; Stratton *et al.*, 2000).

Several studies have identified male gender and older age of onset of diabetes as independent risk factors for proteinuria in T2DM (Ballard *et al.*, 1988; Gall *et al.*, 1991; Klein *et al.*, 1995). From this study, sex and for that matter being a male was not a significant risk factor for proteinuria as observed from the multivariate logistic regression analysis. However, older age of onset, specifically age ≥50 years was significantly associated with proteinuria. It therefore suffices to infer from the results that irrespective of sex, age of onset of T2DM greatly modifies the presence or absence of proteinuria.

Elevated blood pressure, be it systolic or diastolic was significantly associated with proteinuria and in previous studies has been found to be an independent risk factor for the development and progression of proteinuria in T2DM (Rossing *et al.*, 2004). Hypertensive nephrosclerosis has been identified as the foremost cause of end stage kidney disease (USRD, 1999). Consequently, treatment with antihypertensives has been shown to reduce the risk of developing proteinuria and also slowing down the progression of renal injury once nephropathy develops (Parving, 1998). A further stratification of the study participants by grade of hypertension showed increases in mild and heavy proteinuria as hyperten-

sive grade increased. The anti-hypertensive proteinuria risk reduction could however not be assessed in this study cohort as per the design of the study, information on anti-hypertensive treatment was not sought. The finding of 15.5% of the study participants with ISH is consistent with previously published works (Trevisan *et al.*, 2002; Bakris, 2004) and could be due to the fact that type 2 diabetic patients are mostly burdened with ISH.

The estimated proteinuria prevalence among the obese participants reported in this study is far lower than that reported from the work of Alwakeel *et al.,* (2011). The observed difference could be attributed to the methodology adapted for proteinuria estimation. In this study, proteinuria was assessed using early morning urine whilst in the study of Alwakeel *et al.,* (2011) proteinuria was assessed utilizing 24 hour urine.

The high rate of obesity with its associated high proteinuria (mild and heavy) observed in this study is in conformity with the findings of (Praga and Morales, 2006). Weight loss, thus, has been identified as an inducer of a reduction in proteinuria among patients with varied causes of proteinuria for which weight gain is an attributable risk factor.

Obesity, hypertension and duration of diabetes independently contribute to the development of proteinuria in T2DM. Elevated BMI has been recognized as a risk factor for increased proteinuria among diabetics in several studies (Anastasio *et al.*, 2000; Ramirez *et al.*, 2002) however no significant association was observed in the classes of BMI and proteinuria from the multivariate analysis conducted in this study. BMI has been touted as being an insensitive method for assessing adiposity and this fact coupled with dietary therapy and restriction in this cohort of study participants could account for the lack of an observed significant difference in the BMI classes and proteinuria. The effect of hyperglycaemia on proteinuria is well documented (Stratton *et al.*, 2000). Fasting glucose concentration was not significantly associated with proteinuria from the multivariate analysis in this study but duration of diabetes (11 – 20 years) was significantly associated with proteinuria. The 15% frequency of heavy proteinuria found in participants with elevated FBS levels in this study could thus be attributed to good glycaemic control practices among this cohort of participants' couples with a reduced duration of diabetes which could be the sole deciding factor. A number of studies (Ramirez *et al.*, 2002; Al-Homrany and Abdelmoneim, 2004) have observed using logistic regression models that those with high SBP and DBP besides longer duration of diabetes have higher levels of proteinuria. This finding is corroborated by results from this study. From the multivariate analysis, the above named factors individually contribute to kidney damage through glomerulosclerosis ultimately resulting in hyperfiltration and consequently proteinuria, which is a cardinal sign of overt nephropathy.

CONCLUSION

The frequency of proteinuria in Ghanaians with T2DM was 13.8%. Significant predictors of proteinuria included age, duration of diabetes, hypertension and duration of diabetes. Strategies to mitigate the occurrence of nephropathy should be targeted at glycaemic and hypertension control.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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