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A prospective study to determine association between serum uric acid and diabetic retinopathy

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Abstract
Aims: To explore the role of serum uric acid (SUA) concentration in diabetic retinopathy (DR) for patients with type 2 diabetes mellitus (T2DM).
Methods: The present prospective observational study was conducted in department of Ophthalmology at Chattrapati Shivaji Subharti hospital from December 2019 to November 2020. The diabetic patients were assigned to one of the following groups based on presence and severity of diabetic retinopathy with the help of fundus photographs and/or fundus fluorescein angiography.
Results: On correlation analysis, it was found that there is significant relationship between Serum Uric Acid and fundus grading of diabetic retinopathy as r=.310 and p <0.016. On regression analysis, the model summary states that 9.6% variation can be explained by serum uric acid on fundus grade as R square =.096 with P=.016 and hence regression model is significant.

Keywords: serum uric acid, diabetic retinopathy

Introduction

Type 2 diabetes mellitus (DM) is an epidemic disorder and has developed as an important public health challenge all over the world [1-3]. Diabetes mellitus is a systemic disease in which blood glucose levels become persistently and often severely raised either because insulin is not released from the pancreatic islet cells (type 1 diabetes), or because the insulin that is secreted is, for a various reasons, less than normally efficient (type 2 diabetes). Because of chronic hyperglycemia, many people develop severe damage to various organs and tissues. Most commonly affected are the kidneys, the heart, the peripheral nervous system, great vessels, and also the retina [4]. The frequency of type 2 diabetes mellitus (T2DM) is increasing rapidly. T2DM is a serious disease affecting the patient's lifestyle and has become a health problem all over the world [5]. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus in people between age 36-69 years and can result to acquired blindness [6]. The incidence of DR in population-based data vary from 10 to 55% and in clinic-based data vary from 11 to 65% [7]. Around 28.5% of blindness is accredited to DR in subjects aged 40 years and older [8]. Diabetic retinopathy remains a main cause of loss of sight among the 3rd-7th decade. As of 2010, diabetic retinopathy affected over 100 million patients all over the world and is expected to rise to more than 190 million by 2030 [9]. Diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) are the main sight-threatening complication of diabetes. Diabetic ischemic maculopathy describes retinal microvascular degeneration in the macular region which can lead to the loss of central visual acuity. All these complication are associated with poor glycemic control and prolonged disease duration. The retina is the source of free radical production in T2DM and the levels as well as the types of oxidative stress products which cause the severity of retinopathy. The serum level of 8-hydroxy-2' deoxyguanosine(8-OHdG) in DR patients is significantly raised as compared to that in patients with diabetes but without retinopathy (NDR) [10]. Uric acid level is the main cause of diabetic microvascular diseases. Uric acid directly exerts pro-inflammatory effects on vascular smooth muscle cells (VSMCs) [11]. Hyperuricemia is caused by the absorption of large amounts of purines [12]. Uric acid production is accompanied by the generation of reactive oxygen species [13]. Serum uric acid can also lead to the endothelial dysfunction by inhibiting the bioavailability of nitric oxide (NO) and the progression of which may be the cause of vascular lesions and even death [14]. Vascular endothelial growth factor (VEGF) is suggested the main factor of the development of both proliferative DR and DME by changing the retinal capillary permeability by increasing the phosphorylation of proteins involved with tight-junctions like zonula occludens [15].

It seemed that uric acid reduces the VEGF. And also, the uric acid is a mediator of inflammation, endothelial dysfunction and vascular diseases. DR is considered as complex range of vasodegenerative lesions within the retinal microvascular bed such as thickening of capillary basement membranes, pericyte and vascular smooth muscle cell (VSMC) dropout, and capillary occlusion and microaneurysms and acellularity [15]. Vitreous uric acid and glucose concentrations were higher in proliferative as compared to non-proliferative DR. UA production in the vitreous is thought to be involved in the pathogenesis and progression of DR.

Material and methods-The present prospective observational study was conducted in department of Ophthalmology at Chattrapati Shivaji Subharti hospital from December 2019 to November 2020. Patients were enrolled in the study after obtaining written informed consent and approval from Institutional Ethical committee. All participants had a test of visual acuity, intra ocular pressure and complete ocular examination including fundus examination with slit lamp biomicroscope using a 90-diopter lens after dilatation of pupils using 1% tropicamide eyedrops. The diabetic patients were assigned to one of the following groups based on presence and severity of retinopathy with the help of fundus photographs and/or fundus fluorescein angiography.

1. Diabetic patients with no retinopathy.
2. Mild Non-Proliferative Diabetic Retinopathy (NPDR).
3. Moderate NPDR.
4. Severe NPDR and
5. Proliferative Diabetic Retinopathy (PDR).

The eye with worse retinopathy was chosen for inclusion in the study examinations. If both eyes have equal retinopathy, the right eye was assigned to the study.

Inclusion criteria

All patients with Type 2 Diabetes Mellitus.

Exclusion criteria

1. History of chronic alcohol intake,
2. Smoking,
3. Intake of hepatotoxic medications within past six months,
4. Pre-existing hepatobiliary abnormalities or chronic liver disease.
5. Patients with pre-existing ocular diseases like glaucoma, high myopia, previous ocular surgery or photocoagulation will be excluded from the study.
6. Patients with hypertension (>160/90 mmHg), anaemia or other systemic diseases like nephropathy which can accelerate the progression of DR will also be excluded from the study.

Statistical analysis

Statistical analysis is performed using IBM, SPSS Statistics version 25 (IBM Corp., New York, NY). Descriptive data is expressed as mean ± standard deviation unless otherwise stated. Continuous variables are compared using t-tests. A one-way analysis of variance (ANOVA) is used to compare differences between the means of independent groups like best corrected vision (BCVA), intraocular pressure (IOP) and total serum uric acid (within group comparisons). P-value less than 0.05 is considered statistically significant. A correlation analysis is performed to study the relationship between serum uric acid and stage of diabetic retinopathy. Pearson correlation coefficient, $p<0.05$ is considered statistically significant. A multiple regression model is applied to observe the impact of serum uric acid levels on the severity of diabetic retinopathy.

Results

Table 1: Age distribution among patients

Age in years	Frequency	Percent
31-40	4	6
41-50	16	27
51-60	27	45
61-70	6	10
71-80	7	12
Total	60	100

The highest proportion i.e. 45% of the patients pertain to age between 51-60. While there is only 6 % of patients from 31-40 age group. Around 27% of the patients are of age between 41-50, and the rest 10% of the patients lies under the age group 61-70, and 12% of patients between 71-80. The mean age of patients was 57.83 and the p value is.000 which is less than P<.05 means it is statistically significant

Table 2: Fundus grading among patients

Fundus grading	Frequency	Percent
Mild NPDR	19	32
Moderate NPDR	12	20
Severe NPDR	8	13
PDR	16	27
No DR	5	8
Total	60	100

32% of the patients had Mild NPDR,20% of the patients had Moderate NPDR,13% of the patients had severe NPDR,27% of the patients had PDR and8% of the patients had No DR. The mean of fundus grading in diabetic retinopathy is 2.60 and p is.00 which is p<.05. It means that it is statistically significant.

Table 3: Distribution of visual acuity among patients

Visual Acuity	Frequency	Percent
0.1-0.6	28	47
0.61-1.2	19	33
More than 1.2	12	20
Total	60	100

47% of the patients had visual acuity between 0.1-0.6 log MAR units, 33% of the patients had visual acuity between 0.61-1.2 log MAR units and 20% of the patients had visual acuity of more than 1.21 log MAR units.

The mean visual acuity is.947 and the p value is.00 which p<.05. It shows that it is statistically significant.

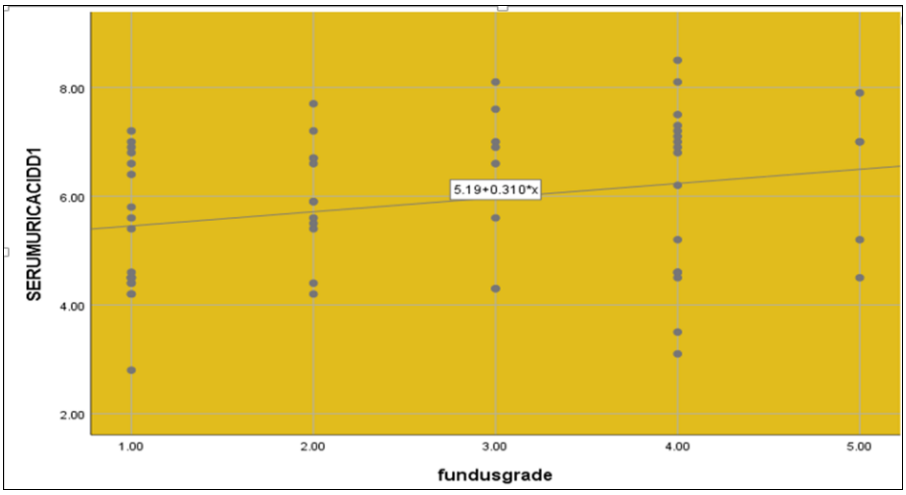
Table 4: Serum uric acid levels among patients

Serum uric acid	Frequency	Percent
Below 5.5	22	37
5.5 or above 5.5	38	63
Total	60	100

There were two categories below and above 5.5 and it has been found that 36% lies below 5.5 level and 63.33% had above 5.5 uric acid level. The mean serum uric acid is 5.87 and p is.00 which is p<.05. It shows that it is statistically significant.

Table 5: Correlational analysis between Serum uric acid levels and Diabetic Retinopathy Fundus gradings.

URIC ACID - diabetic retinopathy fundus grading correlation	Pearson's correlation coefficient (r)	P value
Day1	.310	.016



Graph 1: Correlational analysis between Serum uric acid levels and Diabetic Retinopathy Fundus gradings.

Above table and graph exhibits Pearson's correlation coefficient (r) and Significance (P-value) between Serum Uric Acid and fundus grading, there is a weak positive significant correlation between serum Uric acid and fundus grade as r=.310, P<.016.

Discussion

Diabetes is a public health problem throughout the world and there is no doubt that the situation is more alarming in developing countries which are under grip of the diabetes epidemic. A study by Ramachandran *et al.* [16] found that diabetes develops at a younger age in Asians and consequently, morbidity, mortality and complications occur at a younger age in these people.

In this study, the mean age of patients was 57.83. Jong Jer lee *et al.* [17] in their study the mean age of enrolled patients was 61.9 ±10.1 years (Range 31-87).

Jianfei Xia *et al.* [18] In their study the mean age was 56.20 ± 6.22 years similar to this study. Kiani J *et al.* [19] in their study the mean age of the patients in the case group was 54.6±6.9 and in the control group was 55.8±5.8 years (p=0.389).Chen D *et al.* [20] in their study total number of patients were divided into 3 groups among which NDR group the age was 49.2 ± 8.5, in group NPDR the age was 52.1 ± 13.1 and in group PDR age was 53.5 ± 10.1.Hou L *et al.* [21] in their study included 389 patients with type 2 DM (238 men [61.2%] and 151 women [38.8%]; mean age, 57.93 11.41 years.

Males were slightly more than females in our study. Jong Jer lee *et al.* [17] revealed the similar finding. Jianfei Xia *et al* [18] too had males in majority. Similarly Chen D *et al.* [20] in their study males were comparatively more than the females. Hou L *et al.* [21] also concluded similar finding.

In the present study, it was found that there was a weakly positive significant relationship between Serum Uric Acid and diabetic retinopathy.

Hirohito Kuwata *et al.* [22] in their study concluded that the higher SUA levels were associated with increased risk of developing DR in male patients with type 2 diabetes, but not in female patients. Navin S *et al.* [23] in their study also concluded that increasing levels of serum uric acid were as observed in the group C-DR (diabetics with retinopathy)as compared to those to in the healthy controls and the group B-DM (diabetics without retinopathy). Somlak Chuengsamarn [24] also showed that diabetic retinopathy was significantly correlated with increase of uric acid level. Jong Jer lee *et al.* [17] concluded that that in patients with increase in severity of DR positively associated with SUA (6.47 vs. 5.87 mg/dl, p< 0.001) than did those without change in DR stage.Jianfei Xia *et al* [18] concluded that there is a significant elevation in levels of uric acid (70.55 ± 3.97 mg/L versus 53.81 ± 2.36 mg/L, $P < 0.001$) with diabetic retinopathy compared to diabetes mellitus. Poonam Agrawal [25] in their study divided the patients in 3 groups**.** In group-I, DM patients without retinopathy, DM patients with retinopathy (group-II) and 23 age and sex matched healthy controls (group-III). There was a significant association between serum UA levels and HbA1C (r=-0.45, P=0.05); this association was borderline significant in group-II (r=-0.45, P=0.05) and not statistically significant in group-III (R=-0.46,P=0.09).Ching chao liang *et al.* [26] in their study concluded that there was a higher concentration of serum uric acid in the patients with DR. Avci *et al.* [27] concluded that the mean uric acid level was 3.85 ± 0.91 mg/ dl in the control group and 5.15 ± 1.12 mg/dl in the DR group (p<0.001).The higher serum uric levels may aggravate the progression of Diabetic Retinopathy.

The present study had certain limitations such as absence of a control group to compare the results and the sample size is small. Furthermore, prospective studies with large samples are required to better assess the effects of uric acid on DR.

Conclusion

The patients with diabetic retinopathy had high normal uric acid levels. High SUA levels may be useful for predicting the future risk of developing DR. This study demonstrated a direct relationship between uric acid levels, which could be used to predict the onset of diabetic retinopathy. A large community based, prospective study in the Indian population is needed, to verify the findings.

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