ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

*International Journal of Medical Science and Advanced Clinical Research (IJMACR)*

*Available Online at:www.ijmacr.com*

*Volume – 5, Issue – 6, November – December - 2022, Page No. : 193 - 200*

# Serum Uric Acid - A better diagnostic or prognostic tool to assess severity of diabetic retinopathy, An observational study conducted in a tertiary care Centre

[1]Dr.Prasanth Prasad, Assistant Professor, Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum, Kerala.

[2]Dr.Jarlin John, Assistant Professor, Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum, Kerala.

[3]Dr. Henna Puthiyaveetil Sabeerali, Senior Resident, Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum, Kerala.

[4]Dr.Sumesh Raj, Professor of General Medicine, Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum, Kerala.

**Corresponding Author:** Dr. Sumesh Raj, Professor of General Medicine, Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum, Kerala.

**How to citation this article:** Dr. Prasanth Prasad,Dr. Jarlin John,Dr. Henna Puthiyaveetil Sabeerali,Dr. Sumesh Raj, "Serum Uric Acid - A better diagnostic or prognostic tool to assess severity of diabetic retinopathy, An observational study conducted in a tertiary care Centre", IJMACR-November – December - 2022, Vol – 5, Issue - 6, P. No.193– 200.



**Type of Publication:** Original Research Article

**Conflicts of Interest:** Nil

## Abstract

**Introduction:** Serum uric acid (SUA) is identified as a possible risk factor for T2DM in recent decades. The deranged biochemical profile SUA has been shown to play a significant role in the development of Diabetic Neuropathy and Nephropathy but little knowledge on the relationship between SUA and DR has been shown in literature. Therefore, the identification of a clinical marker is very important for early detection and management of progression of Diabetic Retinopathy (DR).

**Aim:** This study is to find out the role of Serum Uric Acid association in Diabetic Retinopathy. Due to heterogeneity in international studies and the lack of local literature evidence, this research was conducted to explore this interesting relationship between serum uric acid in different grades of Diabetic Retinopathy.

**Methodology:** Study was conducted as observational study design in Department of General Medicine, Trivandrum, Kerala. Patients were allocated into two groups Group 1: 94 T2DM subjects with Diabetic Retinopathy. Group 2: 94T2DM subjects without Diabetic Retinopathy. *Results***:** The levels of Serum Uric Acid increment as severity of diabetic retinopathy progressed & thus found significant association between serum uric acid in severity of diabetic retinopathy.

**Keywords:** serum uric acid, diabetes, microvascular complications, severity and diabetic retinopathy

**Introduction**

Diabetes is increasingly gaining the status of a possible epidemic in India and is currently diagnosed in 77 million people by 2020, according to the International Diabetes Federation (IDF). It is expected that approximately 153 million will suffer from Diabetes Mellitus by 2045. Diabetic Retinopathy (DR), one of the main causes of adult visual impairment and a severe microvascular complication of Diabetes Mellitus. Diabetes prevalence in Kerala ranges from 13.70 per cent to 20 per cent, according to various studies conducted in representative populations in the state, with a trend for a comparatively lower prevalence in Central Kerala.[1]

DR is caused by the deleterious metabolic effects of hyperglycemia, which contributes to extensive and early neurodegeneration, is one of the chronic microvascular complications of Type 2 Diabetes Mellitus (T2DM) [2]. DR is a leading cause of visual disability and blindness in diabetics and it is a microvascular complication that can affect the peripheral retina, the macula or both and [3] DR is a major cause of vision loss in adults [4] which contributes to severe morbidity in patients with diabetes, leading to serious public health issue. Chronic exposure to Diabetes-related metabolic changes may damage the microvasculature of the retina, resulting in DR [5]. Serum uric acid (SUA) is identified as a possible risk factor for T2DM in recent decades. The deranged biochemical profile SUA has been shown to play a significant role in the development of Diabetic Neuropathy and Nephropathy [6] but little knowledge on the relationship between SUA and DR has been shown. Therefore, the identification of a clinical marker is very important for early detection and management of progression of DR. If uric acid is found to be a novel screening tool that predicts the future occurrence of DR, it may be useful for early intervention to mitigate risk, especially in patients with DR complications. Blindness is primarily the result of progressive DR and clinically significant macular edema [7]. The first standardized classification of DR (Airlie House Classification) was developed in 1968. This classification was modified for use in the Early Treatment of Diabetic Retinopathy Study (ETDRS) which became the gold standard for classification of DR. As per ETDRS classification, Diabetic Retinopathy is classified as either proliferative or non-proliferative. DR is a progressive disease comprising several stages including: 1) no DR, in which there are no abnormalities; 2) Mild Non-Proliferative DR 3) Moderate Non-Proliferative DR, 4) Severe Non-Proliferative DR, 5) Very Severe Non-Proliferative DR, 6) Early Proliferative DR, 7) High Risk Proliferative DR and 8) Advanced Diabetic Eye Disease.

Even though it can be effectively treated, Diabetic Retinopathy remains the most common cause of acquired blindness among persons of working age in the industrialized world. The aim of this study is to investigate the Association of Serum Uric Acid in various grades of Diabetic Retinopathy.

**Methods and Materials**

The study design is an observational study which is conducted in Department of General Medicine of Sree Gokulam Medical College and Research Foundation, Trivandrum. The study period was From 1st January 2019 to 31st December 2019. The study was conducted in patients who were diagnosed to have T2DM.

**Inclusion criteria**

T2DM patients, as per ADA criteria who attended the outpatients and inpatients of Department of General Medicine and Department of Ophthalmology, Sree Gokulam Medical College and Research Foundation, Trivandrum, were included in the study.

**Exclusion criteria**

Those who are pregnant, patients treated for cancer in the past 5 years before study enrolment, Those with blood disorders causing hemolysis (e.g., haemolytic anemia), Chronic Kidney Diseases, Hypertensives, Arthritis and Myocardial infarction.

A sample size of 188 subjects. All patients who satisfied the inclusion and exclusion criteria during the study period were included in the study until the sample size attained.

Patients were allocated into two groups

Group 1: 94 T2DM subjects with Diabetic Retinopathy

Group 2: 94T2DM subjects without Diabetic Retinopathy

**ETDRS Classification OF DR** [8]

| Category | Description |
|---|---|
| Mild NPDR | Any or all of; microaneurysms, retinal hemorrhages, exudates, Cotton wool spots<br>No Intra Retinal Microvascular Abnormalities or significant beading |
| Moderate NPDR | SevereRetinalHemorrhagesin1-3quadrantsormild Intra Retinal MicrovascularAbnormalities<br>Significant venous beading in no more than 1 quadrant<br>Cotton wool spots |
| Severe NPDR | Severe retinal hemorrhages in all 4 quadrants Significant venous beading in ≥ 2 quadrants<br>Moderate Intra Retinal Microvascular Abnormalities in ≥ 1 quadrant |
| Very Severe NPDR | ≥ 2 of the criteria of severe NPDR |
| Early PDR | Neovascularisation of the Disc <1/3 Disc area<br>Neovascularisation Elsewhere <1/2 Disc area |
| High Risk PDR | Neovascularisation of the Disc≥ 1/3 Disc area<br>Any Neovascularisation of the Disc with vitreous hemorrhage Neovascularisation Elsewhere ≥ 1/2 Disc area with vitreous hemorrhage |
| Advanced Diabetic Eye Disease | Preretinal(retrohyaloid) hemorrhage, intragel hemorrhage or both Tractional retinal detachment<br>Rubeosis iridis (iris neovascularization -NVI)Neovascular glaucoma |

**Results and Discussion**

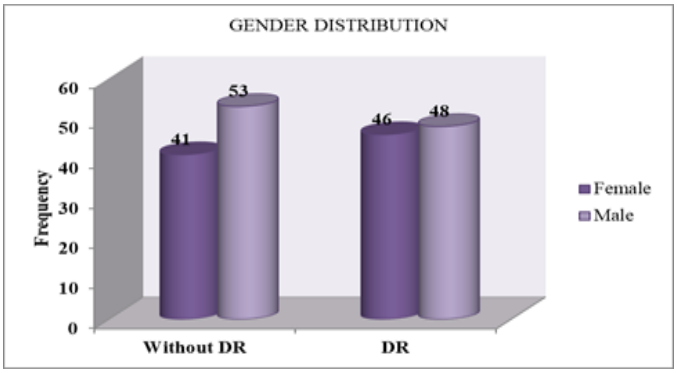
Serum uric acid (SUA) was formerly used to be considered a predominant indicator of gouty diathesis.[9] However, as a Metabolic Syndrome (MetS) marker, by interfering with insulin-stimulated glucose uptake, SUA could worsen insulin resistance and show a positive association between Serum Uric Acid levels and T2DM . The experiments carried out by Cirillo. P et al, Anwar M.M et al. and Tane moto M et al. reported that elevated uric acid levels were associated with microvascular diabetic complications, such as Nephropathy, Retinopathy, and Neuropathy.[10,11,12 ] Purine metabolites are closely associated with the development of diabetic microvascular complications[13], according to Ames BN et al.. Studies conducted by Nakagawa T et al. confirmed that hyperuricaemia has been added to the set of

metabolic anomalies associated with Metabolic Syndrome insulin resistance and/or hyperinsulinemia [14] In the present study, it is clear that the levels of Uric Acid and Lipid Profile showed increment as severity of DR progressed. Apart from age of onset of Diabetes, duration of the disease and glycemic control, we found a significant correlation between serum uric acid and various grades DR.A slightly higher number of the study population were males in without DR group while almost similar gender distribution was seen in DR group. [Table 1 & Figure 1].

Table 1: gender distribution with and without diabetic retinopathy

| Sex | Group | | Total |
|---|---|---|---|
| | Without DR | DR | |
| Female | 41 | 46 | 87 |
| Male | 53 | 48 | 101 |
| Total | 94 | 94 | 188 |

Fig 1: gender distribution with and without diabetic retinopathy

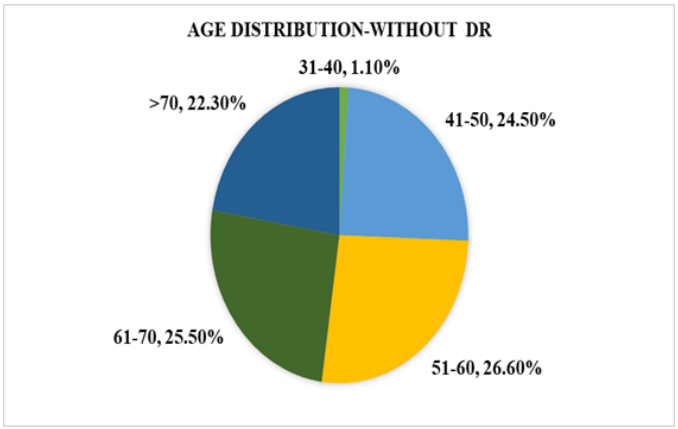



The maximum number of patients without DR in this study were in the age group of 51-60 yrs [Table 2 & Figure 2].

Table 2: Age distribution: without diabetic retinopathy

| Age (Years) | Frequency | Percentage |
|---|---|---|
| 31-40 | 1 | 1.1 |
| 41-50 | 23 | 24.5 |
| 51-60 | 25 | 26.6 |
| 61-70 | 24 | 25.5 |
| >70 | 21 | 22.3 |
| Total | 94 | 100 |

Figure 2: age distribution: without diabetic retinopathy

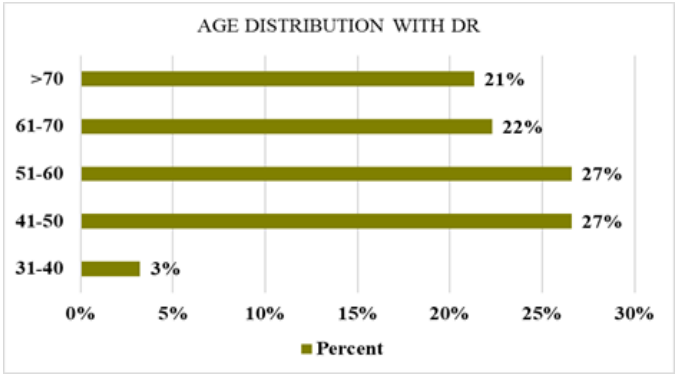



The maximum number of patients with DR in this study were in the age group of 41-60yrs [Table 3 &Figure 3]. In age group of 51-60yrs there were equal number of patients in DR & without DR in this study.

Table 3: age distribution:with diabetic retinopathy

| Age (Years) | Frequency | Percentage |
|---|---|---|
| 31-40 | 3 | 3% |
| 41-50 | 25 | 27% |
| 51-60 | 25 | 27% |
| 61-70 | 21 | 22% |
| >70 | 20 | 21% |
| Total | 94 | 100% |

Figure 3: age distribution:with diabetic retinopathy

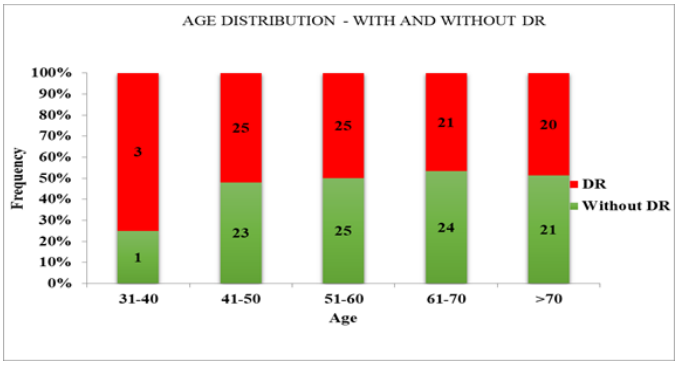


The maximum number of patients with mild, moderate, severe, very severe NPDR in this study were in the age group of 41-50, 61-70, 51-60, 41-50 yrs respectively. The maximum number of patients with early, high-risk PDR in this study were in the age group of 61-70, 51-60 yrs respectively. In our study population, we could not find any patients with advanced diabetic eye disease stage. The mean age of patients studied were almost same in all various grades of DR except in mild NPDR. Significant differences in gender was seen in very severe NPDR & early PDR with more patients were in male &female respectively [Table 4 & Figure 4]

Table 4: age distribution: with and without diabetic retinopathy

| Age | Group | | |
|---|---|---|---|
| (Years) | Without DR | DR | Total |
| 31-40 | 1 | 3 | 4 |
| 41-50 | 23 | 25 | 48 |
| 51-60 | 25 | 25 | 50 |
| 61-70 | 24 | 21 | 45 |
| >70 | 21 | 20 | 41 |
| Total | 94 | 94 | 188 |

Figure 4: age distribution: with and without diabetic retinopathy




Apart from age of onset of Diabetes, duration of the Diabetes showed increase as severity of DR progressed. In CURES, as in our research it was found that the duration of Diabetes significantly increased the severity of Retinopathy.[15]

It was observed that the elevated level of Uric Acid in cases of Diabetic Retinopathy was significant as compared to those without DR [Table 5].

Table 5: mean of hba1c, uric acid, lipid profile: with and without diabetic retinopathy.

| | Group | | P value (independent t test) |
|---|---|---|---|
| | DR | Without DR | |
| HbA1c (%) | 10.21 | 7 | 0.0001 |
| Uric acid (mg/dl) | 6.53 | 3.74 | 0.0001 |
| Total Cholesterol (mg/dl) | 224.53 | 135.71 | 0.0001 |
| Triglycerides (mg/dl) | 154.01 | 87.28 | 0.0001 |
| HDL (mg/dL) | 29.45 | 53.83 | 0.0001 |
| LDL (mg/Dl) | 156.51 | 67.2 | 0.0001 |
| VLDL (mg/dL) | 32.29 | 17.45 | 0.0001 |

It was clearly evident from the study that Uric Acid levels was significantly less in cases of Diabetes Mellitus without Retinopathy as compared to those with DR. However, Uric Acid levels tend to increase with the onset of Retinopathy, a trend which was seen in our study. Among the Diabetic Retinopathy cases, it was much more evident that elevated level of Uric Acid was more significant in proliferative cases as compared to non-proliferative cases [Table 6].

Table 6: mean and standard deviation of duration: various grades of diabetic retinopathy

| Grade of DR | Duration (Year) | |
|---|---|---|
| | Mean | SD |
| Mild NPDR | 5.56 | 0.629 |
| Moderate NPDR | 7.38 | 0.5 |
| Severe NPDR | 9.5 | 0.516 |
| Very severe NPDR | 12.63 | 1.408 |
| Early PDR | 16 | 1.648 |
| High risk PDR | 24.8 | 5.809 |
| P value (ANOVA) | 0.0001 | |

These results agree with the results obtained in a study done by Ashakiran. S et al. [16], found the elevated level of Uric Acid in cases of Diabetic Retinopathy was significant as compared to cases without DR. Among the DR cases, it was much more evident that elevated level of Uric Acid was more significant in proliferative cases as compared to non- proliferative cases.

In the pathogenesis & development of long-term complications associated with Diabetes Mellitus, the amount of Serum Uric Acid plays a significant role. The relationship between Uric Acid and insulin, which plays a vicious cycle for the progression of Diabetes, especially with regard to microvascular changes, is a unique feature that is notable. Studies have shown in the past that insulin release is increased in hyperurecimic subjects in response to oral glucose.[17] Serum Uric Acid levels have also been shown to be directly linked to insulin resistance, regardless of age, sex, excess body weight, fat distribution, and Blood Pressure.[18,19] In addition, physiological hyperinsulinemia is known to acutely reduce Uric Acid and sodium excretion from the kidneys in a coupled fashion.[14]This could explain our study's finding of why Uric Acid tends to increase in cases of Proliferative Retinopathy. It was also noted that Urinary Uric Acid clearance in normal volunteers 69 appears to decrease in proportion to the increase in insulin resistance, which could also contribute to this phenomenon.[20]. As a result, despite adequate or increased insulin concentrations in diabetics, increased Uric Acid levels further complicate the problem of insulin resistance, which could further be associated with the development of complications such as Retinopathy.

Prakash et al. reported in their work that patients with severe DR had a longer duration of Diabetes and higher HbA1c, which could be seen in our study.[21]. Similarly, proliferative cases showed an elevated Glycated Hemoglobin Level, signifying poor glycemic control. Similar findings were made in previous studies on Diabetic Retinopathy on various parameters. Ahsan et al. reported that increased duration of Diabetes and impaired glycemic control are significant factors in the development of Retinopathy [22] which is consistent with our study outcome.

**Conclusion**

The levels of Serum Uric Acid showed increment as severity of DR progressed in our study & thus found significant association between SUA and severity of DR. So regular measurement of Serum Uric Acid Level could be advised to diabetic patients for early management from severity of microvascular complications. Hence this study may put forth that SUA could be a better diagnostic/prognostic tool to assess diabetic retinopathy.

**References**

1. Jose R, Manojan KK, Augustine P, Nujum Z, Althaf A, Haran J, et al. Prevalence of Type 2 Diabetes and Prediabetes in Neyyattinkara Taluk of South Kerala. 2013.

2. Eman M. Aly. FTIR analysis for retina associated with diabetic changes and treatment with oat. Int J Pharm Pharm Sci 2015; 7:277–80.

3. Association, A.D Microvascular Complications and Foot Care ADA 2015. Diabetes Care 38: S58-S66 (2015).

4. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. Diabetes Care 2004;27(10):2540–53

5. Siva Prasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. Surv Ophthalmol 2012;57(4):347–70

6. Kiani J, Habibi Z, Tajziehchi A, Moghimbeigi A, Dehghan A, Azizkhani H. Association between serum uric acid level and diabetic peripheral neuropathy (A case control study). Casp J Intern Med 2014;5(1):17–21.

7. J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo. Diabetes Mellitus: Diagnosis, classification, and Pathophysiology, Harrison's principles of internal medicine. 20th ed. Mc Graw Hill;

8. John S. Kanski's Clinical Ophthalmology, A Systematic Approach. 9th edition.

9. Murea M. Advanced kidney failure and hyperuricemia. Adv Chronic Kidney Dis 2012;19(6):419–24

10. Cirillo P, Sato W, Reungjui S, Heinig M, Gersch M, Sautin Y, et al. Uric Acid, the Metabolic Syndrome, and renal disease. J Am Soc Nephrol 2006;17(12 suppl 3): S165.

11. Anwar MM, Meki A-RMA. Oxidative stress in streptozotocin-induced diabetic rats: effects of garlic oil and melatonin. Comp BiochemPhysiolA Mol Integr Physiol 2003;135(4):539–47.

12. Hsu S-P, Pai M-F, Peng Y-S, Chiang C-K, Ho T-I, Hung K-Y. Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients. Nephrol Dial Transplant 2004;19(2):457–62

13. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78(11):6858–62

14. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, et al. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006;290(3): F625—31

15. Quinones Galvan A, Natali A, Baldi S, Fras Cerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol 1995;268(1 Pt 1): E1-5

16. Ashakiran S, Krishnamurthy N, Navin S, Patil S. Behaviour of serum uric acid and lipid profile in relation to glycemic status in proliferative and non-proliferative diabetic retinopathy. Curr Neurobiol 2011; 2:57–61(the previous 15nth reference was deleted and now total only 22 references)

17. Butturini U, Coscelli C, Zavaroni I. Insulin release in hyperuricemic patients. Acta Diabetol Lat 2007; 14:73–8

18. Sinagra D, Greco D, Scarpitta AM, Bonaventura V. Serum uric acid, insulin secretion and resistance in nonhyperuricemic and hyperuricemic obese female subjects. Int J Obes Relat Me tab Disord J Int Assoc Study Obes 1996;20(11):1041–3.

19. Wang M, Zhao D, Wang W, Liu J, Liu J, Liu S. [A prospective study on relationship between blood uric acid levels, insulin sensitivity and insulin resistance]. ZhonghuaNeiKe Za Zhi 2007;46(10):824–6

20. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266(21):3008–11

21. Prakash G, Agrawal R, Satsangi S, Prakash S. Comparison of serum apolipoproteins and traditional lipids in eyes with diabetic retinopathy in Indian population: A case series. Middle East Afr. J. Ophthalmol.2016;23(2):212–4.

22. Ahsan S, Basit A, Ahmed KR, Ali L, Khanam R, Fawad A, et al. Risk indicators of diabetic retinopathy in patients with type 2 diabetes screened by fundus photographs: Int J Diabetes Dev Ctries 2015;35(3):333–8.