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Original Research Article

Association of serum uric acid in type II diabetes mellitus patients with and without diabetic retinopathy: a case control study

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ABSTRACT

Background: The objective of the study was to assess the association between serum uric acid levels and diabetic retinopathy.
Methods: An analytical case-control study was planned in which a total of 200 diabetic patients aged 40 to 65 years were enrolled divided into 2 groups, 100 diabetic patients with retinopathy and 100 diabetic patients without retinopathy. Both the groups of patients underwent complete ocular examination including assessment of best visual acuity, intraocular pressure, diabetic profile and uric acid assessment.
Results: Prevalence of hyperuricemia was 41% in cases as compared to 19% in controls, thus depicting a significant difference between two groups. Uric acid levels of mild and moderate NPDR cases were significantly lower than that of cases with severe/very severe non-proliferative diabetic retinopathy (NPDR) while proliferative diabetic retinopathy (PDR) cases had higher mean value as compared to all the NPDR types.
Conclusions: The findings of the study suggest that diabetic retinopathy is marked by an increase in uric acid levels and hyperuricemia.

Keywords: Diabetic retinopathy, Uric acid, Hyperuricemia, Diabetic profile, Intraocular pressure

INTRODUCTION

Diabetic retinopathy (DR) is a leading contributor to vision impairment and eye-related health issues, posing a substantial challenge to both public health systems and economic resources.[1] Persistent high blood sugar levels and other metabolic disturbances associated with diabetes can significantly damage multiple organs, resulting in complications such as retinopathy, nephropathy, and neuropathy.[2]

DR is a major eye complication of diabetes. Globally, about 22.27% of individuals with diabetes develop DR and 6.17**%** progress to vision-threatening DR (VTDR).[3,4] VTDR is the leading cause of visual impairment among working-age adults, highlighting DR's status as a principal global health concern.[5]

Uric acid (UA) is the end product of purine metabolism in humans and is widely recognized as the primary marker for gout. Clinical guidelines recommend defining hyperuricemia at a UA concentration of 6 mg/dl, which also serves as the minimum target for UA-lowering therapy in gout patients. [4] Beyond its role in gout, elevated UA has been linked to an increased risk of diabetes as well as diabetic complications, including diabetic peripheral neuropathy and diabetic nephropathy.[5-7]

UA has been demonstrated to promote an inflammatory response to release inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), and a recent meta-analysis showed that IL-6 was associated with the incidence of DR.[8]

In diabetes, chronic hyperglycaemia and mitochondrial dysfunction contribute to increased reactive oxygen species (ROS) production, further exacerbating oxidative stress. This oxidative burden adversely affects various aspects of diabetes, including impaired beta-cell function and insulin resistance, leading to disrupted glucose regulation.

Additionally, oxidative stress-induced damage to blood vessels and impaired endothelial function contribute to the development of diabetic vascular complications such as retinopathy, nephropathy, and cardiovascular diseases.[9]

Objectives

The objectives of the study were: to study the association of increased uric acid level with DR, and to evaluate the serum UA levels and glycaemic status of diabetic retinopathy cases in proliferative and non-proliferative phases.

METHODS

To precisely evaluate the link between DR and serum or plasma UA levels—and to investigate UA's potential as a predictive biomarker for DR in diabetic individuals—we designed this study with the goal of identifying whether elevated UA is significantly associated with DR.

Type of study

A hospital-based analytical case control study.

Selection of cases

Cases were selected from outdoor patients in the Department of Ophthalmology at RAMA Medical College, Kanpur, over a period of 18 months. The study included a total of 200 patients, divided into two groups: group A (cases) comprised 100 patients with type 2 diabetes mellitus (T2DM) showing diabetic retinopathy changes, while group B (controls) included 100 T2DM patients without retinopathy.

Inclusion criteria (cases)

Inclusion criteria for cases were patients of either gender, aged 40–65 years, diagnosed with T2DM and presenting with diabetic retinopathy in the outpatient department.

Exclusion criteria (cases)

Exclusion criteria included pregnant patients, those on xanthine oxidase inhibitors, uricosuric drugs, thiazides, salicylates, oral contraceptives, antitubercular treatment, cytotoxic drugs, and those with conditions such as lymphoma, leukemia, nephrotic syndrome, organ transplant history, or prior laser therapy.

Selection of controls

Controls were selected from amongst type 2 diabetes mellitus patients attending outpatient department fulfilling the same eligibility criteria as for cases but without diabetic retinopathy

Methodology

Patients were categorized into two groups: Group 1 (T2DM with diabetic retinopathy) and Group 2 (T2DM without diabetic retinopathy). Duration of diabetes was calculated from the age at diagnosis to the age at examination. All participants underwent a detailed ophthalmic evaluation including visual acuity assessment using Snellen's chart, intraocular pressure measurement by non-contact tonometry and Goldmann applanation tonometry, pachymetry, slit-lamp examination, and fundus evaluation using slit-lamp biomicroscopy with +90D lens, direct and indirect ophthalmoscopy. Fundus photography and optical coherence tomography (OCT) were performed where required. Vision-threatening diabetic retinopathy (VTDR) was defined as severe NPDR, PDR, or clinically significant macular edema.

Venous blood samples were collected for analysis of serum uric acid (uricase method), HbA1c, fasting and random blood glucose, and lipid profile.

Diagnosis of diabetes mellitus was based on standard criteria: fasting plasma glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL with symptoms, HbA1c ≥6.5%, or 2-hour plasma glucose ≥200 mg/dL after oral glucose tolerance test

Statistical analysis

Data were entered in Microsoft Excel and analyzed using statistical package for the social sciences (SPSS) version 25.0. Quantitative variables were expressed as mean±standard deviation, and qualitative variables as frequencies and percentages. Student's t-test and Chi-square test were used as appropriate. A p value <0.05 was considered statistically significant.

RESULTS

A total of 200 patients were included in the study, comprising 100 cases with diabetic retinopathy and 100 controls without diabetic retinopathy. The mean age of cases and controls was 54.95±5.44 years and 56.31±8.15 years respectively, with no statistically significant difference between the groups. The ages of patients ranged from 40 to 65 years. There was no statistically significant

difference between two groups for mean age (p=0.167). Though the majority of both the cases and controls were males, yet percentage of males was significantly lower in cases (58%) as compared to that in controls (72%) (p<0.001) (Table 2, and Figures 1a and b). Mean UA levels were also significantly higher in cases (6.62±1.72 mg/dl) as compared to that in controls (6.02±1.15 mg/dl) (p=0.004).

Percentage of those with raised uric acid levels was also significantly higher in cases as compared to that in controls (41% versus 19%; p=0.001) (Table 2 and Figures 2a and b). As compared to mild NPDR, moderate, severe and very severe NPDR and PDR patients had significantly higher uric acid levels, thereby showing a significant incremental trend with increasing severity (p<0.001) (Table 3 and Figure 3).

Table 1: Comparison of age and sex profile of cases and controls.

S. no.	Characteristics	Cases (n=100)	Controls (n=100)	Statistical significance
1	Mean age±SD in years	54.95±5.44 (40-65)	56.31±8.15 (40-65)	t=1.388; p=0.167
2	Sex			
	Male	58	72	
	Female	42	28	x^2 =4.308; p<0.001

Table 2: Comparison of serum uric acid levels between cases and controls.

S. no.	Characteristic	Cases (n=100)		Controls (n=100)		Statistical significance	
		Mean	**SD**	**Mean**	**SD**	**'t'**	**'p'**
1	Uric acid (mg/dl)	6.62	1.72	6.02	1.15	2.89	0.004
2	Uric acid status						
	Raised	41		19		χ^2=11.524; p=0.001	
	Normal	59		81			

Table 3: Comparison of uric acid levels in different severity categories and types of retinopathy.

S. no.	Severity	Cases (n=100)	Mean SUA	±SD (mg/dl)
1	Mild NPDR	43	5.98	1.30
2	Moderate NPDR	37	6.56	1.40
3	Severe NPDR	9	7.70	1.86
4	Very severe NPDR	7	7.64	1.82
5	PDR	4	9.87	2.95
Statistical significance (ANOVA)			F=8.618; p<0.001	

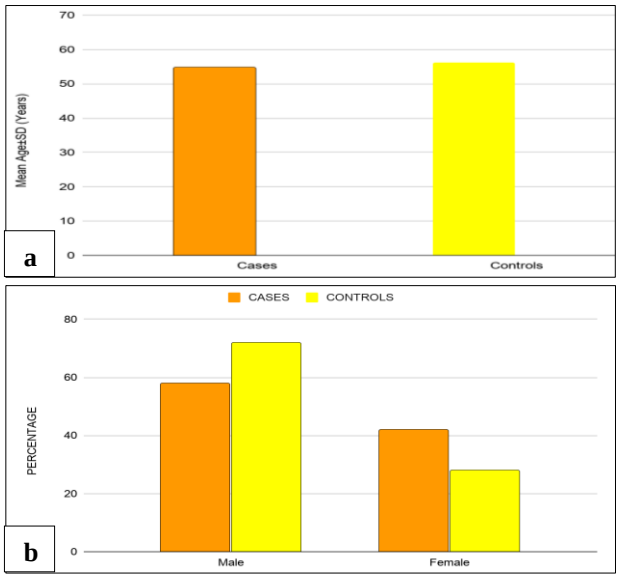

Figure 1: (a) Comparison of mean age of cases and controls, and (b) comparison of sex profile of cases and controls.

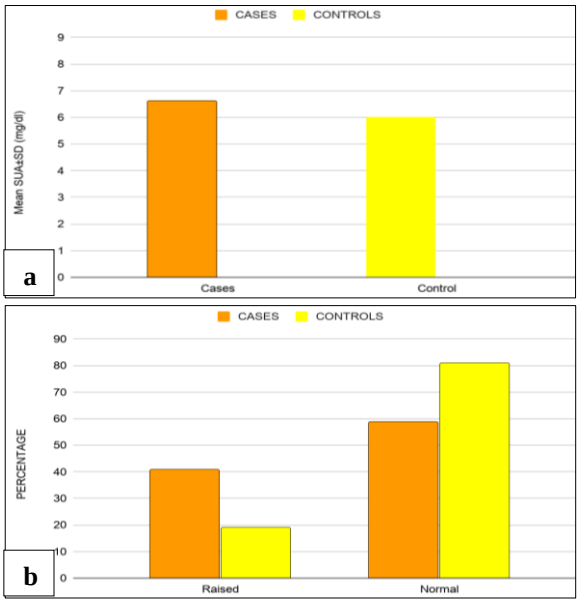

Figure 2: (a) Comparison of (a) SUA and (b) UA status between cases and controls.

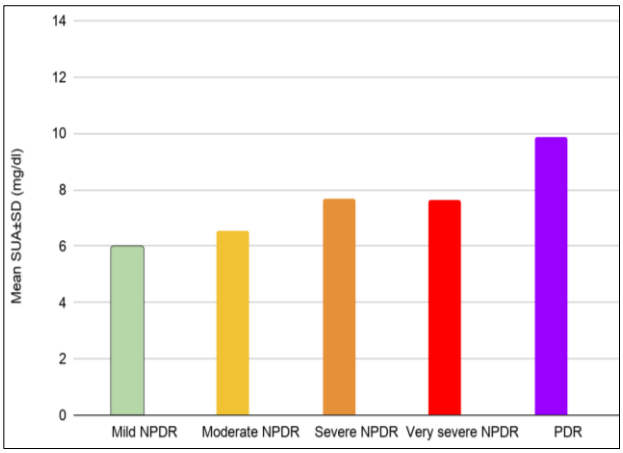

Figure 3: Comparison of uric acid levels in different severity categories and types of retinopathy.

DISCUSSION

The prevalence of diabetes is increasing all over the world; the aim of the study was to study the relationship between serum uric acid and diabetic retinopathy in T2DM and to correlate the grades of DR with serum UA.

In the present study, mean age of cases and controls was 54.95±5.44 and 56.31±8.15 years respectively. Majority of cases (58%) as well as controls (72%) were males, though there was no significant difference between two groups for age but proportion of females was significantly higher in cases as compared to that in controls.

In the present study, mean serum uric acid levels were found to be significantly higher in cases as compared to that in controls. Moreover, prevalence of hyperuricemia was also significantly higher in cases (41%) than in controls (19%). On reviewing the literature, we find a mixed picture regarding this association. Premraj et al in their study found that elevated SUA levels had an association with diabetic retinopathy.[10] Chen et al too observed a significant incremental trend in SUA levels with occurrence and severity of DR.[11]

Guo et al conducted a metanalysis and found that twenty-one studies involving 4,340 patients with DR and 8,595 controls (8,029 controls with diabetes and 566 healthy participants) were included in this meta-analysis and found that patients with DR had significantly higher UA levels than those in the controls with diabetes (WMD=36.28; 95% CI: 15.68, 56.89; p<0.001) and healthy participants (WMD=70.80; 95% CI: 19.85, 121.75; p=0.006).[12]

In contrast, a study conducted by Xia et al found that for patients with T2DM, higher uric acid levels are associated with higher UAE, lower eGFR, and higher prevalence of diabetic neuropathy, but not DR.[13]

Another study by Guo et al provides evidence that UA levels are higher in patients with DR than those in the controls, but this difference is not statistically significant in the early phases. UA might be a potential biomarker for identifying disease severity in patients with DR, rather than predicting the onset of DR among patients with diabetes.[12]

In the present study, UA levels of mild and moderate NPDR cases were significantly lower than that of cases with severe/very severe NPDR while PDR cases had higher mean value as compared to all the NPDR types. Thus, trends in the present study show that progression of diabetic retinopathy was marked by a linear incremental trend of SUA levels.

Rivera-De-la-Parra et al in their study found UA levels to be helpful in differentiating among severe/worse stages of DR and non-severe/mild stages of DR.[14] They derived a cut-off value ≥7.8 mg/dl to be associated with nearly three times higher risk of severe/worse stages of DR. In the present study, we also found mean SUA levels of 7.70 mg/dl or above to be associated with severe and very-severe NDPR and DPR while those with mild to moderate NDPR had mean SUA levels 6.56 mg/dl or lower. Pai et al also observed a linear incremental trend of SUA levels between NPDR to PDR progression and found that DR and its progression had a relationship with SUA levels.[15] Chen et al also observed mean SUA levels in DPR patients to be 1.06 times higher as compared to NPDR patients, thereby showing that increased UA levels were associated with increased severity of DR as also observed in the present study.[11]

Limitations

This study had a relatively small sample size, particularly in advanced stages of diabetic retinopathy. The study did not exclude all potential confounding factors such as other diabetic complications. Additionally, renal and liver function parameters were not assessed, which may have influenced SUA levels.

CONCLUSION

A significant association between elevated SUA levels and the progression of DR in T2DM. We observed significantly higher mean SUA levels in patients with DR compared to controls, with a marked prevalence of hyperuricemia (41% versus 19%). Our study's incremental trend of rising SUA with DR stage supports SUA's potential as a biomarker of DR severity, rather than simply an early predictor. Elevated uric acid may contribute to retinal microvascular damage via oxidative stress, inflammation, and endothelial dysfunction—mechanisms corroborated by both cross-sectional and experimental studies.

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