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Original Article

Frequency of Hyperuricemia in Type-2 Diabetes Mellites and its Relation with Diabetic Nephropathy

Gulzar Ali, Muhammad Asif Kamran*, Muhammad Amir, Babar Mumtaz, Imran Khan, Muhammad Tariq

Combined Military Hospital Peshawar/National University of Medical Sciences (NUMS) Pakistan, *64 Medical Battalion Field Hospital, Miran-Shah Pakistan

ABSTRACT

Objectives: To determine the frequency of Hyperuricemia in patients with type-2 Diabetes Mellitus and to compare frequency of Diabetic Nephropathy in Hypouricemic vs Normouricemic patients with type-2 Diabetes.
Study Design: Cross-sectional analytical study.
Duration and Place of Study: Medicine Department Combined Military Hospital Peshawar, from Dec 2018 to May 2019.
Methodology: Patients from both genders with type 2 Diabetes having glycosylated hemoglobin (HbA1c) ≥6.5%, Fasting Blood glucose ≥ to 7.0 mmol/L or random blood glucose ≥11.1 mmol/L were recruited from out Patient department. Participants were tested for serum uric acid, fasting blood glucose, Glycosylated hemoglobin (HbA1c) and Spot Urine Albumin Creatinine Ratio after 8 hours fasting.
Results: Out of 111 patients enrolled Hyperuricemia was present in 40 (36.04%) patients of which 21 (52.50%) were male and 19 (47.50%) were female. Diabetic Nephropathy was present in 43(38.74%). Out of 43 patients having diabetic nephropathy, 25 (58.14%) were having hyperuricemia. The study observed a linear relationship between serum uric acid and type-2 diabetes duration, fasting blood glucose levels, glycosylated hemoglobin (HbA1c) and urinary Albumin creatinine ratio.
Conclusion: Hyperuricemia is positively linked with diabetic complications in majority of patients with type-2 diabetes. Serum uric acid levels can be used as an early diagnostic parameter and can prognosticate diabetic nephropathy.

Keywords: Diabetes mellitus, Diabetic nephropathy, Hyperuricemia, Microalbuminuria.

How to Cite This Article: *Ali G, Kamran MA, Amir M, Mumtaz B, Khan I, Tariq M. Frequency of Hyperuricemia in type-2 Diabetes Mellites and its Relation with Diabetic Nephropathy. Pak Armed Forces Med J 2023; 73(1): 199-203. DOI: https://doi.org/10.51253/pafmj.v73i1.3916*

INTRODUCTION

Diabetes accounts for 4 million deaths per year which makes it the fifth leading cause of death worldwide.[1] Among the three major types of Diabetes, Type II is the more prevalent one, affecting 90-95% of all affected individuals. In Pakistan, Diabetes is affecting more than 26.3% of the population.[2] Nephropathy is themost debilitating complication of diabetes, ultimately leading to End Stage Renal Disease (ESRD). A study has shown that 66.7% of the patients in Pakistan with newly diagnosed type 2 diabetes who had poor glycemic control, were having Diabetic Nephropathy.[3] High Mortality is found to be associated with Microalbuminuria.[4]

Uric acid is synthesized by the conversion of xanthine to uric acid by xanthine oxidoreductase. Uric Acid has antioxidant as well as pro-oxidant properties. Uric Acid is an important player in homeostatic, metabolic, and hemodynamic abnormalities such as insulin resistance, central obesity, hyperlipidemia and metabolic syndrome. Many researchers have studied serum uric acid (SUA) implication in oxidative stress, inflammatory response and its contributionto endothelial dysfunction and vascular remodeling.[5,6] Serum uric acid has been found to cause damage to vascular endothelium, anti-proliferative manifestations, increased oxidative stress and formation of free radicals.[7] Individual shaving raised levels of uric acid in the blood have relatively higher values of endothelial-dysfunction (ED) markers, increased urinary albumin creatinine ratio (ACR) and blood endothelin levels.[8]

The interest of the researchers in studying hyperuricemia and its associated disorders has grown past gout, such as hypertension, atherosclerosis, cardiovascular disease, Insulin Resistance & Diabetes.[9,10] Furthermore, studies have shown the beneficial effect of urate lowering therapy in preservation of glomerular filtration rate (GFR) in Hyperuricemic patients with chronic kidney disease(CKD).

The objective of our study was to determine the frequency of hyperuricemia in diabetic patients in local population and study its relationship with diabetic nephropathy. On the basis of this study, it can be recommended as a routine test to identify patients at risk for development of nephropathy, and urate

Correspondence: Dr Gulzar Ali, Senior Registrar Medicine CMH Peshawar-Pakistan
Received: 07 Apr 2020; revision received: 02 May 2020; accepted: 08 May 2020

lowering therapy may be advised to those with raised levels, to prevent or retard the disease.

METHODOLOGY

We performed this cross-sectional-analytical study at the Outpatient Department, Combined Military Hospital Peshawar from December 2018 to May 2019 over six months. After approval from the hospital ethical review committee (ERB certificate no-0039),

Inclusion Criteria: Patients of either gender, age 20-65 years, qualifying working definition of type 2 Diabetes Mellitus (having glycosylated hemoglobin (HbA1c) ≥ to 6.5%, fasting blood glucose ≥ to 7.0 mmol/L or random blood glucose ≥11.1 mmol/L) were inlcluded in the study.

Exclusion Criteria: All those patients having type-1 DM, end stage renal disease (ESRD), myeloproliferative disorders, lymphoproliferative disorders and those taking drugs affecting uric acid metabolism were excluded.

Sample size was calculated using world health organization (WHO) sample size calculator with confidence level of 95% and anticipated population proportion of 17%.[11] After informed written consent, Serum uric acid level, fasting blood glucose, glycosylated hemoglobin (HbA1c) and spot Urine albumin creatinine ratio (ACR) samples were collected after minimum 8 hours of fasting and analysis was done with Selectra XL Chemistryanalyzer. Data was recorded on specially designed proforma.

Data was analyzed on Statistical Product and Service Solutions-20 (SPSS-20). Descriptive statistics were calculated for both qualitative and quantitative variables. For quantitative variables like serum Uric Acid, FBG and Glycosylated hemoglobin (HbA1c), microalbuminuria (urinary albumin creatinine ratio (ACR), Mean±SD were calculated. For qualitative variables like gender, hyperuricemia and nephropathy, frequency and percentages were calculated. Chi-square test was used to assess association of dichotomous variables including gender and status of hyperuricemia in patients with diagnosis of diabetic nephropathy. Prior to running chi-squared test, an expected frequency counts >5 was ensured for each category. Scatter plots were made to see relation between serum uric acid levels, age of participants, diabetes duration and other laboratory parameters.

RESULTS

Out of 111 patients gender wise distribution showed 60 (54.10%) male and 51(45.90%) female individuals. Mean age was 52.77 ± 9.16 years. Mean duration of diabetes was 9.20 ± 3.77 years. Mean fasting blood glucose levels were 9.21 ± 2.32 mmol/L. Mean glycosylated hemoglobin was 7.82 ± 1.28%, Mean urinary albumin creatinine ratio 63.66 ± 77.87 mg/g and mean serum uric acid levels were 5.95 ± 1.31 mg/dl (Conventional unit).

Diabetic Nephropathy was present in 43 (38.74%). Hyperuricemia was present in 40 (36.04%) patients out of which 21 (52.50%) were male and 19 (47.50%) were female (Figure-1).

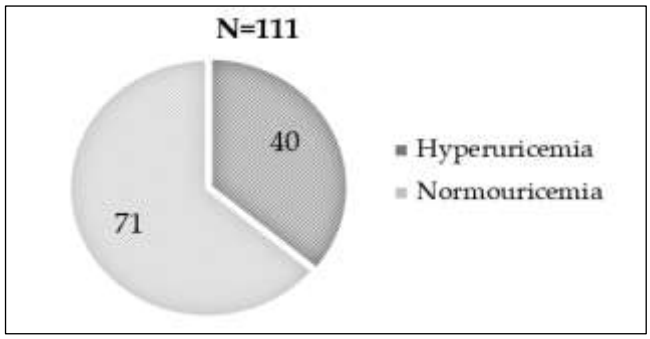

Figure-1: Distribution of Hyperuricemia among study cases.

Out of 43 patients having diabetic nephropathy, 25 (58.14%) were having hyperuricemia. A linear relationship was found between serum uric acid levels and urinary albumin creatinine ratio (ACR) (Figure-2).

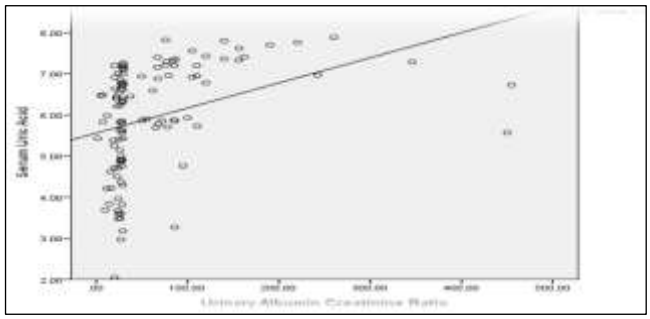

Figure-2: Relation between serum uric acid levels and urinary albumin creatinine ratio (ACR).

Chi-square and t-test were run to assess association of demographic and lab characteristics of patients with nephropathy. It showed that a significantly higher proportion of hyperuricemic females with poor Diabetes control had a diagnosis of nephropathy. Detailed results have been given in (Table-II & Table-III).

Regression analysis yielded a significant model predicting diabetic nephropathy among participants (82.90%, p<0.001). It showed that hyperuricemic

patients had 11 times higher odds of having diabetic nephropathy than their counterparts (Table-I).

Table-III: Association of Demographic and Lab characteristics of patients with nephropathy (n=111).

Variables	Diagnosis of Nephropathy		t-statistic *p* Values
	Absent	Present	
	Mean ± SD	Mean ± SD	
Age	49.37 ± 9.40	58.14 ± 5.55	-6.18 (p<0.001)
Duration of Diabetes	7.69 ± 3.52	11.74 ± 2.68	-6.46 (p<0.001)
Fasting Blood glucose	8.70 ± 2.06	10.02 ± 2.50	-3.03 (p<0.01)
HbA1c	7.46 ± 1.16	8.39 ± 1.26	-3.98 (p<0.001)

A better understanding of the disease and advancement in research has led to certain new predictors that can be used to assess these complications. In this regard, serum uric acid level has been studied, and association of hyperuricemia with complications in Diabetes has been established. Multiple mechanisms have been postulated to link Hyperuricemia with diabetic complications especially Diabetic nephropathy.[14]

Our study was aimed to demonstrate an association between diabetic nephropathy and hyperuricemia. A total of 111 patients were selected from outdoor clinics of Medicine department. Results showed elevated mean blood uric acid levels in diabetics with higher urinary albumin creatinine ratio (ACR) levels.

Table- I: Regression model Presenting Probability of Diabetic Nephropathy among Hyperuricemic Patients (n=43).

Variables	B	S.E	*p*-value	Odds Ratio (OR)	95% C.I For OR	
					Lower	Upper
Constant	-8.164	3.007	0.007	0		
Age	0.098	0.077	0.200	1.103	0.949	1.283
Gender	-1.600	0.572	0.005	0.202	0.066	0.619
Duration Since Diabetes	0.238	0.171	0.165	1.268	0.907	1.775
Hyperuricemia	2.400	.661	< 0.001	11.026	3.016	40.310

Lemeshow Statistic p= 0.37; Cox & Snell R2= 42%, Nagelkerke R2= 57%

Table-II: Association of Demographic and lab Characteristics of Patients with Nephropathy (n=111).

Variables	Sub-Cat	Diagnosis of Nephropathy		χ2
		Absent	Present	
		n(age%)	n(age%)	
Gender	Male	43(71.7%)	17(28.3%)	0.02 (p<0.05)
	Female	25(49.0%)	26(51.0%)	
Hyperuricemia	Absent	53(74.6%)	18(25.4%)	14.89 (p<0.001)
	Present	15(37.5%)	25(62.5%)	

DISCUSSION

Diabetes Mellitus is a worldwide epidemic aecting both Western world and in particular people of Asian ancestry including Pakistan. As of 2014, Diabetes Mellitus has reached an astounding global prevalence of 422 million.[12] While staggering, these numbers fall short of conveying the full magnitude of the problem. The effects of diabetes on human life are multifactorial and devastating including physical complications, psychosocial implications, economic hardships and wasting of the most creative and productive years of human life. Optimum treatment of diabetes though challenging, has been proven to reduce the complications of diabetes.[13] Diabetes is linked with two-fold increased deaths from cardiovascular disorders, debilitating microvascular manifestations aecting vision, renal and nervous system, as well as with pronounced associations including malignancies, infections and psychosocial stigmata. If not treated, the microvascular complications result in blindness, Kidney dysfunction, chronic lower limb ulcers and loss of limbs due to amputations.

Another large population-based, prospective cohort study by Dehghan A *et al*, reported that patients with hyperuricemia were at higher risk of T2DM and that one-quarter of diabetes cases could be associated to a high serum uric acid level.[12]

Similarly, Nakanishi *et al,* reported that an elevation of serum UA concentration increased the risk of T2DM.[13] In the study done by Safi *et al,* diabetes was significantly associated with high SERUM URIC ACID(SUA) levels.[14] Another study by Pavithra V *et al,* strongly established an association between UA and Glycosylated hemoglobin (HbA1c) (p<0.0001) thereby linking Uric Acid to DM, particularly T2DM.[15]

In a large cross-sectional study (n=3212) Yan D *et al.* Found the prevalence of diabetic renal dys-function much higher in Hyperuricemic patients than normouricemics (68.3% vs 41.5%), and the prevalence of DKD increased with increasing uric acid (p<0.0001).

Uric acid was positively correlated with Ualbumin Creatinine Ratio (ACR) and serum creatinine ($p<$ 0.0001) after adjusting for confounding factors.[16]

A study by Behradmanesh *et al*, concluded that hyperuricemia in T2DM plays a significantpart in the development of nephropathy.[17] Sunita *et al*. found that elevated plasma uric acid level has a linear relationship with albumin excretion in urine (r-value = 0.323, and *p*-value <0.05). They also observed positive association with age (r-value=0.337, *p*-value <0.05), age at the onset (r-value=0.341, *p*-value <0.05) & with totaldiabetes years (rvalue=0.312, *p*-value <0.05).[18] Suryawanshi and colleagues reported a positive correlation between microalbuminuria and serum uric acid levels ($p<0.001$), thus concluding that hyperuricemia and microalbuminuria were helpful in the early diagnosis of kidney dysfunction and other cardiovascular diseases.[19]

Another study in Mayo Hospital Lahore comprising of 200 subjects with diabetic nephropathy reported meanuric acid level of 6.99±1.01 mg/dL while urinary albumin creatinine ratio (ACR) of 5.63±1.08 mg/mmol, hence concluding a positive correlation (r-value was 0.0838).[20]

Various other studies have also studied the uric acid role in diabetes as well as diabetic nephropathy, and have yielded almost similar results, linking hyperuricemia with early onset & much rapid progression of chronic kidney disease due to diabetes mellitus. Increased uric acid is connected with kidney dysfunction in the form of glomerular hypertrophy and fibrosis. Thus, early diagnosis of hyperuricemia in diabetics and timely intervention mayretard the development of renal failure. This may lead to the use of serum uric acid levels as a tool for the timely detection and control of Diabetic nephropathy, improving morbidity and mortality in future.

CONCLUSION

Hyperuricemia is positively linked with diabetic complications in majority of type-2 diabetics. Serum uric acid levels canbe used as an early diagnostic parameter and can prognosticate diabetic nephropathy. Regular testing of serum uric acid levels is recommended in patients of Diabetic Nephropathy along with other clinical and lab-based parameters.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

GA & MAK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

MA & BM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

IK & MT: Conception, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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