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Original Research Article

A Hospital Based Cross Sectional Assessment of Hyperuricemia A Prognostic Marker in Chronic Kidney Disease (CKD)

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Conflict of interest: Nil

Abstract

Aim: Study of hyperuricemia a prognostic marker in chronic kidney disease

Methods: This cross-sectional study was carried out in the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India.

Results: 100 patients were included in this study. The prevalence of hyperuricemia amongst our study participants was 65% (95% CI: 58.3–75.7%). On bivariate analysis, patient's age (β: 0.54, 95% CI: 0.25–0.84), eGFR (β: -0.67, 95% CI: -0.91 - -0.43), CKD stage 4 (β: 20.55, 95% CI: 10.32–30.76) or CKD stage 5 (β: 20.82, 95% CI: 9.55–32.09), spot urine PCR (β: 3.76, 95% CI: 1.12–6.40), severe proteinuria (β: 16.51, 95% CI: 6.56–26.46), no hypertension (β: -17.83, 95% CI: -27.17 - -8.48), systolic (β: 0.25, 95% CI: 0.09–0.40) and diastolic (β: 0.58, 95% CI: 0.14–1.01) blood pressures, diabetes (β: 9.01, 95% CI: 0.87–17.14), low protein diet (β: -8.31, 95% CI: -16.07 - -0.55), low-Carb diet (β: 8.36, 95% CI: 0.64– 16.07), ULT (β: 22.71, 95% CI: 16.00–29-42), loop diuretics (β: 11.94, 95% CI: 3.75–20.13), body mass index (β: 1.06, 95% CI: 0.07–2.05) and no anaemia (β: -27.42, 95% CI: (− 39.02 - -15.82) were significantly associated with serum uric acid. Mean serum uric acid significantly differed across CKD stages (F: 7.91, p value < 0.001) severity of proteinuria (F: 5.46, p value = 0.006) Also, on bivariate logistic regression, patient's age (OR: 1.05, 95% CI: 1.02–1.09), eGFR (OR: 0.93, 95% CI: 0.89– 0.96), CKD stage 4 (OR: 9.11, 95% CI: 2.01–33.21) or CKD stage 5 (OR: 6.67, 95% CI: 1.63–27.27), spot urine PCR (OR: 1.52, 95% CI: 1.01–2.30), severe proteinuria (OR: 4.71, 95% CI: 1.59–13.99), no hypertension (OR: 0.06, 95% CI: 0.01–0.30), systolic (OR: 1.03, 95% CI: 1.01–1.06) and diastolic (OR: 1.05, 95% CI: 1.00–1.11) blood pressures, low protein diet (OR: 0.42, 95% CI: 0.18–0.98), low fat diet (OR: 3.09, 95% CI: 1.06–9.02), ULT (OR: 6.71, 95% CI: 2.32–19.37), loop diuretics (OR: 3.73, 95% CI: 1.29–10.82), obesity (OR: 6.65, 95% CI:1.36–32.61) and no anaemia (OR: 0.04, 95% CI: 0.00– 0.29) were significantly associated with hyperuricemia. On multivariate analysis, after adjusting for patient's age, eGFR, spot urine PCR, systolic blood pressure, ULT, loop diuretics and haemoglobin level, patient's age (β: 0.49, 95% CI: 0.24–0.74), eGFR (β: -0.36, 95% CI: -0.57 - -0.16), CKD stage 4 (β: 17.49, 95% CI: 9.52–25.45) or CKD stage 5 (β: 13.28, 95% CI: 4.41–22.16), spot urine PCR (β: 3.06, 95% CI: 1.09–5.04), severe proteinuria (β: 13.94, 95% CI: 4.92– 22.95), no hypertension (β: -18.37, 95% CI: -28.67 - -8.06), systolic (β: 0.14, 95% CI: 0.02–0.25) and diastolic (β: 0.35, 95% CI: 0.03–0.66) blood pressures, ULT (β: 18.84, 95% CI: 12.98–24.71), loop diuretics (β: 6.62, 95% CI: 0.25–12.99) and no anaemia (β: -18.08, 95% CI: (− 27.55 - -8.61) were significantly associated with serum uric acid.

Conclusions: Hyperuricemia was independently associated with patient's age, eGFR, spot urine PCR, hypertension, ULT, loop diuretics, obesity and anaemia.
Keywords: Hyperuricemia, Anaemia, Hypertension.

Introduction

Serum uric acid is commonly elevated in subjects with chronic kidney disease (CKD) but was historically viewed as an issue of limited interest. Recently, uric acid has been resurrected as a potential contributory risk factor in the develop- ment and progression of CKD. Most studies documented that an elevated serum uric acid level independently predicts the development of CKD. Raising the uric acid level in rats can induce glomerular hypertension and renal disease as noted by the development of arteriolosclerosis, glomerular injury and tubulointerstitial fibrosis. Pilot studies suggest that lowering plasma uric acid concentrations may slow the progression of renal disease in subjects with CKD. While further clinical trials are necessary, uric acid is emerging as a potentially modifiable risk factor for CKD.

Gout was considered a cause of CKD in the mid-nineteenth century [1] and, prior to the availability of therapies to lower the uric acid level, the development of end-stage renal disease was common in gouty patients. In their large series of gouty subjects Talbott and Terplan found that nearly 100% had variable degrees of CKD at autopsy (arteriolosclerosis, glomerulo-sclerosis and interstitial fibrosis) [2]. Additional studies showed that during life impaired renal function occurred in half of these subjects [3]. As many of these subjects had urate crystals in their tubules and interstitium, especially in the outer renal medulla, the disease became known as *gouty nephropathy*. The identity of this condition fell in question as the presence of these crystals may occur in subjects without renal disease; furthermore, the focal location of the crystals could not explain the diffuse renal scarring present. In addition, many subjects with gout also had coexistent conditions such as hypertension and vascular disease, leading some experts to suggest that the renal injury in gout was secondary to these latter conditions rather than to uric acid *per se [4]. T*he effects of hyperuricemia were particularly impressive in animals with pre-existing renal disease, where it accelerated glomerular hypertension and the vascular lesions, resulting in worsening proteinuria and renal failure associated with worsening glomerulosclerosis and tubulointerstitial disease [5].

Material and methods

This cross-sectional study was carried out in the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India.

Socio-demographic data (age, gender) and relevant clinical information (aetiology of CKD, comorbidities, dietary regimens, use of medications known to influence serum uric acid and creatinine levels) were recorded from the patient's medical chart or obtained by interviewer-administered questionnaire. Anthropometric data including height and weight were obtained using a stadiometer (measured to the nearest 0.1 cm, without any foot or head wear) and a manual weighing scale (measured to the nearest 0.1 kg, with light clothing and no footwear) respectively. Blood pressure was measured according to World Health Organisation (WHO) guidelines [6] using an automatic blood pressure machine (OMRON® M2, HEM-7121-E). The most recent (less than 3 months) values of haemoglobin, serum

high-density lipoprotein cholesterol (HDL-c), serum low-density lipoprotein cholesterol (LDL-c), serum total cholesterol, serum triglycerides and plasma creatinine in patient's medical charts were recorded. Uric acid in the serum specimen was measured using the direct kinetic uricase method [7]. A clean-catch mid-stream urine specimen from all participants was collected for spot protein and creatinine assessment using the Benzethonium Chloride [8] and Jaffé method [9] respectively.

Definitions and calculations

Estimated glomerular filtration rate (eGFR) was computed from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. CKD was defined by eGFR < 60 ml/min per 1.73 m^2 for more than 3 months [11]. CKD was classified according to Kidney Disease: Improving Global Out-comes (KDIGO guidelines) into Stage 1/G1 (eGFR

≥90 ml/min per 1.73 m^2), Stage 2/G2 (eGFR = 60– 89 ml/min per 1.73 m^2), Stage 3/G3a (eGFR = 45–59 ml/ min per 1.73 m^2), Stage 3b/G3b (eGFR = 30–44 ml/min per 1.73 m^2), Stage 4/G4 (eGFR = 15–29 ml/min per 1.73 m^2), Stage 5/G5 (eGFR< 15 ml/min per 1.73 m^2) 1 [1] Proteinuria was classified into normal or mild in- crease/A1 (spot urine protein-creatinine ratio [PCR] <

150 mg/g), moderate increase/A2 (spot urine PCR = 150–500 mg/g) and severe increase/A3 (spot urine PCR > 500 mg/g) [11].

Renal disease was Glomerular if manifesting with glomerular range proteinuria, and/or haematuria (deformed or red blood cells cast), associated with hypertension and/or oedema; Tubulointerstitial if manifesting with sterile leukocyturia, and low urine specific gravity, associated with or without non-glomerular haematuria and proteinuria; Vascular if presence of hypertension, with moderate proteinuria and normal urine sediment. Mixed renal involvement was renal disease manifesting with a combination of 2 or more of glomerular, tubulointerstitial and vascular involvement.

Hyperuricemia was defined as serum uric acid > 70 mg/l in males and > 60 mg/l in females [12]. Hyper- tension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 or current use of antihypertensive drugs. Diabetes was de- fined as history of diabetes confirmed in the patient's medical records and/or current use of blood glucose control medications. Gout was defined as history of gouty arthritis confirmed in the patient's medical records and/or current use of urate lowering therapy (ULT) against gout. Low protein, low-carb and low-fat diet were defined as a dietary regimen poor in proteins (less than 30 g daily), sugars and lipids respectively, as pre- scribed by a dietician. Body mass index (BMI) was classified as; underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25– 29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) [13]. Anaemia was defined as haemoglobin < 13.0 g/dl in males and <

12.0 g/dl in females [14]. Dyslipidaemia was defined as total cholesterol ≥240 mg/dl (6.21 mmol/l) or low-density lipoprotein cholesterol (LDL-c) > 160 mg/dl (4.14 mmol/l) or high-density lipoprotein cholesterol (HDL-c) < 40 mg/dl (1.03 mmol/l) or triglycerides ≥150 mg/dl (1.69 mmol/l) [15].

Statistical analysis

Statistical analyses were done using statistical package for Social Sciences (SPSS), version 23 Inc., Chicago, Illinois, USA). Level of statistical significance was set at $\alpha < 0.05$. Sensitivity analyses were done, defining hyperuricemia as serum uric acid > 70 mg/l in males and > 60 mg/l in females or current use of ULT. The results were very similar to our current results.

Results

100 patients were included in this study. Mean age of our study participants was 55.78 ± 12.58 years, and 59 (59%) were males. The median (IQR) eGFR was 17.00 (11.00) ml/min per 1.73m^2, and median (IQR) spot urine PCR ratio was 803.0 (1120.0) mg/g. More than two-thirds of participants were at an advanced stage of CKD with 48% at stage 4 and 25% at stage 5. The most common comorbidities identified were hypertension (87%), diabetes (34%) and gout (21%). The types of renal involvement included glomerular (60%), vascular (19%), tubuloinsterstitial (12%), and mixed (9%). 40 (40%) participants were on ULT (Allopurinol), 31 (31%) were on loop diuretics (Furosemide), while 5 (5%) were on angiotensin receptor blockers (Losartan). The mean serum uric acid of the study participants was 76.03 ± 20.50 mg/l. Table 1

The prevalence of hyperuricemia amongst our study participants was 65% (95% CI: 58.3–75.7%).

Factors associated with hyperuricemia in chronic kidney disease

On bivariate analysis, patient's age (β: 0.54, 95% CI: 0.25–0.84), eGFR (β: -0.67, 95% CI: -0.91 - -0.43), CKD stage 4 (β: 20.55, 95% CI: 10.32–30.76) or CKD stage 5 (β: 20.82, 95% CI: 9.55–32.09), spot urine PCR (β: 3.76, 95% CI: 1.12–6.40), severe proteinuria (β: 16.51, 95% CI: 6.56–26.46), no hypertension (β: -17.83, 95% CI: -27.17 - -8.48), systolic (β: 0.25, 95% CI: 0.09–0.40) and diastolic (β: 0.58, 95% CI: 0.14–1.01) blood pressures, diabetes (β: 9.01, 95% CI: 0.87–17.14), low protein diet (β: -8.31, 95% CI: -16.07 - -0.55), low-Carb diet (β: 8.36, 95% CI: 0.64– 16.07), ULT (β: 22.71, 95% CI: 16.00–29-42), loop diuretics (β: 11.94, 95% CI: 3.75–20.13), body mass index (β: 1.06, 95% CI: 0.07–2.05) and no anaemia (β: -27.42,

95% CI: (− 39.02 - -15.82) were significantly associated with serum uric acid. Mean serum uric acid significantly differed across CKD stages (F: 7.91, p value < 0.001) severity of proteinuria (F: 5.46, p value = 0.006) Also, on bivariate logistic regression, patient's age (OR: 1.05, 95% CI: 1.02–1.09), eGFR (OR: 0.93, 95% CI: 0.89– 0.96), CKD stage 4 (OR: 9.11, 95% CI: 2.01–33.21) or CKD stage 5 (OR: 6.67, 95% CI: 1.63–27.27), spot urine PCR (OR: 1.52, 95% CI: 1.01–2.30), severe proteinuria (OR: 4.71, 95% CI: 1.59–13.99), no hypertension (OR: 0.06, 95% CI: 0.01–0.30), systolic (OR: 1.03, 95% CI: 1.01–1.06) and diastolic (OR: 1.05, 95% CI: 1.00–1.11) blood pressures, low protein diet (OR: 0.42, 95% CI: 0.18–0.98), low fat diet (OR: 3.09, 95% CI: 1.06–9.02), ULT (OR: 6.71, 95% CI: 2.32–19.37), loop diuretics (OR: 3.73, 95% CI: 1.29–10.82), obesity (OR: 6.65, 95% CI:

1.36–32.61) and no anaemia (OR: 0.04, 95% CI: 0.00– 0.29) were significantly associated with hyperuricemia. On multivariate analysis, after adjusting for patient's age, eGFR, spot urine PCR, systolic blood pressure, ULT, loop diuretics and haemoglobin level, patient's age (β: 0.49, 95% CI: 0.24–0.74), eGFR (β: -0.36, 95% CI: -0.57 - -0.16), CKD stage 4 (β: 17.49, 95% CI: 9.52–25.45) or CKD stage 5 (β: 13.28, 95% CI: 4.41–22.16), spot urine PCR (β: 3.06, 95% CI: 1.09–5.04), severe proteinuria (β: 13.94, 95% CI: 4.92–22.95), no hypertension (β: -18.37, 95% CI: -28.67 - -8.06), systolic (β: 0.14, 95% CI: 0.02–0.25) and diastolic (β: 0.35,

95% CI: 0.03–0.66) blood pressures, ULT (β: 18.84, 95% CI: 12.98–24.71), loop diuretics (β: 6.62, 95% CI: 0.25–12.99) and no anaemia (β: -18.08, 95% CI: (− 27.55 - -8.61) were significantly associated with serum uric acid. Table 2.

On multivariate logistic regression, after adjusting for patient's age, eGFR, spot urine PCR, systolic blood pres- sure, ULT, loop diuretics and haemoglobin level, patient's age (OR: 1.08, 95% CI: 1.03–1.13), GFR (OR: 0.94, 95% CI: 0.90–0.98), CKD stage 4 (OR: 24.66, 95% CI: 3.63–167.63) or CKD stage 5 (OR: 7.73, 95% CI: 1.63– 27.27), spot urine PCR (OR: 1.83, 95% CI: 1.07–3.12), severe proteinuria

(OR: 6.27, 95% CI: 1.66–23.60), no hypertension (OR: 0.09, 95% CI: 0.02–0.46), systolic blood pressure (OR: 1.04, 95% CI: 1.01–1.07), ULT (OR: 4.99, 95% CI: 1.54–16.16), loop diuretics (OR: 3.39, 95%. CI: 1.01–11.42), obesity (OR: 6.12, 95% CI: 1.15–32.55) and no anaemia (OR: 0.04, 95% CI: 0.00–0.46) were significantly associated with hyperuricemia. Table.2

Table 1a: age and gender of study participants

Age	N (%)
20–29 years	2 (2)
30–39 years	9 (9)
40–49 years	18 (18)
50–59 years	32 (32)
60–69 years	22 (22)
> 70 years	16 (16)
Male gender, n (%)	59 (59)
Duration of CKD diagnosis (months), mean ± SD	14.67 ± 18.05

Table 1b: Basic parameter of study participant

Systolic Blood Pressure (mmHg), mean ± SD	142.3 ± 30.3
Diastolic Blood Pressure (mmHg), mean ± SD	88.3 ± 21.3
Weight (kg), median (IQR)	75.00 (18.40)
Height (m), median (IQR)	1.66 (0.10)
BMI (kg/m^2), median (IQR)	26.30 (6.04)
Haemoglobin (g/dl), mean ± SD	10.27 ± 1.76
Total Cholesterol (mmol/l), mean ± SD	2.06 ± 0.56
HDL-c (mmol/l), mean ± SD	0.55 ± 0.19
LDL-c (mmol/l), mean ± SD	1.25 ± 0.42
Tryglycerides (mmol/l), median (IQR)	1.04 (0.72)
Plasma creat (mg/dl), median (IQR)	3.65 (1.55)
eGFR (ml/min per 1.73m^2), median (IQR)	17.00 (11.00)
Spot urine protein (mg/dl), median (IQR)	1.07 (1.06)
Spot urine creat (mg/dl), median (IQR)	1.47 (1.14)
Spot urine PCR (mg/g), median (IQR)	803.0 (1120.0)
Serum uric acid (mg/l), mean ± SD	76.19 ± 20.25
Hyperuricemia, n (%)	67 (67)

Table 2a: Factors associated with serum uric acid and hyperuricemia in chronic kidney disease

Variable	Serum uric acid			Hyperuricemia	
	Bivariate analysis β (95% CI)	[a]Multivariate analysis β (95% CI)		Bivariate analysis cOR (95% CI)	[a]Multivariate analysis aOR (95% CI)
Age	0.54 (0.25–0.84)	0.49 (0.24–0.74)		1.05 (1.02–1.09)	1.08 (1.03–1.13)
Male gender	0.15 (− 1.79–14.41)	1.96 (− 4.41–8.34)		0.85 (0.37–1.98)	0.58 (0.17–1.91)

Duration of CKD diagnosis (months)	– 0.01 (− 0.23–0.22)	−0.11 (− 0.26–0.05)		1.01 (0.99–1.04)	0.99 (0.96–1.03)
GFR (ml/min per 1.73m^2)	−0.67 (− 0.91 - -0.43)	−0.36 (− 0.57 - -0.16)		0.93 (0.89–0.96)	0.94 (0.90–0.98)
CKD stage					
Stage 2/G2	– 15.08 (− 34.64–4.48)	2.68 (− 17.85–12.49)		–	–
Stage 3a/G3a	3.61 (− 11.61–18.83)	10.79 (− 1.16–22.75)		1.2 (0.20–7.18)	5.44 (0.45–65.66)
Stage 3b/G3b	Ref.	Ref.		Ref.	Ref.
Stage 4/G4	20.55 (10.32–30.76)	17.49 (9.52–25.45)		9.11 (2.01–33.21)	24.66 (3.63–167.63)
Stage 5/G5	20.82 (9.55–32.09)	13.28 (4.41–22.16)		6.67 (1.63–27.27)	7.73 (1.06–56.30)
Spot urine PCR (mg/g)	3.76 (1.12–6.40)	3.06 (1.09–5.04)		1.52 (1.01–2.30)	1.83 (1.07–3.12)
Proteinuria					
No or Mild/A1	Ref.	Ref.		Ref.	Ref.
Moderate/A2	8.81 (−3.08–20.70)	5.41 (− 5.26–16.07)		1.99 (0.57–6.90)	1.65 (0.39–6.90)
Severe/A3	16.51 (6.56–26.46)	13.94 (4.92–22.95)		4.71 (1.59–13.99)	6.27 (1.66–23.60)
Type of renal involvement					
Glomerular	Ref.	Ref.		Ref.	Ref.
Tubulointerstitial	−3.31 (− 15.63–9.02)	5.76 (− 3.47–14.99)		0.77 (0.22–2.72)	1.71 (0.30–9.67)
Vascular	7.36 (− 2.69–17.41)	4.39 (− 2.97–11.74)		1.10 (0.25–4.83)	2.25 (0.43–11.71)
Mixed	−8.92 (− 22.86–5.02)	−5.67 (− 15.70–4.36)		2.20 (0.65–7.40)	1.57 (0.24–10.19)
No Hypertension	−17.83 (− 27.17 - -8.48)	−18.37 (− 28.67 - -8.06)		0.06 (0.01–0.30)	0.09 (0.02–0.46)
Systolic Blood Pressure (mmHg)	0.25 (0.09–0.40)	0.14 (0.02–0.25)		1.03 (1.01–1.06)	1.04 (1.01–1.07)
Diastolic Blood Pressure (mmHg)	0.58 (0.14–1.01)	0.35 (0.03–0.66)		1.05 (1.00–1.11)	1.06 (0.99–1.13)

Diabetes	9.01 (0.87–17.14)	4.34 (− 2.72–11.40)	2.09 (0.83–5.29)	1.40 (0.47–4.18)
HIV	−8.70 (− 20.45–3.04)	−5.15 (− 13.87–3.57)	0.76 (0.23–2.53)	1.37 (0.27–6.99)
Low protein diet	−8.31 (− 16.07 - -0.55)	−1.45 (− 7.70–4.80)	0.42 (0.18–0.98)	0.80 (0.29–2.21)
Low-Carb diet	8.36 (0.64–16.07)	−0.67 (− 7.18–5.84)	2.10 (0.91–4.86)	1.09 (0.41–2.91)
Low fat diet	6.20 (− 2.47–14.88)	−0.92 (− 7.16–5.32)	3.09 (1.06–9.02)	1.73 (0.44–6.81)
[b]Urate lowering therapy	22.71 (16.00–29-42)	18.84 (12.98–24.71)	6.71 (2.32–19.37)	4.99 (1.54–16.16)
[c]Loop diuretics	11.94 (3.75–20.13)	6.62 (0.25–12.99)	3.73 (1.29–10.82)	3.39 (1.01–11.42)
[d]Thiazide diuretics	4.82 (− 35.34–44.98)	−6.43 (− 34.72–21.86)	–	–
[e]ARB	−1.46 (− 19.78–16.87)	1.54 (11.69–14.77)	0.73 (0.12–4.57)	2.38 (0.08–69.14)
BMI (kg/m^2)	1.06 (0.07–2.05)	0.49 (−0.35–1.32)	1.12 (0.99–1.26)	1.04 (0.89–1.21)
BMI class				
Normal	Ref.	Ref.	Ref.	Ref.
Overweight	4.99 (− 3.61–13.59)	5.52 (−1.38–12.41)	1.38 (0.57–3.35)	1.59 (0.56–4.53)
Obesity	11.29 (0.57–22.02)	4.34 (−4.48–13.16)	6.65 (1.36–32.61)	6.12 (1.15–32.55)
Haemoglobin (g/dl)	−2.82 (− 5.00 - -0.63)	−1.61 (− 3.26–0.04)	0.77 (0.61–0.99)	0.86 (0.64–1.15)
No anaemia	– 27.42 (− 39.02 - -15.82)	−18.08 (− 27.55 - -8.61)	0.04 (0.00–0.29)	0.04 (0.00–0.46)
Total Cholesterol (mmol/l)	4.85 (− 8.33–18.0)	9.24 (− 2.54–21.02)	1.64 (0.38–7.40)	1.05 (0.11–9.77)
HDL-c (mmol/l)	– 29.28 (− 67.02–8.46)	−4.16 (− 33.53–25.22)	0.11 (0.01–7.30)	0.01 (0.00–30.34)

LDL-c (mmol/l)	4.81 (−12.63–22.25)	−1.06 (− 14.88–12.76)		1.81 (0.24–13.82)	0.38 (0.21–6.91)

Table 2b: Factors associated with serum uric acid and hyperuricemia in chronic kidney disease

Variable	Serum uric acid			Hyperuricemia	
	Bivariate analysis β (95% CI)	[a]Multivariate analysis β (95% CI)		Bivariate analysis cOR (95% CI)	[a]Multivariate analysis aOR (95% CI)
Triglycerides (mmol/l)	5.30 (−7.67–18.27)	3.76 (− 5.59–13.11)		1.34 (0.32–5.67)	1.40 (0.96–12.34)
Dyslipidaemia	10.62 (−4.60–25.85)	11.23 (− 1.58–24.03)		4.25 (0.82–22.13)	2.13 (0.13–34.26)

Discussion

Our study showed that more than half of CKD patients had hyperuricemia. Among a wide range of demographic, clinical and laboratory parameters evaluated, patient's age, eGFR, spot urine PCR, hypertension, ULT, loop diuretics and anaemia were significantly associated with serum uric acid and hyperuricemia in CKD. Hyperuricemia is common in CKD and mostly results from decreased uric acid excretion. The kidneys play a major role in excreting uric acid, an end-product of purine metabolism. These divergent results can be largely attributed to study methodology. In the Nigerian study, the authors evaluated 120 pre-dialysis CKD patients and reported a prevalence of 47.5%. However, they excluded patients with gouty arthritis and patients on ULT. In the Chadian study, after evaluating 712 CKD patients, an even lower prevalence of 15.2% was reported. However, in this Chadian study, no information was provided on whether patients were on maintenance dialysis or not. Our higher prevalence could also be due to the high proportion of advanced CKD (73.2% CKD stages 4 and 5) amongst our study participants. Our prevalence was similar to the 70% reported in a paediatric population of CKD patients in USA [16]. The high proportion of advanced CKD amongst our study participants is due to the fact that our study was conducted in referral nephrology units which receive advanced cases of CKD from peripheral nephrology units.

We found significant association between eGFR, spot urine PCR and serum uric acid. Patients with CKD stages 4 or 5 and had 24.66 and 7.73 times higher significant odds respectively, of having hyperuricemia com- pared to those with CKD stage 3b. Also, patients with severe proteinuria had 6.27 significant higher odds of having hyperuricemia compared to those with no or mild proteinuria. These findings were similar to the results of Krishnan [17]. We also found a significant association between loop diuretics and serum uric acid in our sample of non-dialysed CKD. It is known that loop diuretics predisposes individuals to hyperuricemia [18]. Diuretics cause hyperuricemia by increasing urate absorption and decreasing urate secretion in the kidneys [18]. Loop diuretics used in the management of hyper- tension and fluid retention in CKD should therefore be used judiciously.

We found a significant independent association between hypertension and hyperuricemia. Noone et al. also reported a significant association between hypertension and hyperuricemia in

paediatric patients with CKD [16]. A growing body of evidence suggest uric acid levels play a role in the development of hypertension [19,20]. Uric acid can cause hypertension by mediating pro inflammatory pathways in vascular smooth muscles, inhibition of endothelial nitric oxide and activation of the renin-angiotensin system [19,20]. On the other hand, hypertension increases renal vascular resistance, reducing renal flow, those increasing urate reabsorption. Also, use of antihypertensive drugs like diuretics can in-crease serum uric acid levels [18]. It is however unlikely that in our study, the observed association between hypertension and hyperuricemia is due to use of diuretics as this was adjusted for in our analysis. Sedaghat et al. suggested that hypertension mediates the decline in renal function caused by hyperuricemia [21]. Further research is needed to clarify the relationship between hyperuricemia and hypertension in CKD patients.

Subjects who were obese had 6.12 times significant higher odds of having hyperuricemia. This was in accordance with findings by Noone et al, in their paediatric CKD population [16]. Hyperuricemia seen in obesity has been attributed to insulin resistance and higher leptin production. Insulin resistance in obese individuals causes larger amounts of insulin to be secreted in order to maintain glucose metabolism. The kidney responds to this hyperinsulinemia by decreasing urate clearance [22]. Obesity may therefore be a cause of hyperuricemia in our subjects, but a causal relationship between these two variables was not evaluated in this study.

It is possible that the observed association between hyperuricemia and anaemia is just an incidental finding. Both conditions can be caused by the underlying CKD, and there may not be a direct relationship between the two. However, in our analysis, after adjusting for eGFR and spot urine PCR, we still found a significant association between both variables. CKD patients with no anaemia displayed 0.04 times lower odds of having hyperuricemia after relevant confounder adjustment. To the best of our knowledge, there has been no study to depict the relationship between hyperuricemia and anaemia in CKD. In the Artherosclerosis Risk in the Communities (ARIC) study, McAdams-DeMarco et al [23]. after following up 10,791 individuals for a period of 9 years, reported that anaemia was associated with an approximately two-fold increased risk of ‘self-reported gout independent of renal function. The authors had no clear biological explanation for the link between anaemia and hyperuricemia but hypothesised that this link may be mediated by oxidative stress. Increased oxidative stress seen in anaemia could cause hyperuricemia by in- creasing xanthine oxidase activity and increased cell death/turnover [24]. More research is needed to explicate this relationship.

Conclusions

Hyperuricemia was independently associated with patient’s age, eGFR, spot urine PCR, hypertension, ULT, loop diuretics, obesity and anaemia.

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