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ORIGINAL ARTICLE

Correlation between Uric Acid, Albuminuria and Cardiovascular Outcome in Patients with Diabetes Mellitus

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ABSTRACT

Background: Many studies have shown an association between uric acid (UA) and cardiovascular (CV) outcome in general population and diabetes, also the association between albuminuria and cardiovascular outcome is well established. The link between serum UA levels and albuminuria with subsequent CV affection is not yet clear. For this reason, we aimed to study such association. **Methods:** One hundred and eight individuals with type 2 diabetes which were divided into two groups each constitute of 54 individuals according to presence or absence of CV disease. Routine laboratory investigations together with serum UA and urinary albumin to creatinine ratio (uACR) was analyzed in the two groups they were then correlated to each other and to different study parameters and future CV event using Framingham risk score (FRS). **Results:** The present study proved that there is statistical significant difference as regard risk of CVD as calculated by FRS being higher in diabetic patients with high serum UA (SUA) levels compared to those with low uric acid levels; the same apply for those with high urinary ACR. Serum UA was found to be correlated with urinary albumin excretion in patients with diabetes with and without CVD (n=108, r=0.450, p<0.0001), there is statistical significant positive correlation between serum UA, urinary ACR and FRS (n=54, r=0.305, p=0.025, n=54, r=0.432, p=0.001 respectively). Conclusions: This study concluded that higher SUA levels were associated with urinary albumin excretion with subsequent increase in risk of future CV events.

Keywords: Uric acid; albuminuria; diabetes mellitus; cardiovascular outcome; Framingham risk score.

INTRODUCTION

The leading cause of disability and death in individuals with diabetes mellitus is atherosclerotic cardiovascular disease (ASCVD), which includes current or previous attacks of acute coronary syndrome (ACS), coronary revascularization, ischemic stroke, transient ischemic attacks, or atherosclerotic peripheral arterial disease. Common coexisting conditions such as type 2 DM, dyslipidemia, hypertension and hyperuricemia are considered a risk for ASCVD development, diabetes in itself a risk factor for ASCVD development **[1]**.

Uric acid (UA) - which constitutes the final product in purine pathway - is associated with obesity, dyslipidemia, diabetes mellitus, impaired glucose tolerance (IGT) & diabetes which contribute to development and progression of ASCVDs, albeit it is yet not clear if such link is causal or inadvertent **[2]**.

Albuminuria is linked to development of atherosclerotic cardiovascular disease, such association could be explained by a common aetiopathologic process, and this includes endothelial dysfunction and/or the state of chronic low grade inflammation. It is of note that, presence of albuminuria in patients with or without diabetes gives rise to increased cardiovascular morbidity and mortality **[3]**.

Accumulating data revealed that endothelial dysfunction, chronic inflammation and procoagulant imbalance are greatly associated with nephropathy, retinopathy, and cardiovascular disease in individuals with diabetes **[4]**. The link between serum UA levels, inflammation and endothelial dysfunction has been shown **[5]**. However, the putative relation between serum UA levels, and CVD in individuals with diabetes and albuminuria is not yet clear. For this reason, we aimed to study such association.

Our aim is to early detect cardiovascular complications related to diabetes in those individuals in order to improve cardiovascular outcome and delay such devastating sequel together with assessment of the reliability of uric acid, and albuminuria as indicators of future CV events.

METHODS

Study design

Retrospective case control study that was carried out in Internal Medicine and Clinical Pathology Departments, Faculty of Medicine, Zagazig University Hospitals between August 2017 and December 2018.

Study Population

Assuming that the mean of atherogenic index of plasma (AIP) among subjects with diabetes with atherosclerotic cardiovascular disease (ASCVD) events is 0.33 ± 0.25 & among those with diabetes without prior ASCVD events is 0.18 ± 0.3, and at power of test 80% and CI 95%. The sample size is calculated to be 108 (54 in each group) using Open Epi program.

Diagnosis of diabetes was done by history from patients together with enclosed laboratory data (either the fasting plasma glucose (FPG) value ≥ 126 mg/dL or the 2-hour plasma glucose during oral glucose tolerance test (OGTT) ≥ 200 mg/dL, or hemoglobin A1C criteria ≥ 6.5%, one blood sample is sufficient to be used to establish diagnosis of diabetes by any of two mentioned criteria [**6]**.

We included two groups, group I include patients with diabetes and proven CVD as evidenced with history, clinical examination, ECG, echocardiography, neuroradiologic investigations or Doppler ultrasound. Group II includes patients with diabetes and no proven CVD.

Inclusion criteria: Age: > 18 years and of either sex, patient with type 2 diabetes mellitus.

Exclusion criteria: Individuals who are under 18 years old. Apparent inflammatory conditions e.g. chest infection, urinary tract infection, skin. Presence of malignancy anywhere. Patients with history of gout or gout treatment. Patients receiving urate lowering therapy (ULT).

Approval for performing the study was obtained from internal medicine department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. All the procedures used in the present study were in keeping with the current revision of the Helsinki Declaration. All participants were informed of the various aspects of the study, and they were enrolled only after providing a signed consent form.

All subjects of the study were subjected to full history and thorough clinical examination As well as drug prescriptions. General examination and local examination of different systems with thorough cardiovascular examination. Routine investigations were done according to protocol of clinical pathology and laboratories of Zagazig University Hospital: complete blood count (CBC), liver function tests, renal function tests, hemoglobin A1c, lipid profile.

Serum uric acid: System: Roche/Hitachi Cobas 8000 (Cobas c702), reference range **(7)**: Males: 3.4-7.0 mg/dL, females: 2.4-5.7 mg/dL. Urinary albumin to creatinine ratio: System: Roche/Hitachi Cobas 6000, (Cobas c501), reported as mg albumin per gram creatinine (mg albumin/g creatinine) in urine after measuring albumin and creatinine separately in spot urine sample. Urinary ACR ≥ 30 mg/g cr characterize presence of albuminuria.

Cardiovascular risk assessment for patients with diabetes who do not have CVD

Framingham risk score (FRS) used in this study is used to calculate the 10-year risk of cardiovascular disease, it is available on this website: https:/www.cvdriskchecksecure.com/ FraminghamRiskScore.aspx/ FRS is used to predict the 10-year risk of developing a CV event, we can then classify the risk of

individuals using FRS as low (< 10 percent), moderate r (10 – 20 percent) and high river risk. **[8]**.

Diagnosis of CVD

Taken generally, CVD consisting of coronary heart disease, cerebrovascular ischaemic accident, transient ischemic attack (TIA) and peripheral artery disease (PAD), presence of any of the earlier in the thread-mentioned CVD. Our study included both individuals with diabetes with and without CVD. After thorough history and complete physical examination, the presence or absence of CVD was established.

CAD includes all of the following: myocardial infarction, angina, revascularization procedures, ischemic cardiomyopathy (a secondary heart failure to ASCVD). Stroke includes either ischemic cerebrovascular accident (where the neurological deficit extends beyond 24 hours) or TIA (where the neurological deficit was framed within 24 hours). PAD was assessed from history taking as intermittent claudication, gangrene of the lower limbs and revascularization procedures.

Patients with no medical history of CVD, asymptomatic and had negative investigations were considered to have no CVD.

Statistical analysis

We analyzed raw data using MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Continuous variables were checked for normal Gaussian distribution by using Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± standard deviation (SD), or median and (minimum - maximum) according to normality of data. Categorical data were expressed as a number (percentage). For quantitative variables, independent sample *t* test was used for comparison in case of normally distributed data, while it's non parametric equivalent Mann–Whitney *U* (MW) test was used for non-Gaussian distribution. For comparisons of quantitative variables among the three groups, one-way ANOVA was used if data was parametric, while Kruskal-Wallis (KW) test was used if data was non parametric. For categorical variables, they were compared using the Chi-square ($\chi 2$). Pearson correlation coefficient was used to assess correlation between uric acid, AIP and levels of albuminuria and study parameters if data is parametric while Spearman's rank correlation was calculated to assess the correlations between the aforementioned parameters if data is non parametric. Linear regression analysis served to assess the impact of uric acid, or levels of albuminuria on FRS (numerical value) by both univariate and multivariate models (while adjusting for confounders). A p value < 0.05 was considered statistically significant (S).

RESULTS

We included one hundred and eight individuals' [45 male (41.7%) and 53 female (58.3%)] in the current study. The mean age of the study participants was 61.02 ± 4.83 years. Mean diabetes duration was 17.11 ± 5.87 years. The glycated hemoglobin (HbA1c) of 18 (16.7%) patients were below 7% and 90 (83.3%) patients were considered to be uncontrolled. Urinary albumin excretion of 38 patients (35.2%) were within normal limits while 70 patients (64.8%) had albuminuria level above 30 mg/g creatinine.

SUA levels were found to be higher in patients with diabetes with proven CVD "group I" (M=7.18, SD=1.49) compared to those without CVD "group II" (M=5.78, SD=1.59); t(106)= -4.72, p<0.0001 (Figure1). As regard albuminuria there was statistical significant difference as regard ACR between patient with diabetes and CVD (Mdn=212.89) and patients with diabetes but without CVD (Mdn=29.03); U=541, p<0001 (Figure 2). Other baseline characteristics between both the two main groups (diabetic patients with or without CVD) are summarized in table 1.

The FRS in diabetic patients without CVD varied between 5.39 % and 63.5 % with a mean of 23.38 ± 13.73 %. 10 participants (18.5 %) had a low risk of CVD (FRS<10 %), 17 participants (31.5 %) had a moderate risk (FRS=10–20 %), and 27 participants (50 %) had a high risk of CVD (FRS>20 %).

We compared between patients with high SUA (SUA ≥6 mg/dL) and those with low SUA (SUA <6mg/dL) as regard many parameters which were summarized in Table 2.

There were statistically significant differences with respect to hypertension, DM duration, serum albumin, TG, LDL-c, HDL-c and urinary ACR between groups.

When we classify our patients into two groups according to urinary ACR [ACR < 30 mg/g cr, another group with ACR ≥ 30 mg/g cr]; there were statistically significant difference between both groups as regard SBP, DM duration, serum UA, TG, HDL-c, and serum albumin (Table 3).

The correlation between serum UA, albuminuria and other study parameters were tested using appropriate correlation analysis. Positive correlation between urinary albumin excretion and SUA in total population (n= 108, r = 0.450, *P* < 0.001), serum UA and FRS (n= 54, r = 0.305, *P* = 0.025), albuminuria and FRS (n= 54, r = 0.432, *P* = 0.001) were determined (figures 2).

Significant relationship between the FRS (as the dependent variable) and the UA serum (β = 2.63, 95 percent CI: 0.35–4.92 ; p = 0.025 ; R2 = 0.09) and between FRS and urinary ACR (β = 0.10, 95 percent CI: 0.05–0.15 ; p = 0.0002 ; R2 = 0.24) by using univariable linear regression analysis. In multivariable regression model with adjusting for DM duration, and SBP, serum UA did not affect CVD risk. In this adjusted model, the adjusted β coefficient for serum UA was -0.02 (p = NS). Notably, urinary ACR (adjusted β = 0.05; p = 0.025), DM duration (adjusted β = 0.89; p = 0.0006) and SBP (adjusted β = 0.35; p < 0.0001) were independent factors affecting future CVD risk (higher FRS).

Table 1. Demographic, clinical and laboratory features between study groups (n=108)

	Group I (n=54)		Group II (n=54)		Test	P
	No	**%**	**No**	**%**		
Age (Years) *Mean± SD*	61.80 ± 4.33		60.24 ± 5.22		**t** -1.69	0.094 (NS)
Sex *Male* *Female*	 21 33	 38.9% 61.1%	 24 30	 44.4% 55.6%	χ^2 0.152	0.696 (NS)
Smoking Status *Non Smoker* *Smoker*	 38 16	 70.4% 29.6%	 39 15	 72.2% 27.8%	χ^2 0.0001	0.999 (NS)
Hypertension *No* *Yes*	 17 37	 31.5% 68.5%	 21 33	 38.9% 61.1%	χ^2 0.365	0.546 (NS)
DM duration (Years) *Median (Range)*	20 (10 – 35)		13 (8 – 30)		**MW** 5.35	**0.0001** **(S)**
Serum Albumin (g/dL) *Mean± SD*	3.46 ± 0.65		4.17 ± 0.50		**t** 5.67	**<0.0001** **(S)**
Creatinine (mg/dL) *Mean± SD*	1.06 ± 0.30		1.04 ± 0.29		**t** -0.255	0.799 (NS)
BUN (mg/dL) *Median (Range)*	20 (3.7 – 79.4)		20 (5 – 36.5)		**MW** 0.63	0.526 (NS)
HbA1c (%) *Mean± SD*	8.92 ± 1.48		8.52 ± 2.05		**t** -1.15	0.255 (NS)
Total Cholesterol (mg/dL) *Mean± SD*	205.97 ± 50.24		213.58 ± 36.41		**t** 0.90	0.370 (NS)
TG (mg/dL) *Median (Range)*	147.5 (63 – 325)		130 (70 – 294)		**MW** 1.84	0.066 (NS)
Uric acid (mg/dL) *Mean± SD*	7.18 ± 1.49		5.78 ± 1.59		**t** -4.72	**<0.0001** **(S)**
ACR (mg/g) *Median (Range)*	212.89 (15 – 1826.1)		29.03 (3.8 – 277)		**MW** 5.64	**<0.0001** **(S)**

t = Independent sample (t) test, MW = Mann Whitney U test, χ^2 Chi-squared test, DM = Diabetes mellitus, BUN = blood urea nitrogen, HbA1c= hemoglobin A1c, TG= triglycerides, ACR= albumin to creatinine ratio.

Table 2. Demographic, clinical and laboratory features of the subjects according to uric acid levels (n=108)

	Diabetic patients with normal uric acid values (Uric Acid < 6 mg/dL) (n=44)		Diabetic patients with high uric acid values (Uric Acid ≥ 6 mg/dL) (n=64)		Test	P
	No	**%**	**No**	**%**		
Age (Years) *Mean± SD*	60.02 ± 4.49		61.70 ± 4.98		**t** 1.79	0.076 (NS)
Sex *Male* *Female*	 20 24	 45.5% 54.5%	 25 39	 39.1% 60.9%	χ^2 0.215	0.643 (NS)
Hypertension *No* *Yes*	 27 17	 61.4% 38.6%	 11 53	 17.2% 82.8%	χ^2 22.31	**<0.0001** **(S)**
DM duration (Days) *Median (Range)*	14.5 (8 – 25)		20 (8 – 35)		**MW** 3.21	**0.001** **(S)**
BMI (kg/m^2) *Median (Range)*	29 (26 – 34.9)		29.3 (25.3 – 35)		**MW** 0.146	0.884 (NS)
SBP (mmHg) *Median (Range)*	140 (110 – 180)		150 (90 – 190)		**MW** 1.27	0.204 (NS)
Creatinine (mg/dL) *Mean± SD*	1.03 ± 0.29		1.06 ± 31		**t** 0.49	0.624 (NS)
Serum Albumin (g/dL) *Mean± SD*	4.05 ± 0.65		3.66 ± 0.65		**T** -2.73	**0.008** **(S)**
Total Cholesterol (mg/dL) *Mean± SD*	202.91 ± 33.9		214.5 ± 49.23		**T** 1.45	0.150 (NS)
TG (mg/dL) *Median (Range)*	125.3 (63 – 294)		150 (68.6 – 325)		**MW** 2.87	**0.004** **(S)**
HDL-c (mg/dL) *Mean± SD*	51.35 ± 15.30		41.03 ± 14.59		**T** -3.54	**0.0006** **(S)**
LDL-c (mg/dL) *Mean± SD*	124.96 ± 34.27		141.23 ± 47.7		**t** 2.06	**0.042** **(S)**
ACR (mg/g) *Median (Range)*	29.6 (3.8 – 1826.09)		150 (5.2 – 1182.19)		**MW** 5.14	**<0.0001** **(S)**
HbA1c (%) *Mean± SD*	8.60 ± 2.12		8.79 ± 1.56		**t** 0.48	0.634 (NS)

t = Independent sample (t) test, MW = Mann Whitney U test, χ^2 Chi-squared test, DM = Diabetes mellitus, BUN = blood urea nitrogen, HbA1c= hemoglobin A1c, TG= triglycerides, ACR= albumin to creatinine ratio, LDL-c= low density lipoprotien cholesterol, HDL-c= high density lipoprotein cholesterol

Table 3. Demographic, clinical and laboratory features of the subjects according to urinary albumin execretion (uACR mg/g) (n=108)

	Diabetic patients with urinary ACR < 30 (n=38)		Diabetic patients with urinary ACR ≥ 30 (n=70)		Test	P
	No	**%**	**No**	**%**		
Age (Years) *Median (Range)*	60 (52 – 70)		61 (50 – 71)		**MW** 0.287	0.774 (NS)
Sex *Male* *Female*	19 19	50% 50%	26 44	37.1% 62.9%	χ^2 1.19	0.276 (NS)
Hypertension *No* *Yes*	17 21	44.7% 55.3%	21 49	30% 70%	χ^2 1.74	0.187 (NS)
SBP (mmHg) *Median (Range)*	130 (110 – 170)		150 (90 – 190)		**MW** 2.77	**0.006 (S)**
DM duration (Days) *Median (Range)*	15 (8 – 30)		20 (8 – 35)		**MW** 2.25	**0.024 (S)**
Creatinine (mg/dL) *Mean± SD*	0.997 ± 0.29		1.08 ± 0.30		**T** 1.23	0.223 (NS)
Serum Albumin (g/dL) *Mean± SD*	4.12 ± 0.52		3.68 ± 0.70		**T** -2.96	**0.004 (S)**
Total Cholesterol (mg/dL) *Mean± SD*	203.98 ± 33.91		212.92 ± 48.32		**T** 1.12	0.265 (NS)
TG (mg/dL) *Median (Range)*	106.5 (63 – 180)		166.5 (69 – 325)		**MW** 5.90	**<0.0001 (S)**
HDL-c (mg/dL) *Mean± SD*	56.96 ± 13.97		38.87 ± 12.6		**T** -6.86	**<0.0001 (S)**
LDL-c (mg/dL) *Mean± SD*	124.50 ± 38.22		140.09 ± 45.16		**T** 1.81	0.074 (NS)
Uric acid (mg/dL) *Mean± SD*	5.71 ± 1.47		6.90 ± 1.66		**T** 373	**0.0003 (S)**
HbA1c (%) *Mean± SD*	8.46 ± 1.86		8.86 ± 1.75		**T** 1.09	0.277 (NS)

t = Independent sample (t) test, MW = Mann Whitney U test, χ^2 Chi-squared test, DM = Diabetes mellitus, BUN = blood urea nitrogen, HbA1c= hemoglobin A1c, TG= triglycerides, LDL-c= low density lipoprotien cholesterol, HDL-c= high density lipoprotein cholesterol

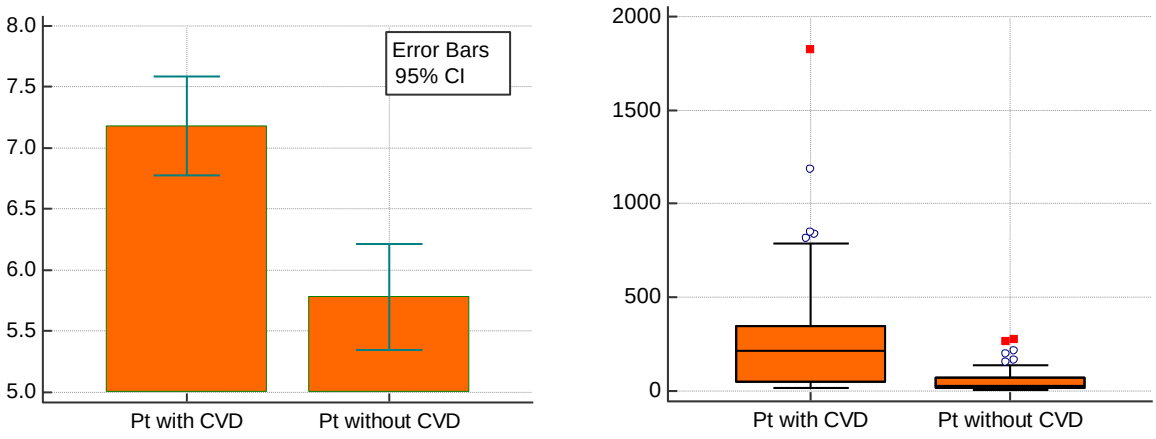

Figure 1. Column chart showing difference between both groups as regard uric acid & ACR

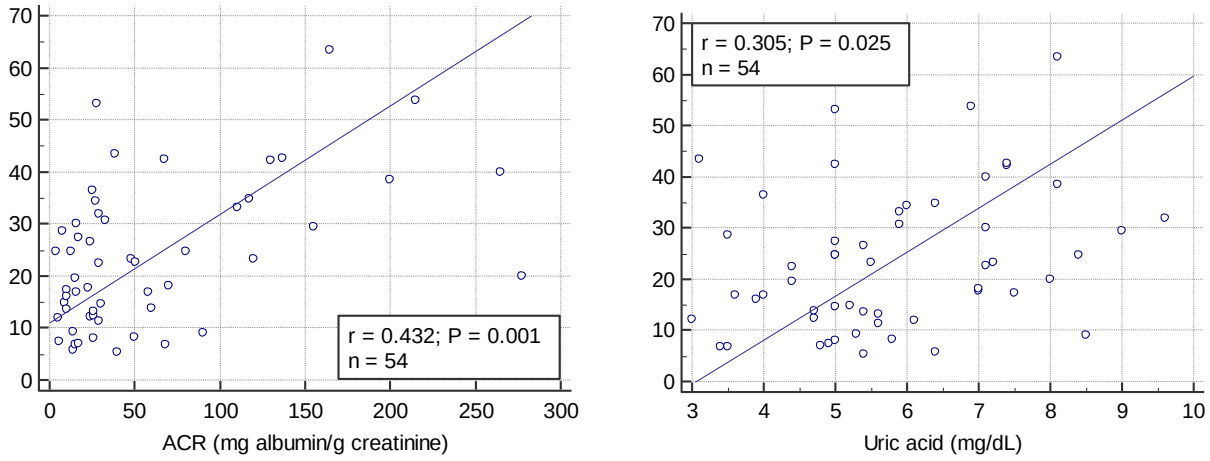

Figure 2. Correlation coefficient between both uric acid, ACR and FRS:

DISCUSSION

Albuminuria in diabetic and non-diabetic patients increases cardiovascular mortality and is associated with the development of ASCVD due to endothelial dysfunction with advanced procoagulant imbalance and chronic low-grade inflammation status **[9]**.

UA as independent risk for future CVD is a matter of debate, indeed the Framingham Heart Study (FHS) had assessed this association, and is considered as bad companion to metabolic syndrome components definitely contribute to development and progression of ASCVDs**[10]**.

The main question addressed in this study was whether the level of serum uric acid and urinary albumin excretion in patients with diabetes are independent risk factors for CVD and whether in the spectrum of cardiorenal connection they are related to one another.

First, uric acid level was found to be higher in patients with diabetes with proven CVD "group I" (M=7.18, SD=1.49) compared to those without CVD "group II" (M=5.78, SD=1.59); t(106)= -4.72, p<0.0001.

There is increasing evidence that hyperuricaemia may be associated with cardiovascular disorders and metabolic disorders that may affect survival of patients **[11]**. Hyperuricemia is strongly associated with traditional cardiovascular risk factors with increased likelihood of developing complications related to microvascular and macrovascular diabetes. Including 15,773 individuals, the Third National Health and Nutrition Examination Survey (NHANES) showed an increase in CV mortality and increased mortality from any cause correlated with SUA levels. The hazard ratio increase per 1 mg / dL of SUA was 1.32, which remained 1.15 after other risk factors and comorbidities were adjusted **[12]**.

Our findings are supported by Niskanen et al. study, including 1,423 middle-aged men, found that SUA levels could strongly anticipate CV deaths, regardless of other risk factors commonly associated with either hyperuricemia or metabolic syndrome [**13]**. Loachimescu et al. found that the mean SUA levels were significantly higher in patients with CVD compared to control (6.3 ± 1.7 mg / dl versus 5.9 ± 1.6 mg / dl ; $p < 0.001$), while diabetic patients also had SUA values more than other participants in the study. In addition, in patients who died during the study period, SUA levels were significantly higher than those who survived (7.1 ± 2.1 mg / dl versus 6.0 ± 1.6 ; $p < 0.001$) **[14]**. A study conducted by Kivity et al. evaluated the relationship between SUA and CVD outcomes; found that SUA was considerably higher in CVD patients versus non-CVD patients **[15]**.

Several studies associate SUA with CHD as an independent risk factor. SUA and low-density lipoprotein levels were found to be independent indicators of ASCVD in a study conducted on Asian Indian diabetic patients **[16]**. Another large prospective cohort study on elderly Austrian ladies of 62.3 years of age was conducted to evaluate the role of SUA in cardiovascular mortality, showing that SUA is

an independent determinant of all causes CV mortality **[17]**.

In our study, patients with high uric acid levels (> 6 mg/dL) were more likely to be, hypertensive, slightly hypoalbuminic with significant albuminuria, moreover, they had more duration of diabetes. No difference between both males and females, and no difference as regard A1c values or BMI. Compared to our study, *Panero et al.* found that people with higher levels of SUA were more likely to be male, being elderly, being overweight or obese, to have hypertension, to have impaired kidney function, abnormal lipid profile, to be insulin-treated, and to have coronary heart disease history **[18]**.

In our study, the group of patints with diabetes who have no history of CVD, after calculation of FRS, it was found to be statistically significantly higher in patients with high uric acid (M=29.13, SD=14.53) than patient with low uric acid (M=19.72, SD=12.03); t(52)= 2.58, p=0.013. This is also consistent with Kivity et al. findings, there was higher CVD in patients with high SUA and the higher calculated FRS was linked to high SUA at baseline [**15]**.

In the current study, we found significant correlation between, uric acid and CVD outcome as calculated with FRS. Kivity et al. also noted, in agreement with our finding, that the correlation between SUA and future CVD risk was significant, as determined by the Framingham risk score **[15]**. Likewise, many epidemiological studies such as Feig et al. and Bos et al. showed that raised SUA could predict the risk of CHD **[19, 20]**.

On the other hand, Skak-Nielsen et al. study to evaluate the relationship between SUA and CVD risk showed that SUA was not an independent predictor of future CV events or mortality associated with CV **[21]**.

The current study, there was statistical significant difference between patients with low and high uric acid levels as regard urinary albumin creatinine ratio, being higher in patients with high SUA. The damage component appears to be identified by all accounts with the progression of preglomerular arteriolar disease that debilitates the autoregulatory reaction of the renal and subsequently causes glomerular hypertension **[22]**. Lee et al. found a link between SUA and urinary albumin excretion and that high SUA is considered as an independent predictor of both albuminuria development with subsequent renal dysfunction **[23]**.

Once more, it has also been widely demonstrated in literature that the high SUA along with albuminuria play a key role in the development and progression of renal function **[4]**. Study by *Anyanwagu et al.*, which included a large cohort of patients treated with insulin, showed that, together with increased urinary albumin excretion, reduced eGFR was associated with a high risk of premature CV death, followed by patients with reduced eGFR but normal urinary albumin levels **[24]**. In this regard, our study show that there was statistical significant difference as regard ACR between patient with diabetes and CVD (Mdn=212.89) and patients with diabetes but without CVD (Mdn=29.03); U=541, p<0001. Albuminuria is known for its association with CVD and is regarded as an independent risk factor in diabetic patients for cardiovascular morbidity and mortality **[25]**. It was reported in a systematic review that microalbuminuria is associated with a 2.4-fold increase in cardiovascular death in patients with T2DM compared with those who have never developed albuminuria **[26]**. Gimeno-Orna et al. assessed albuminuria effect in T2DM patients after categorizing their cohort into 4 groups based on CVD or albuminuria. Patients with no cardiovascular disease but albuminuria had a 2.8-fold increase in risk of cardiovascular disease compared to patients with no albuminuria. In addition, patients with no baseline CVD and albuminuria had the same risk of a subsequent cardiovascular incident than those with previous CVDs had been shown to occur prior to study enrollment **[27]**. Gerstein et al. concluded that any degree of urinary albumin excretion raises the risk of developing CVD in people with or without diabetes; and that risk goes up as the level of albuminuria increases, even below the previously known cutoff for microalbuminuria **[28]**.

Hyperuricemia, and albuminuria are common findings in spectrum of

cardiometabolic syndrome **[4]**. Results from this study showed that hyperuricemia, albuminuria and the risk of CVD (assessed by the FRS) were significantly correlated with each other, though this correlations were diverse (r = 0.305, 0.432 respectively). Furthermore, after confounder adjustment (DM duration and SBP), only urinary ACR seems to have been an independent factor from the above described parameters which could determine the risk of future CVD.

SUA can be useful markers of future CVD together with urinary albumin excretion. They have the benefit that they are readily available and being cheap tests. However, it is necessary to further determine their predictive values. There are some limitations in our study. Our study's retrospective nature is less reliable than prospective ones. Second, the small sample size, it may not represent the general population. Third, the inclusion of participants in a hospital setting could overstate their CVD risk.

In conclusion, the current study showed that the common association between serum UA levels and albuminuria. Together with other traditional risk factors, we should look for such common combination and be aware of the higher risk of developing CVD in these patients. We need other interventional study to assess the importance of SUA and albuminuria modification with urate lowering therapy and with other treatment that target urinary albumin excretion to establish the cause effect relationship.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding information

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