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RESEARCH ARTICLE

Serum Uric acid is a better indicator of kidney impairment than serum uric acid to creatine ratio ; a cross sectional study of type 2 diabetes mellitus patients

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Abstract

Background Type 2 diabetes mellitus (T2DM) patients are likely to develop kidney disease. The need to identify more accessible and cheaper diagnostic biomarkers cannot be overemphasized. This study investigated the ability of serum uric and uric acid to creatinine ratio in assessing the kidney function of T2DM patients and determined the relationship between serum uric acid to creatinine ratio and estimated glomerular filtration rate (eGFR).

Methods One hundred and fifty-five (155) consented T2DM patients were recruited from the diabetes clinic of the Cape Coast Teaching hospital. Anthropometric variables and blood pressure were measured. Serum uric acid (SUA), serum creatinine and urine protein were estimated using standard protocols. Uric acid to creatinine ratio (UA:CR), eGFR were then calculated.

Results From the receiver operator characteristic (ROC) curve obtained, serum uric acid was found to be a better predictor of impaired renal function than UA:CR at p = 0.0001. The uric acid levels of participants in the fourth quartile of each category was found to be significant at p = 0.010 and can be used as indicators of kidney function in these participants. According to the odds ratio, the UA:CR will not be suitable to be used as an indicator of kidney function in any of the participants because their odds ratios were all less than 1. A total of 29(18.7 %) participants were found to have CKD with their eGFR falling below 60 ml/mins per 1.73 m^2. A significant positive relationship was found between serum uric acid and the staging of CKD according to eGFR whiles a negative relationship was found with UA:CR and CKD ($p < 0.0001$).

Conclusions Serum uric acid is a better indicator of renal impairment (eGFR < 60 ml/mins per 1.73 m^2) than UA:CR in patients with type 2 diabetes mellitus.

Keywords Uric acid · Creatinine · Type 2 diabetes mellitus · Estimated GFR · Kidney disease

Introduction

Uric acid is produced as the end product of purine metabolism in humans. The accumulation of serum uric acid can lead to various diseases, and most notably uric acid is causally involved in the pathogenesis of gouty arthritis [1]. Recent studies have suggested that high level of serum uric acid is a risk factor for the development of cardiovascular disease (CVD) in the general population [2, 3]. However, despite the clinical and epidemiological evidence, some authorities have considered that the association was confounded by other well-established risk factors for CVD [4]. Recently, growing evidence demonstrates that serum uric acid may play a role in the development and pathogenesis of metabolic syndrome (MetS) [5, 6]. Recent studies in animals' models report that uric acid may play a causal role in the development of MetS and

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decreasing uric acid levels can prevent or reverse features of the MetS [5]. Serum creatinine (Cr) is a commonly used indicator for detecting small changes in glomerular filtration rate (GFR), hence a good biomarker of early stage CKD [7]. Increased circulating levels of creatinine were found to be associated with increased risk of CVD, obesity and hypertension. Similarly, increased levels of serum uric acid (UA) has been reported by studies to be a marker for decreased renal function and a risk factor for hypertension and CVD [8]. Studies also suggest that serum UA is a strong indicator for type 2 diabetes mellitus (T2DM) independent of other confounding factors [8].

Al Daghri et al. [8], established an inverse relationship between fasting glucose and serum UA/Cr; fasting glucose decreased from lower to higher serum UA/Cr tertiles and also inversely correlated with serum UA/Cr. Al Daghri further established that chronic high fasting glucose in T2DM patients promotes hyper filtration state resulting in increased renal excretion of uric acid [8]. According to Gu et al., [9] among T2DM patients in China, renal function normalised indexes such as serum uric acid to creatinine ratio can be used as a better predictor of incident chronic kidney disease in those with preserved kidney function than serum uric acid alone. There is scarcity of research data on the use of uric acid to creatinine ratio in assessing the kidney function of T2DM patients in Ghana and sub-Saharan Africa, where there is high prevalence of T2DM. Hence, we sought to assess the kidney function of T2DM patients using the uric acid to creatinine ratio. We believe these markers are readily available and will increase the number of tests available for the diagnosis and management of CKD.

Materials and methods

Study design and setting

This cross-sectional study was conducted at the diabetic clinic of Cape Coast Teaching Hospital. The hospital is located in Cape Coast in the Central Region of Ghana. The hospital offers both general and specialist care services in internal medicine, general surgery, obstetrics and gynaecology, dental and eye care and serves as the main facility for referrals in the Central Region of the country. The 400-bed facility admits over 5000 patients annually.

Study population/ eligibility criteria

Male and female T2DM patients who visited the Cape Coast Teaching Hospital (CCTH) diabetes clinic from January to May 2018 were enrolled. The study recruited participants who had not been diagnosed previously with kidney disease and were not on medication that will interfere with renal function.

Sample Size/ sampling technique/ethical clearance

Of the 202 participants recruited and given questionnaires, only 155 were considered eligible as 45 participants could not provide complete data or voluntarily opted out of the study. The study was approved by the Cape Coast Teaching Hospital Ethical Review Committee. The protocol identification number of the ethical clearance for this study was CCTHERC/RS/EC/2018/17.

Data collection

Data collection/anthropometric variables/blood pressure measurement

Demographic data (age, sex, level of education and occupation) and clinical data (duration of diabetes mellitus, type of medication given, presence of microvascular complications) were obtained from patients records and with the help of a questionnaire. Waist circumference, weight and height were measured using standard protocols [10]. BMI was calculated as weight kg/height squared (kg/m²) and subjects were considered as normal weight if their BMI was < 25 kg/m², overweight if their BMI was from 25 to 29 kg/m² and obese if their BMI was ≥ 30 kg/m² [11]. Blood pressure was measured by a trained health personnel following standard procedures.

Sample collection and laboratory procedures

After an overnight fast, 5 mls of blood was collected from each participant into a gel separator tube. The blood was allowed to clot and spun at 3000 rpm for 5 minutes and the entire serum was then transferred into a non-heparinized tube and stored at -20 degrees until laboratory analysis. Creatinine was estimated based on the Jaffe's technique and uric acid on the uricase method. The ratio was then calculated as follows:

$$\textit{Serum uric acid to serum creatinine ratio}\ (UA : CR) = \frac{\textit{serum uric acid}}{\textit{serum creatinine}}$$

Calculation of Estimated Glomerular Filtration Rate and determination of urine protein: The eGFR was calculated using the creatinine based four (4) variable MDRD equation [12];

$$\mathrm{GFR}\left(\mathrm{mL/min/1.73m^2}\right) = 175 \times \left(\mathrm{S_{cr}}\right)^{-1.154} \times (\mathrm{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \quad \text{(conventional units)}$$

Table 1 Clinical characteristics and anthropometric indices of participants stratified by gender

Variable	Total (n=155)	Male (n=75)	Female (n=80)	*P*-value
Age (years)	57.10±9.77	57.16±9.01	57.05±10.49	0.944
Age categories				0.253
<40	6 (3.87)	1 (1.33)	5 (6.25)	
40–49	30 (19.35)	18 (24.00)	12 (15.00)	
50–59	52 (33.54)	22 (29.33)	30 (37.50)	
60–69	49 (31.61)	26 (34.67)	23 (28.75)	
≥70	18 (11.61)	8 (10.67)	18 (22.50)	
Blood pressure (mmHg)				
SBP	140.22±22.68	137.87±20.95	142.43±24.11	0.212
DBP	81.61±13.09	80.95±10.90	82.24±14.90	0.541
FBG, mmol/l	8.66±3.61	7.87±3.54	9.40±3.53	0.008*
WC, cm	99.93±13.90	97.59±12.78	102.12±14.62	0.042*
BMI, Kg/m2	29.50±6.51	27.85±5.35	31.05±7.13	0.002*
BMI, n (%)				0.011*
Underweight	1 (0.65)	1 (1.33)	0 (0.0)	
Normal	43 (27.74)	29 (38.67)	15 (18.75)	
Overweight	43 (27.74)	21 (28.00)	22 (27.50)	
Obese	68 (43.87)	25 (33.33)	43 (53.75)	
Duration of T2DM (years)				0.353
<5	65 (41.94)	37 (49.3)	28 (35.0)	
5–10.	49 (31.61)	20 (26.7)	29 (36.3)	
11–15	17 (10.97)	8 (10.7)	9 (11.3)	
>15	24 (15.48)	10 (13.3)	14 (17.4)	

WC = Waist Circumference, BMI = body Mass Index, T2DM = type 2 diabetes mellitus, *significant at $p < 0.05$

Freshly voided urine was collected from eligible participants and urine protein measured using dipstick (URIT 10V, URIT Medical Electronic Co., Ltd. China).

Data analysis

The analysis was then done with Statistical Package for Social Sciences (SPSS) version 22.0. The data was expressed as means and standard deviations. The statistical tools used for the analysis were T-test, chi-square, correlation and regression. Comparison of means were done using the independent 't' test. Statistical significance of $p < 0.05$ was considered. Sensitivity and specificity was done using "Area under Curve" (AUC) analysis. The correlation and correlation coefficients were done using correlation.

Results

Table 1 shows the clinical characteristics and anthropometric indexes of the participants. Of the total of 155 participants recruited, 75 were males and 80 were females. Majority of the participants 52(33.54 %) were between the ages of 50 to 59, but the mean ages were similar ($p = 0.944$). The means of FBG ($p = 0.008$), BMI ($p = 0.002$) and WC ($p = 0.042$) for females were significantly higher than in males; more females were overweight and obese than males ($p = 0.011$).

Table 2 shows the dipstick urine protein, uric acid, creatinine levels, eGFR and renal function of study participants. Fifty four (54) participants were positive for urine protein with more being females ($p = 0.333$). The mean serum uric acid ($p < 0.001$) and serum creatinine ($p < 0.001$) values in males were higher than in females.

Figure 1 presents the serum uric acid (SUA) and serum uric acid to creatinine ratio (UA:CR) according to eGFR staging. There was a significant trend between SUA levels and the serum UA:CR and eGFR staging. Serum uric acid levels significantly increased as the staging of eGFR moved from stage 1 through to stage 3 and slightly declined in stage 4. This implies that a positive relationship exists between serum uric acid levels and the stage of CKD, hence the higher the stage of CKD the higher the serum uric acid levels. From the same figure, there is a negative relationship between UA:CR ratio and the stages of CKD. Hence serum uric acid to creatinine ratio decreased as CKD progressed.

Table 2 Dipstick urine protein, serum uric acid, serum creatinine levels, eGFR and the renal function among study participants

Variable	Total	Male	Female	*P*-value
Proteinuri				0.333
Positive	54 (34.84)	29 (38.67)	25 (31.25)	
Negative	101 (65.16)	46 (61.33)	55 (68.75)	
Proteinuria grades				0.494
Mild	45 (83.33)	24 (80.00)	21 (87.50)	
Moderate	8 (14.81)	5 (16.67)	3 (12.50)	
Heavy	1 (1.85)	1 (3.33)	0 (0.0)	
Uric acid, µmol/l	404.27±104.75	444.68±101.98	366.38±92.96	<0.001*
Creatinine, µmol/l	99.05±30.01	109.27±28.98	89.46±27.88	<0.001*
UA:CR	4.24±1.11	4.20±1.09	4.14±1.11	0.905
eGFR (mL/mins per 1.73 m^2)	81.01±22.31	83.92±23.31	78.32±21.14	0.121
eGFR n (%)				0.100
<60	22 (14.84)	7 (9.45)	15 (18.75)	
≥60	132 (85.16)	67 (90.54)	65 (81.25)	
eGFR Staging N (%)				0.229
G1: ≥ 90	47 (30.32)	26 (35.14)	21 (26.25)	
G2: 60–89	85 (54.83)	41 (55.40)	44 (55.00)	
G3a: 45–59	17 (10.97)	5 (6.75)	12 (15.00)	
G3b: 30–44	3 (1.93)	2 (2.70)	1 (1.25)	
G4: 15–29	2 (1.29)	0 (0.0)	2 (2.50)	

UA:CR = Uric acid: creatinine ratio, eGFR = Estimated Glomerular Filtration Rate, G1 = Stage One CKD, G2 = Stage Two CKD, G3 = Stage three CKD, G4 = Stage four CKD, CKD = Chronic Kidney Disease. *significant at $p < 0.05$

Figure 2 shows the relationship between serum uric levels and the grades of proteinuria and also the relationship between UA:CR and the degree of proteinuria. Serum uric acid significantly increased as the grades of proteinuria increased (p = 0.0003). UA:CR generally decreased as the grades of proteinuria increased (p = 0.0503).

Figure 3 shows the correlations between serum uric acid levels, serum uric acid to creatinine ratio and eGFR. A negative correlation exists between serum uric acid levels and estimated glomerular filtration rate (r= -0.4224; $p < 0.0001$). Also, serum uric acid to serum creatinine ratio correlated with eGFR (r = 0.452; $p < 0.0001$).

Figure 4 shows the correlation between serum uric acid and serum creatinine levels. A weak positive correlation exists between the serum uric acid levels and the serum creatinine levels (r = 0.454: $p < 0.0001$). Also, a weak negative correlation was found to exist between serum uric acid to creatinine ratio and serum creatinine levels (r= -0.475: $p < 0.0001$).

Table 3 shows the relationship between demographic, clinical biochemical and anthropometric variables and SUA and

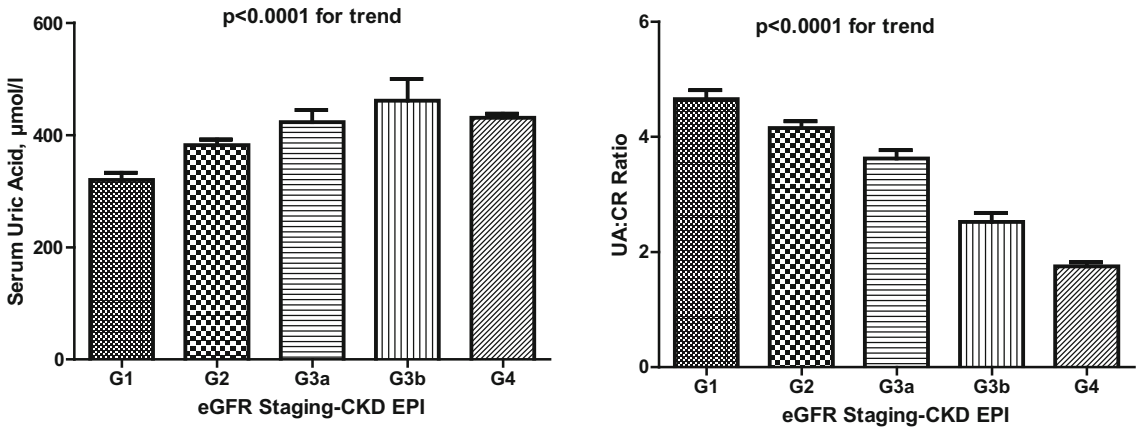

Fig. 1 Serum uric acid levels and serum uric acid: creatinine ratio according to eGFR staging. Bars are shown as means ± SE; $P < 0.05$

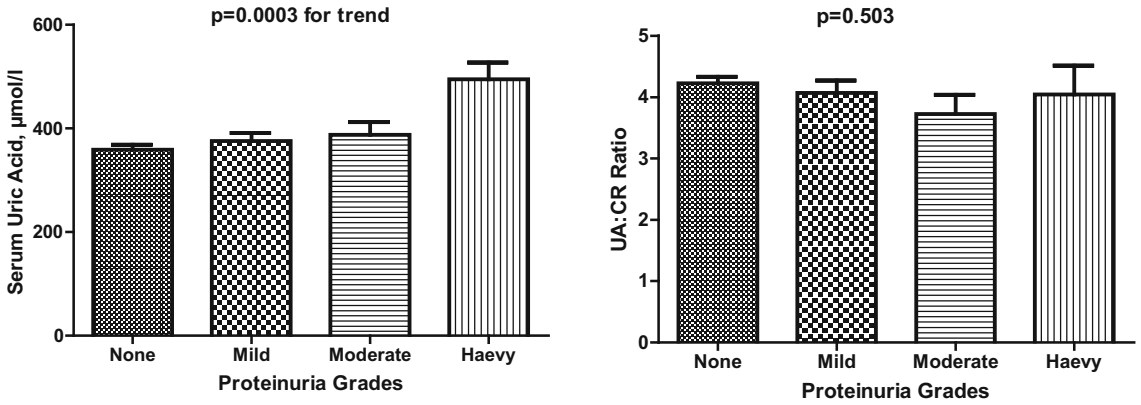

Fig. 2 Serum uric acid levels and serum uric acid: creatinine ratio according to the proteinuria grades. Bar are shown as means ± SE; $P < 0.05$

serum UA:CR. There is a significant relationship between age (r = 0.022; p = 0.003), FBG (r=-0.006; p = 0.024), WC (r = 0.024; p = 0.022) and BMI (r = 0.010; p = 0.040) and serum uric acid. However, only age(r = 1.619; p = 0.022) and FBG (r=-0.519; p = 0.048) showed a significant relationship with serum uric acid to creatinine ratio.

Figure 5 shows the ROC curve for serum uric acid and uric acid: creatinine ratio as predictors of impaired renal function (eGFR < 60). The higher the AUC value the better the parameter can predict a disease than the other parameter it is being compared with. Serum uric acid had a greater AUC (0.708) than serum uric acid to creatinine ratio which had an AUC value of 0.205 (p < 0.0001), hence from the curve, serum uric acid can be said to be a better predictor of chronic kidney disease than serum uric acid to creatinine ratio.

Table 4 shows the serum uric acid quartiles and serum uric acid: creatinine ratio quartiles as indicators of impaired renal function (eGFR < 60 mL/mins per 1.73 m^2). In multivariate Cox regression analysis, the third (Q3) and fourth quartile (Q4) had 9(40.91 %) and 7(31.81 %) participants respectively with a uric acid level in that range and this parameter can be used as an indicator of impaired renal function in these participants because at a 95 % confidence interval the odds ratio is greater than 1 (p < 0.05). The serum uric acid to creatinine ratio for the participants in the third and fourth quartile was significant at a p-value of 0.007 and 0.005 respectively, but they cannot be used as indicators of renal function because at a 95 % confidence interval, participants in both quartiles had odds ratios below 1.

Discussion

This study was undertaken to determine the ability of serum uric acid and serum uric acid to creatinine ratio to assess the kidney function of T2DM patients. The study also sought to find any relationship between these parameters in this group of patients.

The uric acid level of one participant with eGFR < 60 ml/mins per 1.73 m^2 significantly fell into the fourth quartile(Q4) and from the odds ratio it implies that this parameter can be used as an indicator of kidney function in this participant. Also 38 participants with eGFR > 60 ml/mins per 1.73 m^2 had their uric acid levels significantly falling into the fourth quartile(Q4)

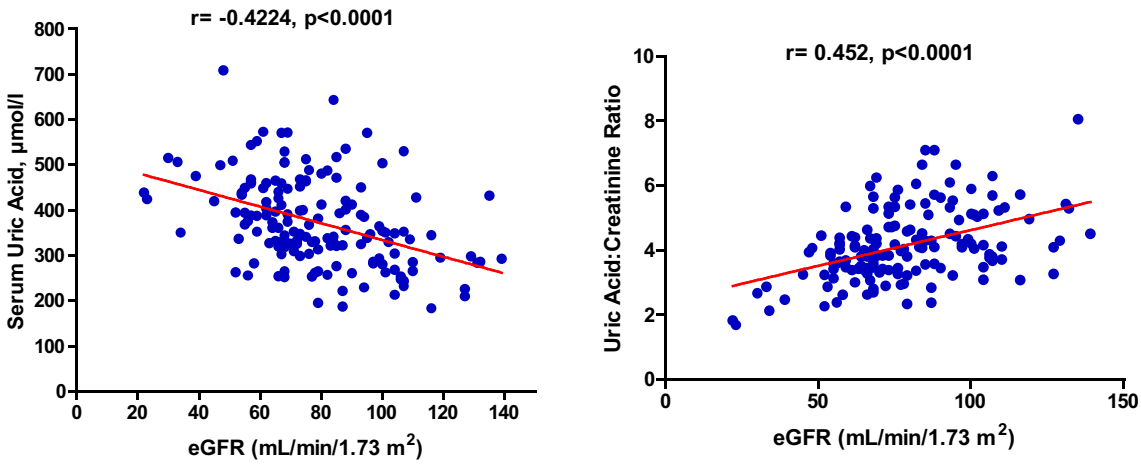

Fig. 3 Correlation relationship between serum uric acid levels and serum uric acid: creatinine ratio and eGFR

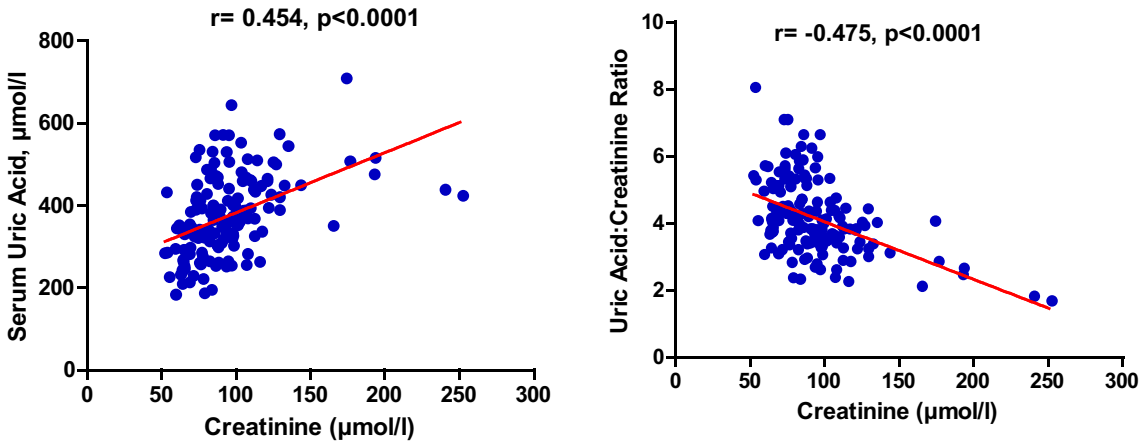

Fig. 4 Correlation relationship between serum uric acid levels and serum uric acid: creatinine ratio and creatinine

and also from the odds ratio, it implies that uric acid can be used as an indicator of renal function in this set of participants. According to Gu et al. [9] in T2DM serum uric acid levels in the fourth quartile was significant and can be used as an indicator of renal function in these participants because their odds ratio was greater than 1. From our study, 10 and 15 participants with eGFR < 60 had their UA:CR ratio significantly falling into the third(Q3) and fourth(Q4) quartiles respectively, but this parameter cannot be used as an indicator of renal function in these participants because their odds ratio was below 1. Also, 30 and 23 participants with eGFR > 60 ml/mins per 1.73 m^2 had their UA:CR ratio significantly falling into the third(Q3) and fourth(Q4) quartiles respectively but this parameter cannot be used as an indicator of renal function in this set of participants. The ROC curve obtained from our study points out that serum uric acid is significantly a better indicator of renal function in this group of patients than serum uric acid to creatinine ratio (UA, AUC = 0.708; UA:CR AUC = 0.250). However, if SUA is really a risk factor of renal disease progression, the baseline renal function-normalized SUA, which may reflect the net production of UA, will be better than SUA as the predictor of incident CKD [9].

The mean UA:CR and estimated glomerular filtration rate though higher in males as compared to that of females was not significant. Again from our study, 18.7 % (p > 0.05) of the participants were having eGFR less than 60 ml/mins per 1.73 m^2 and according to the KDIGO guidelines [13] can be said to be having CKD. Serum uric acid levels increased steadily from stage 1 CKD through to stage 4 and then decreased slightly in stage 5. The steadily rising uric acid level could be due to the increasing inability of the kidney to excrete urine uric acid as CKD progresses. This was expected because most studies have demonstrated a positive relation between serum uric acid levels and CKD stages. In consonance with the findings of Zoppini et al., [14], we recorded a positive relationship between serum uric acid levels and the stages of CKD. Also, as the CKD stage increased the UA:CR level decreased steadily. This could be because, uric acid can be excreted through the gastrointestinal tract and kidneys while

Table 3 Relationship between some selected variables and serum uric acid and uric acid to creatinine ratio

Parameters	Serum Uric acid		UA:CR ratio	
	R	*p*-value	R	*p*-value
Age (years)	0.022	0.003*	1.619	0.022
FBG (mmol/l)	-0.006	0.024*	-0.519	0.048
SBP, mmHg	0.022	0.204	-2.459	0.137
DBP, mmHg	0.011	0.294	0.199	0.835
WC	0.024	0.022*	1.332	0.189
BMI	0.010	0.040*	0.132	0.068

r = correlation coefficient, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, WC = Waist Circumference, BMI = Body Mass Index, *significant at $p < 0.05$

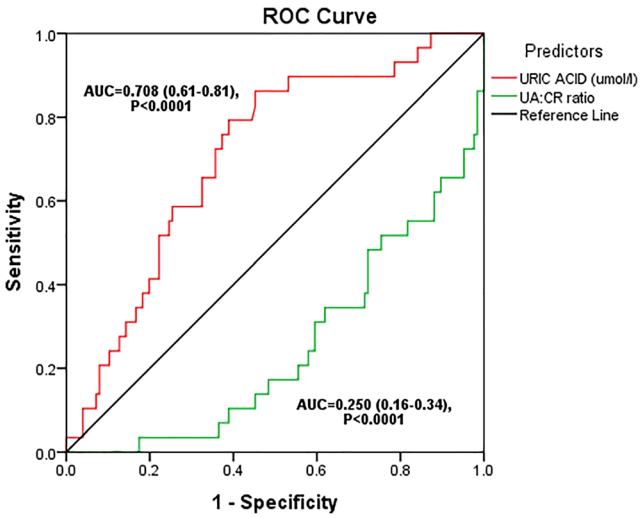

Fig. 5 ROC for serum uric acid and uric acid: creatinine ratio as predictors of impaired renal function (eGFR < 60)

Table 4 Serum uric acid Quartiles and serum uric acid: creatinine ratio quartile as indicators of impaired renal function (eGFR < 60 mL/mins per 1.73 m^2)

Parameter	eGFR<60	eGFR≥60	P-value	OR (95% CI)	*P*-value
Uric acid quartiles			0.047*		
Q1 (187.00–325.00)*	1 (4.54)	36 (27.27)		Reference	
Q2 (325.10–400.00)	5 (22.73)	35 (26.52)		5.14 (0.57–46.27)	0.144
Q3 (400.10–471.10)	9 (40.91)	30 (22.73)		10.8 (1.29–90.16)	0.028*
Q4 (471.20–708.40)	7 (31.81)	31 (23.48)		8.13 (0.95–69.76)	0.046
UA:CR quartiles			<0.001*		
Q1 (1.82–3.43)*	12 (54.55)	23 (17.42)		Reference	
Q2 (3.44–4.06)	6 (27.27)	33 (25.00)		0.35 (0.35–1.06)	0.064
Q3 (4.07–4.74)	3 (13.64)	38 (28.79)		0.15 (0.04–0.59)	0.007*
Q4 (4.75–7.09)	1 (4.54)	38 (28.79)		0.05 (0.01–0.41)	0.005*

creatinine is mostly excreted through the kidneys hence as CKD progresses more creatinine tends to build up in the blood since its excretion is impaired. Some of this uric acid is excreted through the renal route hence the level of creatinine tends to build up more than that of uric acid decreasing the UA:CR ratio as CKD progresses.

In agreement with the study of Gu et al. [14] we observed that the estimated glomerular filtration rate positively correlated with SUA: CR ratio. However, serum uric acid level significantly correlated positively with creatinine ($p < 0.0001$: $r = 0.454$), and this was expected because when there is kidney disease, the ability of the kidney to excrete both uric acid and creatinine is impaired hence these renal markers build up in the blood. Also, there was a significant negative correlation between UA:CR ratio and creatinine ($p < 0.001$: r=-0475). Serum uric was also found to increase steadily as the grade of proteinuria rises. This was expected because proteinuria is an indicator of renal disease and when there is renal disease the ability of the kidney to excrete uric acid is impaired. UA:CR ratio showed an insignificant decline as the grade of proteinuria rises. The reason for this is unclear. Our inability to employ a lager sample size, standardize the measurement of creatinine by the use of isotope dilution mass spectrometry (IDMS) and the fact that the eGFR equation used has not been validated among the Ghanaian population served as the major limitations of this study.

Conclusions

Our study showed that serum uric acid is a better indicator of renal impairment (eGFR < 60 ml/mins per 1.73 m^2) than UA:CR in patients with T2DM. Though serum uric acid was found to be a better indicator of CKD and negatively correlated well eGFR, we would recommend that UA:CR ratio should also be added to the list of markers used as indicators of CKD in T2DM since UA:CR also correlated positively with eGFR and also reflects the net production of uric acid.

Declarations

Conflict of interest The authors declared that they have no conflict of interest.

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