An Observational Analytical Study on Correlation of Serum Uric Acid and HbA1C in Prediabetic and Diabetic Patients

ABSTRACT

Aims: Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia caused by either deficiency in insulin production or insulin action, or both. HbA1c is a commonly accessible test indicated by most doctors to assess the long term glycaemic control in diabetes patients over the duration of past 3 months. Oxidative stress can be predicted in both diabetic and non-diabetic patients through the serum uric acid levels. Therefore, this study aimed at finding out the association between serum uric acid and glycaemic control (HbA1c).
Study design: Analytical Observational Cross Sectional Study
Place and Duration of Study: Department of General Medicine, KLES Dr. Prabhakar Kore Hospital, Belagavi; conducted between 1st January 2020 to 31st December 2020.
Methodology: A one year analytical observation type of study was conducted on 108 patients between the ages of 30 and 70 years diagnosed with Type 2 Diabetes Mellitus and Prediabetes were included in this research. Patients diagnosed with myeloproliferative or lymphoproliferative illnesses, psoriasis, pregnancy, gout and those on medications for gout, and chronic alcoholics were excluded. Enzymatic approach was used to measure serum uric acid (UA) using an automated device and HPLC technique was used to measure whole blood HbA1c.
Results: 108 patients were included in the research out of which, 67 were diabetics and 41 were pre-diabetics. A majority of the participants were males, with a mean age of 59.12±14.06 years. The serum uric acid was substantially greater amongst the patients with diabetes mellitus (6.76±3.1mg/dL) compared to participants with pre-diabetes (5.5±1.9mg/dL). The serum HbA1c and the serum uric acid have a mild positive significant association in diabetics.
Conclusion: There is a weak association of serum uric acid with HbA1c among diabetic patients. Diabetes mellitus patients have greater serum uric acid levels than those with prediabetes mellitus.

Keywords: Diabetes mellitus, HbA1c, Prediabetes, Serum Uric acid

1. INTRODUCTION

Diabetes mellitus is a group of diseases characterised by hyperglycaemia and is caused due to either poor insulin production or insulin action, or both. It consists of two types: Type-1 and Type-2. Type-1 diabetes mellitus is characterised by a severe or near-severe lack of insulin. Type-2 diabetes mellitus shows insulin resistance which is diminished capacity of insulin to act on the peripheral tissue. However, it is possible for the cells of the pancreas to generate enough insulin in the early stages of insulin resistance in order to control blood glucose levels. Type-2 diabetes mellitus can occur as a result of failure of

pancreatic cells caused by insulin overproduction. Chronic hyperglycaemia is related with long term damage, malfunction and failure of multiple organs including eyes, kidneys, nerves and heart(1).

Poor glucose tolerance or low fasting glucose levels are the characteristics of prediabetes, which is a disorder of glucose homeostasis. Although it is possible to reverse the intermediate hyperglycaemic stages, it increases the risk of acquiring type 2 diabetes(1).

The prevalence of diabetes mellitus is rising at an alarming rate over the world and is on its way to amount to pandemic proportions. People (aged 20–79) with diabetes account for 6.4% of the global population in 2010, rising to an estimate of 406 million adults in 2018 and 511 million adults in 2030, according to the World Diabetes Atlas. India has the greatest number of diabetes patients in the world projected to be roughly 69.2 million in the year 2015 and is anticipated to climb to approximately 87 million by the year 2030(2). Wild et al have anticipated a similar two fold escalation in the prevalence of diabetes in the globe as a whole, with a highest increase in India impacting up to 79.4 million people(3). Therefore, diabetes is a serious health care concern in India.

Serum uric acid levels can be used for predicting the renal damage of both diabetic and non-diabetic patients (4). It can also be a predictor of oxidative stress (5, 6). Uric acid production occurs as the final waste product of the purine metabolism by xanthine oxidase's enzymatic activity and finds its way into the bloodstream (7). Normal range of serum uric acid for males is considered to be 2.5 to 7 mg/dL while in females it is 1.5 to 6 mg/dL. High serum uric acid levels can indicate its poor elimination from the body, thereby reflecting the kidneys' filtration efficiency.

Glycated haemoglobin (HbA1c) is an established marker of the mean blood glucose and can be used to assess the long term glycaemic control in diabetes patients over the duration of the past 2-3 months. A1c in haemoglobin binds non-enzymatically to circulating glucose and therefore these levels will rise as a result of increased glucose levels in the bloodstream(8). HbA1c is also a biomarker of risk factors for diabetic micro and macro-vascular problems and provides information on the degree of hyperglycaemia.

Table 1: HbA1c values*

Diagnosis	**HbA1c (%age)**
Normal	Less than 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	6.5% or higher

*As adapted from American Diabetes Association

Thus, the current study aimed to understand the correlation of HbA1c and serum uric acid in patients of diabetes and prediabetes.

2. MATERIAL AND METHODS

2.1 Study design

A one year hospital based observational cross sectional study was conducted from 1st January 2020 to 31st December 2020. The study protocol was approved by the institutional ethical committee of JN Medical College Belagavi, Karnataka. All participants signed an informed consent form prior to taking part in the study.

Study population included patients with previously diagnosed diabetes and pre-diabetes, aged between 30 to 70 years admitted in the ICU and wards of KLES Dr. Prabhakar Kore Hospital, Belagavi. Patients on medications for hyperuricaemia, alcoholics, those suffering from myeloproliferative disease, lymphoproliferative disease and psoriasis, pregnancy and those diagnosed with gout were excluded.

After a detailed history and clinical examination, venous blood obtained from each patient following overnight fasting was used for biochemical analysis. Serum Uric Acid (UA) was tested through an automated device by enzymatic method whereas whole blood HbA1c was assessed by HPLC technology.

2.2 Statistical analysis

IBM SPSS version 23 was used to perform statistical analysis on the data. The data was provided as mean, standard deviation, and quartile range. The mean difference between all of the subjects' baseline attributes was compared using a student t-test. An independent t-test was used to compare the baseline in age and gender groups. The link between uric acid and HbA1c levels in both groups of patients was assessed using Pearson's correlation coefficient and multinomial logistic regression analysis for association. A p-value of < 0.05 was judged statistically significant.

3. RESULTS AND DISCUSSION

Majority of the participants of the study were male, and the mean age of the total study population was 59.12 ± 14.06 years. A summary of demographic data is shown in Table 1.

Table 2. Demographics for the entire study population

Gender	**Female** 41 (38%)	**Male** 67 (62%)	
	Minimum	**Maximum**	**(Mean ±SD)**
Age (n=108)	21	87	59.12 ± 14.06
Height (in cm)	153	172	161.12 ± 3.974
Weight (in kg)	58	102	75.44 ± 8.189

Comparison of weight between the diabetic and prediabetic group was found to be statistically significant (p= 0.02). Similarly, comparison of HbA1c values of both groups was found to be statistically significant with a p value of 0.001. Mean HbA1c value in diabetic population was 9.2 indicating poor glycaemic control as compared to pre diabetic population with a mean HbA1c value of 6. The serum uric acid was substantially greater among the patients with diabetes mellitus (6.76 ± 3.1mg/dL) compared to participants with pre-diabetes

(5.5 ± 1.9 mg/dL). Serum uric acid values were also statistically significant on comparison (p = 0.03). A comparison of mean of continuous variables of the two groups by student t- test is shown in Table 2.

Table 3. Mean of continuous variables compared between the two groups.

	Diabetes Mellitus	**Pre-diabetes Mellitus**	**Total**
Frequency (n)	67	41	108
Percentage (%)	62%	38%	100%
	Mean ± SD	**Mean ± SD**	**p value**
Age in yrs	60.27 ± 13.99	57.24 ± 14.15	0.28
Height in cm	161.55 ± 4.30	160.41 ± 3.30	0.150
Weight in kg	76.79 ± 9.34	73.22 ± 5.21	0.02*
BMI in kg/m^2	29.43 ± 3.80	28.38 ± 2.31	0.114
HBA1C in %	9.2 ± 2.3	6.0 ± 0.2	0.001**
Serum Uric Acid in mg/dl	6.76 ± 3.1	5.5 ± 1.9	0.03*
	Frequency	**Frequency**	**p value**
Habits- Smoker	16	7	0.442
Habits- Tobacco chewing	10	4	
Diabetic Retinopathy	49 (73.1%)	0	0.001
***p<0.05 is considered statistically significant; **p<0.001 is considered statistically highly significant.**			

The incidence of diabetic retinopathy in the participants was found to be significantly higher in diabetics (n=49, 73.1%), as compared to prediabetic individuals in which none of the individuals developed diabetic retinopathy.

Chi square analysis of diabetic and prediabetic population who had habits of smoking and tobacco chewing did not yield any significance. Similarly, t-tests of BMI of diabetic and prediabetic group were not statistically significant. HbA1c and the serum uric acid have a mild positive significant association in diabetics (p= 0.014) by Pearson's correlation. (Refer Fig.1)

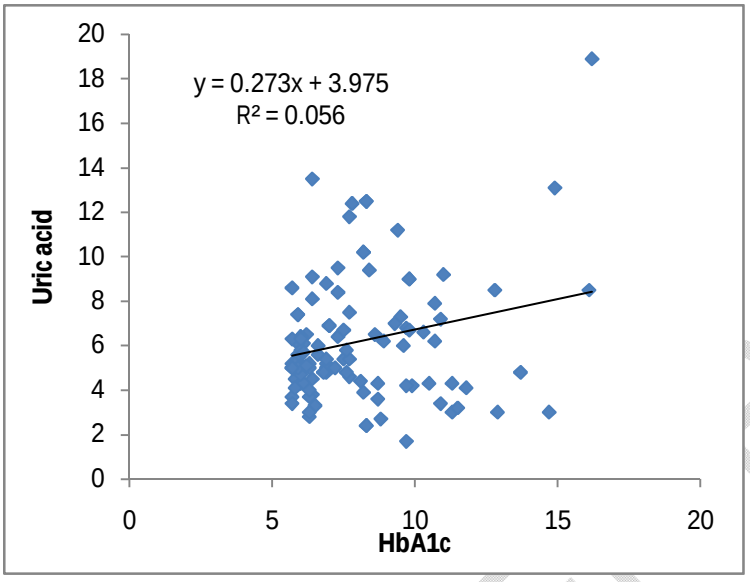

Fig.1: Correlation between HbA1c and serum uric acid

3.1 DISCUSSION

Glycated haemoglobin (HbA1c) levels are often used to predict diabetes in individuals with high blood sugar levels or suspected diabetics(9) . It is used as an indicator of the average glucose levels of the individual for the past two to three months. HbA1c levels can also be used to monitor and manage diabetes. A value between 5.7% and 6% is considered prediabetic, while that ≥ 6.5% is diagnosed as diabetic. In the current study, the mean HbA1c was found to be (9.2±2.3) in patients with diabetes mellitus and (6.0±0.2) in participants with pre-diabetes.

Diabetes is known to be associated with several other conditions including retinopathy, neuropathy, nephropathy, macrovascular diseases, cardiomyopathy, non alcoholic fatty liver disease and other such complications that lead to a poor prognosis (10). The current study evaluated the participants for retinopathy and habits that lead to them like tobacco chewing and smoking since it was commonly found in such cases (11). It was observed that out of the 67 patients with diabetes, 49 had diabetic retinopathy thus placing diabetics at a significantly higher incidence than those with pre-diabetes mellitus. Twenty-three of the total 108 participants smoked cigarettes, while 14 of them had a habit of chewing tobacco. However, there was no discernible difference between the two groups in terms of the distribution of habits.

Serum uric acid is a reflection of the purine catabolism within an individual, and can be significantly elevated in those with metabolic diseases, chronic kidney disease and

atherosclerotic changes. Recently, a number of researchers have been interested in finding out the correlation between serum uric acid levels and diabetes mellitus. However, it is unclear whether the uric acid levels rise or fall with an increasing blood glucose level as shown by HbA1c values. Some studies have referred to this phenomenon as the 'bell fit', wherein, initially uric acid levels increase with an increasing blood glucose level, and later serum uric acid levels decrease with a continued rise in blood glucose levels(12–14). Evaluation of the serum uric acid levels in both, diabetes and prediabetes population can be helpful in indicating the progression or severity of diabetes along with Hb1Ac.

In the current study, serum uric acid was substantially greater among the patients with diabetes mellitus (6.76±3.1mg/dL) as compared to participants with pre-diabetes (5.5±1.9mg/dL). Rao et al., in a research similar to this one, found a greater mean of serum uric acid in those with diabetes and pre-diabetes mellitus (15). Haque T et al. found that the serum uric acid level in diabetes mellitus patients was lower than in those with pre-diabetes, which is in contrast to the current study (16).

The mean age of participants in the present study was found to be 59.12±14.06yrs of age, with male predominance. At a mean age of 57.24 ±14.15 years for those with prediabetes and mean age of 60.27± 13.99 years for those with diabetes, there was no statistically significant difference in age between the two groups. The mean weight among the patients with diabetes mellitus was significantly higher (76.79±9.34 kg) than in the group of pre-diabetes (73.22±5.21 kg). In a study similar to this one, Haque T et al. found that men were more likely than women to have diabetes or pre-diabetes (16).

A correlation of HbA1c and serum uric acid levels in diabetes and prediabetes can help in understanding the patterns of these entities with advancing disease progression. In this observational investigation, HbA1c levels were correlated with uric acid levels in patients with prediabetes and type 2 diabetes mellitus. 41 patients had prediabetes in while 67 patients were diagnosed as diabetes mellitus.

In this study, it has been observed that there is a weak positive significant correlation between serum HbA1c with the serum uric acid. However, studies by Dehghan A et al. and Chien K-L et al have found that serum uric acid, blood glucose and HbA1c levels were significantly associated (17,18). According to a study by Cui Y et al, this correlation between serum uric acid and HbA1c is dependent on insulin levels in the patients of diabetes and prediabetes, which might influence the results (14). Studies by Kramer CK et al. and Kodama S et al. have identified a link between serum uric acid and diabetes (19, 20). However, in a 16 year follow-up study of Japanese people, uric acid was found to be unrelated to a statistically significant increase in the risk of T2DM(21). Another study by Wu Q et al has concluded that an increased serum level poses a higher risk of developing T2DM and prediabetes in women when compared to men (22). A recent study by Modi AS and Sahi N in diabetic persons in India revealed no significant association between SUA and FBG (23). A study on National Health and Nutrition Examination Survey Participants indicated that serum uric acid levels were inversely associated with T2DM (24).

4. CONCLUSION

According to our study, there appears to be a poor association between HbA1c and serum uric acid among the participants diagnosed with diabetes and prediabetes. Participants identified as pre-diabetes mellitus had a lower serum uric acid level those with diabetes

mellitus. Although an association between serum uric acid levels and HbA1c is seen in persons with diabetes mellitus, the correlation found was modest.

5. LIMITATION OF THE STUDY

A small sample size forms the limitation of this study. A larger sample size with a long term follow up of the prediabetic population can be helpful in carrying out a detailed study to find out if serum uric acid can be used as a marker to measure oxidative stress and evaluate for microvascular and macrovascular complications as a result of diabetes in the Indian population.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this original article.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

REFERENCES

1. Association AD. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2013;37(Supplement_1):S81–90. Available from: https://doi.org/10.2337/dc14-S081

2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018 Feb;14(2):88–98.

3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047–53.

4. Lin F, Zhang H, Huang F, Chen H, Lin C, Zhu P. Influence of changes in serum uric acid levels on renal function in elderly patients with hypertension: a retrospective cohort study with 3.5-year follow-up. BMC Geriatr [Internet]. 2016;16(1):35. Available from: https://doi.org/10.1186/s12877-016-0209-2

5. Ok EJ, Kim K, Park SB. Association between Serum Uric Acid and Oxidative Stress in Korean Adults. Korean J Fam Med. 2018 Sep;39(5):295–9.

6. Xiong Q, Liu J, Xu Y. Effects of Uric Acid on Diabetes Mellitus and Its Chronic Complications. Int J Endocrinol. 2019;2019:9691345.

7. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016 Jun;213:8–14.

8. Kilpatrick ES. Glycated haemoglobin in the year 2000. J Clin Pathol. 2000 May;53(5):335–9.

9. Al-Ghamdi AA. Role of HbA1c in management of diabetes mellitus. Saudi Med J [Internet]. 2004 Mar;25(3):342—345. Available from: http://europepmc.org/abstract/MED/15048173

10. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol [Internet]. 2022;18(9):525–39. Available from: https://doi.org/10.1038/s41574-022-00690-7

11. Durlach V, Vergès B, Al-Salameh A, Bahougne T, Benzerouk F, Berlin I, et al. Smoking and diabetes interplay: A comprehensive review and joint statement. Diabetes Metab [Internet]. 2022;48(6):101370. Available from: https://www.sciencedirect.com/science/article/pii/S1262363622000520

12. Whitehead TP, Jungner I, Robinson D, Kolar W, Pearl A, Hale A. Serum urate, serum glucose and diabetes. Ann Clin Biochem. 1992 Mar;29 (Pt 2):159–61.

13. Choi HK, Ford ES. Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels--the Third National Health and Nutrition Examination Survey. Rheumatology (Oxford). 2008 May;47(5):713–7.

14. 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;2016:7184123.

15. M. S, Sahayo B. A STUDY OF SERUM URIC ACID IN DIABETES MELLITUS AND PREDIABETES IN A SOUTH INDIAN TERTIARY CARE HOSPITAL. J Heal Allied Sci NU. 2012;02:18–23.

16. Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. Diabetol Metab Syndr [Internet]. 2019;11(1):49. Available from: https://doi.org/10.1186/s13098-019-0446-6

17. Dehghan A, van Hoek M, Sijbrands EJG, Hofman A, Witteman JCM. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008 Feb;31(2):361–2.

18. Chien K-L, Chen M-F, Hsu H-C, Chang W-T, Su T-C, Lee Y-T, et al. Plasma uric acid and the risk of type 2 diabetes in a Chinese community. Clin Chem. 2008 Feb;54(2):310–6.

19. Kramer CK, von Mühlen D, 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 Jul;32(7):1272–3.

20. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association between serum uric acid and development of type 2 diabetes. Diabetes Care. 2009 Sep;32(9):1737–42.

21. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens. 2001 Jul;19(7):1209–15.

22. Wu Q, Guan Y, Xu CZ, Wang N, Liu X, Jiang F, et al. [Relationship of serum uric acid with prediabetes and newly detected type 2 diabetes mellitus]. Zhonghua Liu Xing Bing Xue Za Zhi [Internet]. 2022 Oct;43(10):1603—1610. Available from: https://doi.org/10.3760/cma.j.cn112338-20220117-00041

23. Dr. Anuj Satishkumar Modi*1 DNS. Serum uric acid levels in type 2 diabetes mellitus. J Cardiovasc Dis Res. 2020;11(3):56–9.

24. Bandaru P, Shankar A. Association between Serum Uric Acid Levels and Diabetes Mellitus. Int J Endocrinol. 2011;2011:604715.