Journal of Global Diabetes & Clinical Metabolism

Research Article

# An Independent Risk Factor for Diabetic Retinopathy: Uric Acid

This article was published in the following Scient Open Access Journal:
Journal of Global Diabetes & Clinical Metabolism
**Received** November 08, 2017; **Accepted** November 24, 2017; **Published** November 30, 2017

**Avcı Deniz[1]*, Karahan Samet[1], Cetinkaya Ali[1], Karagoz Hatice[1], Esmeray Kubra[1], Bugday Irfan[1], Erden Abdulsamet[2], Bulut Kadir[1] and Ortakoyluoglu Adile Irfan[1]**

*[1]Kayseri Training and Research Hospital, Internal Medicine, Kayseri, Turkey*

*[2]Hacettepe University Hospital, Division of Rheumatology, Department of Internal Medicine, Ankara, Turkey*

## Abstract

**Objective**: Diabetic retinopathy is the leading cause of vision loss in working-age. Blindness caused by Diabetes Mellitus currently affects approximately 150 million people worldwide. It is revealed that uric acid can directly exert pro-inflammatory effects on vascular smooth muscle cells (VSMCs). This study aims to analyse the uric acid levels on DR regarding its pro-inflammatory effects on VSMCs.

**Materials and Methods**: Patients with Diabetes mellitus who undergone to ophthalmic examination as patients of Diabetes Clinic of Kayseri Training and Research Hospital during the period of February 2012-November 2015 were prospectively examined.

Patients who had conditions that may affect uric acid levels such as chronic renal failure, medications and infectious diseases were excluded. Remaining patients with DM were divided into two groups; 73 of them had DR and 90 patients' eye examinations were normal. The uric acid levels of these two groups were compared.

**Results**: There was no significant difference in terms of age and gender between the groups (p=0.066 and p=0.290, respectively). 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).

**Conclusion:** It is becoming clarified that, uric acid has other roles in the organism apart being an etiologic factor in gout, nephrolithiasis, renal and cardiovascular diseases. In light of evidence about the effects of uric acid as a mediator of endothelial dysfunction, inflammation and vascular disease and serious implications of uric acid to VSMCs and PDGF, we it is concluded that higher serum uric acid levels may worsen the progression of Diabetic Retinopathy. High serum uric acid levels can be considered as an independent risk factor for Diabetic Retinopathy.

**Conclusion:** increased serum uric acid levels can be considered as an independent risk factor for Diabetic Retinopathy.

**Keywords**: Diabetes mellitus, diabetic retinopathy, uric acid, vascular endothelial growth factor, vascular smooth muscle cell

## Introduction

Diabetic retinopathy (DR) is one of the leading causes of vision loss in working-age patients in the world. Blindness caused by Diabetes Mellitus (DM) currently affects approximately 150 million people worldwide, and according to estimates of World Health Organization it will double in 2025 [1]. The prevalence of diabetic macular edema (DME) in diabetics of 15-year duration is approximately 20% in patients with Type 1 DM and 25% in patients with Type II DM that are on treatment and 2% of them become blind over the years [2-4].

In patients with DM, the main cause of vision impairment is DME [3]. DME may develop at any stage of proliferative or non-proliferative DR. Based on angiographic findings, there are two types of macular edema: focal or diffuse. Diabetic maculopathy caused by leaking microaneurysms is classified as focal, while leakage at the level of the capillary beds leads to diffuse. On the other hand there are two types of macular edema: ischemic or non-ischemic [5].

Vascular endothelial growth factor (VEGF) is suggested as an important factor in the development of both proliferative DR and DME, altering retinal capillary permeability by increasing the phosphorylation of proteins involved with tight-junctions such as zonula occludents [6]. It is suggested that uric acid reduces VEGF. On the other hand uric acid is a mediator of endothelial dysfunction, inflammation and vascular disease. Many conflicting studies discussed about uric acid are a cause or a result of some diseases

***Corresponding author:** Deniz AVCI, MD, Department of Internal Medicine, Kayseri Training and Research Hospital, 38010 Kayseri, Turkey, Email: denav38@gmail.com

such as hypertension and renal failure. One of the difficulties of implicating uric acid in the pathogenesis of hypertension and kidney disease is that most of the traditional risk factors are also associated with elevated uric acid [7-9].

DR is characterized by a complex array of vasodegenerative lesions within the retinal microvascular bed; such as thickening of capillary basement membranes, pericyte and vascular smooth muscle cell (VSMC) dropout, microaneurysms, and capillary occlusion and acellularity [9]. Kanellis, et al. revealed that uric acid can also directly exert proinflammatory effects on VSMCs [10] and because of the proinflammatory effects of uric acid on VSMCs we designed this study and aimed to analyze the effect of high uric acid levels on DR. Although recent literatures have shown the association between DR and serum uric acid levels, the clear pathway has not been described. Furthermore, the role of uric acid in the course of DR is largely unknown.

In the present study, we aimed to show the elevation of serum uric acid levels in DR patients.

## Materials and Methods

This prospective research was performed with the patients admitted to the Diabetes Mellitus polyclinic of Kayseri Training and Research Hospital between the dates of February 2012-November 2015. The patients were sent to fundoscopic examination and blood examination. Parameters such as height, weight and waist circumference were recorded. Blood examinations were performed in the same center by the same device.

Since the uricosuric drugs (allopurinol, probenecid), renal failure, purine metabolism defect, atherosclerotic heart disease, hypothyroidism and infections could affect the blood uric acid levels; therefore the patients in with such conditions were excluded from the study. If the date of fundoscopic examination was not certain, patients' history was unknown, diabetes duration was unknown or if there is no suitable laboratory finding the patients were excluded. After these exclusion criteria patients were divided into two groups: The first group including the patients who had DR was called DR Group, and the second group including the patients with normal findings of eye examination was called as Control Group. After these exclusions there were 73 patients in the DR Group and 90 patients in the Control Group.

## Statistical Analysis

Continuous variables were tested for normal distribution by the Shapiro-Wilk test and histograms. We reported continuous data as mean and standard deviation or median and percentiles where suitable. We compared normally distributed continuous variables using student t-test and the continuous variables which are not normally distributed continuous variables by using Mann Whitney U test between the groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation analyses are used in analysis of relation between DR and control DM groups. The receiver operating characteristic (ROC) curves were used to evaluate the performance of variables to indicate the presence of DR in diabetes mellitus patients. Univariate binary logistic regression analyses (adjusted for DM duration) were used to examine the risk factors to influence the development of Diabetic retinopathy. $p<0.05$ was considered as significant. For statistical analysis, the statistical package for the social sciences (SPSS version 22) was used.

## Results

The excluding criteria mentioned above were applied to the patients with DM admitted to Kayseri Training and Research Hospital. Finally, available 73 patients with DR and 90 patients with normal fundoscopic examination were included. On both sides there were Diabetes Mellitus. Regarding to gender factor, there was no significant difference between DR and control groups ($p=0.290$). The mean age was 56.74 ± 9.54 years in the control group, while it was 58.26 ± 8.70 years in DR group. The difference was not statistically significant ($p<0.066$). The median DM duration of DR group was higher than the control group. It was 6.0 (2.0-11.0) years in the control group and 13.0 (7.0-20.0) years in DR group. The difference was statistically significant ($p<0.001$). Although the mean HBA1c value was slightly higher in the study group when compared to the control group (7.84 ± 2.93 versus 8.59 ± 2.67, respectively), it did not reach to a statistical significance ($p=0.610$).

The mean serum uric acid level was 3.85 ± 0.91 mg/dl in the control group whereas it was 5.15 ± 1.12 mg/dl in the DR group. The levels were found to be statistically significant ($p<0.001$) (Figure 1).

There was a weak, positive and significant correlation between DM duration and serum uric acid levels ((r=0.331, p=0.001). The correlation between BUN (Blood Urea Nitrogen) and uric acid was also weak, positive and statistically significant (r=0.255, p=0.001). Similarly, the correlation between serum creatinin and serum uric acid was weak, positive and statistically significant (r=0.249, p=0.001).

The receiver operating characteristic (ROC) curves were used to evaluate the performance of variables to indicate the presence of DR in diabetes mellitus patients. AUC value of uric acid was 0.828, CI: 0.532-0.855, $p<0.001$. AUC of BUN was 0.764, CI: 0.561-0.857, $p<0.001$. AUC of diabetes mellitus duration was 0.709, CI: 0.561-0.857, p=0.012.

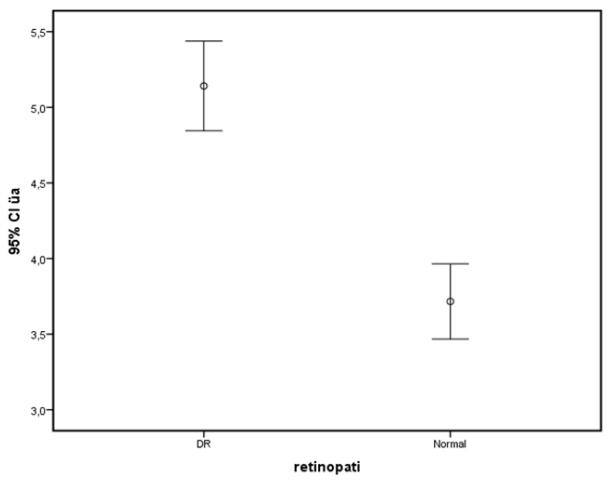


**Figure 1:** Uric acid levels are higher in DR group.

Univariate binary logistic regression analyses were performed to identify the effects of the parameters on DR. Serum uric acid levels were found to be an independent risk factor for DR with an OR of 3.610 with 95% CI of (2.360-5.520) (p<0.001). On the other hand, serum BUN levels were significant with an OR of with 95% CI of (1.198 1.095-1.311) (p<0.001). When the variables performing by the univariate binary regression analyses adjusted to DM duration were calculated, serum uric acid levels were remained significant with an adjusted OR of 4.678 (2,337-9,362), p<0.001. Serum BUN levels were also remained significant; OR: 1.184, CI: 1.043-1.343, p=0.009.

Some features and laboratory findings of the patients were summarized in Tables 1, 2 and 3.

We performed logistic regression to have the adjusted values for the same parameters because of the significant difference in the DM duration values of the two groups. In this condition, uric acid was still had a strong significance (p<0.001) (OR: 4.678, CI: 2.337-9.362).

## Discussion

The pathophysiology of DR is quite often being studied as it has been the most important cause of non-congenital vision loss. The primary findings in this study were demonstrating elevation of serum uric acid levels during the period of DR diagnose and the relation between serum uric acid levels and the pathogenesis of DR.

In our study, data from 73 diabetic patients with DR and 90 diabetic patients with normal ophthalmologic examination were

**Table 1.** Comparison of normal diabetes mellitus and diabetics with Diabetic Retinopathy.

| Continious VARİABLES | Referance Values | Total | Diabetes Mellitus Groups | | *p* value |
|---|---|---|---|---|---|
| | | | NON RETİNOPATHİC DİABETİCS (n=90) | DİABETİC RETİNOPATHY (n=73) | |
| Age (years)* | | 56.74 ± 9.54 | 55.50 ± 10.05 | 58.26 ± 8.70 | *p*=0.066 |
| DM Duration (years)# | | 10.0 | 6.0 (2.0-11) | 13.0 (7.0-20.0) | *p*<0.001 |
| BMI (kg/m$^2$)# | | 31.80 (28.79-34.04) | 29.90 (27.33-34.42) | 32.39 (29.75-33.89) | *p*=0.229 |
| Glucose (fasting) (mg/dl) | (70-110) | 196.0 (145.0-276.0) | 197.0 (144.25-275.25) | 195.0 (143.0-281.0) | *p*=0.701 |
| BUN (mg/dl)# | (7-20) | 14.81 (12.0-17.0) | 13.0 (11.0-16.0) | 16.0 (13.50-19.0) | *p*<0.001 |
| Creatinin (mg/dl)# | (0.6-1.3) | 0.70 (0.60-0.80) | 0.70 (0.60-0.80) | 0.70 (0.60-0.815) | *p*=0.122 |
| AST (U/L)# | (<35) | 19.0(16.0-24.0) | 19.0 (16.0-23.0) | 19.0 (17.0-24.75) | *p*=0.468 |
| ALT (U/L)# | (<35) | 21.0 (16.0-27.0) | 20.0 (16.50-27.50) | 21.0 (14.75-26.25) | *p*=0.507 |
| Total cholesterol (mg/dl)* | (0-200) | 212.30 ± 47.38 | 208.71 ± 44.60 | 216.65 ± 50.25 | *p*=0.298 |
| Uric Acid (mg/dl)* | (2.6-7.2) | 4.45 ± 1.19 | 3.85 ± 0.91 | 5.15 ± 1.12 | *p*<0.001 |
| HBA1c* | (<6.5) | 8.17 ± 2,81 | 7,84 ± 8.95 | 8.59 ± 2.63 | P=0.091 |
| Categoric VARİABLES | | n(162) | n(90) | n(73) | |
| Sex M/F (%) | | 30.1% /69.9% | 33.3% / 66.7% | 26.0% / 74.0% | *P*=0.290 |

BMI: Body Mass Index, BUN: blood urea Nitrogen, AST: Aspartate amino transferase, ALT: Alanine amino transferase, M:Male, F: Female

**Table 2:** ROC analysis for Diabetes Mellitus patients to detect Area Under Curves (AUC) of fasting glucose, HBA1c, creatinin, BUN, total cholesterol, uric acid, and ALT due to presence of Diabetic Retinopathy.

| VARIABLE | AUC | 95% CI | *p* VALUE |
|---|---|---|---|
| Uric acid | 0.816 | 0.750-0.883 | *p*<0.001 |
| DM duration | 0.754 | 0.653-0.854 | *p*<0.001 |
| BUN | 0.693 | 0.613-0.773 | *p*<0.001 |
| Creatinin | 0.570 | 0.482-0.658 | *p*=0.125 |
| HBA1c | 0.556 | 0.467-0.645 | *p*=0.222 |
| Total cholesterol | 0.545 | 0.454-0.636 | *p*=0.331 |
| ALT | 0.468 | 0.373-0.564 | *p*=0.508 |

**BUN:** Blood urea nytrogen, **ALT:** alanin amino transferase

**Table 3:** Odds ratios and 95% confidence intervals (CI) from univariate binary logistic regression of the likelihood of DR in Diabetes Mellitus patients.

| VARİABLES | ODDS RATİO | 95% CI | p | ODDS RATİO | 95% CI | p |
|---|---|---|---|---|---|---|
| GENDER | 0.704 | 0.356-1.392 | *P*=0.313 | 1.130 | 0.386-3.307 | p=0.824 |
| AGE | 1.032 | 0.998-1.067 | *p*=0.068 | 1.043 | 0.989-1.101 | *p*=0.122 |
| DM duration | 1.153 | 1.070-1.242 | *p*<0.001 | | | |
| BMI | 1.012 | 0.936-1.096 | *p*=0.760 | 1.031 | 0.940-1.130 | *p*=0.519 |
| Waist circumference | 1.013 | 0.969-1.058 | *p*=0.582 | 1.0007 | 0.958-1.059 | *p*=0.778 |
| CREATİNİN | 0.107 | 0.670-60.987 | *p*=0.107 | 16.241 | 1.067-474364 | *p*=0.105 |
| BUN | 1.198 | 1.095-1.311 | *p*<0.001 | 1.184 | 1.043-1.343 | *p*=0.009 |
| TOTAL CHOLESTEROL | 1.004 | 0.997-1.010 | *p*=0.296 | 1.001 | 0.992-1.011 | *p*=0.833 |
| URİC ACİD | 3.610 | 2.360-5.520 | *p*<0.001 | 4.678 | 2,337-9,362 | *p*<0.001 |
| ALT | 0.994 | 0.964-1.026 | *p*=0.727 | 0.991 | 1.054-1.258 | *p*=0.743 |
| HBA1c | 1.103 | 0.984-01.237 | *p*=0.093 | 1.051 | 0,848-1.1303 | *p*=0.648 |

**BUN:** Blood urea nitrogen, **ALT:** Alanine amino transferase, BMI: Body mass index.

compared each other after applying exclusion criteria. The mean uric acid level was 3.85 ± 0.91mg/dl in the control group whereas it was 5.15 ± 1.12 mg/dl in the DR group. It was statistically significant. Uric acid was found to be an independent risk factor for DR. In our study population, duration of diabetes mellitus was longer in DR group. In terms of gender and age the groups were similar.

The studies on DR pathogenesis and associated conditions become increasingly intensive, including those reporting common pathogenesis with Parkinson disease [11], and association with depression and memory loss [12] or cardiovascular conditions [13] in recent years. In a recent study, Alcubierre et al. reported that vitamin D deficiency is associated with DR [14]. In addition, factors predicting DR have also been evaluated [15-17]. It was reported that increased LRP6 level (intravitreal low-density lipoprotein receptor-related protein 6) in vitreous was correlated with vascular endothelial growth factor in DR [16]. In Chinese population, elevated serum mannose-binding lectin levels were found to be DR [17]. In the last decade, it has become evident that uric acid levels are not only associated with gout disease or chronic renal failure but also associated to many conditions in which inflammation plays a role in the pathogenesis [18,19]. Serum uric acid levels have been studied in diabetic complications. Papanas, et al. observed significantly higher serum uric acid levels in diabetic patients with peripheral neuropathy compared to those without [20].

In a study published in 2007, findings of Mohor, et al. concluded that serum uric acid and ceruloplasmin levels were higher in patients with diabetic retinopathy accompanied by diabetic foot [21]. In a study from China, Yuan Zhi et al. reported that hyperuricemia was associated with retinal arterioles and larger retinal venules regardless of known cardiovascular risk factors [22]. Presumably, retinal vascular injury is related to reduction in local endothelia NO synthesis by uric acid which directly enters to vascular smooth muscles. This induces smooth muscle proliferation. Rao and colleagues have shown that uric acid stimulates VSMC proliferation by increasing platelet-derived growth factor a-chain expression [23] and also Kanellis have confirmed this observation and also reported that uric acid-induced VSMC proliferation is mediated by the activation or induction of extracellular signal-regulated kinase mitogen-activated protein kinases (MAPK) and cyclooxygenase-2 [10,23].

In agreement with literature, serum uric acid levels were found to be higher in diabetic patients with diabetic retinopathy in this study. The receiver operating characteristic (ROC) curves were used to evaluate the performance of variables to indicate the presence of DR in diabetes mellitus patients. AUC value of uric acid was 0.828, $p<0.001$. Due to the fact that renal insufficiency is a condition that could lead to increase serum uric acid levels, we proposed to exclude the patients with impaired renal functions. The highest serum creatinin level was 1.0 mg/dl in all groups. Although the renal functions, represented by BUN and serum creatinin, were in normal ranges, there were weak, positive and significant correlations between serum uric acid and serum creatinin levels and between serum uric acid and serum BUN levels ($p<0.001$ and $p<0.001$). Therefore, the question appears to be; could it be the elevation of serum uric acid levels is due to a subclinical deterioration in renal functions rather than an inflammatory pathway? Is the elevation we found only the effect of an impairment of renal functions? In order to answer these questions, univariate binary logistic regression analyses were performed to determine the risk factors to influence the development of DR. Based on these analyses, it's possible to suggest that uric acid is an independent risk factor in the course of DR [summarized in Table 3].

## Conclusion

Uric acid levels were associated with inflammation of vascular smooth muscles. It may have role in pathogenesis of retinal vascular involvement in DR. With regard to the findings of this study, uric acid levels are significantly higher in patients with DR when compared to those without DR. In the literature, there is no current available information about the effect of lowering uric acid levels on the course Diabetic retinopathy. The following research on this subject may focus this question.

## References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care.* 1998;21(9):1414-1431.
2. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91(12):1464-1474.
3. World Health Organization (www.who.int). Geneva. Diabetes fact sheet number 312. [updated on 2011 Aug]; http://www.who.int/mediacentre/factsheets/fs312/en (Accessed November 2013)
4. Gupta N, Mansoor S, Sharma A, et al. Diabetic Retinopathy and VEGF. *Open Ophthalmology J.2013;7*:4-10.
5. Simo R, Hernandez C. Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. *Diabetologia*. 2008;51(9):1574-1580.
6. Hsu CC, Yin MC, Tian R. Ascorbic acid and uric acid suppress glucose induced fibronectin and vascular endothelial growth factor production in human endothelial cells. *J Diabetes Complications.* 2005;19(2):96-100.
7. Kanbay M, Solak Y, Dogan E, Lanaspa MA, Covic A. Uric Acid in Hypertension and Renal Disease: The Chicken or the Egg? *Blood Purif.* 2010;30:288-295.
8. Kanellis J and Kang DH. Uric Acid as a Mediator of Endothelial Dysfunction, Inflammation, and Vascular Disease. *Semin Nephrol*. 2005;25(1):39-42.
9. Gardiner TA, Archer DB, Curtis TM, Stitt AW. Arteriolar involvement in the microvascular lesions of diabetic retinopathy: implications for pathogenesis. *Microcirculation.* 2007;14(1):25–38.
10. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension.*2003;41(6):1287-1293.
11. Tian T, Li Z, Lu H. Common pathophysiology affecting diabetic retinopathy and Parkinson's disease. *Med Hypotheses*. 2015;85(4):397-398.
12. Rovner BW, Casten RJ, Murchison AP, Ho AC, Henderer J, et al. Depression and Memory Loss in African Americans with Diabetic Retinopathy. *J Am Geriatr Soc*. 2014;27(2):114-118.
13. Raum P, Lamparter J, Ponto KA, et al. Prevalence and Cardiovascular Associations of Diabetic Retinopathy and Maculopathy: Results from the Gutenberg Health Study. 2015;10(6):e0127188.
14. Alcubierre N, Valls J, Rubinat E, et al. Vitamin D Deficiency Is Associated with the Presence and Severity of Diabetic Retinopathy in Type 2 Diabetes Mellitus. *J Diabetes Res*. 2015;2015:374178.
15. 15. Xu L, Zhou B, Li H, et al. Serum Levels of Progranulin Are Closely Associated with Microvascular Complication in Type 2 Diabetes. *Dis Markers*. 2015;2015:357279.
16. Gao X, Ma K, Lu N, Xu Y, Hong T, Peng X. Elevated LRP6 levels correlate with vascular endothelial growth factor in the vitreous of proliferative diabetic retinopathy. *Mol Vis*. 2015;21:665-672.
17. Huang Q, Shang G, Deng H, Liu J, Mei Y, et al. High Mannose-Binding Lectin

Serum Levels Are Associated with Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes. *PLoS One*. 2015;2;10(7):e0130665.

18. Kanbay M, Yilmaz MI, Sonmez A, et al. Serum Uric Acid Level and Endothelial Dysfunction in Patients with Nondiabetic Chronic Kidney Disease . *Am Nephrol*. 2011;33(4):298-304.

19. Yalcin Solak Y, Akilli H, Kayrak M, et al. Uric Acid Level and Erectile Dysfunction in Patients with Coronary Artery Disease. *J Sex Med.* 2014;11(1):165-172.

20. Papanas N, Demetriou M, Katsiki N, et al. Increased serum levels of uric acid are associated with sudomotor dysfunction in subjects with type 2 diabetes mellitus. *Exp Diabetes Res*. 2011;2011:346051.

21. Mohora M, Vîrgolici B, Coman A, et al. Diabetic foot patients with and without retinopathy and plasma oxidative stress. *Rom J Intern Med*. 2007;45(1):51-57.

22. Yuan Y, Ikram MK, Jiang S, et al. Hyperuricemia Accompanied with Changes in the Retinal Microcirculation in a Chinese High-risk Population for Diabetes. *Biomed Environ Sci*. 2011;24:146-54.

23. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. *J Biol Chem*. 1991;266(13):8604-8608.