

Behaviour of serum uric acid and lipid profile in relation to glycemic status in proliferative and non-proliferative diabetic retinopathy

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Abstract

Diabetic retinopathy is emerging as one of the important causes of blindness in both developing and developed countries. High hemoglobin A1c level, high 2-hr blood glucose level, low uric acid level and positivity for proteinuria were found to be significantly associated for the development diabetic retinopathy. The study was done on a total of 75 subjects. They were divided into 3 groups as: Group 1 - 25 subjects of Diabetes mellitus with retinopathy, Group 2 - 25 subjects of Diabetes mellitus without retinopathy & Group 3 - 25 Healthy Normal subjects. 7 cases were diagnosed as Proliferative Diabetic Retinopathy and other 18 cases as Non-Proliferative Diabetic Retinopathy based on fundoscopic examination. Results clearly indicate that there exists a poor glucose homeostasis & lipid derangement as a metabolic consequence in diabetic retinopathy cases. Uric acid levels were significantly less in cases of diabetes mellitus without complications, as compared to normal controls. Uric acid levels showed an increasing trend in retinopathy group. Conclusion: Serum uric acid level plays an important role in the pathogenesis & progression of long term complications associated with diabetes mellitus. Uric acid levels have tendency to decrease before retinopathy complication sets in and tends to increase with the onset of retinopathy. Behaviour of uric acid levels may thus indicate along with co-existence of lipid derangements, the ongoing pathophysiology in diabetes in relation to glycemic control, insulin resistance, onset and progression of complications such as retinopathy and nephropathy.

Key Words: Glycated Hemoglobin, Lipid Profile, Proliferative & Non-proliferative Diabetic Retinopathy, Uric Acid

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Introduction

Diabetic retinopathy is an ocular manifestation of systemic disease which affects up to 80% of all patients who have had diabetes for 10 years or more, which can eventually lead to blindness [1]. Diabetic retinopathy is emerging as one of the important causes of blindness in both developing and developed countries. The World Health Organization has estimated that, the number of adults with diabetes in the world would increase alarmingly: from 135 million in 1995 to 300 million by 2025. Factors already known to be significantly related to occurrence of retinopathy are age of the patient, duration of diabetes, presence of ischaemic heart disease, presence of hypertension, a high fasting capillary glucose level as well as elevated serum levels of urea, creatinine, cholesterol and triglycerides [2]. High hemoglobin A1c level, high 2-hr blood glucose level on the glucose loading test, low uric acid level and positivity for proteinuria were found to be significantly associated for the development diabetic retinopathy [3].

The association of high serum uric acid with insulin resistance has been known since the early part of the 20th century. A prospective follow-up study has shown that high serum uric acid is associated with higher risk of type 2 diabetes independent of obesity, dyslipidemia and hypertension [4]. In fact, hyperuricemia has always been presumed to be a consequence of insulin resistance rather than its precursor [5].

Elevated serum uric acid is a consistent feature of the insulin resistance syndromes, which are also characterized by elevated fasting and post-carbohydrate plasma insulin level, blood glucose concentration with serum triglyceride concentration, and raised body mass index and waist-hip ratio [6] [7]. The behaviour of uric acid levels in diabetes mellitus has shown to be quite different in patients with & without complications associated with the disease.

Material & Methods

The study was done on a total of 75 subjects. They were divided into 3 groups namely:

- Group 1: 25 subjects of Diabetes mellitus with retinopathy
 Group 2: 25 subjects of Diabetes mellitus without retinopathy
 Group 3: 25 Healthy Normal subjects

Diabetic retinopathy cases were diagnosed on the fundoscopic findings by an Ophthalmologist, which was further classified in to Proliferative & Non-Proliferative Diabetic Retinopathy. Subjects with H/O arthritis, H/O angina or myocardial infarction, leukemia, other complications of diabetes mellitus such as nephropathy, neuropathy & diabetic ulcers or any such conditions which is known to alter directly serum uric acid levels were excluded from the study. 5 ml fasting sample was collected from median cubital vein under aseptic precautions. 1.5 ml was transferred to fluoride bulb for glucose analysis by GOD-POD method [8] ; 1.5 ml was transferred to EDTA bulb for Glycated Hemoglobin estimation by Cat-ion exchange resin method [9] ; remaining 2 ml was centrifuged after allowing to clot for about 15 min in a plain bulb and then centrifuged to obtain serum. Serum was analysed for Urea by Urease-GLDH method [10] , Creatinine by Jaffe-kinetic method [11] , Total Cholesterol was done by Cholesterol oxidase method [12] , Triglycerides by GPO-POD method [13] , HDL by Precipitation-Cholesterol oxidase method [14] and Uric acid by Uricase method [15]. LDL was calculated by using Friedwald's formula [16].

The statistical analysis was carried out by using Student 't' test. Mean & standard deviation was calculated and parameters were compared of Group 1 with Group 3 and Group 2 with Group 3. Various parameters were also compared among diabetic retinopathy group with reference to Progressive Diabetic Retinopathy (PDR) & Non-Progressive Diabetic Retinopathy (NPDR).

Significance of difference in values was determined by the 'p' value < 0.05. Correlation of Glucose, Total Cholesterol, Triglycerides, LDL -Cholesterol & Glycated Hemoglobin was done within each group with reference to uric acid. Significance of correlation was decided based on 'r' & 'p' values.

Results

Group 1 consisted of 25 cases retinopathy, among which 7 cases were diagnosed as Proliferative Diabetic Retinopathy and remaining 18 cases as Non-Proliferative Diabetic Retinopathy based on fundoscopic examination. 25 cases of Diabetes Mellitus without retinopathy changes were included in Group 2. Age and sex matched 25 healthy normal controls constituted Group 3. Among the 25 cases of diabetic retinopathy, only 2 cases were females.

The mean and standard deviation of parameters namely Glucose, Urea, Creatinine, Total Cholesterol, Triglycerides, HDL-Cholesterol, LDL-Cholesterol, Glycated Hemoglobin and Uric acid in Group 1 (Diabetic Retinopathy), Group 2 (Diabetes Mellitus without retinopathy) and Group 3 (Normal Controls) has been shown in Table 1.

Table 2 shows mean and standard deviation values of parameters namely Glucose, Urea, Creatinine, Total Cholesterol, Triglycerides, HDL-Cholesterol, LDL-Cholesterol, Glycated Hemoglobin & Uric acid among Diabetic Retinopathy Group in Proliferative and Non-Proliferative cases.

Table 3 shows the correlation findings of Uric acid with Glucose, Total Cholesterol, Triglycerides, LDL-Cholesterol and Glycated Hemoglobin in Group 1, Group 2 and Group 3.

Table 1. Mean and standard deviation of diabetic profile, kidney profile, lipid profile & uric acid in Diabetic retinopathy, Diabetes mellitus without retinopathy and healthy controls.

Groups	Glucose	Urea	Creatinine	Total Choles-	Triglycerides	HDL-C	LDL - C	Gly Hb	Uric acid
Group 1 (DM + R)	184.56* ± 46.18	27.88± 2.28	1.14 ± 0.20	202.84* ± 23.45	211.04* ± 33.55	32.48 ± 1.98	128.08*± 19.15	6.84* ± 1.10	4.94* ± 0.56
Group 2 (DM - R)	143.28* ± 39.39	27.92± 6.59	1.09 ± 0.17	173.20* ± 22.02	172.60 ± 41.27	33.84 ± 2.76	104.76* ± 17.81	6.60* ± 0.89	3.49* ± 0.44
Group 3 (Normal)	81.36 ± 8.00	25.08± 5.06	1.01 ± 0.11	160.68 ± 20.18	171.40 ± 29.07	33.48 ± 2.84	92.96 ± 20.14	5.14 ± 0.30	4.39 ± 0.37

* Group 1 Vs Group 3, Group 2 Vs Group 3: $p < 0.05$

(DM+R = Diabetes mellitus with retinopathy, DM - R = Diabetes mellitus without retinopathy, HDL - C = HDL - Cholesterol, LDL - C = LDL - Cholesterol, GlyHb = Glycated Hemoglobin)

Table 2. Mean and standard deviation of diabetic profile, kidney profile, lipid profile & uric acid in Proliferative and Non-proliferative diabetic retinopathy.

Groups	Glucose	Urea	Creatinine	Total Cholesterol	Triglycerides	HDL-C	LDL- C	Gly Hb	Uric acid
Group 1 PDR (n = 7)	212.14 ± 53.39	31.28* ± 3.72	1.40* ± 0.18	214.71 ± 22.58	224.00 ± 31.26	32.85 ± 2.96	136.85 ± 17.44	7.65* ± 0.58	5.50* ± 0.25
Group 2 NPDR (n = 18)	173.83 ± 39.60	26.55 ± 3.77	1.04 ± 0.20	198.22 ± 22.71	206.00 ± 33.88	32.33 ± 1.53	124.66 ± 19.14	6.52 ± 1.10	4.73 ± 0.50

* Group 1 Vs Group 2: $p < 0.05$

(PDR = Proliferative diabetic retinopathy, NPDR = Non-proliferative diabetic retinopathy, HDL – C = HDL – Cholesterol, LDL – C = LDL – Cholesterol, GlyHb = Glycated Hemoglobin)

Table 3. Correlation findings of Uric acid with Glucose, Total Cholesterol, Triglycerides, LDL-Cholesterol (LDL – C) and Glycated Hemoglobin (Gly Hb) in Group 1, Group 2 and Group 3.

Groups		Glucose	Total Cholesterol	Triglycerides	LDL – C	Gly Hb
Group 1 DM + R	r	0.470	0.538	0.360	0.546	0.588
	p	0.018*	0.006*	0.137	0.005*	0.002*
Group 2 DM – R	r	- 0.400	- 0.800	0.028	- 0.159	- 0.230
	p	0.048*	0.705	0.895	0.449	0.269
Group 3 Normal	r	0.269	0.158	0.266	0.085	- 0.008
	p	0.194	0.451	0.200	0.680	0.970

*Significant

Discussion

In the present study, it is clear that there exists multifactorial involvement in the development of complications related to diabetes such as retinopathy. Apart from age of onset of diabetes, duration of the disease and glycemic control, there exist various biochemical factors which are not only involved in the pathogenesis, but also in predicting and preventing the consequences arising out of complications in diabetes mellitus.

The average age of onset of diabetes mellitus in Group 1 was 17.36, while it was 15.32 in Group 2. Comparing the mean values between Group 1 & Group 3 as depicted in Table 1, it clearly indicates that there exists a poor glucose homeostasis & lipid derangement as a metabolic consequence in diabetic retinopathy cases. It was also observed that the elevated level of uric acid in cases of diabetic retinopathy was significant as compared to controls. 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. Similarly, proliferative cases showed an elevated glycated haemoglobin level along with urea and creatinine values, signifying poor glycemic control,

as shown in Table 2. Similar observations were made in previous studies done on diabetic retinopathy in relation to various parameters as stated above [17].

Although the glycemic control and serum lipid profile showed better picture in Group 2 subjects than in Group 1, there existed a significant abnormality with glucose, total Cholesterol, LDL-Cholesterol & Glycated Hemoglobin, though to a lesser extent, as compared with Group 3. It was clearly evident from the study that uric acid levels were significantly less in cases of diabetes mellitus without complications, as compared to normal controls. It is postulated that uric acid levels have tendency to decrease before complications like retinopathy complication sets in [18], which was observed in our study. However, uric acid levels tend to increase with the onset of retinopathy, more so with the progression of renal involvement, a trend which Group 1 has shown. Correlation between glycemic status indicators and lipid profile parameters with uric acid among the different groups as shown in Table 3, significantly point towards its association in glucose and lipid homeostasis and also in the development of complications in diabetes.

Serum uric acid level has an important role in the pathogenesis & progression of long term complications associ-

ated with diabetes mellitus. A unique feature notable is the relation between uric acid and insulin, which plays a viscous cycle for the progression of diabetes, particularly with reference to microvascular changes. Studies have demonstrated in the past that insulin release in response to oral glucose is enhanced in hyperuricemic subjects [19]. It has also been shown that serum uric acid values were directly related to insulin resistance independent of age, sex, excess body weight, fat distribution and blood pressure [20] [21]. Further, it is known that physiological hyperinsulinemia acutely reduces urinary uric acid and sodium excretion from the kidneys in a coupled fashion [22]. This could explain the observation of our study as to why uric acid tends to increase in proliferative retinopathy cases. Also, it was noted that urinary uric acid clearance appears to decrease in proportion to increase in insulin resistance in normal volunteers, which could also contribute to this phenomenon [23]. As a result, increased uric acid levels further complicates the issue of insulin resistance despite adequate or increased insulin concentration in diabetics, which may further get associated with the progression of complications such as retinopathy and nephropathy.

Conclusion

Diabetic patients with and without complications show a difference in serum uric acid pattern in relation to duration of disease along with glycemic status, lipid derangements and complications associated with the disease. Poor glycemic control and lipid derangements are observed in diabetes may lead to onset as well as worsening of complications. Behaviour of uric acid levels may indicate the ongoing pathophysiology in diabetes in relation to glycemic control & insulin resistance, onset and progression of complications such as retinopathy and nephropathy. Further studies can be undertaken on a larger diabetic population to know the variations in uric acid levels and its implications in the development of complications.

References

1. Kertes PJ, Johnson TM. Evidence-Based Eye Care. Philadelphia: Lippincott Williams & Wilkins; 2007.
2. Ossama AWEH, Mohammed KS. Prevalence and risk factors for diabetic retinopathy among Omani diabetics. Br J Ophthalmol 1998; 82: 901-906.
3. Nomura K, Hotta K. Risk Factors Relating to Development of Diabetic Retinopathy in Diabetic Patients in Health Care-examination Program, Journal of the Eye 2005; 22: 1577-1581.
4. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 2008; 31: 361-362.
5. Cappuccio FP, Strazzullo P, Farinero E, Trevisan M. Uric acid metabolism and tubular sodium handling. Results from a population-based study. JAMA 1993; 270: 354-359.
6. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, et al. Relationship of **uric acid** concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution. The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord 1996; 20: 975-980.
7. Agamah ES, Srinivasan SR, Webber LS, Berenson GS. Serum **uric acid** and its relation to cardiovascular disease risk factors in children and young adults from a biracial community: the Bogalusa Heart Study. J Lab Clin Med 1991; 118: 241-249.
8. Barham D, Trinder P. An improved color reagent for the determination of blood glucose by the oxidase system. Analyst 1972; 97: 142-145.
9. Gabby KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. J Clin Endocrinol Metab, 1977; 44: 859-64.
10. Hallett CJ, Cook JGH. Produced nicotinamide adenine dinucleotide-coupled reaction for emergency blood urea estimation. Clin Chim Acta 1971; 35: 33-37.
11. Bartels H, Bohmer M, Heierli C. Serum creatinine determination without protein precipitation. Clin Chim Acta 1972; 37: 193-197.
12. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974; 20: 470-475.
13. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 1973; 19: 476-482.
14. Demacker PN, Hijmans AG, Vos-Janssen HE, van't Laar A, Jansen AP. A study of the use of polyethylene glycol in estimating cholesterol in high-density lipoprotein. Clinical Chemistry 1980, 26; 1775-1779.
15. Caraway WT. Quantitative determination of uric acid. Clin Chem 1963; 4 : 239-243.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density cholesterol in plasma without use of the preparative centrifuge. Clin Chem, 1972; 18: 499-502.
17. Cai X, Wang F, Ji L. Risk factors of diabetic retinopathy in type 2 diabetic patients. Chinese Medical Journal, 2006, 119 : 822-826.
18. Feldman T, Weitzman S, Biedner B. Retinopathy and serum uric acid in diabetics. Harefuah. 1995; 128: 681-683.
19. Butturini U, Coscelli C, Zavaroni I. Insulin release in hyperuricemic patients. Acta Diabetol Lat. 1977; 14: 73-78.
20. 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 Metab Disord.*1996; 20: 1041-1043.
21. 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. *Chinese Journal of Internal Medicine.* 2007; Vol 46: 824-826.
 22. **Quinones GA**, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. *Am J Physiol Endocrinol Metab* 1995, 268: E1-E5.
 23. 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: 3008-3011.

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