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Research Article

Correlation of Serum Uric Acid Level and Microvascular Complications in Patients with Type 2 Diabetes Mellitus

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Abstract
Diabetes mellitus has become a significant health challenge overall. It is a chronic, heterogeneous metabolic disorder that manifests as hyperglycemia and is characterized by impaired insulin secretion, insulin resistance, and increased hepatic glucose production. Microvascular dysfunction is unique to diabetes and characterized by nonocclusive microcirculatory disease. Hyperuricemia has been found to be associated insulin resistance, and consequently with type 2 diabetes. Potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation. Here an attempt has been made to study the level of serum uric acid in Type 2 diabetes mellitus and correlating it with development of microvascular complications.

Keywords: *Serum Uric Acid, Type 2 Diabetes Mellitus.*

Introduction

Diabetes mellitus has become a significant major health challenge overall. In India alone, the prevalence of diabetes is anticipated to rise from 31.7 million in 2000 to 79.4 million of every 2030.[1]Diabetes mellitus type 2 is a chronic, heterogeneous metabolic disorder that manifests as hyperglycemia and is characterized by impaired insulin secretion, insulin resistance, and increased hepatic glucose production; most cases begin in adulthood, and type 2 accounts for 90% to 95% of cases of diabetes in adults. Microvascular dysfunction is unique to diabetes and characterized by nonocclusive microcirculatory disease and impaired autoregulation of blood flow and vascular tone. Chronic hyperglycemia is essential for development of these changes, and intensive glycemic control delays the onset and slows the progression of microvascular effects.

Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes. Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation, leading to development of diabetic neuropathy and retinopathy. SUA is known to be associated with disease progression in the early stage of diabetic nephropathy.

Some have found a significant & specific independent association between uric acid level and cardiovascular mortality and morbidity, while others have come to an opposite conclusion. But little light has been thrown over the role of increased serum uric acid level and development of microvascular changes in patients with Type 2 Diabetes Mellitus.

Here an attempt has been made to study the level of serum uric acid level in Type 2 diabetes mellitus and correlation with development of microvascular complications.

Aims & Objectives

1. To know the serum uric acid level in patients with Type 2 Diabetes mellitus.
2. To correlate anthropometric measurements with serum uric acid level.
3. To correlate serum uric acid levels and microvascular complications in Type 2 Diabetes Mellitus.

Materials and Methods

The present study was aimed to establish a correlation between serum uric acid level and the development of microvascular changes in patients with Type 2 Diabetes Mellitus and was carried out in Sri Venkateswaraa Medical College Hospital & Research Centre which is a 750 bedded multi disciplinary centre serving the rural population in South India.

Type of Study: Cross sectional analytical study.

Study Centre: Sri Venkateswaraa Medical College Hospital & Research Centre.

Study Population: All diagnosed cases of Type 2 Diabetes Mellitus in the Department of General Medicine in Sri Venkateshwaraa Medical College and Research Institute, who are willing for the study.

Sample Size: 160 cases, with a 5 % non-compliance margin.

Period of study: Nov 2018 to May 2020

Inclusion Criteria

1. Patients with Type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes).
2. Both sexes included.

Exclusion Criteria

1. Patients with renal failure.
2. Pregnancy & lactating mothers.
3. Patients who are on long term diuretics & steroid.
4. Patients who are regularly consuming alcohol.
5. Patients who are on anti metabolite and chemotherapy drugs.
6. Patients who have hepatic & metabolic disorders.
7. Renal transplant patients.

Data Collection, Entry and Analysis

All type 2 diabetic patients who fit the inclusion criteria attending to medical and diabetology department in Sri Venkateswaraa Medical College Hospital & Research Centre were included in the study after obtaining informed consent and description of the procedures. After documenting the demographic data of the patients, a detailed clinical history ,diabetic history, thorough general physical examination and detailed systemic examination was obtained and documented in the Profoma.

Laboratory Data

- Blood urea estimation done using Glutamate dehydrogenase method (GLDH).

- Serum creatinine estimation done by Modified Jaffes method.
- Serum uric acid done by using semi auto analyser, Uricase Pod method.

Statistical Analysis

The data obtained were entered in MS Excel Sheet and data analysisdone with IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Chicago, IL.

Results

The total number of subjects included in this study was 160.

Among those 160 subjects, 100 were males and 60 females. All were diagnosed cases of Type 2 Diabetes Mellitus.

The statistical results are compared at 0.05 level of significance. (p value $\leq$ 0.05 implies significance)

Table 1: Distribution of study participants according to their age (N=160)

SL no.	Age	Frequency	Percentage
1	40-50	36	22.5
2	51-60	47	29.4
3	61-70	51	31.9
4	71-80	26	16.3

Figure 1: Distribution of study participants according to their age

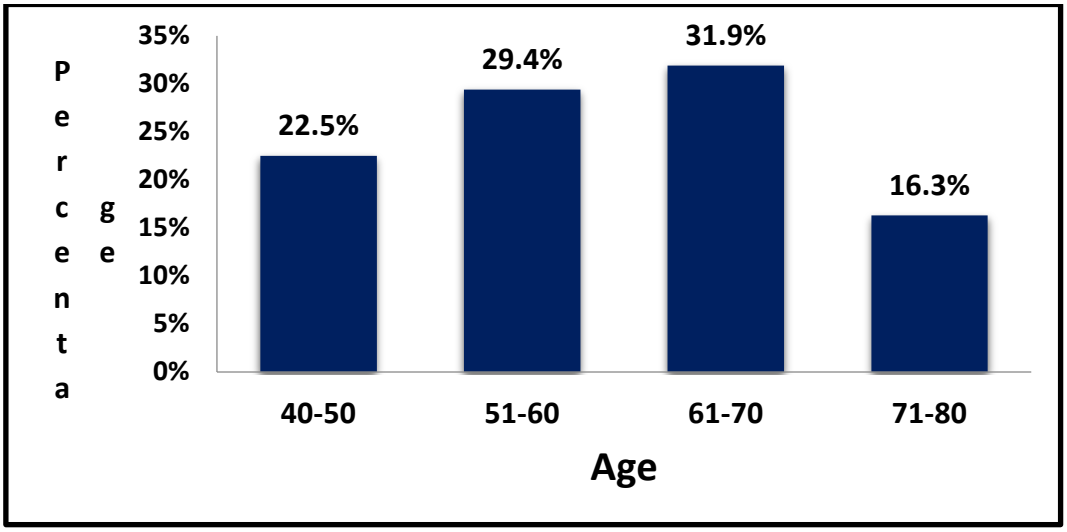


Table 2: Distribution of study participants according to their gender (N=160)

Slno	Gender	Frequency	Percentage
1	Male	100	62.5
2	Female	60	37.5

Figure 2: Distribution of study participants according to their gender (N=160)

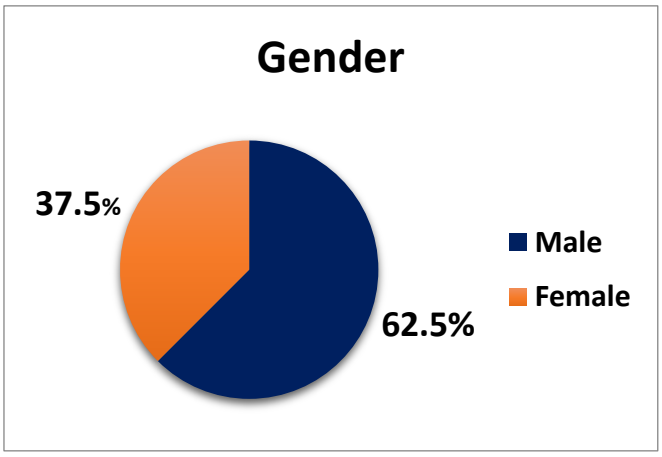


Figure 3: Distribution of BMI among the study participants (N=160)

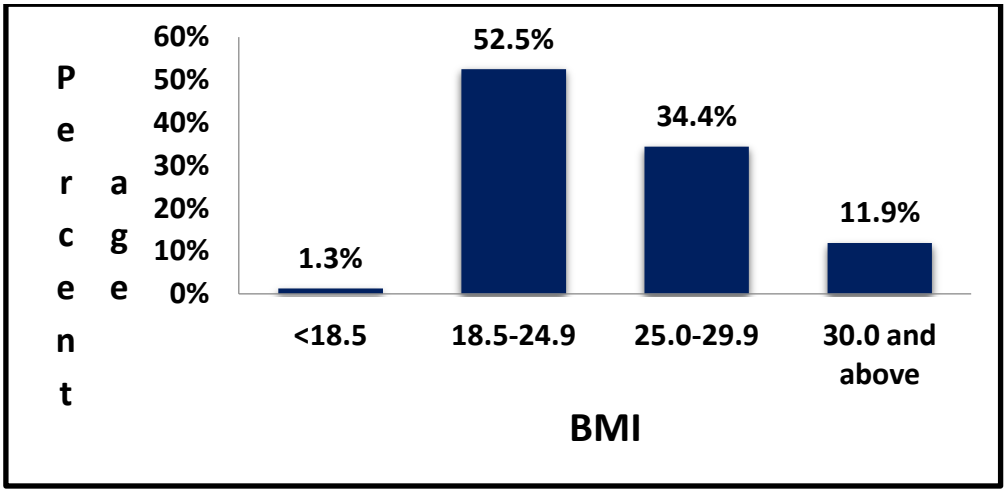


Table 3: Distribution of FBS levels among the study participants (N=160)

Slno	FBS (mg/dL)	Frequency	Percentage
1	110-129	11	6.9
2	130-159	36	22.5
3	160-189	47	29.4
4	190-209	26	16.3
5	210-239	20	12.5
6	240-269	6	3.8
7	270-300	4	2.5
8	>300	10	6.3

Table 4: Distribution of PPBS levels among the study participants (N=160)

Slno	PPBS (mg/dL)	Frequency	Percentage
1	150-180	25	15.7
2	180-210	67	41.9
3	210-240	27	16.9
4	240-270	20	12.5
5	270-300	5	3.1
6	>300	16	10.0

Figure 4: Distribution of uric acid among the study participants (N=160)

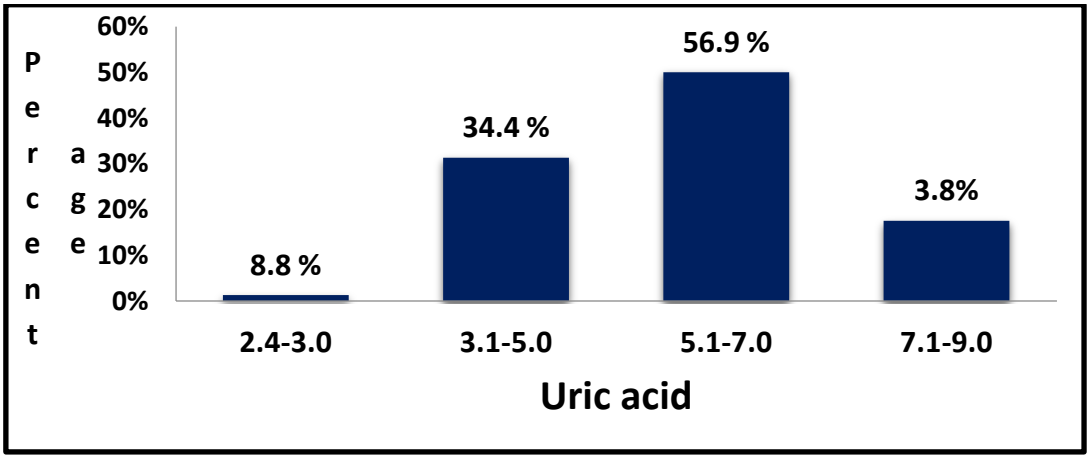


Figure 5: Distribution of uric acid levels in relation to gender

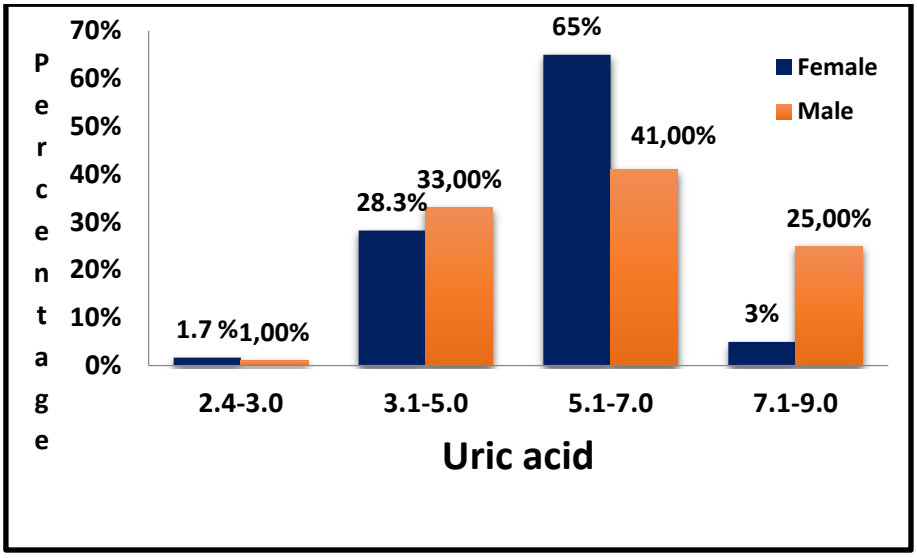
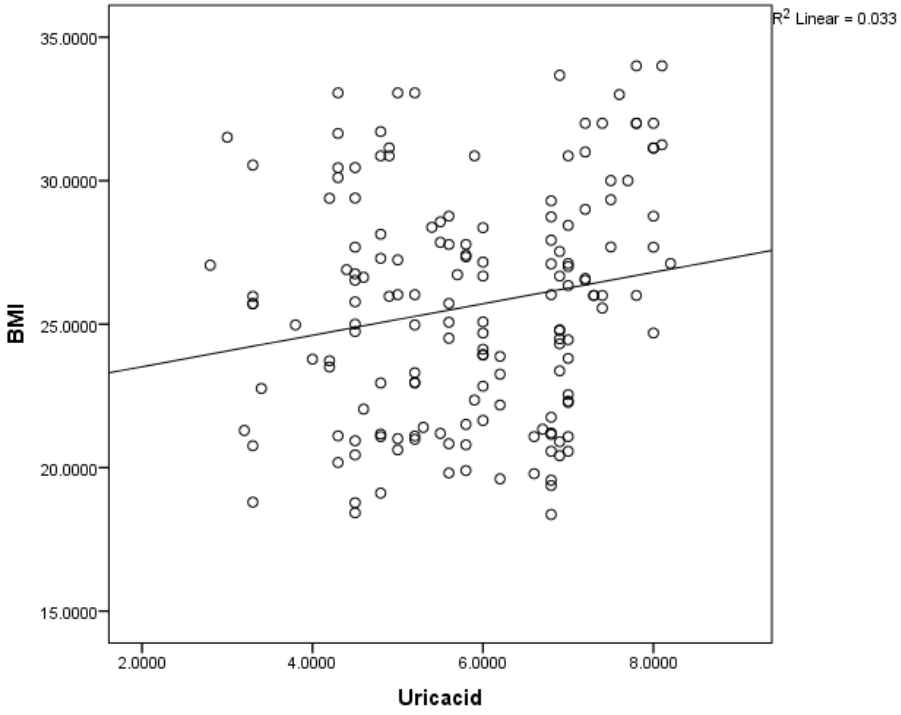


Figure 6: Correlation of BMI with serum uric acid levels (N=160)

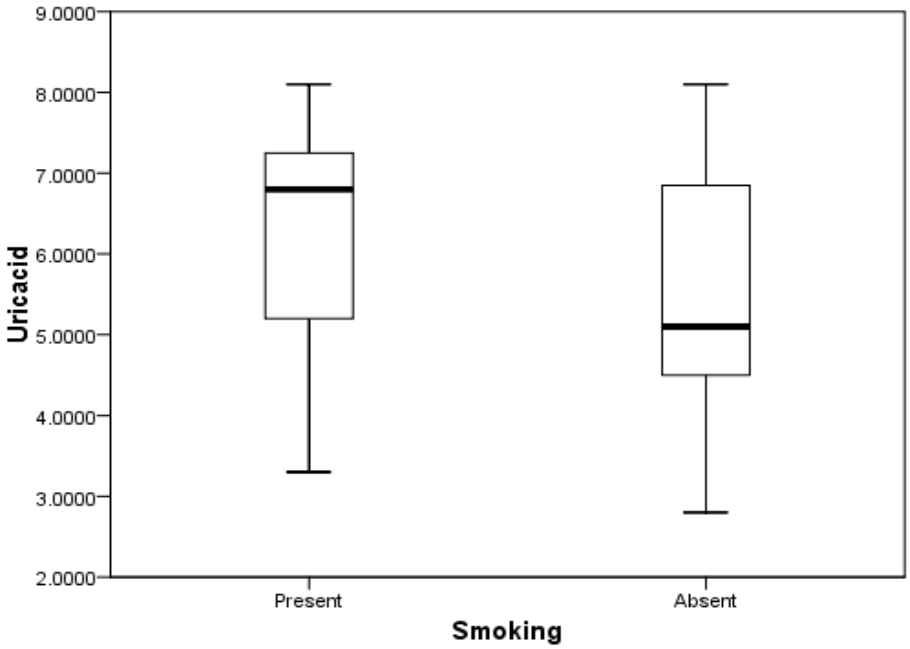


(r=0.182, p=0.021)

Table 5 Correlation of smoking with serum uric acid levels (N=160)

Slno	Variables	Smoking present	Smoking absent
1	Uric acid level	6.26±1.31	5.55±1.48

Figure 7 Correlation of smoking with serum uric acid levels (N=160)



(p<0.001)

Figure 8: Correlation of serum uric acid levels with HBA1C (N=160)

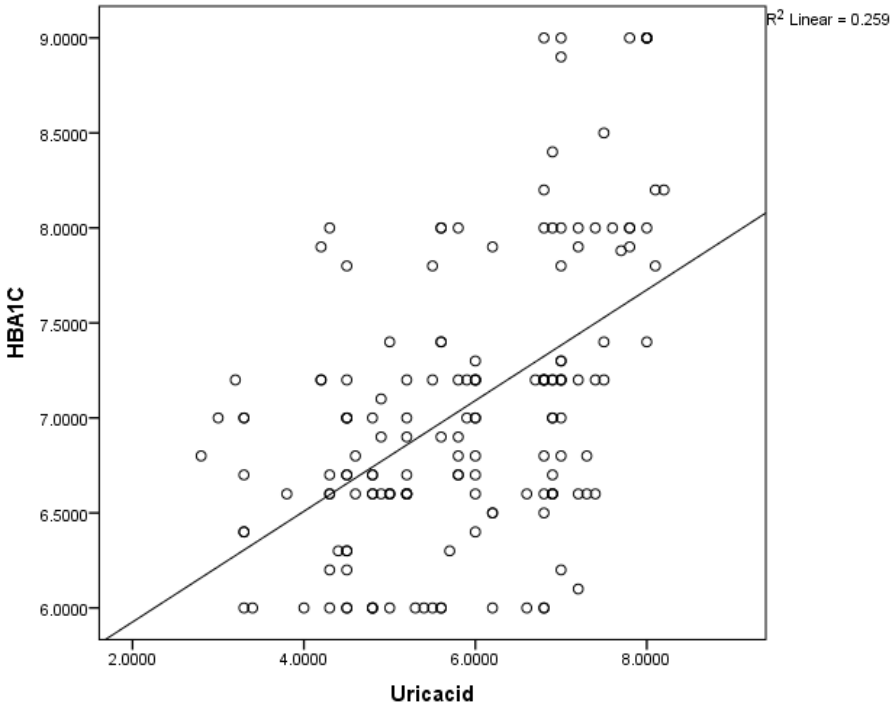


Figure 9: Association of duration of diabetes with serum uric acid levels

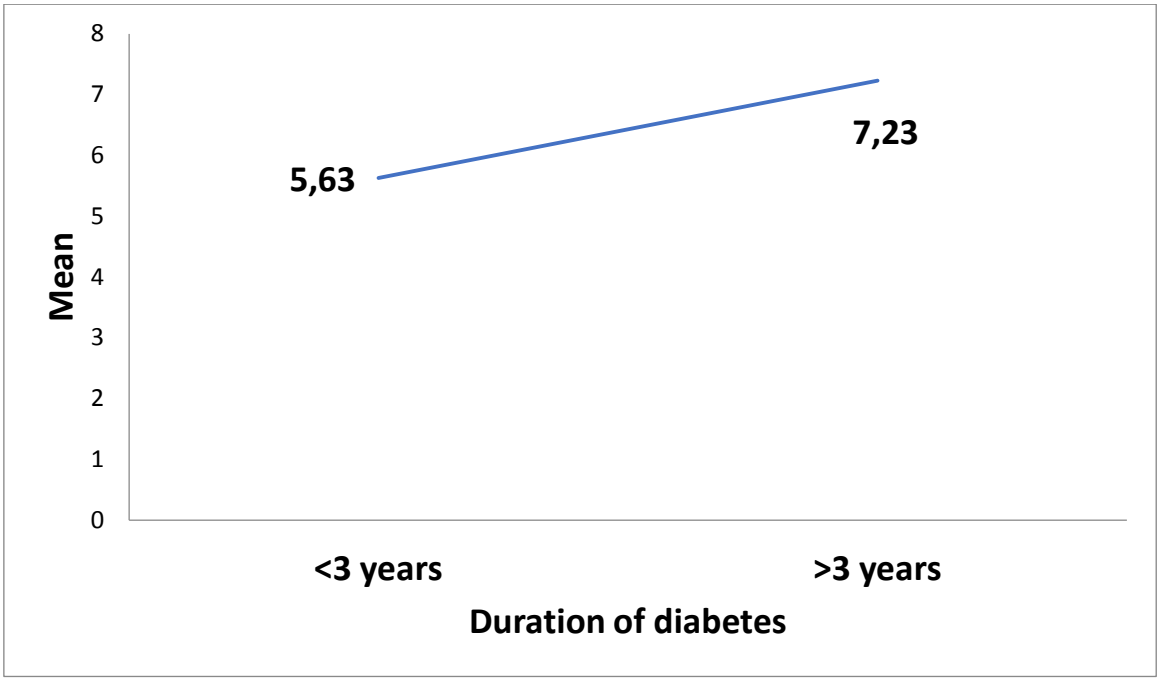


Table 6: Distribution of serum uric acid levels in Diabetic neuropathy

Slno	Variables	Serum uric acid level	p value
1	**Monofilament test**		
	Normal	5.58±1.32	<0.001
	Abnormal	7.83±1.24	
2	**Tone**		
	Normal	5.89±1.30	0.258
	Abnormal	5.46±1.62	
3	**Ulcers**		
	Present	7.05±0.97	0.003
	Absent	5.71±1.29	
4	**Deformities**		
	Present	6.57±0.96	0.06
	Absent	5.80±1.33	
5	**Loss of sensation**		
	(More than 3) Present	7.36±1.32	
	Absent	5.66±1.25	<0.001

Table 7: Distribution of serum uric acid levels in Diabetic retinopathy (N=160)

Slno	Variables	Serum uric acid level	p value
1	**Fundus changes** Present	7.57±0.96	
	Absent	5.8±1.33	<0.001

Table 8: Distribution of serum uric acid levels in Diabetic nephropathy (N=160)

Slno	Variables	Serum uric acid level	p value
1	**Microalbumuria**		
	Present (n=44)	6.68±1.15	<0.001
	Absent (n=116)	5.54±1.25	
2	**Urea**		
	Normal	5.45±1.30	
	Elevated urea	5.92±1.33	0.135
3	**Creatinine**		
	Normal	5.36±1.28	
	Elevated creatinine	6.23±1.24	<0.001

Discussion

The present study was carried out from Nov 2018 to May 2020, at Sri Venkateshwaraa Medical College Hospital & Research Centre, Ariyur, Puducherry, a mutli disciplinary hospital serving the rural population.

In our study, we evaluated 160 patients, all diagnosed cases of type 2 diabetes mellitus, out of which 100 were males and 60 females. Mean age of the participants were 59.69±9.43 years. Majority of them were in the age group of 61-70 years followed by 51-60 years (29.4%), 40-50 years (22.5%). (**Table1-Fig1**)

This is similar to various other studies in our country, some are Warjukar et al, Nugraha et al, the mean age of study group was 59.74±10.58.

Male preponderance seen in our study (62.5%) (**Table 2-Fig 2**).

Hyperuricemia was present in 43.1% of the study participants. The total mean uric acid levels in our study were 5.86±1.33 mg/dL. It clearly shows the prevalence of hyperuricemia in patient with Diabetes Mellitus.

The body mass index seen was normal for about 52.5% followed by 34.4% were overweight and 11.9% were obese. (**Fig 3**). As, BMI increases, serum uric acid levels also increases(r=0.182, p=0.021) (**Fig 6**) .Patients with higher BMI had significantly higher levels of serum uric acid in our study. Mean uric acid was positively correlating with BMI as given by various other studies like the ones by Kawamoto et al, Ali et al and Mukhopadhyay et al.

Serum uric acid levels were high among smokers in our study and was found significant (p<0.001), (**Table 5- Fig 7**) contrary to previous studies which show negative correlation of smoking status with serum uric acid level.

As HBA1C increases, serum uric acid levels also increases and was found to be statistically significant in our study. Majority of the study participants are having HBA1C levels around 6.0-7.0% (57.5%) followed by 7.1-8.0% in 34.4%. Around 8.1% were having around 8.1 to 9.0.(**Fig-8**)

As duration of diabetes increases serum uric acid level increases. (**Fig-9**). Nugraha et al, in 2018, and Kodama et al in 2008, found that as duration of diabetes increases serum uric acid level increases. "The possible reason may be due to increased excretion of uric acid over the years and modification of diet in renal disease."With aging, levels of uric acid increases in serum of diabetic patients.

According to our study, there was statistical significant difference between uric acid levels with abnormal monofilament test, presence of ulcers and presence of loss of sensation. (**Table-6**) Diabetic peripheral neuropathy (DPN) is the main clinical manifestation of sensory and autonomic nerve symptoms, distal symmetry polyneuropathy, and motor neuropathy are the most common types of DPN. Yu et al performed a meta-analysis of 1388 patients with T2DM with peripheral neuropathy and in 4746 patients without peripheral neuropathy and showed that SUA levels were significantly elevated in patients with diabetes complicated with peripheral neuropathy and that increased hyperuricemia was related with increased risk of peripheral neuropathy.

We also found a statistical significant difference between uric acid levels and presence of fundus changes in our study (**Table-7**). Based on the changes of haemodynamics or vascular geometry, vascular injury is considered to be the prime motivator for the initiation and progression of DR, including pericytosis, platelet aggregation, thickening of basement membrane, and neuroglial damage. Uric acid is closely related to these pathological changes. A study reported that increased SUA levels were associated with an increased severity of DR in Taiwan. Kuwata analyzed data from 1839 patients with T2DM in Japan by gender stratification and found that higher SUA levels were associated with an increased risk of DR in men, but not in women. The results showed sex hormones play an important role in the metabolism of uric acid, which deserved to discuss the specific mechanism further.

Microalbuminuria was present in 27.5% of the study participants. (**Table-8**). There was statistical significant difference between uric acid levels with presence of microalbuminuria and elevated creatinine levels. Patients with higher SUA levels have poorer renal function, independent of glycated hemoglobin (HbA1c) or the duration of diabetes. In T2DM, there is an independent and significant positive association between higher blood UA and an increased risk of a reduced glomerular filtration rate (eGFR). Blood UA levels greater than 5.5 mg/dl can predict chronic kidney disease of stage 3 and above in T2DM. Xanthine oxidase (XO) is a very important enzyme that is responsible for the conversion of sulfhydryl groups to UA. Elevation of UA by 1 μmol/l enhanced the probability of albuminuria by 1.5%, and a rise in XO activity of 1 U/l also increased the probability of albuminuria by 1.5%. In diabetes, both XO and uric acid are independently associated with albuminuria.

Conclusion

Complex genetic and environmental factors contribute to causing diabetes, and chronic complications of diabetes may occur throughout the body.

Hyperuricemia is closely related to the development of diabetes and its chronic complications.

Our study found statistical significance in the association of serum uric acid level and its role in the development of diabetic neuropathy, diabetic retinopathy and diabetic nephropathy in patients with Type 2 Diabetes Mellitus. Uric acid may play a role in the pathogenesis of diabetic microvascular diseases. Patients with type 2 diabetes mellitus often had coexisting microvascular complications when the diagnosis of diabetes mellitus was made.

Therefore, identifying a clinical surrogate for the severity of diabetic microvascular complications is needed. Regular measurements of SUA level as a potential marker for the severity of microvascular diseases may be beneficial for patients with diabetes.

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