Correlation between Serum Uric Acid with Type 2 Diabetes Mellitus and its Complications

Jayshri Sadashiv Jankar[1*], Kumud Namdeorao Harley[2] and Roshan Kumar Jha[1]

[1]Department of Biochemistry, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, India.
[2]Department of Biochemistry, Government Medical College, Akola. India.

Authors' contributions

This work was carried out in collaboration among all authors. Author JSJ designed and prepared the manuscript. Authors KNH and RKJ analyzed and interpreted it. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Type 2 diabetes mellitus is becoming more common over the world, making it a major health concern. Many research has been carried a link among both higher uric acid concentrations in the body and a higher incidence of type 2 diabetes mellitus. On a biochemical level, uric acid has been proved to have a negative impact on insulin sensitivity in animals. When nitric oxide, essential for glucose uptake, is suppressed, this occurs. The goal of this study is to review past research on the relationship between serum uric acid and diabetes type II in various parts of the world, as well as the prevalence of such a link. Articles were chosen using the PubMed database and EBSCO Information Services. We used all relevant publications to our review that dealt with the connection among both serum uric acid and diabetes type II, in addition to the other articles. Other publications that were not linked to this field were excluded. In this systematic review, serum uric Acid levels were found to be correlated to type 2 diabetes mellitus, metabolic syndrome and carotid artery disease. Atherosclerosis is more common in people with type 2 diabetes. The reliability of concentrations of uric acid levels in blood in predicting type 2 diabetes and enhancing prevention should be the focus of future study.

Corresponding author: E-mail: jayshrijankar@gmail.com;

Keywords: Hyperuricemia; glucose levels; metabolic syndrome; intima media thickness; prediabetes.

1. INTRODUCTION

Type 2 diabetes mellitus is becoming more prevalent around the world, rendering it a major public health concern. As per recent studies [1], more than 336 million people globally had type 2 diabetes mellitus in 2011. In 2030, this prevalence is estimated to rise far more, with 552 million occurrences expected. Furthermore, the number of experts predict that even this prevalence will continue to rise significantly as long as worldwide obesity levels remain high [2]. To be able to prevent type 2 diabetes mellitus from occurring, recognizing risk factors related to the disease's progression is important. Furthermore, certain reports suggest that uric acid may play a part in the development of a variety of chronic diseases, particularly diabetes type 2, hypertension, and renal failure [3,4].

Because of its role in the suppression of nitric oxide, uric acid could have a harmful effect on insulin resistance in animals on a physiological level. Nitric oxide, on the other hand, is crucial in the glucose uptake mechanisms, thus its inhibition by uric acid will affect insulin role [5,6]. Moreover, insulin resistance will lead to the development of hyperinsulinemia, which will consequently increase concentration of uric acid in blood. This increase occurs as a results of several mechanisms including a reduction of renal secretion of uric acid, and accumulation of uric acid substrate [7]. However, until now no solid evidence is present to establish an independent association among both concentration of uric acid levels in blood and type

2 diabetes mellitus [8]. For this disagreement, researchers have been looking into the relationship between type 2 diabetes mellitus and uric acid levels. Several studies have been published and concluded the presence of this association. Nevertheless, this link does not yet reach the level of causation, which is still a source of debate. In addition, both alcoholism and metabolic syndrome, which are both health risks that are unrelated for type 2 diabetes mellitus, are associated with high uric acid levels, making the correlation among both uric acid and type 2 diabetes mellitus even more complex to assess. Uric acid levels, per some researchers, may be hazard markers instead of risk factors for type 2 diabetes mellitus.

In the view of above, our objective was to systematically evaluate the correlation between serum uric acid with type 2 diabetes mellitus and its complications.

2. METHODOLOGY

The systematic review process was intended to look over previous studies on the relationship between serum uric acid and type 2 diabetes in different parts of the world, as well as the prevalence of such a correlation. I performed a literature survey employing the PubMed database and EBSCO Information Services to discover published research till December 2020. "Type 2 diabetes mellitus," "serum uric acid," "hyperuricemia," and "glucose levels" were being used as search phrases. The search was limited to peer-reviewed articles with an abstract that were published in English. Additional citations that matched our search criteria found in the reference lists of journal papers, were also screened.

2.1 Inclusion Criteria

- In any records events, clinical data on serum urea concentrations in relation with type 2 diabetes mellitus.

2.1 Exclusion Criteria

- Review
- Editorials letters
- Commentaries
- Article with unavailable data

3. RESULTS

There were 105 articles found in the structured literature search. 24 duplicate papers were eliminated, 42 articles were omitted based on titles and abstracts, 7 articles were identified through relevant references, 12 articles were excluded based on inclusion criteria, and 20 articles that met the inclusion and exclusion criteria were chosen. 16 case-control studies, 2 cohort studies, 1 doubleblinded placebo trial, and 1 cross-sectional research were included in the review. The study only focused at articles written in English. Tables 1 and 2 provide a detailed summary of the search approach and results.

Chien et al. conducted a detailed cohort research in which 2,690 ages ranged 35 to 97 years old

without diabetes or any cardiovascular disease at the start of the trial were included in 1990 [9]. After a nine—year follow up, about 548 of included patients developed type 2 diabetes mellitus. When analyzing uric acid levels in the serum of all participants, it was found to have higher concentration in individuals who developed type 2 diabetes mellitus, and been related to the development of metabolic syndrome. When authors compensated with different demographic causes like lifespan, sex, body mass index (BMI) and different contender's relevant factors, they observed that having high uric acid levels increased the likelihood of getting type 2 diabetes mellitus in the serum was 1.63 (95% confidence interval, 1.2-2.23, p<0.001). The findings of this study led to the suggestion of the presence of a mild positive correlation between type 2 diabetes mellitus, and higher serum levels of uric acid.

Nakanishi et al (2003) [10] assessed the presence of a link of concentration of uric acid in blood with type 2 diabetes mellitus. In their study, they included over 2,310 patients and followed them up for six years. All patients were Japanese men office workers, older than 35 years and younger than sixty years. Authors adjusted for all possible risk factors considering an advancement of type 2 diabetes mellitus, and found that the adjusted relative risk for developing diabetes mellitus with high serum levels of uric acid was 1.78 (95% Confidence Interval, 1.11-2.85, p=0.03). The authors discovered that men with a BMI of less than 24.2 kg/m2 had a greater connection between having high serum uric acid levels and acquiring type 2 diabetes mellitus, regardless of the fact that the risk increase is much higher in obese people. These findings may suggest that uric acid levels in the blood and TYPE 2 DIABETES MELLITUS have a strong relationship.

Moreover, Wang (2011) [11] et al performed a study where they examined the potential correlation between developing type 2 diabetes mellitus and having elevated levels of serum uric acid among adult Chinese individuals [11]. In their study, they included 924 Chinese adults aged more than forty years, and without diabetes mellitus. Authors followed participants for 3.5 years, during which, 98 of them developed type 2 diabetes mellitus. They then performed a covariate adjusted cox regression test that there was a major link among both the two higher levels of serum uric acid, and risk of developing type 2 diabetes mellitus.

In fact, patients with increased concentration of u ric acid levels\ in their serum had a 2.71 higher c hance of acquiring TYPE 2 DIABETES MELLITUS than those with normal uric acid lev els in their serum.

The linkage of concentration of uric acid and the likelihood of prediabetes and type 2 diabetes mellitus was investigated Niels van der Schaft et al (2017) [12]. At the start of the study, they divided the subjects into necessarily related incompatible subgroups: normoglycaemia (n = 7,030) and prediabetes (n = 1,337). Incidences of prediabetes (n = 1,071) and type 2 diabetes mellitus (n = 407) were followed up on with these groupings. It was discovered that a standard deviation increase in serum uric acid was strongly correlated with occurrence of prediabetes in persons with normoglycaemia (Hazard Ratio 1.10, 95% confidence interval (CI) 1.01; 1.18), not so much with type 2 diabetes mellitus in people with prediabetes (Hazard Ratio 1.07, 95 percent CI 0.94; 1.21). In addition, serum uric acid was increased with type 2 diabetes mellitus in prediabetic males (Hazard Ratio 1.23, 95 % Confidence Interval 1.01; 1.48) but not in prediabetic women (Hazard Ratio 1.00, 95% Confidence Interval 0.84; 1.19).

Shantan Venishetty et al (2018) [13] investigated 103 diabetic patients with age group between 30 years and 65 years of age. The mean age of the study patients was 54.5 ± 8.4 years with 65% being males and 40.8% having history of hypertension. When analysed mean uric acid levels among males was high compared to females, but was not statistically significant ($P = 0.35$). They found that Carotid atherosclerosis as measured by Caroid Intima Media Thickness (CIMT) is associated with serum uric acid levels in patients with type 2 diabetes mellitus.

Abbas Dehghan et al (2008) [14] investigated 4,536 nondiabetics. 62 participants acquired diabetes over the course of 10.1 years of follow-up. Concentration of uric acid in serum was increased from 107 to 756 µmol/l with a mean ± SD of 323.7 ± 82.2 µmol/l. In comparison to the first quartile, the age- and sex-adjusted hazard ratios (HRs) (95 percent CIs) for diabetes were 1.30 (0.96 −1.76) for the second, 1.63 (1.21–2.19) for the third, and 2.83 (2.13–3.76) for the fourth quartile of concentrations of uric acid in serum. The population-attributable risk of diabetes due to elevated concentrations of uric acid in serum was 0.24 (95% confidence Interval 0.17– 0.30) in the fourth quartile, 0.09 (0.3– 0.15)

in the third quartile, and 0.04 (0.01– 0.10) in the second quartile.

Tangigul Haque et al. (2019) [15] measured fasting Blood Glucose, concentrations of uric acid in serum, and lipid levels in 310 blood samples from 215 male and 95 female participants. Serum Uric Acid concentrations had been used to classify all participants into four quartiles. Researchers reported that prediabetic and diabetic people had lower mean uric acid concentrations in their serum (338.2 101.6 and 290.9 98.2 mol/L, respectively) than healthy people (369.5 110.9 mol/L) (p 0.001). Body Mass Index, triglycerides, and total cholesterol were all significantly correlated with serum Uric Acid, however Fasting Blood Glucose was inversely linked. With increased serum uric acid levels across the quartiles, the prevalence of diabetes was reduced. Serum uric acid levels were inversely related to diabetes mellitus in regression analysis.

T. Murali Venkateswara Rao et al (2016) [16] recruited 70 patients with type 2 diabetes mellitus and 30 healthy individuals in the research. The proportion of diabetic patients with hyperuricemia was 11.43 percent, while none of the controls had hyperuricemia in the study population. The mean uric acid level rose from 4.30 ± 0.77 in people with diabetes for two to four years to 4.57±1.01 in people with diabetes for five to eight years. The mean uric acid level among persons with diabetes during 9 to 12 years was 6.47±1.07. There was a statistically significant link between diabetes duration and blood uric acid level.

120 type 2 diabetics were researched by Akshay Shirsath et al (2019) [17]. Researchers found a significant relationship between serum creatinine and uric acid levels ($p <0.001$), and they noticed that when the participants' serum creatinine levels were elevated, so were their uric acid levels. They discovered a strong link between twenty-hour urine albumin and uric acid levels ($p= 0.025$), and that as uric acid levels rose, microalbuminuria increased. In this research, there had been a statistically significant relationship between HbA1c and uric acid levels ($p <0.001$). The study found a significant link between fasting blood sugar levels and uric acid levels ($p=0.004$).

Walid G Babikr et al (2016) [18] reported a non-significant positive connection between serum uric acid and HbA1c (r=0.135, p=0.026) and a non-significant negative correlation between concentrations of uric acid in serum and fasting blood sugar (r = -0.211, p=0.000) in diabetic individuals.

Table 1. Flowchart of the search strategy and selection process

Structured review

↓

Articles looked in initial pooled search= 105

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Duplicate articles excluded = 24

↓

Excluded based on abstracts and titles= 42

↓

Articled recognised through relevant references = 7

↓

Excluded based on the inclusion criteria = 12
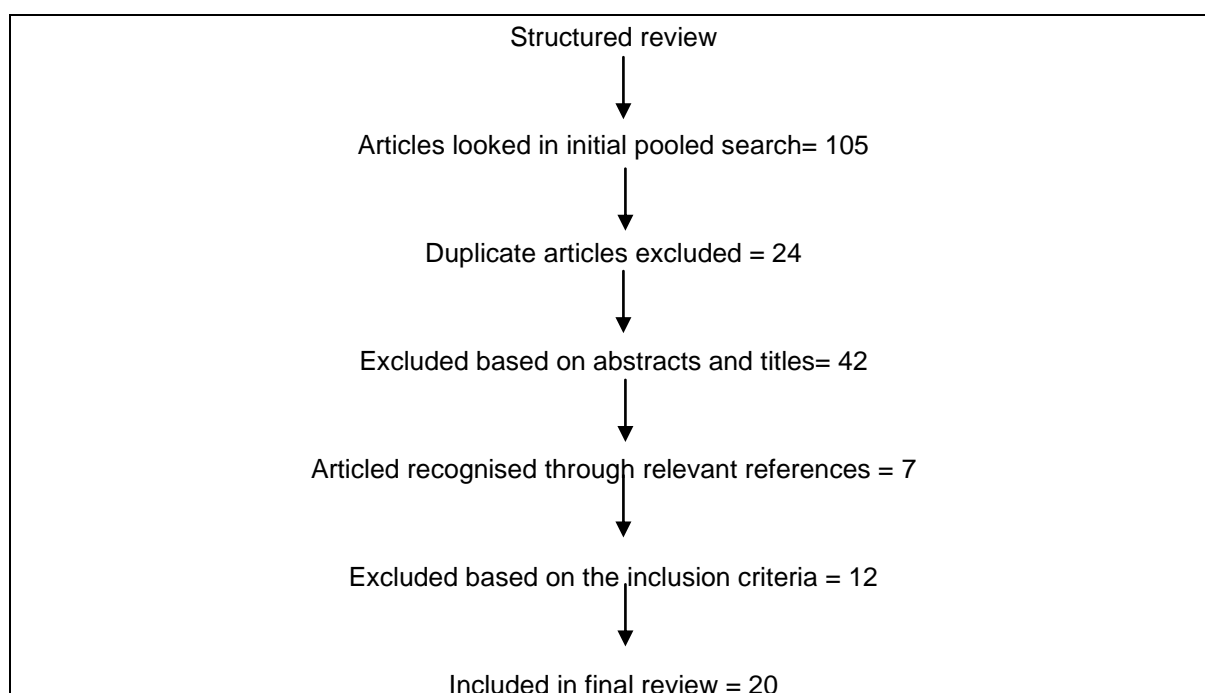
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Included in final review = 20

Table 2. Researchers, Study design, Country, Objective, duration of study, outcome, references

Researchers	Study design	Country	Objective	Duration of study	Outcome	Ref.
Chien et al	Community-based prospective cohort study	China	Investigating the association between plasma serum levels of uric acid and the risk of type 2 diabetes mellitus in Chinese people	9 years	Authors found a mild positive correlation between serum levels of uric acid and type 2 diabetes mellitus in Chinese people and the correlation between hyperuricemia and diabetes was partly mediated through the metabolic syndrome.	10
Nakanishi et al	Cross sectional study	Japan	Examining the correlation between serum levels of uric acid and the development of type 2 diabetes mellitus (non-insulin-dependent)	6 years	This study concluded that SUA is closely correlated with a higher risk of type 2 diabetes mellitus.	11
Wang et al	Prospective cohort study	China	Investigating the correlation between serum levels of uric acid and the risk of type 2 diabetes in middle-aged and elderly Chinese	3.5 years	They found that serum levels of uric acid was an independent risk factor for type 2 diabetes mellitus in middle-aged and elderly Chinese and data indicated the association between serum uric acid and the incidence of type 2 diabetes mellitus was independent from insulin resistance, which plays an important role in the pathology of type2 diabetes mellitus.	11
Niels van der Schaft et al	a prospective cohort study	Netherlands	Evaluating the link between concentrations of serum uric acid in serum and the development of	Incidence of prediabetes is 7.5 years, and type 2 diabetes mellitus is	Researchers showed that while serum uric acid was linked with incidence prediabetes in normoglycaemic females, it was	12

Researchers	Study design	Country	Objective	Duration of study	Outcome	Ref.
			prediabetes and type 2 diabetes mellitus.	7.2 years.	not in normoglycaemic males. Concentrations of uric acid in serum, on the other hand, was reported to be correlated with the establishment of type 2 diabetes mellitus in prediabetic males but not in prediabetic females.	
Shantan Venishetty et al	A cross- sectional observational study	India	The effect of serum uric acid in carotid atherosclerosis in type 2 diabetes mellitus is being explored.	2 years	The researchers noted that concentrations of uric acid in serum are substantially linked to carotid atherosclerosis in type 2 diabetes mellitus subjects.	13
Abbas Dehghan et al	a prospective cohort study	Netherlands	The connection between concentrations of uric acid in serum and the possibility of type 2 diabetes mellitus is being investigated.	10.1 years	The researchers discovered that individuals with higher concentrations of serum uric acid in serum are more likely to acquire type 2 diabetes mellitus.	14
Tangigul Haque et al	A cross sectional study	Bangladesh	The connection between uric acid concentrations in serum and fasting blood glucose (FBG) levels in healthy, prediabetic, and diabetic people was investigated.	-	Non-diabetic individuals had greater uric acid concentrations in serum, but prediabetic and diabetic persons had a decreasing tendency.	15
T. Murali Venkateswara Rao et al	an analytical cross sectional study	India	The significance of uric acid levels in serum and lipid profile variables in type 2 diabetes mellitus is being investigated.	1 year	The researchers concluded that diabetics had considerably higher uric acid concentrations in serum, as well as dyslipidaemia with high triglycerides and hypertension.	16
Akshay Shirsath et al	A Cross Sectional Study	India	Studying the uric acid concentrations in serum in	1.5 years	Investigators found that serum creatinine levels were increased	17

Researchers	Study design	Country	Objective	Duration of study	Outcome	Ref.
			type type 2 diabetes mellitus individuals and relation with microalbuminuria and serum creatinine levels		in type 2 diabetes mellitus patients who had elevated concentrations of uric acid in serum along with microalbuminuria	
Walid G Babikr et al	A cross sectional study	Najran	The relationship between uric acid concentrations in serum and glycemic management in type 2 diabetes mellitus subjects is being investigated.	-	The authors discovered that serum uric acid levels have a negative impact on glycemic tolerance in type 2 diabetes mellitus individuals.	18
Qin Li at al	a population-based cross-sectional survey	China	The relationship between uric acid concentrations in serum and the metabolic syndrome in type 2 diabetes mellitus is being studied.	6 months	In patients with type 2 diabetes, uric acid concentrations in serum were observed to be strongly linked to metabolic syndrome and carotid atherosclerosis.	19
Nobukazu Ishizaka et al	a population-based cross-sectional survey	Japan	Exploring the relationship between uric acid concentrations and metabolic syndrome in Japanese people, as well as determining if uric acid has an indirect association with the occurrence of carotid atherosclerosis in people who are divided by sex and metabolic syndrome condition.	9 years	Researchers observed that uric acid concentrations in serum are related to metabolic syndrome in both males and females, irrespective of age, TC, or smoking habits.	20

In Shanghai, Qin Li et al (2011) [19] carried a population-based cross-sectional survey with 395 males and 631 females ages ranging from 41 to 92 years. B-mode ultrasonography has been used to evaluate the intima-media thickness (IMT) and carotid atherosclerotic plaques (PLQ) in the carotid artery. The new National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans were used to diagnose metabolic syndrome. Uric acid levels were positively associated with body mass index, C-reactive protein, waist circumference, triglyceride levels, systolic blood pressure, albumin/creatinine ratio, homeostasis model assessment index-insulin resistance, and carotid intima-media thickness (all p <0.05) and negatively associated with duration of diabetes, fasting plasma glucose, glycohemoglobin, eGFR, HDL-cholesterol (all p< 0.001). The probabilities of metabolic syndrome were substantially larger in the highest quartile of uric acid levels [odds ratio 3.97, (95 % confidence interval 2.58-6.13)] (P <0.001 for trend) and atherosclerotic plaques in the carotid arteries [odds ratio 2.71 (95% confidence interval 1.62-4.47)]

Cross-sectional data from 8144 individuals who underwent general health screening were evaluated by Nobukazu Ishizaka et al (2005) 20. After adjustment for age, total cholesterol, and cigarette smoking, the odds ratios (95% confidence intervals) for metabolic syndrome in sex-specific quartiles of serum uric acid in women were 1.0, 1.06 (0.60 to 1.87), 2.18 (1.30 to 3.64), and 4.17 (2.56 to 6.79), and in men were 1.0, 0.92 (0.74 to 1.14), 1.52 (1.25 to 1.65), and 1.97 (1.61 to 2.40). Upon controlling for age, serum levels, total cholesterol, and smoking status, carotid plaque was found to be more common in men without metabolic syndrome in the second, third, and fourth quartiles of uric acid levels, with odds ratios (95 percent CI) of 1.24 (1.01 to 1.52), 1.37 (1.11 to 1.68), and 1.31 (1.05 to 1.63, respectively, but not in men with metabolic syndrome or women with metabolic syndrome.

4. DISCUSSION

Type 2 diabetes mellitus is acknowledged as among the most highly prevalent illnesses. It has several long-term consequences and concerns. Type 2 diabetes mellitus incidence and prevalence have been constantly growing over the world, rendering this a world health concern that need critical intervention [21].

According to recent findings, there may be a link between elevated uric acid levels in serum and type 2 diabetes mellitus. In fact, it has been proposed that serum uric acid levels are an independent factor in causing the condition. According to several studies, persons with increased uric acid concentrations in their blood have an increased chance of getting type 2 diabetes mellitus [22,23]. These results have led to the belief that uric acid could possibly be used as an indicator for the presence of type 2 diabetes mellitus and its associated metabolic disorders [24,25].

There are several mechanisms that may be responsible for this association between type 2 diabetes mellitus and uric acid serum levels. For example, a previous study on animal models have concluded that hyperuricemia caused by increased fructose levels can play a crucial component in the advancement of metabolic syndrome. Furthermore, they discovered that lowering uric acid levels in the blood relieved clinical features of metabolic syndrome [26,27].

Another possible mechanism is the induction of endothelial dysfunction by high uric acid levels, which will lead to the reduction of nitric oxide levels [28,29]. Nitric oxide has a crucial role in glucose intake, therefore, its reduction will lead eventually to less intake of glucose in skeletal muscles. The result of all these reactions is to have resistance to insulin and progression of this condition to type 2 diabetes mellitus. Additionally, oxidative stress has been noticed to be increase in patients who have higher serum uric acid concentrations [30,31]. This oxidative stress can significantly affect tissues and thus contributing to the establishment of type 2 diabetes mellitus.

Since uric acid concentrations in serum have been linked to atherosclerosis and the Metabolic Syndrome, [32,33] that's useful to believe about uric acid as a qualified parameter for assessment process and an effective adaptation focus for cardiovascular disease and metabolic syndrome. Surprisingly, some research has shown that decreasing uric acid concentrations with allopurinol enhances endothelial function, peripheral vasodilation ability, and blood circulation also systemic and local, proposing a new treatment target [34-36]. To establish if high uric acid concentrations is a causative factor in the establishment of cardiovascular disease and metabolic syndrome, clinical trials with very well clinical end points are essential.

5. CONCLUSION

The occurrence of metabolic syndrome increases with elevated concentrations of uric acid in type 2 diabetes mellitus subjects. Regular evaluation of concentrations of uric acid in serum can provide information for guessing metabolic syndrome and thus preventing further complications of type 2 diabetes mellitus.

CONTENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71907