THE ASSOCIATION BETWEEN CHRONIC KIDNEY DISEASE, HYPERURICAEMIA AND PROTEINURIA IN ADULT PATIENTS ATTENDING OUTPATIENT CLINICS IN BANJUL, THE GAMBIA

Nkum BC[1], Micah FB[1], Eghan BA[1], Ankrah TC[1], Nyan O[2]
[1]Department of Medicine, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, [2]Department of Medicine, Edward Francis Small Teaching Hospital, The Gambia, [2]Medical Research Council Laboratories, Fajara, The Gambia

Abstract

Background: Chronic kidney disease (CKD) is manifested by irreversible worsening renal function and is associated with proteinuria and hyperuricaemia.
Objective: To determine the prevalence of CKD, hyperuricaemia and proteinuria and explore the relationship between CKD, hyperuricaemia and proteinuria among outpatients in Banjul, The Gambia.
Design: Prospective cross-sectional study
Setting: Outpatient clinics of Edward Francis Small Teaching Hospital and Medical Research Council Laboratories in Banjul.
Methods: Two hundred and eight consecutive patients with hypertension on treatment and 108 non-hypertensive patients aged over 25years were enrolled. A questionnaire was filled and anthropometric measurements were taken. An oral glucose tolerance test was done. Serum uric acid and creatinine were determined from venous blood samples and proteinuria was determined by urine dipsticks. The estimated glomerular filtration rate (GFR) was calculated using the Cockcroft and Gault equation. CKD was defined and classified by The National Kidney Foundation's Kidney Diseases Outcomes Quality Initiative guidelines.
Results: The results of 300 participants were included in this analysis. The prevalence of hyperuricaemia was 36%, proteinuria 25% and CKD 41% (10.7% of participants had Stage 1, 6.7% Stage 2, 21.7% Stage 3, 1.3% Stage 4 and 0.3% Stage 5). The mean uric acid was 0.33 (0.13) mmol/L, mean creatinine 88.1 (54.1) µmol/L and mean GFR was 103.2 (80.2) ml/min/1.73 m^2 .There was a strong and significant association between hyperuricaemia, proteinuria and CKD among these participants before and even after controlling for age, sex, hypertension and diabetes mellitus.
Conclusion: The prevalence of CKD, hyperuricaemia and proteinuria in patients attending clinics in Banjul was high. There was a strong and significant association between CKD, hyperuricaemia and proteinuria.

Key Words: Systemic Hypertension, Chronic Kidney Disease, Renal Failure, Hyperuricaemia, Proteinuria

Introduction

Chronic kidney disease (CKD) is one of the major causes of mortality and morbidity in the developing as well as the developed world[1-4]. The incidence and prevalence of CKD is on the increase and this is especially as a result of the epidemic of hypertension and type II diabetes mellitus (DM) which is occurring worldwide and is consequently fueling this increase[5,6]. There is therefore the need for increased screening and early detection of renal disease generally but especially among hypertensive and DM patients. This is especially crucial in sub-Saharan Africa where there are very few facilities for treatment of CKD and treatment costs are prohibitive[7,8]. The current guidelines recommend screening for CKD using the estimated glomerular filtration rate (GFR) after determining serum creatinine levels[9].

CKD is defined as irreversible, substantial and long-standing loss of renal function. Albuminuria defined as urine albumin-creatinine ratio ≥30 mg/g, is a diagnostic component of CKD[10]. This is particularly in diabetic nephropathy which in the incipient phase is characterised by microalbuminuria (30-300 mg/day) and is followed by the phase of overt proteinuria (>300 mg/day). In DM patients, microalbuminuria is now known as the earliest marker of diabetic nephropathy and is currently the recommended screening test[11]. In hypertensive patients with and without DM, microalbuminuria is a risk factor for hypertensive target end organ damage including kidney disease and is associated with progression to end-stage renal disease[12]. Microalbuminuria is also a marker of increased risk for the development of hypertension in normotensives[13]. CKD is thus associated with proteinuria and examining urine for protein is important in screening for CKD.

Hyperuricaemia is associated with confirmed risk factors for CKD such as DM, hypertension and metabolic syndrome[14]. Severe renal failure of any aetiology may be associated with hyperuricaemia and may in the rare instance result in gout. In certain

Corresponding Author: **Frank B. Micah**
Komfo Anokye Teaching Hospital,
P. O. Box 1934, Kumasi.
Tel: 00233 244135972
Email Address: fbmicah@hotmail.com
Conflict of Interest: None declared

instances the severe renal failure is the cause of the hyperuricaemia while the reverse is also true in other instances. There are some studies which have shown an association between hyperuricaemia and CKD while others have demonstrated otherwise. Wang et al found hyperuricaemia to be a risk factor for CKD in a cohort study involving 94,422 Taiwanese participants[14]. In another Taiwanese study See et al found only a weak association between hyperuricaemia and renal function while hyperuricaemia was strongly associated with metabolic syndrome[15]. The prevalence of gout has been shown to increase with progressing stages of CKD in the US population from National Health and Nutrition Examination Surveys data[16].

There are very few published studies on renal function, CKD, uric acid and urine protein in The Gambia. From a 1996-97 community study conducted in Banjul and Farafenni, van der Sande et al reported mean uric acid and creatinine as well as prevalence of high creatinine and uric acid as part of various reports[17-19]. Recently de la Cruz and others have reported on 69 terminal CKD patients they screened for haemodialysis in Banjul. Mean creatinine for these patients was 1425.6 (366.1) μmol/L and 13% had proteinuria.

As part of our study to determine the relationship between left ventricular hypertrophy and insulin resistance, we determined creatinine, uric acid and urine protein in hypertensive and non-hypertensive Gambians who were seen at outpatient clinics[20,21]. Our main objective for this current study was to determine the prevalence of CKD, hyperuricaemia and proteinuria and also explore the relationship between CKD, hyperuricaemia and proteinuria among patients attending outpatient clinics in Banjul, The Gambia.

Materials and Methods

This was a prospective cross sectional study conducted from January to May 2000. The participants were recruited from the Edward Francis Small Teaching Hospital (EFSTH), Banjul and Medical Research Council (MRC) Laboratories, Fajara, The Gambia. Patients with systemic hypertension who were seen at the hypertension clinic of EFSTH were consecutively recruited into the study. At the Gate Clinic of the MRC Laboratories, patients who reported with minor infectious diseases who had no cardiovascular disease or DM who in addition did not have hypertension were recruited as the non-hypertensives. The exclusion criteria for this study were severe inter-current illnesses, systemic or metabolic diseases, cardiovascular disease (excluding hypertension) or labile hypertension and morbid obesity (BMI > 35 kg / m^2). Known cases of DM were excluded from the study but those who were diagnosed after undergoing an oral glucose tolerance test (OGTT) were included.

A field worker administered a questionnaire using the appropriate local language and this was followed by a physical examination undertaken by one physician. The weight of participants wearing light clothes and without footwear was measured using an electric scale (Secca ® 770, CMS London). Height was measured to the nearest 0.5 cm after participants have removed their footwear and head gear or cap using standardised stadiometers. A plastic tape measure was used to record hip and waist circumferences to the nearest 0.5 cm. The blood pressure was measured on the left arm using a digital blood pressure machine (Omron ® HOM – 705 CP, Japan). Three readings were taken and the mean of the later two readings was used in the analysis[22].

The participants after recruitment reported back the following morning after an overnight fast for urine examination, blood sampling, electrocardiogram and echocardiogram. The patient first collected about 10 to 20mls of urine in a sterile wide-necked leak proof urine specimen container. This was immediately tested for urine protein with Albustix urine dipsticks (Bayer AG, Germany). The results were read and recorded as no proteinuria, 1+ proteinuria, 2+ proteinuria or 3+ proteinuria. Venous blood samples were then collected and analysed for uric acid and creatinine at the MRC Biochemistry Laboratory using a centrifugal biochemical analyzer (Cobas Fara, Roche, UK). Afterwards an OGTT was performed utilising 75g anhydrous glucose in 300 - 350 ml of water. The glucose levels on a fasting, 30 min and 120 min samples were determined immediately upon taking the samples using a Haemocue analyser (Haemocue AB, Sweden). The complete results of the OGTT is in the process of being reported in another article but the results were used in classifying the participants into those with and without DM.

The following definitions were adopted for this study. Hypertension was defined as systolic blood pressure ≥ 140 and / or diastolic blood pressure ≥ 90.mmHg in subjects who are not taking antihypertensive medication[23]. Overall Obesity was defined as Body Mass Index (BMI) ≥30 kg / m^2 while Central Obesity or High Waist Hip Ratio (WHR) was defined as WHR > 0.9 for males and > 0.8 for females[24]. And DM was defined as fasting venous plasma glucose (FPG) ≥ 7.0 mmol/L and or 2h post glucose capillary whole blood ≥ 11.1 mmol/L[25,26]. Hyperuricaemia was defined as uric acid level ≥ 0.36 mmol/L in females and ≥ 0.42 mmol/L for males[27]. Proteinuria was defined as any proteinuria on urine dipstick and this included 1+ proteinuria, 2+ proteinuria and 3+ proteinuria.

The estimated glomerular filtration rate (GFR) was calculated using the Cockcroft and Gault equation; GFR (ml/min/1.73 m^2) = 1.23 (140 - age) x weight (kg) / Plasma creatinine (μmol/l) for males and GFR (ml/min/1.73 m^2) = 1.04 (140 - age) x weight (kg) /Plasma creatinine (μmol/l) for females[28]. The National

Kidney Foundation's Kidney Diseases Outcomes Quality Initiative (NKF KDOQI) guidelines were used in defining and classifying CKD. This classification is based on GFR and the presence or absence of kidney damage. The reduced GFR and or kidney damage must be present for more than 90 days to establish chronicity. In the absence of past data on GFR or markers of kidney damage, chronicity is inferred from clinical presumption of kidney disease for more than 3 months. Based on this assumption CKD was classified into Stage 1 GFR > 90 ml/min/1.73 m^2 and albuminuria, Stage 2 GFR 60 - 89 ml/min/1.73 m^2 and albuminuria, Stage 3 GFR 30 - 59 ml/min/1.73 m^2, Stage 4 GFR 15 - 29 ml/min/1.73 m^2 and Stage 5 GFR < 15 ml/min/1.73 m^2 [29].

The data was analysed using Stata version 8.0 statistical package and Microsoft Excel 2007. The mean and standard deviation were calculated for continuous variables, and were compared using the Student t-test. Percentages were calculated for discrete variables and these were compared using Pearson Chi-square test. The participants were classified further into normotensives with and without DM and hypertensives with and without DM and these four subgroups were captioned as the clinical group. CKD was classified into stage1 to stage 5 and proteinuria into four subgroups (Group 0 – No proteinuria, Group 1 – 1+ proteinuria, Group 2 – 2+ proteinuria and Group 3 – 3+ proteinuria). One-way analysis of variance was used in the analysis of the continuous variables in the different subgroups of the clinical group, CKD and proteinuria. The results of FPG, GFR and creatinine were not normally distributed so a logarithmic transformation was done and this was used in all further analysis using univariate and multivariate linear and logistic regression. For the purpose of logistic regression analysis proteinuria was reclassified into two subgroups, no proteinuria and any proteinuria. P-values of less than 0.05 were taken as statistically significant.

The study was approved by The Gambia Government / MRC Ethical Committee. All the participants gave a formal consent by signing or thumb printing an informed consent form after careful consideration and explanation.

Results

From outpatient clinics 208 consecutive patients (138 females) with systemic hypertension on treatment and 108 non-hypertensive patients (69 females) were enrolled for our initial study[20,21] but only 300 (194 hypertension, 198 females) of these patients were included in this analysis. Ten participants had no results for both creatinine and uric acid while 6 had no urine protein results and were therefore excluded from the analysis. The mean (± standard deviation (sd)) age of the participants was 53.5 (12.0) years. Table 1 show the characteristics of hypertension and normotensive patients.

Table 1: The clinical characteristics of the participants

	Hyper-tension (n=194)	Normal (n=106)	All (n=300)	P
Parameter				
	Number (%)	Number (%)	Number (%)	
Sex				
Male	63 (32.5)	39 (36.8)	102 (34.0)	0.45
Female	131 (67.5)	67 (63.2)	198 (66.0)	0.45
Age range (years)	27 – 85	30 – 80	27 - 85	
BMI ≥ 30	60 (30.9)	18 (17.0)	78 (26.0)	< 0.01
High WHR	153 (78.9)	62 (58.5)	215 (71.7)	< 0.001
DM	35 (18.0)	8 (7.6)	43 (14.3)	0.01
	Mean±sd	Mean±sd	Mean±sd	
Age (years)	55.2 (11.6)	50.5 (12.1)	53.5 (12.0)	< 0.01
Weight (kg)	73.5 (16.2)	66.3 (13.3)	71.0 (15.6)	< 0.001
Height (m)	1.64 (0.08)	1.65 (0.09)	1.64 (0.08)	0.44
BMI (kg/m^2)	27.5 (6.2)	24.6 (5.4)	26.5 (6.1)	< 0.001
Waist circum-ference (cm)	95.4 (12.5)	87.8 (11.9)	92.7 (12.8)	< 0.0001
Hip circum-ference (cm)	106.9 (12.8)	103.2 (12.0)	105.6 (12.6)	0.02
Waist-Hip ratio	0.89 (0.06)	0.85 (0.07)	0.88 (0.06)	< 0.0001
SBP (mmHg)	147.9 (27.1)	115.9 (13.1)	136.6 (27.7)	< 0.0001
DBP (mmHg)	88.8 (13.5)	72.0 (8.4)	82.9 (14.4)	< 0.0001

They were similar in the proportion of males and females but there were significant differences in all the other parameters with the hypertension patients having significantly higher values. Mean FPG was 5.7 (2.4) mmol/L, mean uric acid 0.33 (0.13) mmol/L, mean creatinine 88.1 (54.1) µmol/L and mean GFR was 103.2 (80.2) ml/min/1.73 m^2 (Table 2). Mean FPG was similar in the normal and hypertension groups while it was significantly higher in the DM and DM - hypertension groups. There were significant differences in the mean uric acid in the different clinical groups, the highest in the DM - hypertension group and the lowest in the normal group. The

differences in creatinine and GFR in the clinical groups were not statistically significant.

Table 3 shows the GFR group of participants by the degree of proteinuria. There were no significant differences in the various GFR groups except the 30 – 59 ml/min/1.73 m^2 which included the only 2 participants with proteinuria of 3+. In the GFR group of > 90 ml/min/1.73 m^2, there were 28 participants with proteinuria of 1+ and 4 participants with 2+ and these 32 (10.7%) were classified as CKD stage 1 while in the 60 – 89 ml/min/1.73 m^2 group there were 16 participants with proteinuria 1+ and 4 with 2+ (20 (6.7%)) who were classified as CKD stage 2. Sixty five (21.7%) participants were classified as CKD stage 3, 4 (1.3%) as CKD stage 4 and 1 (0.3%) as CKD stage 5. Overall 122 (40.7%) of the study population had CKD. One hundred and seven (35.7%) of participants had hyperuricaemia and 76 (25.3%) had some degree of proteinuria. Table 4 shows that the patients with hypertension with and without DM had significantly higher prevalence of hyperuricaemia. There were no significant differences in the prevalence of CKD in the different clinical groups while proteinuria was significantly common in the hypertension and DM - hypertension groups. The 4 participants with stage 4 and the single participant with stage 5 CKD were all hypertension patients. From Table 5 there were several significant associations between the various variables. The clinical group was significantly associated with hyperuricaemia, uric acid and proteinuria but not with CKD, creatinine and GFR. Hyperuricaemia was significantly associated with CKD, creatinine and GFR but not with proteinuria. CKD was associated with proteinuria and uric acid while proteinuria was significantly associated with uric acid and creatinine but not with GFR.

The results from the univariate linear regression analysis (Table 6) were similar but not identical to the results from Table 5. There were significant association between uric acid and proteinuria, log of creatinine and log of GFR. Log of creatinine and log of GFR were both significantly associated with proteinuria, hyperuricaemia and uric acid. All these associations were still significant after controlling for age, sex, hypertension and DM in multivariate analysis (Table 7). Table 8 shows the results of univariate logistic regression analysis with proteinuria and hyperuricaemia as the outcome variables. Proteinuria was significantly associated with uric acid, log of creatinine and log of GFR but the relationship with hyperuricaemia was not up to statistical significance. There were significant association between hyperuricaemia and log of creatinine and log of GFR but the association with proteinuria was not statistically significant. After controlling for age, sex, hypertension and DM, the association between proteinuria and both uric acid and hyperuricaemia were not significant. The association between proteinuria and log of creatinine and log of GFR on one hand and the association between hyperuricaemia and log of creatinine and log of GFR on the other hand were both significant in multivariate analysis.

Table 2: Mean FPG, uric acid, creatinine and GFR by clinical group

	Normal (n=98)	DM (n=8)	Hypertension (n=159)	DM-Hypertension (n=35)	All (n=300)	P
FPG (mmol/L)	5.1 (0.6)	12.4 (9.4)	5.2 (0.7)	8.0 (3.3)	5.7 (2.4)	< 0.0001
Uric Acid (mmol/L)	0.29 (0.09)	0.35 (0.16)	0.35 (0.13)	0.39 (0.18)	0.33 (0.13)	< 0.001
Creatinine (μmol/L)	80.4 (19.6)	89.9 (22.4)	92.3 (64.1)	90.5 (72.3)	88.1 (54.1)	0.39
GFR (ml/min/1.73 m^2)	90.4 (32.1)	86.0 (31.5)	107.3 (99.7)	124.6 (78.0)	103.2 (80.2)	0.12

Table 3: GFR group by proteinuria

Proteinuria / GFR	0 (n=224)	1+ (n=62)	2+ (n=12)	3+ (n=2)	All (n=300)	P
> 90	116 (51.8)	28 (45.2)	4 (33.3)	0 (0)	148 (49.3)	0.25
60 - 89	62 (27.7)	16 (25.8)	4 (33.3)	0 (0)	82 (27.3)	0.79
30 - 59	44 (19.6)	15 (24.2)	4 (33.3)	2 (100.0)	65 (21.7)	0.03
15 - 29	2 (0.9)	2 (3.2)	0 (0)	0 (0)	4 (1.3)	0.53
< 15	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (0.3)	0.28

Table 4: Prevalence of hyperuricaemia, CKD and proteinuria by clinical group

	Normal (n=98)	DM (n=8)	Hypertension (n=159)	DM+ Hypertension (n=35)	All (n=300)	P
Hyperuricaemia	14 (14.3)	3 (37.5)	74 (46.5)	16 (45.7)	107 (35.7)	< 0.001
CKD						
Stage 1	4 (4.1)	0 (0.0)	20 (12.6)	8 (22.9)	32 (10.7)	0.10
Stage 2	5 (5.1)	0 (0.0)	11 (6.9)	4 (11.4)	20 (6.7)	0.52
Stage 3	17 (17.4)	3 (37.5)	39 (24.5)	6 (17.1)	65 (21.7)	0.33
Stage 4	0 (0)	0 (0)	3 (1.9)	1 (2.9)	4 (1.3)	0.49
Stage 5	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.3)	0.83
All Stages	26 (26.5)	3 (37.5)	74 (46.5)	19 (54.3)	122 (40.7)	< 0.01
Proteinuria						
0	87 (88.8)	8 (100)	110 (69.2)	19 (54.3)	224 (74.7)	< 0.0001
1	9 (9.2)	0 (0)	40 (25.2)	13 (37.1)	62 (20.7)	< 0.001
2	2 (2.0)	0 (0)	7 (4.4)	3 (8.6)	12 (4.0)	0.35
3	0 (0)	0 (0)	2 (1.3)	0 (0)	2 (0.7)	0.62

Table 5: The association between clinical group, hyperuricaemia, CKD and proteinuria and various variables

	Clinical Group	Hyperuricaemia	CKD	Proteinuria
	P	P	P	P
Sex	0.24 (χ^2)	0.88 (χ^2)	< 0.001 (χ^2)	0.39 (χ^2)
BMI ≥ 30	0.02 (χ^2)	0.30 (χ^2)	0.03 (χ^2)	0.49 (χ^2)
High WHR	< 0.01 (χ^2)	0.86 (χ^2)	< 0.01 (χ^2)	0.35 (χ^2)
Hypertension	N/A	< 0.001 (χ^2)	< 0.01 (χ^2)	< 0.001 (χ^2)
DM	N/A	0.21 (χ^2)	0.42 (χ^2)	0.20 (χ^2)
Clinical group	N/A	< 0.001 (χ^2)	0.07 (χ^2)	< 0.01 (χ^2)
Hyperuricaemia	< 0.001 (χ^2)	N/A	< 0.001 (χ^2)	0.07 (χ^2)
CKD	0.07 (χ^2)	< 0.001 (χ^2)	N/A	< 0.001 (χ^2)
Proteinuria	< 0.01 (χ^2)	0.07 (χ^2)	< 0.001 (χ^2)	N/A
Age	< 0.01 (F)	0.03 (t)	< 0.001 (F)	0.03 (F)
Weight	< 0.001 (F)	< 0.001 (t)	< 0.0001 (F)	0.22 (F)
Height	0.72 (F)	0.60 (t)	0.10 (F)	0.06 (F)
BMI	< 0.001 (F)	< 0.01 (t)	< 0.0001 (F)	0.08 (F)
Waist circumference	< 0.0001 (F)	< 0.001 (t)	< 0.0001 (F)	0.09 (F)
Hip circumference	0.02 (F)	< 0.01 (t)	< 0.0001 (F)	0.16 (F)
Waist-Hip ratio	< 0.0001 (F)	0.04 (t)	0.96 (F)	0.41 (F)
SBP	< 0.0001 (F)	< 0.001 (t)	< 0.001 (F)	< 0.0001 (F)
DBP	< 0.0001 (F)	< 0.01 (t)	0.02 (F)	< 0.0001 (F)
FPG	< 0.0001 (F)	0.09 (t)	0.92 (F)	0.80 (F)
Uric Acid	< 0.001 (F)	N/A	< 0.0001 (F)	< 0.01 (F)
Creatinine	0.39 (F)	< 0.0001 (t)	< 0.0001 (F)	< 0.01 (F)
GFR	0.12 (F)	< 0.001 (t)	N/A	0.36 (F)

Table 6: Univariate analysis with uric acid, log of creatinine and log of GFR as the outcome variable

	Uric Acid		Creatinine		GFR	
	r	P	r	P	r	P
Sex	-0.026	0.10	-0.133	0.02	0.343	< 0.001
BMI ≥ 30	0.029	0.09	-0.030	0.61	0.400	< 0.001
High WHR	-0.006	0.74	-0.113	0.05	0.301	< 0.001
Hypertension	0.064	< 0.001	0.005	0.93	0.048	0.47
DM	0.053	0.01	-0.042	0.57	0.141	0.13
Proteinuria	0.050	< 0.01	0.154	< 0.01	-0.169	0.02
Hyperuricaemia	N/A	N/A	0.402	< 0.001	-0.351	< 0.001
Age	0.002	< 0.001	0.003	0.12	-0.015	< 0.001
Weight	0.001	< 0.01	-0.002	0.30	0.016	< 0.001
Height	0.128	0.17	0.261	0.41	-0.138	0.73
BMI	0.003	0.02	-0.005	0.21	0.039	< 0.001
Waist circumference	0.002	< 0.01	-0.003	0.13	0.018	< 0.001
Hip circumference	0.001	0.08	-0.003	0.11	0.020	< 0.001
Waist-Hip ratio	0.276	0.02	-0.067	0.87	0.262	0.60
SBP	0.001	< 0.001	0.002	< 0.01	-0.004	< 0.01
DBP	0.002	< 0.001	0.003	0.07	-0.002	0.41
FPG	0.070	0.02	0.021	0.84	-0.003	0.98
Uric Acid	N/A	N/A	2.288	< 0.001	-2.293	< 0.001
Creatinine	0.194	< 0.001	N/A	N/A	N/A	N/A
GFR	-0.126	< 0.001	N/A	N/A	N/A	N/A

Table 7: Multivariate analysis with uric acid, log of creatinine and log of GFR as the outcome variable adjusting for age, sex, DM and hypertension

	Uric Acid		Creatinine		GFR	
	r	P	r	P	r	P
Proteinuria	0.033	0.05	0.176	< 0.01	-0.222	< 0.01
Hyperuricaemia	N/A	N/A	0.436	< 0.001	-0.373	< 0.001
Uric acid	N/A	N/A	2.459	< 0.001	-2.251	< 0.001
Creatinine	0.191	< 0.001	N/A	N/A	N/A	N/A
GFR	-0.137	< 0.001	N/A	N/A	N/A	N/A

Table 8: Univariate analysis with proteinuria and hyperuricaemia as the outcome variable

	Proteinuria			Hyperuricaemia		
	OR	CI	P	OR	CI	P
Sex	1.48	0.48-2.63	0.18	0.96	0.58-1.58	0.88
BMI ≥ 30	1.22	0.68-2.18	0.50	1.82	1.08-3.09	0.03
High WHR	1.38	0.75-2.51	0.30	0.95	0.56-1.61	0.86
Hypertension	4.35	2.18-8.69	< 0.001	4.53	2.51-8.18	< 0.001
DM	1.95	0.98-3.85	0.06	1.52	0.79-2.93	0.21
Proteinuria	N/A	N/A	N/A	1.67	0.98-2.85	0.06
Hyperuricaemia	1.67	0.98-2.85	0.06	N/A	N/A	N/A
Age	1.01	0.99-1.03	0.27	1.02	1.00-1.04	0.03
Weight	1.00	0.98-1.01	0.83	1.03	1.01-1.04	< 0.01
Height	0.03	0.00-0.73	0.03	2.20	0.12-39.71	0.59
BMI	1.02	0.98-1.06	0.41	1.07	1.02-1.11	< 0.01
Waist circumference	1.01	0.99-1.03	0.55	1.03	1.01-1.06	< 0.01
Hip circumference	1.00	0.98-1.02	0.93	1.03	1.01-1.05	< 0.01
Waist-Hip ratio	7.58	0.13-443.83	0.33	50.48	1.15-2224.93	0.04
SBP	1.02	1.01-1.03	< 0.001	1.02	1.01-1.03	< 0.001
DBP	1.04	1.02-1.06	< 0.001	1.03	1.01-1.05	< 0.01
FPG	2.16	0.83-5.66	0.12	2.15	0.85-5.47	0.11
Uric Acid	18.17	2.42-136.53	< 0.01	N/A	N/A	N/A
Creatinine	2.21	1.20-4.08	0.01	22.07	8.69-56.05	< 0.001
GFR	0.57	0.35-0.93	0.02	0.26	0.15-0.44	< 0.001

Table 9: Multivariate analysis with proteinuria and hyperuricaemia as the outcome variable adjusting for age, sex, DM and hypertension

	Proteinuria			Hyperuricaemia		
	OR	CI	P	OR	CI	P
Proteinuria	N/A	N/A	N/A	1.17	0.66-2.06	0.59
Hyperuricaemia	1.18	0.67-2.07	0.57	N/A	N/A	N/A
Uric Acid	6.65	0.82-53.94	0.08	N/A	N/A	N/A
Creatinine	2.19	1.20-3.99	0.01	26.67	9.73-73.13	< 0.001
GFR	0.45	0.26-0.78	< 0.01	0.19	0.10-0.36	< 0.001

Discussion

This study has shown that the prevalence of hyperuricaemia in these participants was 36%, that of proteinuria was 25% and CKD 41% though stages 4 and 5 CKD was only 2%. The mean uric acid was 0.33 (0.13) mmol/L, mean creatinine 88.1 (54.1) µmol/L and mean GFR was 103.2 (80.2) ml/min/1.73 m^2 .There was also a strong and significant association between uric acid, proteinuria and CKD among these subjects before and even after controlling for age, sex, hypertension and DM.

In the previous Gambian study the following results were obtained, mean uric acid 0.32 (0.08) mmol/L in urban men, 0.25 (0.07) mmol/L in urban women, 0.30 (0.06) mmol/L in rural men and 0.21 (0.06) mmol/L in rural women. Mean creatinine was 82.6 (49.8) µmol/L in urban men, 66.0 (37.4) µmol/L in urban women, 79.8 (18.6) µmol/L in rural men and 60.7 (21.4) µmol/L in rural women. The prevalence of hyperuricaemia was as follows; 7.4% in urban men, 8.5% in urban women, 1.4% in rural men and 1.3% in rural women while the prevalence of elevated creatinine (defined as creatinine ≥90 µmol/L for women or ≥100 µmol/L for men) were 15.3%, 8.2%, 13.0% and 1.4% for urban men, urban women, rural men and rural women respectively. These mean levels and prevalence levels for the whole population were in all instances lower than that of the hypertensives. In the hypertensive population mean uric acid was 0.36 (0.10) mmol/L in urban men, 0.29 (0.10) mmol/L in urban women, 0.35 (0.07) mmol/L in rural men and 0.23 (0.07) mmol/L in rural women while mean creatinine was 95.0 (88.4) µmol/L in urban men, 80.5 (73.4) µmol/L in urban women, 95.6 (18.4) µmol/L in rural men and 71.8 (32.9) µmol/L in rural women. The prevalence of hyperuricaemia among the hypertensives

was 18.4%, 28.1%, 6.8% and 6.9% while the prevalence of elevated creatinine was 22.2%, 10.9%, 27.0% and 6.9% for urban men, urban women, rural men and rural women respectively[17-19]. These results are similar but not identical to the findings of our present study and further comparison by formal statistical testing is also not possible.

Serum uric acid concentration is maintained through the synthesis and excretion of urate with approximately 70% of uric acid being excreted from the kidneys. Creatinine has been shown to have a strong influence on uric acid levels by Choe et al.[30] while an independent relationship of creatinine and uric acid has been reported by Rathmann and others[31]. Hyperuricaemia has been shown to be an independent risk factor for renal dysfunction in the normal population as well as in patients with CKD, DM and hypertension[32-41]. In animal studies, hyperuricaemia has been shown to be associated with the development of mild renal disease which is characterised by mild proteinuria[42]. Other animal studies have also shown that hyperuricaemia may not only cause new onset renal disease but may worsen already existent renal disease[39]. Clinical studies have demonstrated that lowering uric acid in renal disease patients with asymptomatic hyperuricaemia with allopurinol led to less and slower progression of the renal disease[43]. Other studies have also shown that cessation of allopurinol treatment in patients with CKD resulted in a significant deterioration of renal function[44,45]. The results of our study have shown this association between uric acid and renal function, before and after adjusting for age, sex, hypertension and DM.

Hyperuricaemia therefore has a direct effect on renal function and an indirect effect on urine protein through its effect on the kidneys. Several studies on DM patients have illustrated this relationship between hyperuricaemia and proteinuria. In a study of type 2 DM patients, a significant association was found between hyperuricaemia and serum creatinine and eGFR. In the same study serum uric acid levels was positively correlated to the urinary albumin-creatinine ratio and this relationship remained significant after adjusting for eGFR[46]. Tseng also found serum uric acid to be independently correlated to urinary albumin-creatinine ratio in type 2 DM Taiwanese patients[34] while Fukui et al demonstrated the same association in Japanese men with type 2 DM[47]. In Italy Bo et al found uric acid to be associated independently with macroalbuminuria[48] while Bruno et al established this independent association with both micro- and macroalbuminuria[49]. In type 1 DM, the level of uric acid early in the course of diabetes was demonstrated to be independently and significantly associated with later development of persistent macroalbuminuria but not persistent microalbuminuria[37]. In our study the association between uric acid and proteinuria was significant in univariate but not in multivariate analysis controlling for age, sex, hypertension and DM.

Most of these DM studies have also demonstrated the relationship between renal function and proteinuria. Eghan and others found creatinine and blood urea nitrogen to be significantly higher in type 2 DM patients with microalbuminuria in Kumasi, Ghana[50]. In Dar es Salaam, Tanzania, Lutale et al found serum creatinine to be independently associated with urine albumin concentration measured as average albumin excretion rate in multiple linear regression analysis[51]. The relationship between microalbuminuria and renal function has also been demonstrated in normotensives and hypertension patients with hypertensive target end organ damage[52]. There was a significant association between renal function and proteinuria in these Gambians we studied with urine protein detected with urine dipsticks.

The major strength of our study is that this is one of the few renal studies which have been undertaken in The Gambia. There has been no previous study in The Gambia which sought to determine the relationship between renal function, uric acid and proteinuria. This study has shown a strong association between renal function, proteinuria and uric acid in these participants. Potential limitations of this study include the hospital based cross sectional design which is fraught with biases such as proximity and selection biases. Also instead of only measuring urine protein by using urine dipsticks the ideal would have been to determine the urinary albumin-creatinine ratio or albumin excretion rate on a morning urinary sample or a 24-hour urine sample. However since this was not the primary objective of the original study this was not measured. Further, some participants may have produced a first morning urine sample since the participants were seen early in the morning for the urine examination, but we did not inquire to confirm this neither did we take any measures to rule out ambulatory or orthostatic proteinuria. There is therefore the need generally for more cardiovascular studies, preferably large community based studies in The Gambia and specifically ones that would explore further the relationship between renal function, uric acid and proteinuria.

Conclusion

The prevalence of hyperuricaemia, proteinuria and CKD was high in The Gambia. There was a significant association between renal function, uric acid and proteinuria in these participants and this supports the suggestion that hyperuricaemia may have a direct effect on renal function and therefore indirectly on proteinuria.

References

1. Aitkins RC. The epidemiology of chronic kidney disease. Kidney Int Suppl 2005; 94: S14-S18.
2. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365: 331–340.

3. Naicker S. End-stage renal disease in sub-Saharan and South Africa. Kidney Int Suppl 2003; 83: S119-S122.
4. Mate-Kole MO, Affram RK. Presentation and clinical course of End-stage renal failure in Ghana. A preliminary prospective study. *Ghana Med. J* 1990; 24: 164-168.
5. Plange-Rhule J, Phillips R, Acheampong JW, Saggar-Malik AK, Cappuccio FP, Eastwood JB. Hypertension and renal failure in Kumasi, Ghana. *J Hum Hypertens*. 1999 Jan; 13:37-40.
6. Haroun MK, Jaar BG, Hoffman SC, et al. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol* 2003; 14: 2934-2941.
7. Agaba EI, Lopez A, Ma I, Martinez R, Tzamaloukas, Vanderjagt DJ, Glew RH, Tzamaloukas AH. Chronic haemodialysis in a Nigerian teaching hospital: practice and costs. *Int J Artif Organs* 2003; 26: 991-995.
8. Fogazzi GB, Attolou V, Kadiri S, Fenili D, Priuli F. A nephrological program in Benin and Togo, West Africa. Kidney Int Suppl 2003; 83: S56-S60
9. European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Nephrol Dial Transplant. 2002; 17 Suppl 7:72-87.
10. Saydah SH, Pavkov ME, Zhang C, Lacher DA, Eberhardt MS, Burrows NR, Narva AS, Eggers PW, Williams DE. Albuminuria prevalence in first morning void compared with previous random urine from adults in the national health and nutrition examination survey, 2009-2010. Clin Chem. 2013 Apr; 59(4):675-83. doi: 10.1373/clinchem.2012.195644. Epub 2013 Jan 11.
11. National Institute for Health and Clinical Excellence. CG 66. Type 2 Diabetes: full guidelines. London: NICE, 2008. Acesseed 24 March 2014.
12. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med.* 2003; 139:901 – 906.
13. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE; Prevend Study Group. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med*. 2001; 249:519 – 526.
14. Wang S, Shu Z, Tao Q, Yu C, Zhan S, Li L. Uric acid and incident chronic kidney disease in a large health check-up population in Taiwan. Nephrology (Carlton). 2011 Nov; 16(8):767-76.
15. See LC, Kuo CF, Chuang FH, Li HY, Chen YM, Chen HW, Yu KH. Serum uric acid is independently associated with metabolic syndrome in subjects with and without a low estimated glomerular filtration rate. *J Rheumatol*. 2009; 36:1691-8. doi: 10.3899/jrheum.081199. Epub 2009 Jun 16.
16. Juraschek SP, Kovell LC, Miller ER 3rd, Gelber AC. Association of kidney disease with prevalent gout in the United States in 1988-1994 and 2007-2010. Semin Arthritis Rheum. 2013 Jan 8. pii: S0049-0172(12)00266-1
17. van der Sande MA, Walraven GE, Milligan PJ, Banya WA, Ceesay SM, Nyan OA, McAdam KP. Family history: an opportunity for early interventions and improved control of hypertension, obesity and diabetes. *Bull World Health Organ*. 2001; 79:321-8.
18. van der Sande MA, Ceesay SM, Milligan PJ, Nyan OA, Banya WA, Prentice A, McAdam KP, Walraven GE. Obesity and undernutrition and cardiovascular risk factors in rural and urban Gambian communities. *Am J Public Health*. 2001:91:1641-4.
19. van der Sande MA, Milligan PJ, Nyan OA, Rowley JT, Banya WA, Ceesay SM, Dolmans WM, Thien T, McAdam KP, Walraven GE. Blood pressure patterns and cardiovascular risk factors in rural and urban gambian communities. *J Hum Hypertens*. 2000; 14:489-96.
20. Nkum BC, Nyan O, Corrah T, Ankrah TC, Allen S, Micah FB., et al. Resting electrocardiographic and echocardiographic findings in an urban community in the Gambia. *Journal of Science and Technology*. 2009; 29:130-140.
21. Nkum BC, Micah FB, Ankrah TC Nyan O. Left ventricular hypertrophy and insulin resistance in adults from an urban community in The Gambia: cross-sectional study. *PLoS One*. 2014 4; 9:e93606.
22. Mayet J, Shahi M, Foale RA, Poulter NR, Sever PS, McG Thom SA. Racial differences in cardiac structure and function in essential hypertension. *Br Med J*. 1994; 308:1011-1014.
23. Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L et al. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization.Clin Exp Hypertens. 1999 Jul-Aug; 21(5-6):1009-60.
24. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National

Institutes of Health.Obes Res. 1998 Sep; 6 Suppl 2:51S-209S.
25. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998; 15:539-53.
26. World Health Organisation. Definition and diagnosis diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF Consultation, Geneva, Switzerland. 2006.
27. Harmonisation of Reference Intervals Pathology Harmony Group, Clinical Biochemistry Outcomes,January 2011.Retrieved 24 March 2014.
28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
29. Anonymous. Kidney Disease Outcome Quality Initiative. Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney* Dis 2002; 39 Suppl 1: S1-S246.
30. Choe JY, Park SH, Kim JY, Shin IH, Kim SK: Change in serum uric acid between baseline and 1-year follow-up and its associated factors in male subjects. Clin Rheumatol 2008, 27:483–489
31. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM: Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *Eur J Epidemiol* 2007, 22:439-445.
32. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S: Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens* Res 24: 691-697, 2001
33. Segura J, Campo C, Ruilope LM: How relevant and frequent is the presence of mild renal insufficiency in essential hypertension? *J Clin Hypertens* 4: 332-336, 2002
34. Tseng CH: Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. *Kidney Int* 68: 796–801, 2005
35. Ohno I, Hosoya T, Gomi H, Ichida K, Okabe H, Hikita M: Serum uric acid and renal prognosis in patients with IgA nephropathy. *Nephron* 87: 333–339, 2001
36. Feig DI, Mazzali M, Kang DH, Nakagawa T, Price K, Kannelis J, Johnson RJ. Serum uric acid: a risk factor and a target for treatment? *J Am Soc Nephrol*. 2006; 17(4 Suppl 2):S69-73.
37. Hovind P, Rossing P, Johnson RJ, Parving HH. Serum uric acid as a new player in the development of diabetic nephropathy. *J Ren Nutr*. 2011:21:124-7. doi: 10.1053/j.jrn.2010.10.024.
38. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003; 41(6):1183-90. Epub 2003 Apr 21.
39. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002; 13:2888-97.
40. Heinig M, Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. *Cleve Clin J Med*. 2006; 73:1059-64.
41. Cirillo P, Sato W, Reungjui S, Heinig M, Gersch M, Sautin Y, Nakagawa T, Johnson RJ. Uric acid, the metabolic syndrome, and renal disease. *J Am Soc Nephrol*. 2006; 17:S165-8.
42. Nakagawa T, Mazzali M, Kang DH, Kanellis J, Watanabe S, Sanchez-Lozada LG, Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Hyperuricemia causes glomerular hypertrophy in the rat. *Am J Nephrol*. 2003; 23:2-7.
43. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis*. 2006; 47:51-9.
44. Kanbay M, Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, Uz E, Akcay A, Yigitoglu R, Covic A. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. *Int Urol Nephrol*. 2007; 39:1227-33. Epub 2007 Aug 15.
45. Talaat KM, el-Sheikh AR. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. *Am J Nephrol*. 2007; 27(5):435-40. Epub 2007 Jul 4.
46. Bonakdaran S, Hami M, Shakeri MT. Hyperuricemia and albuminuria in patients with type 2 diabetes mellitus. *Iran J Kidney Dis*. 2011; 5(1):21-4.
47. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, Kadono M, Hasegawa G, Yoshikawa T,Nakamura N. Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism. 2008 May; 57(5):625-9. doi:10.1016/j.metabol.2007.12.005.
48. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. Eur J Clin Invest. 2001 Apr; 31(4):318-21.
49. Bruno G, Cavallo-Perin P, Bargero G, Borra M, Calvi V, D'Errico N, Deambrogio P, Pagano G. Prevalence and risk factors for micro- and macroalbuminuria in an Italian population-based cohort of NIDDM subjects. *Diabetes Care*. 1996 Jan; 19(1):43-7.

50. Eghan BA Jr, Frempong MT, Adjei-Poku M. Prevalence and predictors of microalbuminuria in patients with diabetes mellitus: a cross-sectional observational study in Kumasi, Ghana. Ethn Dis. 2007 autumn; 17(4):726-30.
51. Lutale JJ, Thordarson H, Abbas ZG, Vetvik K. Microalbuminuria among Type 1 and Type 2 Diabetic patients of African origin in Dar Es Salaam, Tanzania. BMC Nephrol. 2007 Jan 15;8:2.
52. Halimi J-M, Hadjadj S, Aboyans V, Allaert F-A, Artigou J-Y, Beaufils M, et al. Microalbuminuria and urinary albumin excretion: French clinical practice guidelines. Diabetes Metab. 2007; 33(4):303 – 309.