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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: *Diabetc nephropathy constitutes the most common cause of end stage rena; 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: *Diabetc nephropathy, serum uric acid, peripheral neuropathy, retinopathy.*

Background

Diabetes mellitus may be one of the oldest disease 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 Indian[3] ·In India kerala is the state with the highest prevelance 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: 1Year 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 6250cases of type 2 diabetic patients attended diabetic clinic, who met inclusion and exclusion criteria were enrolled in the study.

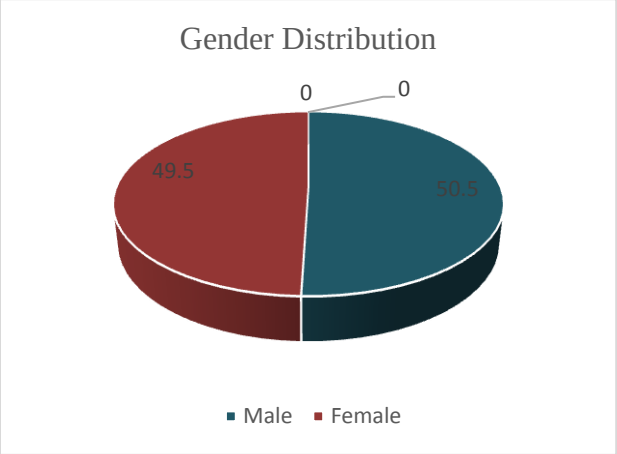
Age and sex distribution

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.

Graph 1: Gender distribution



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

Graph 2: Distribution of sample by age group

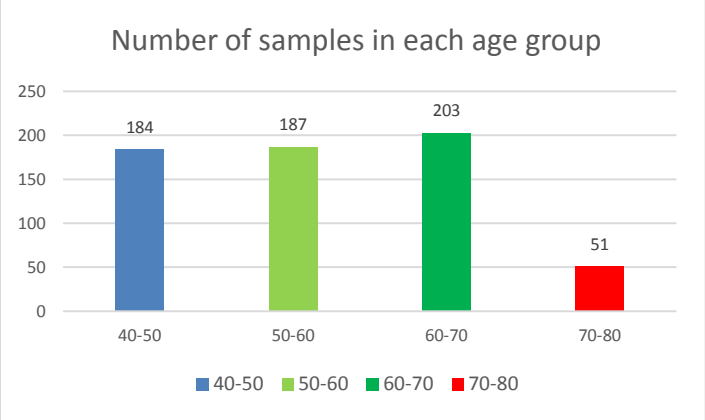
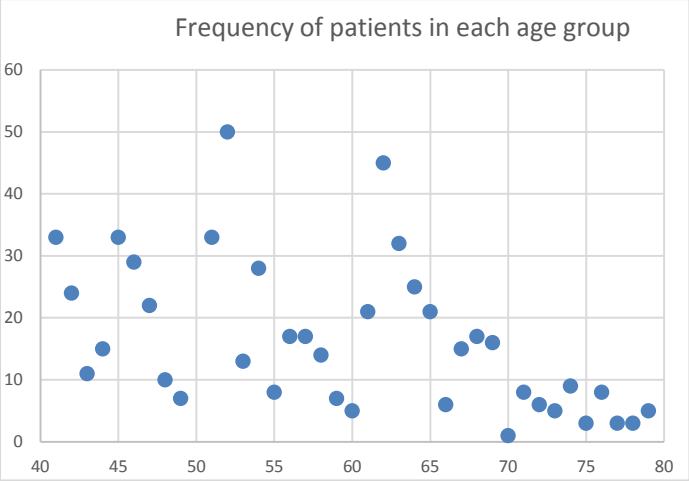


Table 3: Age and sex distribution

Sex	Mean age	No	Std. Deviation
Male	55.604	316	9.8105
Female	56.552	309	9.7586
Total	56.075	625	9.8105

Mean age of the study population was 56.07 years with mean age for male patients 55.6years and for female patients 56.55 years.

Graph 3: Age distribution



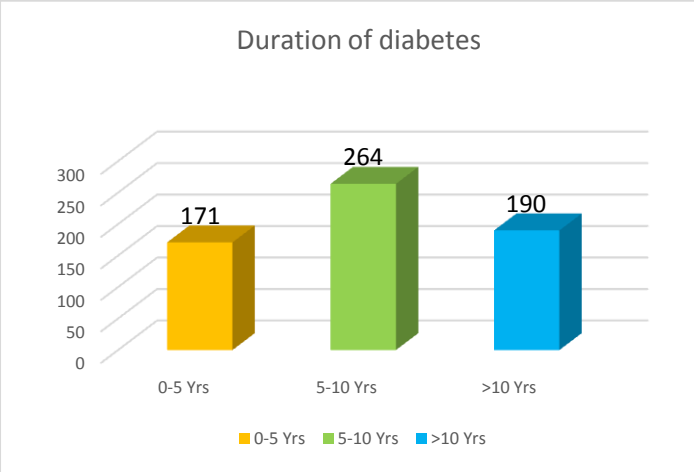
Distribution of samples based on duration of diabetes mellitus

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

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



Distribution of sample by serum uric acid.

Table 5: Mean serum uric acid in males and females

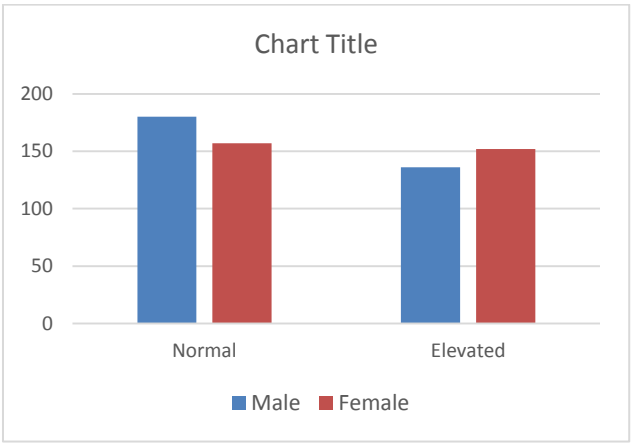
Sex	Mean Serum Uric Acid	No
Male	6.71	316
Female	5.26	309
Total	6.0243	625

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	Sex		Total	P value
	Female	Male		
Normal	157	180	288	0.122
Elevated	152	136	337	
Total	309	316	625	

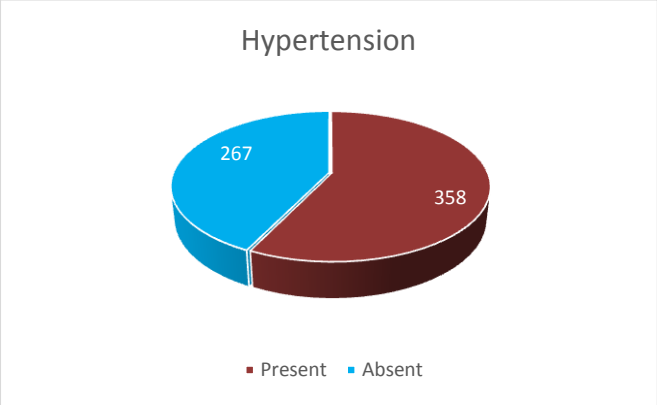
Out of 625 patients serum uric acid was elevated in 288 patients (46.1% of total study population) which included180 males and 157 females.



Distribution of samples based on systemic arterial hypertension

Systemic Hypertension	Frequency	Percentage
Present	358	57.28%
Absent	267	42.72%

Graph 7: Distribution of samples based on systemic arterial hypertension



Out of 625 patients, 358(57.2%) patients were hypertensive and the rest 267(42.7%) were non hypertensive.

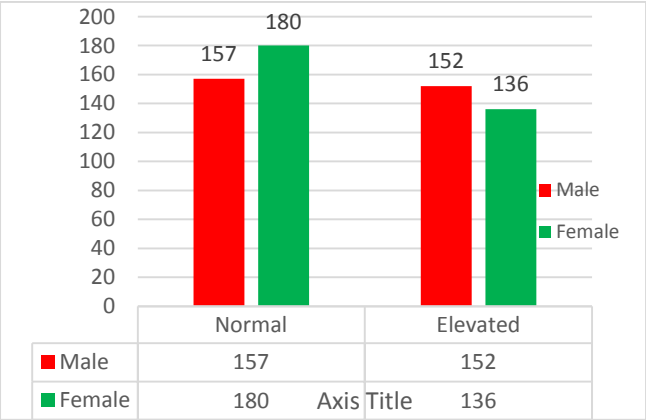
Distribution of samples based on systemic arterial hypertension

Table 9: Distribution based on systemic arterial hypertension

Sex	Hypertension present	Hypertension absent
Male	175	141
Female	183	126
Total	358	267

Out of 625 patients 175males and 183 females were hypertensive.

Graph 7: Distribution of samples based on systemic arterial hypertension



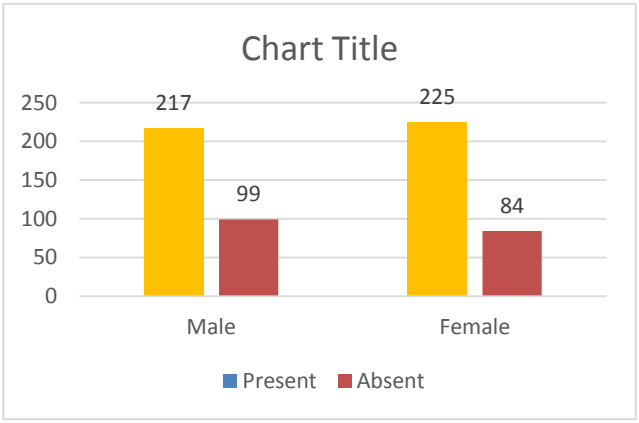
Distribution of samples based on diabetic retinopathy

Table 10: Distribution of samples based on diabetic retinopathy

	Diabetic retinopathy		
Sex	Absent	Present	Total
Male	99	217	316
Female	84	225	309
Total	183	442	625

442 patients enrolled in this study had Diabetic retinopathy which included217 males and 225 females.

Graph 8: Distribution of samples based on diabetic retinopathy



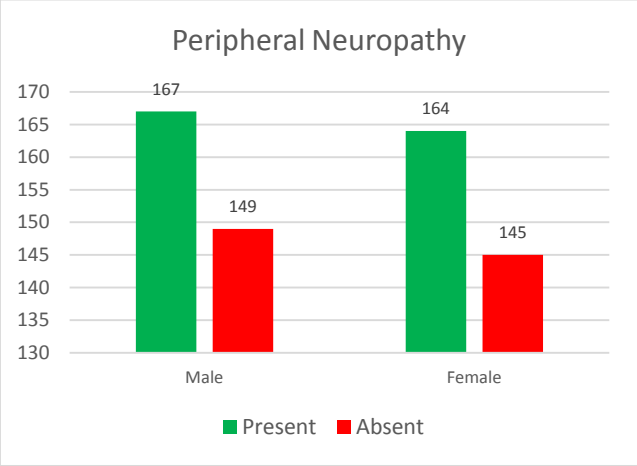
Distribution of population based on diabetic peripheral neuropathy

Table 11: Distribution of population based on diabetic peripheral neuropathy

Sex	Peripheral neuropathy	
	Absent	Present
Male	149	167
Female	145	164
Total	294	331

331 patients (52.9%) had peripheral neuropathy which included167 male patients and 164 female patients.

Graph 9: Distribution of population based on diabetic peripheral neuropathy



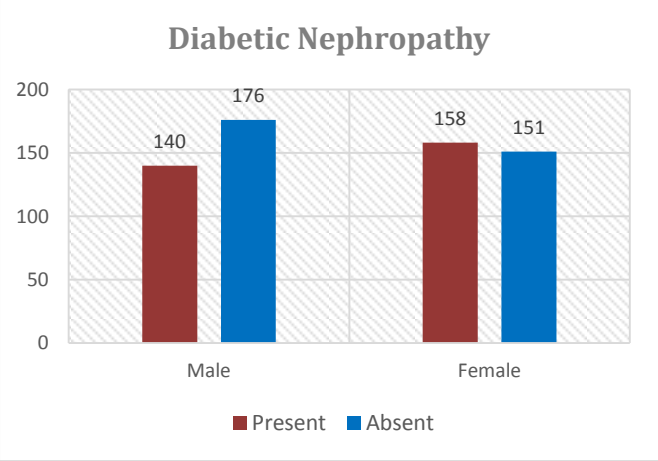
Distribution of samples based on diabetic nephropathy

Table 10: Distribution of samples based on diabetic nephropathy

	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 included140 males and 158 females.

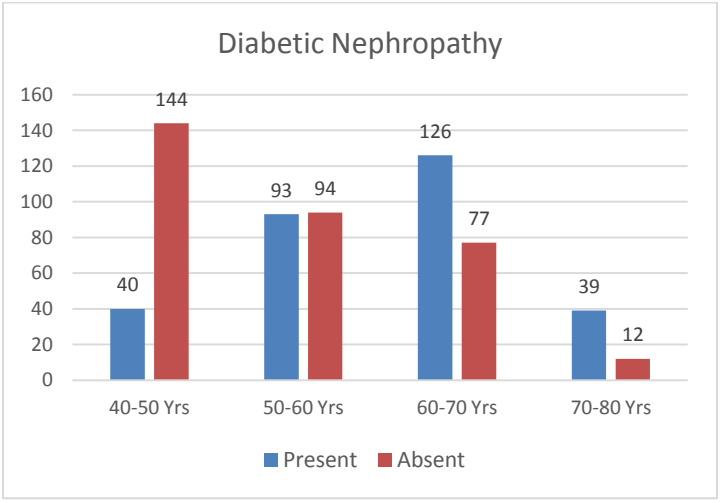
Graph 8: Distribution of samples based on diabetic nephropathy



Distribution of diabetic nephropathy based on age

Age Group	Diabetic Nephropathy		Total	P Value
	Present	Absent		
40-50 Yrs	40	144	184	
50-60 Yrs	93	94	187	
60-70 Yrs	126	77	203	
70-80 Yrs	39	12	51	<0.00001

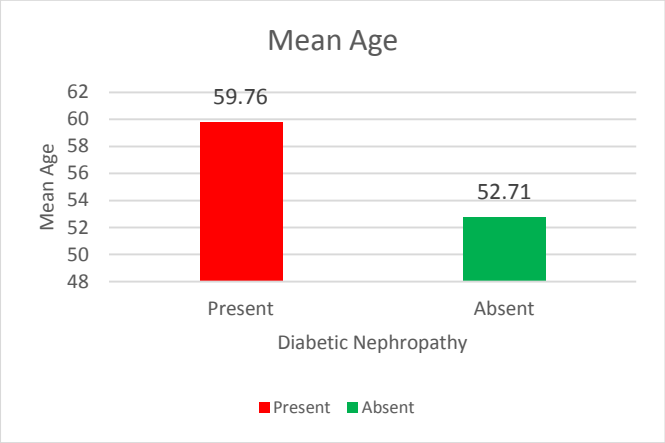
There was a statistically significant difference between association of diabetic nephropathy and advancing age as demonstrated by a p value of <.05.



Distribution of diabetic nephropathy based on age

Diabetic Nephropathy	Mean Age	P value
Present	59.768	
Absent	52.709	<.0001

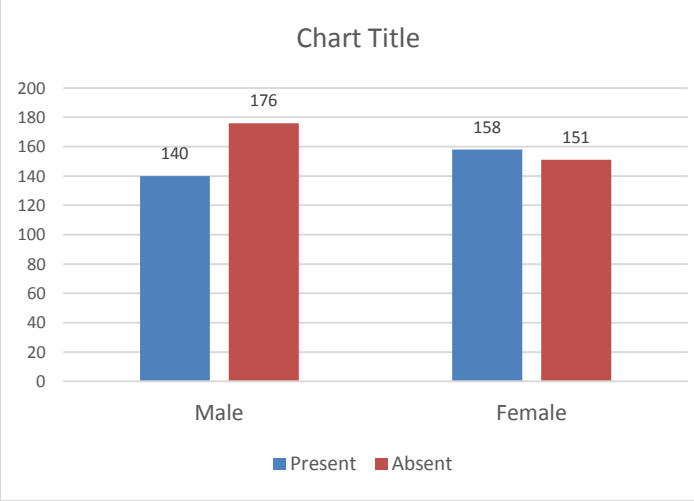
The mean age of patients that developed nephropathy was 59.76 while that of patients with no nephropathy was 52.70. This was found to be statistically significant. i.e. as the age advances the chances of developing nephropathy also increased.



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.

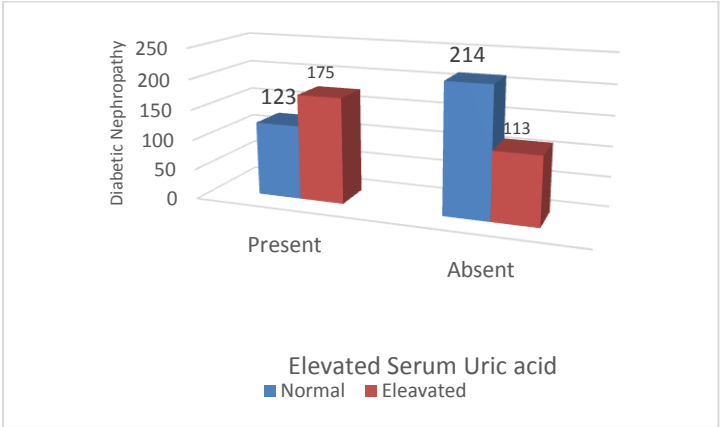


Crosstab showing association between serum uric acid andnephropathy

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).

Graph 10: Association between Serum Uric Acid and Nephropathy

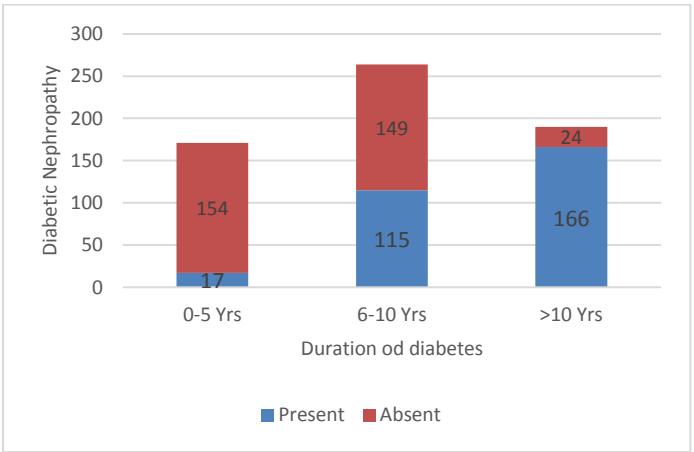


Association between duration of diabetes mellitus and nephropathy

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	

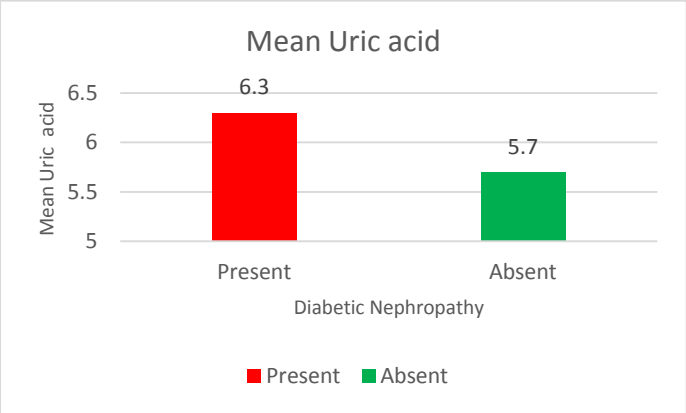
There was significant statistical association between duration of diabetes and development of nephropathy .i.e. as the duration increased the prevalence of nephropathy also increased.



Association between mean uric acid and diabetic nephropathy.

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

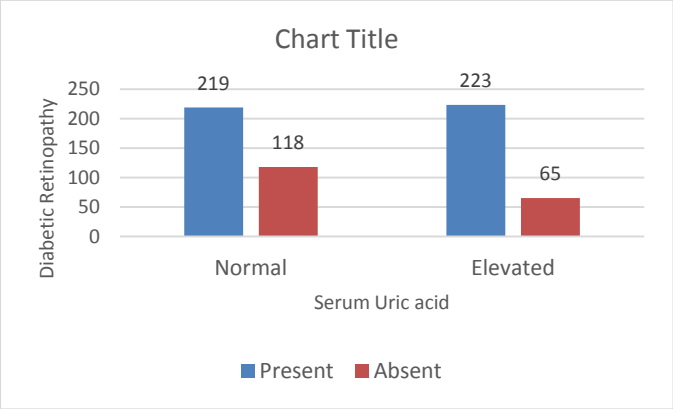
The mean uric acid level of those patients with nephropathy was 6.31 and that of patients with no nephropathy was 5.68. This was found to be statistically significant (p<0.0001)



Association between serum uric acid and retinopathy

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

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



Association between serum uric acid and peripheral neuropathy

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

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[8] 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).

Bonakdaranet al[9] 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[8] was 4.5 ± 0.15 mg/dL, there was no statistically significant difference between male and female population.

Bonakdaranet al[65] 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 JavadKiani[10] 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 [11] 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 nephropathy and duration of diabetes

Out of 298 patients with diabetic nephropathy; 17 patients having <5 year duration of diabetes

115 patients having 5-10 year duration, 166 having >10 year duration.

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. P value was 0.00001. Jiji Inassi, Vijayalakshmy R[12] studied duration of diabetes and development of nephropathy.

Association between serum uric acid and nephropathy

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.[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 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 55.6years 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 included180 males and 157 females.

358(57.2%) patients were hypertensive and the rest 267(42.7%) were normotensive. 175males 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

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