HYPERURICEMIA AS AN ADDITIONAL RISK FACTOR FOR MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS

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Key words: SUA, DN, DR

ABSTRACT

This study is to evaluate hyperuricemia as additional risk factor for development of microvascular complications in diabetic patients. **Methods:** this was a hospital based observational study which included total of 100 diabetic patients visiting PMCH opd and admitted indoor and out of which 50 had microvascular complications and 50 were without microvascular complications based history taking and examinations. Serum uric acid was measured in both the groups of patients and compared. **RESULTS:** Out of 50 patients with microvascular complications 23 had hyperuricemia and 27 had serum uric acid within normal range while out of 50 patients without microvascular complications just 8 had hyperuricemia with P value 0.000604 which is highly significant value. Out of 19 patients with retinopathy 10 had hyperuricemia and 9 had SU within normal range with P value 0.0019. Out of 16 patients with neuropathy 5 had hyperuricemia and 11 had SU in normal range with P value 0.181. Out of 24 patients with nephropathy 16 had hyperuricemia and 8 hade SU in normal range with P value 0.000013. **CONCLUSION:** Serum Uric acid is elevated in microvascular complication as a whole group when compared to those without microvascular complication group and furtherhyperuricemia is strongly associated with Nephropathy and Retinopathy but not neuropathy.

Introduction

Uric Acid (UA) (C5H4N403) a prevalent of urine metabolism is predominantly used as a predictor of gouty diabetes. However as association of metabolic syndrome uric acid would worsen insulin resistance by disturbing insulin stimulator glucoseuptake. Elevated serum uric acid has been an independent risk factor for development of vascular complications in a diabetic patient. Hence is it essential for secondary and tertiary prevention.The kidney is an important regulator for circulating UA as is responsible for 60 to 70% of total body UA excretion. The remaining uric acid is secreted into the intestine followed by the bacterial uricolysis. Diabetes mellitus is undoubtedly one the most challenging health problem in this century. Complications due to diabetes are a major cause of disability and reduce quality of life. The number of patient diagnosed with complications each year is rising. Diabetic nephropathy is the leading cause of death for people with Type2 DM. Vascular complications of diabetes mellitus are classified into microvascular and macrovascular complication.

Microvascular Complications:

- DiabeticNephropathy
- DiabeticNeuropathy
- DiabeticRetinopathy

Macrovascular Complications:

- Coronary Artery Diseases
- CerebrovascularDiseases
- Peripheral VascularDiseases

Diabetes Mellitus

- FBS greater or equal126mg/dl
- PPBS greater or equal200mg/dl
- HbA1c greater or equal6.5
- Diabetic Retinopathy - FundusExamination
- Diabetic Neuropathy - General Physical Examination, Neurological Examination
- Diabetic Nephropathy - Microalbuminuria, Creatininelevels.

Materials and Methods

Types of Study: Hospital based observational study

Place of Study: Patna medical college and hospital,Patna

Duration of Study: One and half year (January 2019-June 2020

INCLUSION CRITERIA:

- Diabetic patients diagnosed by ADAcriteria
- Age 20 to 80years
- Male andfemale

EXCLUSION CRITERIA

- DKA/HONK
- GDM
- CKD

Methodology:

- Obtained consent from all those who participated in this study.
- This study was based on observational collection of data of diabetic patients with and without microvascular complications.
- Patients underwent a history taking with general physical examination. (Age, sex, duration of disease)
- Patients were scanned for diabetes by ADA criteria.
- Patients were examined for vascular complications.

We divided them into 2groups.

I. **Group I:**Patients with diabetes with microvascularcomplication
II. **Group II:** Patients with diabetes and without microvascularcomplications.

- Uric acid levels were observed for both thegroups
- Age, sex, duration of the disease was all most equal in both the groups.

Result were computed to see if Hyperuricemia was an added risk factor for microvascular complications in diabetic patients

Patients were examined in detail and they were diagnosed diabetes

based on ADA criteria.

	Pre-Diabetes	Diabetes
FPG*	100-125 mg/dL 5.6 mmol/L – 6.9 mmol/L	126 mg/dL and over 7.0 mmol/L and over
OGTT* after 75 g glucose load	140 mg/dL - 199 mg/dL 7.8 mmol/L – 11.0 mmol/L	200 mg/dL and over 11.1 mmol/L and over
A1c†	5.7 % - 6.4%	6.5% and over

*FPG and OGTT guidelines for GDM are different;†A1c does not apply to diagnosis of type 1 diabetes or to GDM.

Diabetic complications were diagnosed by:

Diabetic retinopathy: Fundus examination (ophthalmologist) medical records, diagnosed by a medical practitioner.

Diabetic neuropathy: nylon monofilament,general physical examination, medical record, diagnosed by a medical practitioner.

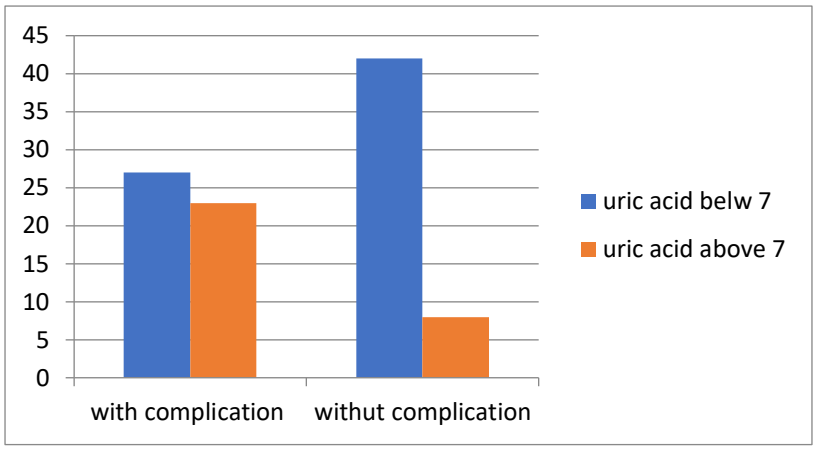
Diabetic nephropathy: albuminuria, creatinine, medical records, diagnosed by a medical practitioner.

Results:

FREQUENCY DISTRIBUTION OF URIC ACID (WITH COMPLICATION AND WITHOUTCOMPLICATION)

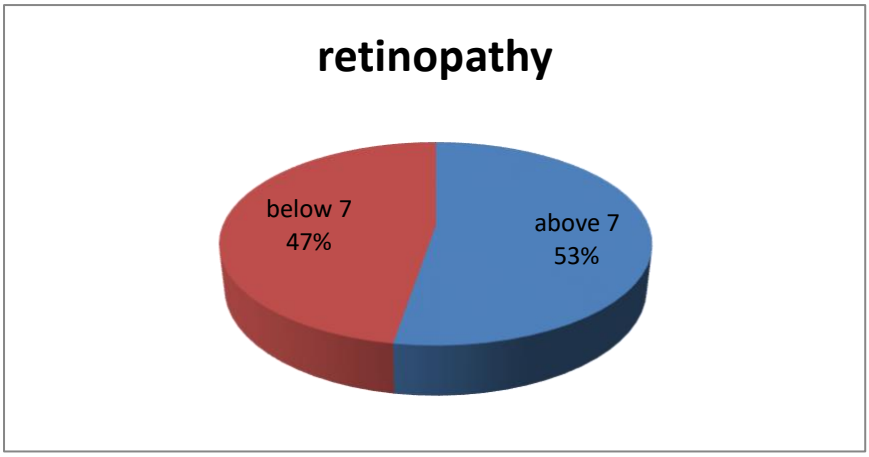
S NO	URIC ACID LEVEL	With Complication	%	Without Complication	%
1	BELOW 7	26	52%	42	84%
2	ABOVE 7	24	48%	8	16%
	TOTAL	50	100	50	100

Above table reveals, that hyperuricemia (Uric acid above 7**) is thrice as elevated in the Microvascular Complication group (48%)** when compared with those without microvascular complication (16%).

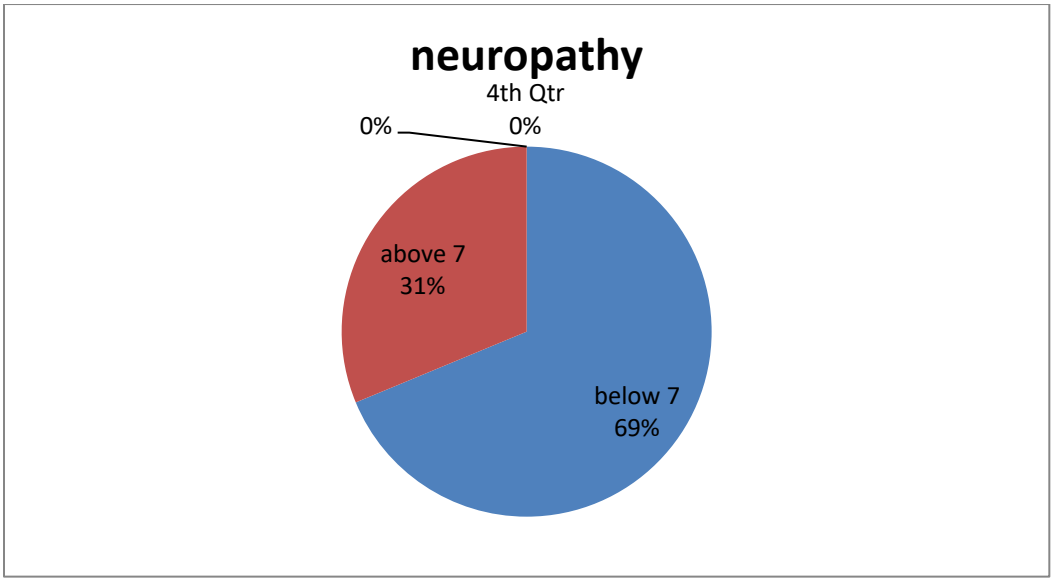


Frequency distribution of uric acid		
s.no	**Serum uric acid**	**Retinopathy**
1	Below 7	9
2	Above 7	10
	Total	19

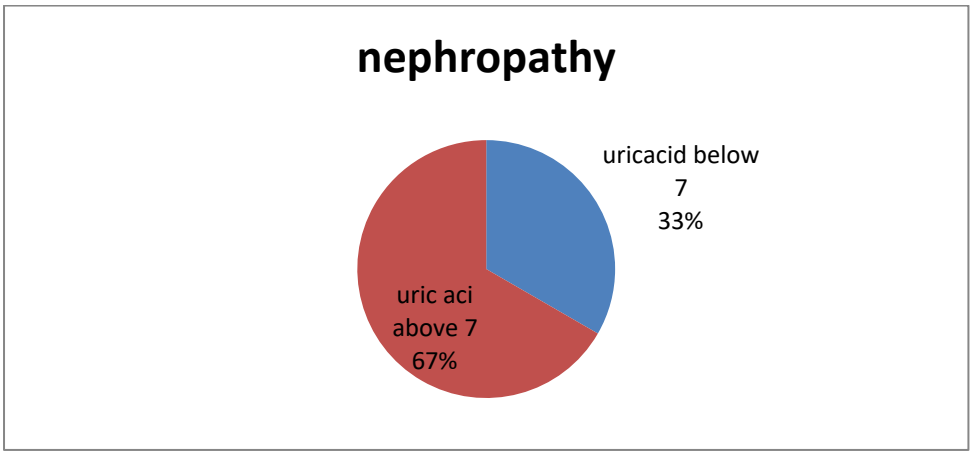
Out of the 19 patients with diabetic retinopathy, 10 patients had elevated serum uric acid levels



Frequency distribution of uric acid		
s.no	**Serum uric acid**	**Neuropathy**
1	Below 7	11
2	Above 7	5
	Total	16



s.no	**Serum uric acid**	**Nephropathy**
1	Below 7	8
2	Above 7	16
	Total	24



CHI-SQUARE TEST (HYPERURICEMIA AND MICROVASCULAR COMPLICATION)

Null hypothesis: There is no association between Uric acid and microvascular complication.

H_0: Uric acid and microvascular complication are independent

H_1: Uric acid and microvascular complications are not independent.

	value	DF	Significant value
Pearson chi square	11.76	1	0.000604
No. of valid cases	50	1	
Odds ratio	4		

Pearson chi-square value is 11.76 with degree of freedom of 1. The significant value is 0.000604 (i.e. P value). Since P value is less than 0.05, the difference between observed value and expected value is significant. Therefore Null hypothesis is rejected. **Thus there is strong association between hyperuricemia and overall microvascular complications**.

CHI-SQUARE TEST (HYPERURICEMIA AND RETINOPATHY)

Null hypothesis: There is no association between Uric acid and Retinopathy

H_0: Uric acid and retinopathy are independent

H_1: Uric acid and retinopathy are not independent

	Value	Df	Asymp. Sig (2 sided)
Pearson chi-square	9.58	1	0.0019
N. of Valid cases	50		

Pearson chi-square value is 9.58 with degree of freedom of 1. The significant value is 0.0019 (i.e. P value). Since P value is less than 0.05, the difference between observed value and expected value is significant. Therefore Null hypothesis is rejected. **Thus there is strong association between hyperuricemia and Retinopathy.**

CHI-SQUARE TEST (HYPERURICEMIA AND NEPHROPATHY)

Null hypothesis:There is no association between Uric acid and Nephropathy

H_0: Uric acid and Nephropathy are independent

H_1: Uric acid and Nephropathy are notindependent

	Value	Df	Asymp. Sig (2 sided)
Pearson chi-square	18.99	1	0.000013
N. of Valid cases	50		

Pearson chi-square value is 18.99 with degree of freedom of 1. The significant value is 0.000013 (i.e. P value). Since P value is less than 0.05, the difference between observed value and expected value is significant. Therefore Null hypothesis is rejected . **Thus there is strong association between hyperuricemia and nephropathy.**

CHI-SQUARE TEST (HYPERURICEMIA AND NEUROPATHY

Null hypothesis: there is no association between Uric acid and neuropathy

H_0: Uric acid and neuropathy are independent

H_1: Uric acid and neuropathy are not independent

	Value	Df	Asymp. Sig (2 sided)
Pearson chi-square	1.78	1	0.181
N. of Valid cases	50		

Pearson chi-square value is 1.78 with degree of freedom of 1. The significant value is 0.181 (i.e. P value). Since P value is more than 0.05, the difference between observed value and expected value is not significant. Therefore Null hypothesis is accepted . **Thus there is no association between hyperuricemia and neuropathy.**

Discussion

Diabetes Mellitus is one of the earliest diseases portrayed in an Egyptian Manuscript from around 1500 BC, the first described case being type 1 DM. Diabetes is caused either due to insufficient production of insulin by the pancreatic islets or due to peripheral receptor level resistance to insulin despite adequate circulating insulin levels.

Increasing amounts of uric acid in the serum causes Gout and this is one of the most significant features of lifestyle-related disorder. Uric acid is primarily a purine metabolic waste protect about 70% of it gets excreted in the kidneys. Hence decreased excretion of uric-acid is an important cause of hyper-uricemia. There is no method for detecting the uric acid production in humans. Uric acid production is indirectly estimated through serum Uric acid level and urine excretion.

Development of vascular complications were predicted independently by serum uric acid . In a study conducted by Agrawal et al. it was concluded that the Uric acid levels are raised in patients with diabetes. They found lower levels of uric acid in diabetic subjects compared to healthy controls but higher level of uric acid in subjects of diabetes with retinopathy. This is consistent with the finding of Navin S et al where they have suspected the pro-oxidant role of uric acid in causation of oxidative stress leading to diabetic complication like diabetic retinopathy, though they could not clearly state that the hyperuricemia in diabetic retinopathy is either a protective response (due to its antioxidant role) or a primary cause of it (due to its pro-oxidant role). In our study we found that out of the 50 patients with micro-vascular complications 19 (38%) had retinopathy and out of this 9 patients (52.63%) had increased uric acid levels. This was also corroborated with a study conducted by Ching-Chao Liang et al.,where he concluded that there was increased serum uric acid levels which correlated with the severity of diabetic Retinopathy.

In another study by JavadKiani et al., he showed that there was increased level of serum uric acid in diabetic patients with diabetic neuropathy.However in our study we found that there was no significant correlation between uric acid levels and diabetic neuropathy.

In a study conducted by YiliXu et al. he concluded that the patients with vascular complications had increased serum uric acid levels. He also said that this could be an independent predictor of vascular complications.We found similar results in our study in

which out of 50 patients with vascular complications there were 23 patients (46 %) withincreased levels of uric acid as opposed to only 8 patients (16%) in patients without microvascular complication.

Nazir Shah et al. conducted a study in 2013 in 163 patients of diabetes mellitus (type 2) and proposed that elevation in the levels of uric acid was more in the diabetic patients with nephropathy (50%). In our study, it was found that 64% of patients with diabetic nephropathy had hyperuricemia which was similar to the study done by Nazir Shah et al. In a study conducted in 60 diabetic patients by Nasri et al. , it was proved that there was a significant association between diabetic nephropathy and the levels of uric acid in the patient's serum which was in accordance with the results of our study.

Su-Mi Kim et al. demonstrated that HUA contributes to the development of nephropathy in diabetic patients. In our study, we found that 16 out of 24 patients with diabetic nephropathy had elevated uric acid levels.

In a study conducted by NS Nekiet al. in 400 diabetic patients, it was shown that there is a linear correlation between serum uric acid and development of nephropathy in patients with diabetes, which was also proved in the study done by us.

In a review by Qing Xiong etal. with the deepening of the researches on uric acid, especially in the study of metabolic diseases, uric acid has been found to be closely related to obesity, metabolic syndrome, nonalcoholic fatty liver disease, diabetes, and other metabolic diseases. Uric acid causes a series of pathophysiological changes through inflammation, oxidative stress, vascular endothelial injury, and so on and thus subsequently promotes the occurrence and development of diseases. This review confirmed the positive correlation between uric acid and diabetes mellitus and its chronic complications through the pathogenesis and clinical studies aspects.

In clinical studies conducted by Ching-Chao Liang etal. serum uric acid concentration has been found to be associated with DR and DN. In multivariate logistic regression analysis, a high uric acid concentration was a risk factor for albuminuria (odds ratio (OR), 1.227; 95% confidence interval (CI) = 1.015–1.482; p = 0.034) and DR (OR, 1.264; 95% CI = 1.084–1.473; p = 0.003). It was also demonstrated that there was a higher concentration of serum uric acid in the patients with more severe albuminuria and DR. In conclusion, an increased serum uric acid level was significantly correlated with the severity of albuminuria and DR in Taiwanese patients with type 2 DM.

Reference

1. "About diabetes". *World Health Organisation*. Retrieved April 2020.
2. RSSDI textbook of diabetes mellitus. *(Rev. 3rd ed.). New Delhi: Jaypee Brothers Medical Publishers. p. 215-44.* ISBN 9789351520900. *(20140.*
3. "Update 2019". *IDF. International Diabetes Federation diabetes atlas 9th edition 2019.*
4. *Williams textbook of endocrinology(14thed.) Philadelphia:Elsevier/Saunders(pub date-6thdec2019). pp. 1371–1435. ISBN 978-0-32355-5396-8.*

5. "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications" *Harrisons Principal Of Internal Medicine 20th edition Page no 2850-2882*
6. *Qing Xiong, Jie Liu, Yancheng Xu, "Effects of Uric Acid on Diabetes Mellitus and Its Chronic Complications", International Journal of Endocrinology, vol. 2019, Article ID 9691345, 8 pages, 2019.*
7. *Ching-Chao Liang,1 Pi-Chen Lin,2 Mei-Yueh Lee,2,3,4 Szu-Chia Chen,3,4,5 Shyi-Jang Shin,2,4,6 Pi-Jung Hsiao,2,4 Kun-Der Lin,2,4,7 and Wei-Hao Hsu2,3,* Lu Cai, Academic Editor Int J Mol Sci. 2016 Aug; 17(8): 1248.Published online 2016 Aug 2. doi: 10.3390/ijms17081248PMCID: PMC5000646 PMID: 2749053*
8. *Xu Y, Zhu J, Gao L, Liu Y, Shen J, et al. (2013) Hyperuricemia as an Independent Predictor of Vascular Complications and Mortality in Type 2 Diabetes Patients: A Meta-Analysis. PLoS ONE 8(10): e78206*
9. *Navin S, Krishnamurthy N, Ashakiran S, Dayanand CD. The association of hypomagnesaemia, high normal uricaemia and dyslipidaemia in the patients with diabetic retinopathy. J Clin Diagn Res. 2013;7(9):1852*
10. *Nazir Shah, Amanullah, Sheraz Jamal and Mumtaz Ali Marwat. Association Of Hyperuricemia With Diabetic Nephropathy Intype 2 Diabetes Mellitus. Khyber Journal of Medical Sciences.*