ASSOCIATION BETWEEN SERUM URIC ACID AND HbA1c IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A CASE-CONTROL STUDY

Verma Indu[1], Nimesh Archana[2]

[1]*Senior Demonstrator, Department of Biochemistry,*
University College of Medical Sciences and GTB Hospital, Delhi, India.
[2]*Assistant Professor, Department of Clinical Biochemistry,*
College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia.

ABSTRACT

Background and Aim: Uric acid is a pro-oxidant molecule that might be implicated in increasing oxidative stress and insulin resistance in type 2 diabetes mellitus patients. Hence, the aim of the study was to assess serum uric acid and HbA1c level (an indicator of glycemic control) in these patients and speculate the association between the two. Methods: 40 newly diagnosed cases of Type 2 diabetes mellitus (20 males and 20 females) with age ranging between 35-70 years were statistically compared against 40 age and sex-matched healthy subjects with respect to their uric acid and HbA1c levels. Demographic data like the height and weight of patients was also recorded and statistically compared. Results: No statistical difference in age, height and weight were observed in type 2 diabetes cases vs. controls indicating that the groups were comparable. HbA1c and uric acid levels of males and females with type 2 diabetes mellitus were significantly higher in comparison to normal males and females (controls). Correlation analysis showed a positive and significant correlation between HbA1c and uric acid levels in male and female cases of type 2 diabetes mellitus. Conclusion: Uric acid might have a role in the development or worsening of type 2 diabetes mellitus. However, further studies are required with a larger sample size to clearly establish the relationship between uric acid and glycemic control in type 2 diabetes mellitus since studies in the literature have shown conflicting results and hence the understanding of the etiopathogenesis of type 2 diabetes mellitus remains poorly understood with respect to uric acid.

Keywords: Type 2 diabetes mellitus; Uric acid; HbA1c; Etiopathogenesis; Correlation.

INTRODUCTION

Type 2 diabetes mellitus is a clinical condition characterized by hyperglycemia and hyperinsulinemia as a result of insulin resistance in the body. Globally the prevalence of diabetes mellitus has been dramatically rising. The International Diabetes Federation (IDF) estimated that globally 1 in 11 adults aged 20–79 years (415 million adults) had diabetes mellitus in the year 2015 [1]. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM) [2,3].

Type 2 diabetes mellitus if not controlled medically, can lead to a wide array of medical and surgical complications like nephropathy, cardiovascular disorders, hypertension, obesity, stroke, neuropathies and many such conditions. Thus, type 2 diabetes mellitus can lead to multi-organ dysfunction and could be highly debilitating to the patients afflicted with it leading to decreased life expectancy. There has been a tremendous amount of research that has been going on worldwide in exploring the mechanisms that could lead to an increase in insulin resistance, the main factor responsible for the development of type 2 diabetes mellitus.

It is a well-known fact that type 2 diabetes mellitus is characterized by increased oxidative stress in the body which might lead to an increase in insulin resistance in the body. So it is rational to think that any biomolecule that could increase the oxidative stress in the body might be associated with diabetes mellitus. Uric acid is a pro-oxidant molecule produced in the body as a result of purine catabolism and thus might be implicated in increasing the oxidative stress in the body [4].

In this study, we wanted to explore whether uric acid levels are altered in patients with type 2 diabetes mellitus and if it is so then is it related to the glycemic control (determined by HbA1c) of the patient or not. Studies in literature have reported conflicting results with respect to uric acid levels in type 2 diabetes mellitus, hence its role is not clear in type 2 diabetes mellitus. Therefore, the objective of the study was to assess the serum uric acid concentration and HbA1c level in patients with type 2 diabetes mellitus and speculate the association between the two.

MATERIAL AND METHODOLOGY

Study design: It is a case-control study

Ethics approval: The study was approved by the research committee and the institute's ethics' committee for human studies. Informed consent was taken from the subjects enrolled in the study.

Study population and place: The study was carried out from January 2014 to March 2015 in the Department of Biochemistry in collaboration with the Department of Medicine in Maharishi Markandeshwar Institute of Medical Sciences and Research, Ambala, India.

Correspondence: Indu Verma, Senior Demonstrator, Department of Biochemistry, University College of Medical, Sciences and GTB Hospital, Delhi, India. Email: induyashu1406@gmail.com

Inclusion criteria: The case group included 40 newly diagnosed cases of Type 2 diabetes mellitus (20 males and 20 females) with age ranging between 35-70 years. The control group comprised of 40 age and sex-matched healthy subjects (20 males and 20 females). The subjects enrolled in the study were categorized into cases and controls based on the criteria recommended by the American Diabetes Association (ADA).

Exclusion criteria: Individuals having any other concurrent disease besides Type 2 DM and those who were taking any medication were excluded from the study to avoid confounding results. Anemic individuals and female subjects who were pregnant were excluded as well from the study.

Sample size: 40 in case group and 40 in the control group

Methodology:

The cases were enrolled in the study when they came to the OPD (of Department. of Medicine) with symptoms suggestive of type 2 DM. Their blood samples were collected and analyzed in the Department of Biochemistry for fasting and 2 hours postprandial glucose levels using the glucose oxidase peroxidase enzymatic method in the autoanalyzer based on turbidimetry. The results so obtained were used to categorize them into case groups as per the ADA criteria. Age and sex-matched healthy volunteers also provided their fasting and postprandial blood samples for blood glucose estimation and, if levels were found to be in the normal range, were included in the control group for further study. After categorizing the subjects into case and control group, their blood samples were analyzed for HbA1c level and Uric acid concentration. HbA1c level in subjects was measured using resin columns-based ion-exchange chromatography. Serum uric acid was estimated turbidimetrically in autoanalyzer using enzymatic kits (uricase method). The demographic data (age, height, weight) and biochemical data of subjects were recorded for further statistical analysis and computation of results.

Statistical analysis: The data was analyzed for normality. Since the parameters followed a normal distribution, the data has been as expressed as Mean ± SD (standard deviation). Independent student t-test has been used to compare parameters between cases and control group. Pearson's correlation analysis has been used for determining the association between HbA1c and uric acid levels. The statistical work has been carried out using the software, SPSS version 20. P-value ≤ 0.05 has been considered statistically significant.

RESULTS

The parameters shown in Table 1 denote the demographic data of the subjects. There is no statistically significant difference between the cases and controls with respect to age, height and weight indicating that the two groups are comparable.

Table 1shows that HbA1c and uric acid levels were significantly higher in males with type 2 diabetes mellitus in comparison to normal males (controls). Likewise, the HbA1c and uric acid levels were found to be significantly higher in female cases with type 2 diabetes mellitus in comparison to normal females (controls). Further

correlation analysis showed a positive and significant correlation between HbA1c and uric acid levels in male and female cases of type 2 diabetes mellitus (Table 2; fig. 1 and 2).

Table 1: Demographic data of type 2 diabetes mellitus (T$_2$DM) patients and controls.

	T$_2$DM (N=40)	Controls (N=40)	P
Age (years)	51.95±12.48	47.85±11.79	0.13
Height (feet)	5.37±0.36	5.43±0.21	0.38
Weight (Kg)	64.78±8.97	64.48±10.66	0.89
Male (n=20)			
HbA1$_C$ (%)	7.960±1.01	4.809±0.45	0.000*
Uric acid (mg/dl)	5.795±1.42	4.449±0.76	0.001*
Female (n=20)			
HbA1$_C$ (%)	8.084±1.06	4.738±0.60	0.000*
Uric acid (mg/dl)	4.671±1.56	3.776±0.71	0.028*

*p-value ≤ 0.05 is considered significant

Table 2: Correlation between HbA1$_c$ and uric acid levels in T$_2$DM in male and female patients.

	Correlation coefficient (r)	P-value
Male with Type 2 DM (HbA1$_c$ and uric acid)	0.536	0.015*
Females with Type 2 DM (HbA1$_c$ and uric acid)	0.461	0.041*
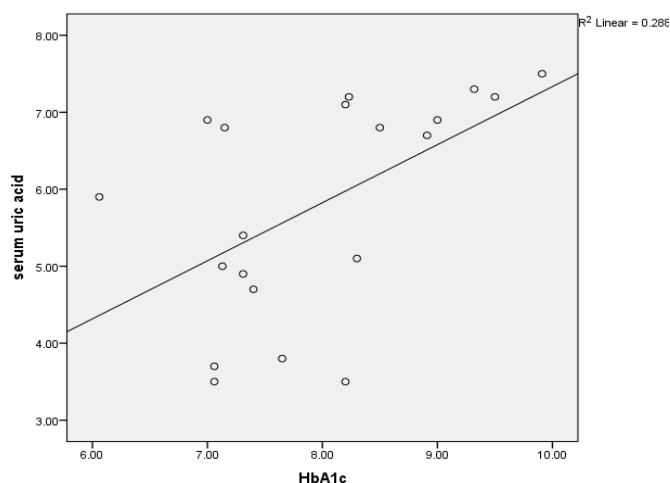
* P-value ≤ 0.05 is considered significant

Fig 1: Correlation between HbA1$_c$ and uric acid levels in male patients with T$_2$DM

DISCUSSION

The results of our study show that men and women with type 2 diabetes mellitus exhibit a comparatively higher level of uric acid in the blood in comparison to controls which positively correlated with the HbA1c levels. This could hint the possibility of uric acid playing a role in the etiopathogenesis of type 2 diabetes mellitus (T2DM).

Uric acid is a breakdown product of purine catabolism and acts as a pro-oxidant molecule thereby increasing the oxidative stress in the body which might contribute towards the insulin resistance in patients of type 2 diabetes mellitus.
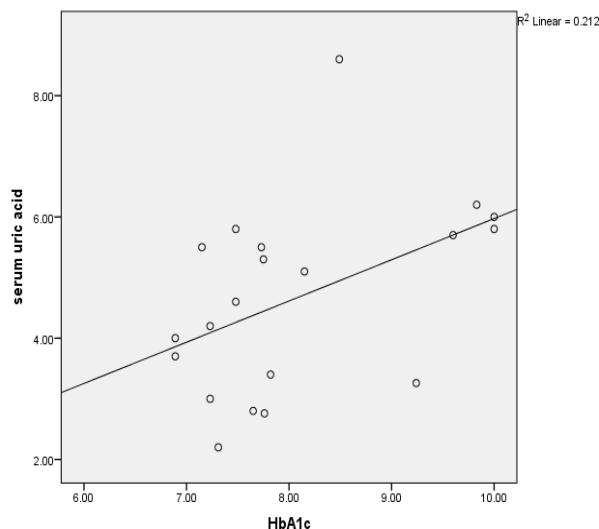

Fig 2: Correlation between HbA1$_c$ and uric acid levels in female patients with T$_2$DM

Two recently published studies in the literature have also found a similar positive correlation between uric acid and HbA1c levels in type 2 diabetes mellitus patients [5,6]. A study in T2DM patients by Atak BM et al showed higher uric acid values in patients with poor glycemic control (high HbA1c) in comparison to patients with good glycemic control and healthy controls [7]. Research in literature also shows that therapy to decrease uric acid level is found to improve insulin resistance and blood glucose levels [8].

There are studies that show that an increased level of uric acid is found to be associated with other metabolic conditions as well as atherosclerotic cardiovascular diseases owing to oxidative stress [9,10]. Another study shows that uric acid has been found to be associated with insulin resistance and metabolic syndrome [11]. The role of uric acid levels has been implicated in chronic kidney disease as well in a study conducted by Johnson RJ et al [12]. Research has also shown that uric acid is found to be associated with hypertension [13].

Thus, from the above studies, it is found that the role of uric acid has been implicated in several metabolic diseases by virtue of its pro-oxidant nature. However, regarding its role in diabetes mellitus, it is still not clear whether an increase in uric acid leads to diabetes mellitus or is it that diabetes mellitus associated with hyperinsulinemia and hyperglycemia leads to decreased excretion of uric acid via kidneys resulting in higher blood uric acid concentration. In our study, we found higher uric acid concentration in type 2 diabetes mellitus like a few other studies [14-17]. A literature search has also revealed studies showing no association [18] or an inverse relation as well [19]. Another study by Cui Y et al too found an inverse correlation between serum uric acid level and HbA1c level in T2DM patients with high insulin level but no such correlation was found by them in T2DM patients with low insulin level [20].

Thus, from the studies available in literature the role of uric acid in type 2 diabetes mellitus cannot be clearly ascertained. Hence, the number of studies are required to be carried out on a large group of patients to clearly establish the relationship between the uric acid and glycemic control in patients with type 2 diabetes mellitus. This would help in a better understanding of the etiopathogenesis of T2DM and whether uric acid concentration can be used as a predictor for the development or worsening of T2DM or not. Further studies are also needed to speculate on the role of uric acid lowering drugs in improving the glycemic profile of the person to clarify the role of uric acid in the etiopathogenesis of T2DM.

CONCLUSION

Male and female patients of type 2 diabetes mellitus exhibited a significantly higher level of HbA1c and serum uric concentration in comparison to healthy controls. The serum uric acid concentration positively correlated with HbA1c level in type 2 diabetes mellitus prompting that uric acid might have a role to play in the development or worsening of type 2 diabetes mellitus

REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas — 7th Edition. Diabetes Atlas http://www.diabetesatlas.org/ (2015)

[2] Holman, N., Young, B. & Gadsby, R. Current prevalence of type 1 and type 2 diabetes in adults and children in the UK. Diabet Med. 2015; 32:1119–20

[3] Bruno G. Incidence of type 1 and type 2 diabetes in adults aged 30–49 years: the population-based registry in the province of Turin, Italy. Diabetes Care. 2005; 28:2613–9

[4] Silva RP, Patricio ES, Bonifacio JPPL, Carvalho LAC, Filho ABC, Miyamoto S, et al. 116 - Pro-Oxidant Effect of Uric Acid Metabolites in Inflammatory Cells. Free Radical Biology and Medicine 2016;100:S60.

[5] Pavithra V, K Revathy and Swaminathan S. Association between Uric acid and HbA1c in type 2 Diabetes Mellitus in Comparison with Controls. Int J Curr Microbiol App Sci 2016;5(4):585-9

[6] Duman TT, Kocak MZ, Atak BM, Erkus E. Serum Uric acid is correlated with HbA1c levels in type 2 diabetes mellitus.Exp Biomed Res 2018;1(1):6-9

[7] Atak BM, Duman TT, Kocak MZ, Savli H. Serum uric acid level is associated with type 2 diabetes mellitus and diabetic regulation.Exp Biomed Res 2018;1(4):135-9

[8] Takir M, Kostek O, Ozkok A, Elcioglu OC, Bakan A, Erek A, et al. Lowering Uric Acid With Allopurinol Improves Insulin Resistance and Systemic Inflammation in Asymptomatic Hyperuricemia. J Investig Med 2015 Dec;63(8):924-9

[9] Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis 2007;17(6):409-14

[10] Su P, Hong L, Zhao Y, Sun H, Li L. Relationship Between Hyperuricemia and Cardiovascular Disease Risk Factors in a Chinese Population: A Cross - Sectional Study. Med Sci Monit 2015 Sep 12;21:2707-17

[11] Osgood K, Krakoff J, Thearle M. Serum uric acid predicts both current and future components of the metabolic syndrome. Metab Syndr Relat Disord. 2013;11(3):157-62

[12] Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant. 2013;28(9):2221-8

[13] Kuwabara M, Hisatome I, Niwa K, Hara S, Roncal -Jimenez CA, Bjornstad P, et al. Uric Acid Is a Strong Risk Marker for Developing Hypertension From Prehypertension: A 5-Year Japanese Cohort Study. Hypertension 2018;71(1):78-86

[14] Dehghan A, van HM, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 2008;31 (2):361-2

[15] Chien KL, Chen MF, Hsu HC, Chang WT, Su TC, Lee YT, et al. Plasma uric acid and the risk of type 2 diabetes in a Chinese community. Clin Chem 2008;54(2):310-6.

[16] Kramer CK, von MD, Jassal SK, Barrett-Connor E. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose: the Rancho Bernardo Study. Diabetes Care 2009;32(7):1272-3.

[17] Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol 2003;18(6):523-30

[18] Rusdiana, Widjaja SS, Syahputra M, Savira M. Association between Haemoglobin A1c and Uric Acid Levels among Patients with Diabetes Mellitus Type 2 at a Primary Health Care Clinic in North Sumatera, Indonesia. Open Access Maced J Med Sci 2018;6(9):1633-5

[19] Wei F, Chang B, Yang X, Wang Y, Chen L, Li WD. Serum Uric Acid Levels were Dynamically Coupled with Hemoglobin A1c in the Development of Type 2 Diabetes. Scientific reports. 2016;6(1):28549

[20] Cui Y, Bu H, Ma X, Zhao S, Li X, Lu S. The Relation between Serum Uric Acid and HbA1c Is Dependent upon Hyperinsulinemia in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. J Diabetes Res 2016:7184123