

SERUM URIC ACID LEVELS IN TYPE 2 DIABETES PATIENTS: EXPLORING THE ASSOCIATION WITH CARDIOVASCULAR DISEASE - A SYSTEMATIC REVIEW

S. Kumaresan¹, S. Palanisamy¹¹Assistant Professor, Department of General Medicine, Government Medical College, Pudukkottai, Tamilnadu, India

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Corresponding Author:

Dr. S. Palanisamy,
 Email: drsamypdkt@gmail.com

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**Abstract**

The increasing global prevalence of type 2 diabetes underscores the critical need for comprehensive insights into associated cardiovascular risks. This review explores serum uric acid levels as a potential link for understanding the intricate relationship between type 2 diabetes and heightened cardiovascular disease risk. The primary objective of this study was to explain the multifaceted connections between serum uric acid levels, type 2 diabetes, and cardiovascular health. By synthesising the existing literature, this review provides a comprehensive framework for understanding the metabolic changes contributing to cardiovascular risks in individuals with type 2 diabetes. A systematic examination of relevant studies investigating serum uric acid levels in patients with type 2 diabetes and their association with cardiovascular outcomes was conducted. The methods used in these studies, including participant demographics, measurement techniques, and statistical analyses, were critically assessed to ensure a robust foundation for synthesising findings. The synthesis of current research revealed complex links between elevated serum uric acid levels in patients with type 2 diabetes and an increased risk of cardiovascular diseases. Mechanisms encompassing inflammation, oxidative stress, and endothelial dysfunction have been explored, shedding light on the potential contributory role of serum uric acid in exacerbating cardiovascular complications in diabetic patients.

INTRODUCTION

The global surge in type 2 diabetes mellitus (T2DM) has evolved into a multifaceted health crisis with profound implications extending beyond glycemic control. Amidst the intricate landscape of metabolic dysregulation associated with T2DM, the quest to identify predictive markers and elucidate the underlying mechanisms that drive complications, particularly cardiovascular disease (CVD), is of paramount importance. One emerging candidate in this narrative is serum uric acid.

Background

T2DM, characterised by insulin resistance and hyperglycaemia, significantly affects global health. In addition to immediate metabolic disturbances, individuals with T2DM are confronted with an increased susceptibility to cardiovascular complications, thereby intensifying the urgency to unravel the complex interplay between metabolic perturbations and cardiovascular well-being.

Serum uric acid levels as a metabolic indicator

Traditionally considered a by-product of purine metabolism and a diagnostic marker for gout, serum

uric acid has emerged as a pivotal player in the metabolic discourse. Recent studies have highlighted its potential involvement in insulin resistance, inflammation, and oxidative stress, prompting a more thorough examination of its implications in T2DM.

Justification for Investigation

This review examined the association between serum uric acid levels and the risk of cardiovascular disease in patients diagnosed with type 2 diabetes mellitus. The justification for this investigation stems from the imperative need to fully grasp the state of metabolic well-being beyond conventional markers while recognising the potential of serum uric acid as a marker and a factor in the complex network of metabolic dysfunction within the diabetic population.

Objectives

The primary aim of this review was to consolidate the existing literature and investigate the levels of uric acid in the bloodstream of patients with T2DM and their connection with cardiovascular outcomes. We aspire to contribute nuanced perspectives that may reshape our approach to managing metabolic health in the continually expanding T2DM landscape by

critically analysing methodologies, synthesising findings, and exploring potential mechanisms. In subsequent sections, we will navigate through the current body of literature, closely examine analytical approaches, unravel the intricacies of mechanistic pathways, and highlight the clinical implications, all with the overarching objective of offering comprehensive insights into the intricate relationship between UA levels of uric acid in the bloodstream, T2DM, and cardiovascular disease.

MATERIALS AND METHODS

1. Literature Search Strategy

A systematic and comprehensive search was conducted across major scientific databases, including PubMed, Scopus, and the Web of Science, to identify relevant studies published up to January 2024. The search strategy employed a combination of keywords such as "serum uric acid", "Type 2 Diabetes", "cardiovascular disease", and related terms.

2. Inclusion and Exclusion Criteria

Studies were included if they met the following criteria.

- Focusing on serum uric acid levels in patients with type 2 diabetes.
- The association between serum uric acid levels and cardiovascular disease outcomes was also investigated.
- Included Human Subjects.
- Published in peer-reviewed journals.

Studies were excluded if they were as follows:

- Published in languages other than English.
- Case reports, reviews, or conference abstracts.
- It did not provide sufficient information on methodologies or outcomes.
- Studies conducted on animals.

3. Synthesis of Findings

The data synthesis involved a narrative summary of the study's characteristics, methodologies, and key findings. Heterogeneity of the study designs.

4. Ethical Considerations

Ethical approval was not applicable, as this review was based on analysing previously published studies. All the included studies adhered to ethical standards, as outlined in their respective publications.

RESULTS

Serum Uric Acid levels and cardiovascular disease

Numerous studies have consistently presented evidence to support the notion that there is a positive correlation between increased serum uric acid concentrations and high susceptibility to CVD in individuals diagnosed with type 2 diabetes. To illustrate, Kanieeth D et al. (2023) conducted an investigation that uncovered a significant association between elevated uric acid levels and cardiovascular events among patients with diabetes.^[1] This tendency was further reinforced by Yang et al. (2021) through

a meta-analysis that amalgamated data from multiple studies, thereby reinforcing the autonomous role of uric acid in elevating the risk of cardiovascular ailments.^[2]

Mechanisms Underlying the Association

The intricate mechanisms connecting elevated levels of uric acid in the bloodstream to an increased risk of cardiovascular disease in individuals with type 2 diabetes have been the subject of a thorough investigation. A study conducted by Martínez et al. (2021) delved into the role of uric acid in promoting insulin resistance, proposing a plausible pathway through which uric acid could contribute to the development and progression of cardiovascular complications.^[3] Furthermore, the research conducted by Myke-Mbata et al. (2021) provided insights into the pro-inflammatory pathways triggered by elevated levels of uric acid, suggesting a link between uric acid-induced inflammation and an elevated risk of cardiovascular disease.^[4] These findings collectively indicate that uric acid has the potential to be not only a bystander but also an active participant in the complex network of cardiovascular complications associated with type 2 diabetes.

Clinical Relevance

Understanding the relationship between increased uric acid levels in the blood and cardiovascular disease in individuals with type 2 diabetes is of significant clinical importance. In addition to its potential use as a biomarker, the connection between uric acid and inflammation, oxidative stress, and blood vessel dysfunction suggests that uric acid could indicate the overall metabolic environment. With this knowledge, healthcare professionals can take a more nuanced approach to assessing cardiovascular risk in patients with diabetes. A study conducted by Li et al. (2023) investigated interventions aimed at reducing uric acid levels, thereby suggesting a potential strategy for mitigating the risk factors for cardiovascular disease in individuals with type 2 diabetes. Incorporating serum uric acid monitoring into regular clinical evaluations can provide a more extensive understanding of the cardiovascular environment in individuals with type 2 Diabetes.^[5] Furthermore, this information can guide individualised therapeutic approaches, emphasising glycaemic regulation and managing underlying metabolic disturbances associated with increased uric acid levels.

To effectively manage cardiovascular risk in individuals with type 2 diabetes, it is crucial to have a deep understanding of the link between serum uric acid levels and cardiovascular disease. As research progresses, by uncovering the complexities of this relationship, the opportunity for precise interventions and enhanced risk assessment arises. This study offers a valuable path for refining clinical strategies for individuals with type 2 diabetes and cardiovascular health.

Clinical Implications

1. Monitoring serum uric acid Levels in Type 2 Diabetes:

The clinical management of T2DM could benefit from the practical use of serum uric acid level monitoring. Elevated uric acid levels might be an early indicator of metabolic disruption, providing clinicians with a valuable means of assessing risk beyond traditional markers. Consistent monitoring could enable a proactive strategy, enabling healthcare providers to identify individuals at increased cardiovascular risk and tailor interventions accordingly. Myke-Mbata et al. (2021) conducted a systematic review highlighting the importance of integrating serum uric acid assessment into regular evaluations for patients with T2DM.⁴ This allows healthcare providers to detect individuals with high uric acid levels and promptly implement interventions to manage blood sugar levels and cardiovascular risk factors.

2. Interventions and lifestyle modification

Considering the correlation between increased serum uric acid levels and cardiovascular risk in individuals with type 2 diabetes mellitus, interventions directed at lowering uric acid levels may show potential. Lifestyle adjustments such as dietary modifications and increased physical activity have been investigated as prospective approaches. Akbaş et al. (2023) illustrated that reducing uric acid levels via lifestyle adjustments could decrease cardiovascular risk factors in patients with type 2 diabetes mellitus.⁶ Furthermore, preliminary studies have indicated the potential of pharmacological interventions, such as urate-lowering agents, to regulate uric acid levels. Investigating these interventions not only corresponds with the principles of personalised

medicine but also emphasises the potential impact of uric acid as a modifiable risk factor for cardiovascular health in individuals with T2DM.

3. Implications for Healthcare Providers.

Incorporating serum uric acid monitoring into current treatment approaches necessitates heightened awareness among healthcare providers about the clinical significance of elevated uric acid in T2DM patients. Clinicians must acknowledge uric acid not only as an indicator for gout but also as a possible factor in the wider metabolic environment, particularly cardiovascular risk.^[7] Healthcare professionals must be prepared to analyse uric acid levels in conjunction with traditional biomarkers to develop a thorough understanding of each patient's metabolic characteristics. Incorporating uric acid assessments into risk prediction models can enhance risk stratification, enabling the implementation of more precise preventive strategies that align with an individual patient's metabolic profile.

In summary, monitoring serum uric acid levels in individuals with T2DM provides clinicians with a valuable opportunity to improve risk assessment and tailor treatment strategies. A personalised approach can be adopted by considering lifestyle changes and potential interventions to reduce the cardiovascular risk associated with elevated uric acid levels. This represents a shift in how individuals at the intersection of T2DM and cardiovascular health are comprehensively managed. As research progresses, healthcare providers have the potential to gain insights that could reshape their approach to patient care in this complex metabolic landscape.

Table 1: Characteristics of Included Studies

Study	Design	Participants	Measurement Techniques
Kanieeth et al, ^[1] (2023)	Cross-sectional, population-based study.	2976 participants	Anthropometric measurements and blood samples.
Yang et al, ^[2] (2021)	Meta-analysis	49,800 participants	Cardiovascular or all-cause mortality, coronary artery disease (CAD), stroke, and major adverse cardiovascular events (maces)
Martínez et al, ^[3] (2021)	Cross-sectional study	354 participants	Oral glucose tolerance test (OGTT), Blood sample Analysis
Myke-Mbata et al, ^[4] (2021)	Cross-sectional study	101 participants	HbA1c (glycated Haemoglobin)
Li et al, ^[5] (2023)	Prospective cohort study	7,101 participants	Cardiovascular or all-cause mortality, CAD, Hazard Ratios, and maces
Akbaş et al, ^[6] (2023)	Retrospective Observational study	174 participants	Hba1c, Albuminuria, Uric Acid, lipid profile, urea, creatinine, Glomerular filtration rate (GFR) and albumin levels

Table 2: Key Findings on Serum Uric Acid and Cardiovascular Risk

Studies	Key Findings
Kanieeth et al, ^[1] (2023)	Association between elevated uric acid levels and the occurrence of cardiovascular events among patients with diabetes.
Yang et al, ^[2] (2021)	Elevated uric acid levels were significantly associated with an increased risk of cardiovascular or all-cause mortality, coronary artery disease, and major adverse cardiovascular events in hypertensive patients.
Martínez et al, ^[3] (2021)	The role of uric acid in promoting insulin resistance contributes to the development and progression of cardiovascular complications.
Myke-Mbata et al, ^[4] (2021)	Proposed a link between uric acid-induced inflammation and an elevated risk of cardiovascular disease.
Li et al, ^[5] (2023)	Higher serum uric acid levels are associated with increased risks of all-cause and cardiovascular mortality in diabetes.
Akbaş et al, ^[6] (2023)	Lifestyle changes, like diet, exercise, and weight management, impact uric acid levels and cardiovascular health in diabetes.

DISCUSSION

In the ever-changing environment of T2DM, investigations of uric acid levels in the blood have revealed a multifaceted connection with significant consequences for both metabolic well-being and cardiovascular outcomes. Our understanding of the intricate network of T2DM is improved by amalgamating the primary discoveries from the existing literature. Nevertheless, this study highlights the potential importance of serum uric acid as a biomarker with extensive implications.

Key Findings and Implications

The body of evidence reviewed consistently underscores the positive correlation between elevated serum uric acid levels and increased cardiovascular disease risk in individuals with T2DM. This association extends beyond mere coincidence, revealing potential mechanistic links between inflammation, oxidative stress, and endothelial dysfunction. As we unravel these intricacies, it becomes evident that serum uric acid, once relegated to the periphery, plays a central role in understanding the broader metabolic health landscape of T2DM.

Serum Uric Acid level as a biomarker

Serum uric acid, traditionally viewed as a marker of gout, has emerged as a biomarker of considerable significance in T2DM. Its potential role as a marker and active participant in the metabolic dysregulation characteristic of diabetes underscores the need for a paradigm shift in clinical assessments. By incorporating serum uric acid into routine monitoring, healthcare providers gain a nuanced tool that extends beyond traditional glycemic markers, offering a holistic perspective on metabolic health.^[8,9]

Importance of Continued Exploration

In conclusion, it is imperative to underscore the importance of continued exploration in this evolving field. The insights gained from ongoing research are key to refining risk stratification, tailoring interventions, and ultimately enhancing patient care. Serum uric acid, once a peripheral player, emerges as a protagonist in the narrative of T2DM, urging researchers, clinicians, and stakeholders to collaborate in uncovering its full potential for improving patient outcomes.^[10]

Challenges and Limitations in Current Research

- **Diversity in Study Designs:** Exploring serum uric acid in T2DM revealed substantial heterogeneity in study design, participant characteristics, and methodologies. This diversity presents challenges in comparing findings across studies and extracting generalised conclusions.^[11]
- **Confounding Elements:** Numerous studies may lack sufficient control over confounding variables, such as diet, medication usage, and comorbidities. These confounding elements can introduce complexity into result interpretation, affecting the credibility and dependability of

associations noted between serum uric acid levels and cardiovascular outcomes.^[6]

- **Limited Interventional Studies:** The scarcity of interventional studies exploring the direct impact of reducing uric acid levels on cardiovascular outcomes in T2DM patients hinders our understanding of causality. Addressing this limitation is crucial for establishing causal relationships and informing potential therapeutic strategies.

Proposals for Future Studies

- **Longitudinal Interventional Trials:** Future studies should prioritise well-designed longitudinal intervention trials to investigate the impact of lowering serum uric acid levels on cardiovascular outcomes in individuals with T2DM. This could involve exploring lifestyle modifications and pharmacological interventions and assessing long-term efficacy and safety.
- **Standardised Measurement Protocols:** Ensuring uniformity in measuring serum uric acid levels across studies enhances comparability. Implementing consistent methodologies is vital for facilitating more resilient meta-analyses and systematic reviews. This, in turn, will contribute to a more coherent understanding of the association between serum uric acid levels and cardiovascular risk in T2DM patients.
- **Inclusion of Diverse Populations:** Future studies should strive to include diverse populations, considering factors such as age, sex, and ethnicity. This approach ensures a more comprehensive understanding of how serum uric acid levels vary across different demographic groups and how these variations affect cardiovascular risk in T2DM.

Impact on Clinical Practice and Patient Outcomes

- **Precision Medicine Approaches:** Addressing current gaps in knowledge has the potential to be used in a new era of precision medicine for T2DM patients. Tailoring interventions based on an individual's metabolic profile, including serum uric acid levels, could optimise cardiovascular risk management and improve patient outcomes.^[12]
- **Risk Stratification Models:** Integrating serum uric acid into existing risk stratification models may refine cardiovascular risk assessments in T2DM patients. This approach could guide healthcare providers in implementing targeted preventive strategies, ultimately reducing the burden of cardiovascular complications in this population.^[13]
- **Patient-Centred Care:** A nuanced understanding of the relationship between serum uric acid and cardiovascular outcomes empowers healthcare providers to deliver patient-centred care. By addressing metabolic perturbations associated with elevated uric acid, clinicians can optimise therapeutic approaches, improving overall patient outcomes and quality of life.^[14,15]

In summary, addressing the challenges and directing future research efforts toward methodological standardisation, diverse population inclusion, and longitudinal intervention trials can significantly advance our understanding of the role of serum uric acid in cardiovascular risk in individuals with type 2 diabetes. In turn, this has the potential to reshape clinical practice and improve patient outcomes in this complex and evolving landscape.

CONCLUSION

Investigating serum uric acid levels in T2DM presents a multifaceted connection with substantial implications for metabolic health and cardiovascular outcomes. This thorough review consolidates the current literature, particularly emphasising the potential importance of serum uric acid as a biomarker. Evidence consistently supports a positive association between elevated serum uric acid levels and an increased risk of cardiovascular disease in T2DM, revealing mechanistic links involving inflammation, oxidative stress, and endothelial dysfunction. Serum uric acid, traditionally linked to gout, is a pivotal biomarker of T2DM, necessitating a shift in how clinical assessments are conducted. Including serum uric acid in routine monitoring equips healthcare providers with a nuanced tool beyond traditional glycaemic markers, providing a comprehensive perspective on metabolic health. Future research should investigate the causality and interventions targeting uric acid levels to elucidate their impact on cardiovascular outcomes in patients with T2DM. Methodological standardisation, including diverse populations and longitudinal studies, is crucial to advancing our understanding. Continued exploration of this field is essential for refining risk stratification, tailoring interventions, and enhancing patient care. Serum uric acid, once on the periphery, has emerged as a central character in the narrative of T2DM, inviting collaboration to unlock its full potential. The journey ahead promises a deeper understanding of the role of serum uric acid, paving the way for innovative strategies and personalised interventions. In this endeavour, the symbiotic relationship between research and clinical practice becomes integral to advancing care in the ever-evolving landscape of type 2 diabetes.

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