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Frequency and Correlation of Serum Uric Acid to Different Stages of Albuminuria in Type II Diabetic Nephropathy

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ABSTRACT

Background: Albuminuria is considered the gold standard of onset and progression of diabetic nephropathy (DN). Higher levels of serum insulin may decrease uric acid clearance by the kidneys leading to hyperuricemia, which has injurious effect on kidneys.

Objective: To evaluate the frequency and relationship of uric acid to different levels of albuminuria in type II diabetes mellitus.

Patients and Method: This cohort study included 56 T2DM patients classified according to stages of DN into: Group I that including 12 patients with normoalbuminuria, group II included 26 patients with microalbuminuria, and group III including 18 patients with macroalbuminuria. All of them were evaluated for serum creatinine and albumin, CBC, ACR, UAE, HbA1c, ESR, Serum TSH and serum uric acid (SUA).

Results: Hyperurecemia frequency was (62.5%) and it had highly statistical significant difference with albuminuria in the three studied groups. There was strong significant positive correlation of SUA with UAE ($p < 0.014$), Cr ($p < 0.037$), ACR ($p < 0.006$), HbA1c ($p < 0.017$) in macroalbuminuria and UAE ($p<0.042$) and ACR ($p < 0.043$) in microalbuminuria group, and TLC ($p < 0.024$) in normoalbuminuria group. While there was a significant negative correlation between UA with albumin ($p < 0.029$) in macroalbuminuria group.

Conclusions: Hyperinsulinemia and chronic inflammation associated with type IIDM leads to hyperuricemia, which had high frequency in our study (62.5%) and carry a hazardous effect on kidney function contributing to progressive increase of albuminuria. So we must search for management of elevated UA in these patients to delay onset & progression of its morbidity.

Keywords: Uric Acid, Type II diabetes mellitus, Albuminuria, Egypt.

INTRODUCTION

The overall effects of hyperglycaemia leading to release of proinflammatory and profibrotic mediators that cause alterations in intra-renal haemodynamics resulting in the classic structural and functional alterations of diabetic kidney disease with alterations in glomerular permeability, and, ultimately, the development of glomerulosclerosis and interstitial fibrosis [(1)].

Elevated UA is associated with endothelial dysfunction, insulin resistance, and progression of non-diabetic renal disease [(2)]. These findings have led us to find out the role of uric acid in the onset and progression of diabetic nephropathy [(3, 4)]. The aim of the present work was to evaluate frequency and correlation of hyperuricemia with albuminuria in type II DM patients.

PATIENTS AND METHODS

Cohort study had been carried out in Outpatient Clinic of Endocrinal and Nephrology Units of Internal Medicine Department, Zagazig University Hospitals, from October 2017 to November 2018. We conducted this study on 56 T2DM patients (27 females and 29 males) diagnosed according to The National Diabetes Data Group and World Health Organization diagnostic criteria [(5)]. FBS ≥ 126 mg/dl, 2-h PPG ≥ 200 mg/dl and HbA1c ≥ 6.4% in 2 repeated times. The patients were classified into **group I** including 12 diabetic patients with normoalbuminuria (ACR < 30 mg/g), UAE (12.2 ± 8.4), (8 males and 4 females) and eGFR of 92.33 ± 12.45 ml/min/1.73 m^2, **group II** including 26 diabetic patients with microalbuminurea (ACR = 30-300 mg/g), UAE (95.1 ± 60.9) (10 males and 16 females), eGFR of 72.23 ± 12.72 ml/min/1.73 m^2, and **group III** including 18 diabetic patients with macroalbuminurea (ACR > 300 mg/g), UAE of 366.6 ± 26.3 (11 males and 7 females) and eGFR of 42.11 ± 11.82 ml/min/1.73 m^2.

Inclusion criteria: Age equal or more than 18 years, T2DM patients and patients on antidiabetic management or insulin therapy.

Exclusion criteria including: Age < 18 years or more than 65 years, patients refusing to participate in the study, presence of type1DM, diabetic ketoacidosis, chronic glomerulonephritis, transplanted recipients, liver disease, evidence of current infection or inflammation, blood diseases, blood transfusion or malignancy, pregnancy, or taking UA lowering agents

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or diuretics, hypothyroid and patients with GFR< 30 ml/min/1.73 m^2.

Ethical approval:

After complete explanation of the procedure steps and nature of the research, written consents were taken from all persons sharing in this study. The study was approved by Zagazig University, Faculty of Medicine Ethical Committee (Zu-IRB # 4111/13-2-2017).This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All persons included in this study were subjected to the following:

- Complete clinical history and physical examination, lab investigation: like complete blood count, urinalysis, serum albumin and creatinine, ESR, UAE, enzymatic photometric test was used to measure SUA. Immunoturbidimetric assay was used to measure urine albumin. Urine creatinine was measured using creatinine Jaffe method on Olympus AU400 analyzer. Albumin creatinine ratio (ACR) was calculated by dividing urine albumin concentration with urine creatinine concentration. HbA1c, eGFR calculated by MDRD4 equation in addition to TSH, FT4 and lipid profile.
- All blood samples withdrawals were performed by nursing staff when they were fasting.

Data management:

Collected data revised, verified, edited on P.C, and then analyzed statistically using SPSS statistical package for the social science version 24.

The following statistical tests were used:

Qualitative variables were represented by frequency and percentage. Description of quantitative variables in the form of mean and standard deviation, (mean ± SD). Chi-square (x2) test and Fisher exact were used for comparison of qualitative variables with each other. Comparison between quantitative variables was carried out using Student t-test of two independent samples. For comparison of more than two quantitative groups one-way ANOVA F- test was used for categorical data. Significance level (p) was expressed as following: P- Value > 0.05 is not significant. P - Value ≤ 0.05 is significant. P- Value < 0.001 is highly significant. Pearson correlation coefficient was used to calculate correlation between quantitative variables.

RESULTS

Table (1) showed that there was significant difference between the three studied groups regarding BMI and serum uric acid (SUA). While, there were no statistical significance differences as regarding age, gender and diabetic retinopathy.

Table (1): Demographic-clinical data of the studied population (N= 56)

		Group I (N=12)	Group II (N=26)	Group III (N=18)	F / χ^2	P
Age (years) Mean ± SD		**46.17 ± 13.63**	**47.85 ± 18.46**	**53.2 ± 12.28**	**.394**	**0.679**
Sex	**Male**	**8 (66.7%)**	**10 (38.5%)**	**11 (61.1%)**	**1.559**	**0.459**
	Female	**4 (33.3%)**	**16 (61.5%)**	**7 (38.9%)**		
BMI (kg/m^2) Mean ± SD		**25.35 ± 2.48**	**26.94 ± 2.72**	**28.9 ± 2.07**	**6.469**	**0.006**
High UA (mg/dl)		**3(25%)**	**17(65.4%)**	**15(83.3%)**	**3.476**	**0.028**
Normal UA		**9(75%)**	**9(34.6%)**	**3(16.7%)**		
DR	**II**	**10 (83.3%)**	**18 (69.2%)**	**8 (44.4%)**	**2.388**	**0.303**
	III	**2 (16.7%)**	**8 (30.8%)**	**10 (55.6%)**		

DR - diabetic retinopathy. BMI - body mass index. SD- standard deviation UA - uric acid

Table (2) showed that there were high statistical significant differences between different groups regarding S. creatinine, urea, UA, ACR and UAE, S. albumin, total protein, TLC, HbA1c and 1^{ST}ESR while there were no statistical significance differences regarding blood Hb, TG and TSH.

Table (2): Comparison of basal lab values among different groups

	Group I (N=12) (Mean ± SD)	Group II (N=26) (Mean ± SD)	Group III (N=18) (Mean ± SD)	F	P
Uric acid (mg/dl)	5.81 ± 1.49	7.55 ± 1.59	10.86 ± 1.32	13.623	0.000
ACR (mg/g)	22.8 ± 2.49	95.88 ± 2.55	342.2 ± 14.74	59.154	0.000
UAE (mg/24h)	12.2 ± 2.41	95.15 ± 6.99	366.6 ± 6.3	5.135	0.015
Creatinine (mg/dl)	0.85 ± 0.15	1.00 ± 0.24	1.70 ± 0.36	6.951	0.000
BUN (mg/dl)	22.4 ± 3.89	38.38 ± 3.61	67.6 ± 3.84	28.217	0.000
T. protein (mg/dl)	7.1 ± 1.12	6.82 ± 1.37	4.82 ± 0.319	6.314	0.007
S.Albumin (g/dl)	5.01 ± 0.405	4.15 ± 0.994	2.78 ± 0.488	10.497	0.001
ALT (U/L)	31.33 ± 2.46	31.92 ± 6.86	32.20 ± 1.61	0.027	0.973
AST (U/L)	43.33 ± 9.27	29.02 ± 2.05	31.4 ± 3.28	2.095	0.148
Hemoglobin (g/dl)	11.25 ±1.5	10.86 ± 2.28	9.36 ± 1.71	1.173	0.329
TLC (10^3 /µL)	5.77 ± 1.81	7.17 ± 1.47	8.9 ± 1.11	6.985	0.005
HbA1c (%)	5.08 ± .773	5.41 ± 1.12	7.78 ± 0.289	13.880	0.000
1st ESR (mm/hr)	29.1± 3.5	31.5 ± 5.71	74.2 ± 101.37	7.347	0.001
Cholesterol(mg/dL)	104.5 ± 4.67	181.1 ± 2.96	231.1 ± 5.05	9.991	0.000
TG (mg/Dl)	124.0 ± 3.35	127.17 ± 6.38	170.4 ± 4.79	1.872	0.179
TSH(mlU/L)	1.95 ±0 .096	2.71 ± 0.08	2.96 ± 0.27	1.407	0.267
fT4 (ng/dL)	1.14 ±0 .423	1.23 ± 0.05	1.434 ± 0.07	0.608	0.554

TLC: total leukocyte counts. HbA1c: hemoglobin A1c. TG: triglyceride. TSH: thyroid stimulating hormone. FT4: free T4. AST: aspartate transferase enzyme. ALT: alanine transferase enzyme.

Table (3) showed that there was statistical significant positive correlation between uric acid and TLC in normoalbuminuria group, UAE & ACR in microalbuminuria group and S. creatinine, UAE, ACR and HbA1c in macroalbuminuria group. While, there was statistical significant negative correlation between uric acid with albumin in macroalbuminuria group.

Table (3): Correlation between uric acid with other parameters in all the studied population

		Uric acid in normoalb.	***Uric acid in microalb.***	***Uric acid in macroalb.***
Age (years)	Pearson Correlation (Sig.)	.107 (.840)	-.280 (.354)	.428 (.472)
BMI (kg/m^2)	Pearson Correlation(Sig.)	.577 (.230)	.311 (.301)	.333 (.585)
UAE (mg/24h)	Pearson Correlation(Sig.)	.040 (.940)	.443* (.042)	.847* (.014)
Creatinine (mg/dl)	Pearson Correlation(Sig.)	.124 (.815)	.377 (.060)	.508* (.037)
Urea (mmol/day)	Pearson Correlation(Sig.)	.216 (.681)	.186 (.542)	.201 (.102)
ACR (mg/g)	Pearson Correlation(Sig.)	.282 (.588)	.569* (.043)	.618**(.006)
TLC (10^3 /µL)	Pearson Correlation(Sig.)	.870 (.024)*	-.406 (.168)	.122 (.845)
Hb (g/dl)	Pearson Correlation(Sig.)	.639 (.172)	-.506 (.078)	.238 (.700)
HbA1c (%)	Pearson Correlation(Sig.)	-.437 (.386)	.410 (.165)	.697* (.017)
Albumin (g/dl)	Pearson Correlation(Sig.)	.689 (.130)	-.356 (.232)	-.589* (.029)
Total protein (mg/dl)	Pearson Correlation(Sig.)	-.555 (.253)	.303 (.315)	-.411 (.091)
LDL (mg/dL)	Pearson Correlation(Sig.)	-.377 (.462)	.391 (.187)	.095 (.897)
TC (mg/dL)	Pearson Correlation(Sig.)	.311 (.548)	-.169 (.581)	.060 (.924)

* significant ** high significant UAE: urine albumin excretion. ACR: albumin creatinine ratio. LDL: low density lipid. TC: total cholesterol.

DISCUSSION

A common complication of type II diabetes is diabetic nephropathy, which is a leading cause of end-stage renal disease in developed countries **Hayashino *et al.* [6].**

Hyperinsulinemia resulting from insulin resistance in T2DM negatively affects renal excretion (by activating the transporter of UA) and increases rates of production and renal reabsorption of uric acid. Metabolic component abnormality could be rising microalbuminuria and serum uric acid in DM this may be due to increase excretion of purine metabolism [7], glomerular hypertension and trans vascular albumin leakage [8].

Hyperurecemia and microalbuminuria levels have been shown to play wire roles in induction of some inflammatory cytokines (hs-CRP, IL-6, and TNF-α), and oxidative stress. Both of them were speculated to the pathogenesis of diabetic vascular complications [9]. Prevalence of elevated uric acid in our study was 62.5% (35 out of 56 study subjects). It is similar to **Singh *et al.* [10]**, who showed a high prevalence of hyperuricemia (UA >7 mg/dl males and > 6 mg/dl females) in 23 (46%) out of 50 study subjects. The probable reason for this could be that the shared persons were not taking any treatment for hyperuricemia or suppression of UA excretion by exogenous insulin.

Our study showed that serum UA level progressively increased in group **I** (6.18 ± 1.49), **II** (7.55 ± 1.59) and **III** (10.86 ± 1.32) ($P < 0.000$). Also, UAE was progressively increased in group **I** (12.2 ± 8.41), **II** (95.15 ± 60.99) and **III** (**366.6 ± 26.3**). There was statistically high significant positive correlation between UA and UAE in micro- ($P < 0.042$) & macroalbuminuria ($P < 0.014$) groups. The same results were observed by **Behradmanesh *et al.* [11]** who established confirmed correlation of albuminuria and uric acid in diabetic nephropathy. Proteinuria (median and mean ± SD) were 303.5 mg/dl and 388 ± 28.7 respectively, while in patients of DM type 2, uric acid (mean ±SD was 4.5 ± 0.15 mg/dl. Also, **Dehghan *et al.* [12]** and **Kodama *et al.* [13]** stated that elevation of microalbuminuria and uric acid level may be prophesy occurrence of DM.

Positive significant correlation of serum UA level with serum creatinine, blood urea in relation to albuminuria in the studied groups. Our result is in accordance with **Unnikrishnan *et al.* [14]** and **Johnson *et al.* [15]** who showed that level of uric acid in serum was a major pathological factor in the development of nephropathy in Type-2 diabetic patients. Hyperuricemia was associated with kidney damage manifested by glomerular hypertrophy and sclerosis. This is in harmony with **Tanaka *et al.* [16]** in his study**;** level of uric acid was evaluated to study its association with reduction in kidney function at overt nephropathy onset in diabetic patients type II. They observed that risk of duplication of serum creatinine was linked to higher level of UA.

There was positive correlation of UC with TLA, which was significant in normoalbuminuria but not significant in micro & macroalbuminuria. it was explained by a state of immune dysfunction and immune depression that was associated with the progressive renal impairment.

Uric acid levels in the studied patients were correlated inversely with serum albumin ($P < 0.029$), total proteins ($p < 0.091$) and blood Hb ($p < 0.078$). This is due to malnutrition, inflammation complex, increase permeability of basement membrane and low level of erythropoietin due to development of renal impairment. Serum UA was believed as an inflammatory factor and have a significant act on dysfunction of endothelium, which is pathogenic cause of DN in type 2DM **Leung *et al.* [3] and Cai *et al.* [4].**

Positive but not significant correlation of UA with BMI was found in our patients. In contrary to **Zhang *et al.* [17]** who recruited 5888 individuals aged 45 to 96 years and reported that general linear model analysis adjusted for confounding factors did not reveal interaction between BMI and SUA levels. However, SUA independently linked to SBP both in males and females with BMI < 24.0 kg/m^2, and SUA independently was associated with DBP in females with BMI ≥ 24.0 kg/m^2. This may be due to ethnicity, study protocols, methods of evaluation and size of study.

Our study declared that there was a positive correlation of SUA with HbA1c, which is non-significant in microalbuminuria and significant in macroalbuminuria due to deterioration of glycemic control. This is against **Rusdiana *et al.* [18]** who found that level of uric acid has no relation to HbA1c in the studied subjects.

CONCLUSION AND RECOMMENDATION

From the aforementioned study, it could be concluded that uric acid have high prevalence in DM type 2 and high positive correlation with stages of albuminuria. So, we recommend to make it as one of routine investigations for early detection of the disease and good management to delay or protect from complication.

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