Serum Uric Acid Levels in Patients with Type 2 Diabetes and Its Association with Diabetic Nephropathy in Patients Attending a Tertiary Care Centre in South Kerala

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Abstract

Introduction: Diabetic nephropathy constitutes the most common cause of end stage renal disease worldwide. Inflammation and endothelial dysfunction appear to play a central role in the onset and progression of diabetic nephropathy. Recent evidences has emerged in the last decade to suggest that uric acid is an inflammatory factor and may play a role in endothelial dysfunction. Hence this study tries to evaluate any such correlation between diabetic nephropathy and serum uric acid.

Aim: To correlate Serum Uric Acid level with microvascular complications of Diabetes Mellitus.

Materials & Methods: It is a Cross sectional study of 1 year duration. The sample size was 625. Data analyzed using SPSS version 1.5.

Results: The mean uric acid value of the study population was 6.02 mg/dl. The mean uric acid level of those patients with nephropathy was 6.31 and that of patients without nephropathy was 5.68. There was no significant statistical association between elevated serum uric acid and with development of peripheral neuropathy. There was significant statistical association between elevated uric acid levels and development of retinopathy.

Conclusions: There is significant correlation between the microvascular complications of diabetes mellitus and serum uric acid level except peripheral neuropathy.

Keywords: Diabetic nephropathy, serum uric acid, peripheral neuropathy, retinopathy.

Background

Diabetes mellitus may be one of the oldest diseases known to mankind. The disease was mentioned in Egyptian manuscripts some 3000 years ago.¹ It is estimated that 387 million people have DM in 2015; by 2030 this would have risen to 552 million.² India is the “diabetes capital of the world” with 41 million Indians having diabetes, every fifth diabetic in the world is an Indian³. In India Kerala is the state with the highest prevalence of diabetics, 20% as compared to the national average of 8%⁴,⁵.
Diabetes is associated with increased risk of macro vascular and micro vascular complications such as coronary artery disease, stroke, peripheral arterial disease, end stage renal disease, peripheral neuropathy, retinopathy etc. Of all these complications kidney diseases may be the one that could be most attributed to diabetes. Diabetic nephropathy is the leading cause of chronic kidney disease requiring hemodialysis support. Until the 19th century, type 2 diabetes was relatively infrequent. With increasing wealth and obesity, there is a progressive increase in the frequency of type 2 DM. Proteinuria in type 2 diabetes had been well known in the 19th century, but end stage renal disease in type 2 diabetic patients was rare because most patients died of complications. As the life span of diabetic patient increased there is a dramatic increase in dialysis requiring diabetic kidney disease. The presence of Diabetic Nephropathy increases mortality in both type I and type II diabetes. The presence of nephropathy increases the mortality by 20-200% in diabetic patients.6,7

Potential mechanisms by which uric acid could mediate diabetic nephropathy includes endothelial dysfunction, increased activity of the Renin angiotensin aldosterone system, and induction of inflammatory cascades all of which have been demonstrated to contribute to progression of renal injury in diabetic nephropathy. Hyperuricemia has been reported to be associated with increased risk of renal insufficiency as well as cardiovascular events.

The objective of this study is to evaluate the association between serum uric acid level and nephropathy in type 2 diabetic patients.

Aims and Objectives of Study

- To study the level of serum uric acid in type 2 diabetes mellitus
- To correlate serum uric acid level with Fasting Blood Sugar (FBS)
- To correlate Serum Uric Acid level with microvascular complications of Diabetes Mellitus

Materials and Methods

Study design: Cross sectional study
Study period: 1 Year from date of ethical clearance
Sample size: 625

Inclusion Criteria:
1. All type 2 diabetes patient
2. Both sexes
3. Duration of disease more than 3 tears

Exclusion Criteria:
1. Patients with gout
2. Patient taking drugs which cause hyperuricemia
3. Patient with malignancy
4. Patient with CKD
5. Patient with CLD
6. Patients with chronic alcoholism
7. Patients failing to give consent

Written informed consent was obtained from all the study subjects. The subjects underwent a detailed history taking, general physical examination, Systemic examination, relevant laboratory investigations including:
- Complete Blood Count
- Liver Function Test (LFT), Prothrombin Time (PT), International Normalised Ratio (INR)
- Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS)
- Microalbuminuria
- Fasting lipid profile
- Fasting Serum uric acid

The subjects will be explained about the nature and purpose of the study.

Study variables

Diagnosis of type 2 Diabetes mellitus (as per ADA guidelines)'
Symptoms of diabetes with,
Fasting plasma glucose of 126mg/dl or more
HbA1c of 6.5% or more
Two hour plasma glucose of 200mg/dl or more during an oral glucose tolerance test with 75g glucose
Fasting blood sugar was assessed by Randox Daytona autoanalyser, which works on
colorimetric method without deproteinisation, using venous blood sample.
Fasting serum uric acid was measured by Randox Imola autoanalyser working on colorimetric method using venous blood sample.

**Diabetic retinopathy:** assessed by clinical fundoscopic evaluation

**Diabetic nephropathy:** assessed from kidney function test and presence of albumin in the urine sample

**Diabetic neuropathy:** assessed by clinical examination of motor system and sensory system of the individual to evaluate the involvement of peripheral nerves.

**Statistical Analysis:** Data was entered in Microsoft excel and analyzed using SPSS version 1.5 or higher. Categorical variables were analysed using chi-square tests. Independent t-test will be used to compare continuous variables among the group with hyperuricaemia and with the normouricaemic group. Pearson correlation coefficient determination was performed to evaluate the degree of association between uric acid and various clinical and biochemical parameters. Quantitative data was expressed as mean and standard deviation (SD). P values of < 0.05 was considered to be statistically significant

**Observations**
A total of first consecutive 6250 cases of type 2 diabetic patients attended diabetic clinic, who met inclusion and exclusion criteria were enrolled in the study.

**Age and sex distribution**

**Table 1: Gender distribution**

| Sex      | Number | Percentage |
|----------|--------|------------|
| Male     | 316    | 50.5       |
| Female   | 309    | 49.5       |
| Total    | 625    | 100        |

Out of 625 cases studied 316 were male and 309 were female. 50.5% were males and 49.5% were females.

The sample population included patients of age 40 to 80 years

**Table 2: Distribution of sample by age**

| Age | Frequency | Percent |
|-----|-----------|---------|
| 40-49 | 184       | 29.4    |
| 50-59 | 187       | 29.9    |
| 60-69 | 203       | 32.4    |
| 70-79 | 51        | 8.2     |
| Total | 625       | 100.0   |

Mean age of the study population was 56.07 years with mean age for male patients 55.6 years and for female patients 56.55 years.
Distribution of samples based on duration of diabetes mellitus

The minimum duration of diabetes mellitus in this study population was 1 year and maximum duration 26 years. Most of the cases were having duration of diabetes between 5 and 10 years.

Table 4: Distribution of samples based on duration of diabetes mellitus

| Duration of diabetes mellitus | Frequency | Percent |
|------------------------------|-----------|---------|
| 1-5 years                    | 171       | 27.36   |
| 6-10 years                   | 264       | 42.25   |
| More than 10 years           | 190       | 30.4    |
| Total                        | 625       | 100.0   |

Distribution of sample by serum uric acid.

Table 5: Mean serum uric acid in males and females

| Sex   | Mean Serum Uric Acid | No. | P value |
|-------|----------------------|-----|---------|
| Male  | 6.71                 | 316 |         |
| Female| 5.26                 | 309 |         |
| Total | 6.0243               | 625 |         |

The mean uric acid value of the study population was 6.02 mg/dl (mean uric acid for males was 6.71 and that of females was 5.26 mg/dl)

Table 6: Distribution of serum uric acid

| S. Uric acid | Male | Female | Total | P value |
|--------------|------|--------|-------|---------|
| Normal       | 180  | 157    | 337   | 0.122   |
| Elevated     | 136  | 152    | 288   |         |
| Total        | 316  | 309    | 625   |         |

Out of 625 patients serum uric acid was elevated in 288 patients (46.1% of total study population) which included 180 males and 157 females.

Distribution of samples based on systemic arterial hypertension

| Systemic Hypertension | Frequency | Percentage |
|-----------------------|-----------|------------|
| Present               | 358       | 57.28%     |
| Absent                | 267       | 42.72%     |
Out of 625 patients, 358 (57.2%) patients were hypertensive and the rest 267 (42.7%) were non hypertensive.

**Graph 7: Distribution of samples based on systemic arterial hypertension**

442 patients enrolled in this study had Diabetic retinopathy which included 217 males and 225 females.

**Graph 8: Distribution of samples based on diabetic retinopathy**

331 patients (52.9%) had peripheral neuropathy which included 167 male patients and 164 female patients.
Graph 9: Distribution of population based on diabetic peripheral neuropathy

Distribution of samples based on diabetic nephropathy

Table 10: Distribution of samples based on diabetic nephropathy

| Sex    | Absent | Present | Total |
|--------|--------|---------|-------|
| Male   | 176    | 140     | 316   |
| Female | 151    | 158     | 309   |
| Total  | 327    | 298     | 625   |

298 patients (47.68%) enrolled in this study had Diabetic nephropathy which included 140 males and 158 females.

Graph 8: Distribution of samples based on diabetic nephropathy

Distribution of diabetic nephropathy based on age

| Age Group | Diabetic Nephropathy | Total | P Value |
|-----------|----------------------|-------|---------|
| 40-50 Yrs | 40                   | 144   | 184     |
| 50-60 Yrs | 93                   | 94    | 187     |
| 60-70 Yrs | 126                  | 77    | 203     |
| 70-80 Yrs | 39                   | 12    | 51      |

There was a statistically significant difference between association of diabetic nephropathy and advancing age as demonstrated by a p value of <.05.

The mean age of patients that developed nephropathy was 59.76 while that of patients with no nephropathy was 52.70. This was found to be statistically significant, i.e. as the age advances the chances of developing nephropathy also increased.
Distribution of diabetic nephropathy based on gender

| Gender | Diabetic Nephropathy | Total | P Value |
|--------|----------------------|-------|---------|
|        | Present              | Absent|        |
| Male   | 140                  | 176   | 326    | .0875  |
| Female | 158                  | 151   | 309    |        |

There was no statistical difference between development of diabetic nephropathy and gender.

Crosstab showing association between serum uric acid and nephropathy

| Diabetic Nephropathy | Serum Uric Acid | Total | P Value |
|----------------------|-----------------|-------|---------|
|                      | Normal          | Elevated|    |
| Present              | 123             | 175    | 298    | 0.00001 |
|Absent                | 214             | 113    | 327    |        |
|TOTAL                 | 337             | 288    | 625    |        |

Analysis done using chi square test showed significant association between serum uric acid and diabetic nephropathy (p value = 0.00001).

Association between duration of diabetes mellitus and nephropathy

Table 16: Comparison between duration of diabetes mellitus and nephropathy

| Duration of diabetes | Diabetic Nephropathy | Total | P Value |
|----------------------|----------------------|-------|---------|
|                      | Present              | Absent|        |
| 0-5 Yrs              | 17                   | 154   | 171    | <0.00001 |
| 6-10 Yrs             | 115                  | 149   | 264    |        |
| >10 Yrs              | 166                  | 24    | 190    |        |

There was significant statistical association between duration of diabetes and development of nephropathy i.e. as the duration increased the prevalence of nephropathy also increased.
Association between mean uric acid and diabetic nephropathy.

| Diabetic Nephropathy | Mean uric acid | P value |
|----------------------|----------------|---------|
| Present              | 6.31           | <.0001  |
| Absent               | 5.68           |         |

The mean uric acid level of those patients with nephropathy was 6.31 and that of patients with no nephropathy was 5.68. This was found to be statistically significant (p<0.0001)

Association between serum uric acid and retinopathy

| Serum Uric acid | Peripheral Neuropathy | P Value |
|----------------|-----------------------|---------|
| Normal         | Present 168 Absent 169 Total 337 | 0.0921 |
| Elevated       | Present 163 Absent 125 Total 288 |         |

There was significant statistical association between elevated uric acid levels and development of retinopathy

There was no significant statistical association between elevated serum uric acid and with development of peripheral neuropathy.

**Discussion and Conclusions**

The aim of the study is to find out the association of serum uric acid with nephropathy in patients with type 2 diabetes mellitus. This study was conducted in 625 who were willing for the study and who fulfilled inclusion and exclusion criteria.

**Age and sex distribution.**

Out of 625 cases studied 311 (50.5%) were male and 309(49.5%) were female. The age range from 40 to 80 years. Majority of cases between 60 to 70 years(32.4%)

Behradmanesh et al. in their study of Association of serum uric acid with proteinuria in type 2 diabetic patients conducted in 60 patients.age range from 41 to 81 years, with mean age of 57 ± 8.3 years (.56.7% female and 43.3% males).

Bonakdar an et al. in their study on ‘Hyperuricemia and Albuminuria in Patients With Type 2 Diabetes Mellitus’ is a cross-sectional study of 1275 patients (43% males and 57% females) with mean age of the patients was 52.45 ± 10.11 years old.

Distribution of samples by duration of diabetes mellitus.

In my study out of 625 patients studied 171 patients are diagnosed to have diabetes less than 5 years, 264 patients having diabetes for 5 to 10 years and 190 patients had diabetes for more than 10 years.

**Distribution of samples by uric acid.**

The mean uric acid value of the study population was 6.024 mg/dl. the mean value for the male population was 6.71 and for female population
5.26 mg/dl. This difference in uric acid values is statistically significant with a p value of 0.001.

Out of 625 patients serum uric acid was elevated in 288 patients (46.1% of total study population) which included 180 males and 157 females. Mean ± SE of serum uric acid in study conducted by Behradmanesh et al was 4.5 ± 0.15 mg/dL, there was no statistically significant difference between male and female population.

Bonakdaran et al in their study the mean serum uric acid concentration was 4.56 ± 1.33 mg/dL, which was significantly higher in men than in women (4.89 ± 1.36 mg/dL versus 4.30 ± 1.24 mg/dL, respectively; P < .001).

### Association between uric acid and diabetic peripheral neuropathy

331 patients (52.9%) had peripheral neuropathy which included 167 male patients and 164 female patients. out of 331 patients having peripheral neuropathy,163 having elevated uric acid and p value was 0.0921 which was not statistically significant.

A study by Javad Kiani et al showed the higher level of serum uric acid level in diabetic patients with diabetic neuropathy. In their study the mean serum uric acid was 4.70±0.96 in diabetic patients with DPN and 4.36±0.89 mg/dl in patients without DPN (p=0.019). My findings were contrary to the above study.

### Association between serum uric acid and diabetic retinopathy

Out of 625 patients, 442 having retinopathy. Out of that 223 patients having elevated uric acid. P value of 0.00065 which was statistically significant.

The finding in this study goes hand in hand with the result of various early studies. Jianfei Xia et al studied the levels of purine metabolites and its association to diabetic retinopathy. They compared uric acid, xanthine, adenosine and inosine in patients with diabetes, with and without retinopathy. They concluded the levels of these four metabolites, especially the level of adenosine, may be useful for monitoring the progression of diabetic retinopathy and evaluating the treatment. High level of uric acid is associated with diabetic complications. It may be related to Uric acid by its physiologic functions including activation of the rennin angiotensin system and direct actions on endothelial cells and vascular smooth muscle cells. These functions are related to development of diabetic complications including diabetic retinopathy.

### Distribution of diabetic nephropathy

Out of 625 patients, 298 having nephropathy ie 47.68%. 140 were males and 158 were females. p value was 0.0875. There was no significant association between gender and nephropathy.

### Association between nephropathy and age

Out of 298 patients having diabetic nephropathy, 40 patients were between 40-50 years, 93 were between 50-60 years, 126 were between 60-70 years, 39 were between 70-80 years.

Mean age of patients with diabetic nephropathy were 59.768 and without nephropathy were 52.709. This association was statistically significant with a p value of 0.0001.

### Association between serum uric acid and diabetic retinopathy

Out of 625 patients serum uric acid was elevated in 288 patients. 175 patients with elevated uric acid level were having diabetic nephropathy also. Analysis done using chi square test showed significant association between serum uric acid and diabetic nephropathy (p value = 0.00001).
The mean uric acid level of those patients with nephropathy was 6.31 and that of patients with no nephropathy was 5.68. This was found to be statistically significant (p<0.0001). Ficociello et al.\textsuperscript{13} investigated the impact of baseline serum uric acid levels on nephropathy. They evaluated data of 355 participants and observed a significant association (P < 0.0002) between uric acid levels and nephropathy. This was a cross sectional study done in 625 patients who were enrolled in this study and underwent thorough clinical examination to look for evidence of hypertension and complications of diabetes mellitus. Investigations like 24 hour urine protein, FBS, serum uric acid and serum creatinine done. The conclusions obtained from this study are given below.

Out of 625 cases studied 316 were male and 309 were female. 50.5% were males and 49.5% were females. Mean age of the study population was 56.07 years with mean age for male patients 55.6 years and for female patients 56.55 years. The minimum duration of diabetes mellitus in this study population was 1 year and maximum duration 26 years. Most of the cases were having duration of diabetes between 5 and 10 years.

The mean uric acid value of the study population was 6.02 mg/dl (mean uric acid for males was 6.71 and that of females was 5.26 mg/dl). Out of 625 patients serum uric acid was elevated in 288 patients (46.1% of total study population) which included 180 males and 157 females. 358 (57.2%) patients were hypertensive and the rest 267 (42.7%) were normotensive. 175 males and 183 females were hypertensive.

442 patients enrolled in this study had Diabetic retinopathy which included 217 males and 225 females. 331 patients (52.9%) had peripheral neuropathy which included 167 male patients and 164 female patients. 298 patients (47.68%) enrolled in this study had Diabetic nephropathy which included 140 males and 158 females.

There was a statistically significant difference between association of diabetic nephropathy and advancing age as demonstrated by a p value of <.05. The mean age of patients that developed nephropathy was 59.76 while that of patients with no nephropathy was 52.70. This was found to be statistically significant, i.e. as the age advances the chances of developing nephropathy also increased.

There was no statistical difference between development of diabetic nephropathy and gender. Analysis done using chi square test showed significant association between serum uric acid and diabetic nephropathy (p value = 0.00001). There was significant statistical association between duration of diabetes and development of nephropathy i.e. as the duration increased the prevalence of nephropathy also increased.

The mean uric acid level of those patients with nephropathy was 6.31 and that of patients without nephropathy was 5.68. This was found to be statistically significant (p<0.0001).

There was significant statistical association between elevated uric acid levels and development of retinopathy. There was no significant statistical association between elevated serum uric acid and with development of peripheral neuropathy.

References
1. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002. Apr; 23(4):373-378
2. Global burden of diabetes. International Diabetes federation. Diabetic atlas fifth edition 2011, Brussels. Available at http://www.idf.org/diabetesatlas
3. Joshi SR, Parikh RM India-diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007 May; 55:323-4.
4. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. Mar 2007;125(3):217-230.
5. Reddy KS, Prabhakaran D, Chaturvedi V, et al. Methods for establishing a surveillance system for cardiovascular
diseases in Indian industrial populations. *Bull World Health Organ.* Jun 2006;84(6):461-469.

6. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Eng J M* 1999; 341:1127-1133.

7. Adler AI, Stevens RJ, SE, et al: Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes study (UKPDS 64).*Kidney Int* 2003; 63:225-232.

8. Behradmanesh S, Horestani MK, Baradaran A et al Association of serum uric acid with proteinuria in type 2 diabetic patients. Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran;Journal of Reseach in Medical Science. 2013;18 (1):44-6

9. Bonakdaran S, Hami M, Shakeri MT Hyperuricemia and albuminuria in patients with type 2 diabetes mellitus. Division of Endocrinology, Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, Iran published in Iran J Kidney Dis. 2011;5(1):21-4.

10. Javad Kiani, Zahra Habibi,Ali Tajziehchi, Abbas Moghimbeigi, Arash Dehghan, and Homeyra Azizkhani. Association between serum uric acid level and diabetic peripheral neuropathy (A case control study). Caspian J Intern Med. 2014 Winter; 5(1): 17–21.

11. Jianfei Xia, Zonghua Wang, and Feifei Zhang. Association between Related Purine Metabolites and Diabetic Retinopathy in Type 2 Diabetic Patients. International Journal of Endocrinology Volume 2014, Article ID 651050, 9.

12. Jiji Inassi, Vijayalakshmy R Assistant Professor, Physiology, Govt. Medical College, Kozhikode, Kerala; Professor &