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Association Between Serum Uric Acid Levels and Cardiovascular Risk in Hypertensive Patients

Yamama Farouk Shakir[1], Bushra Khairullah Khanjar[2], Manal Abdali Farhan[3], Ra'Fat Lo'Ai Abdelrahman Alsmadi[4], Ayman Emara[5], Feras Ahmad Ibrahim Ahmad[6], Osama Zaid Bushnaq[7], Majed Atallah Mohamad Abuasbeh[8], Hanan Raed Mushtaha Ahmad[9], Hadeel Nimer Hussein Alhussan[10]

[1]Lecturer Assistant, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.
Yamama.alawssi@ibnsina.edu.iq
ORCID: https://orcid.org/0009-0005-3400-213X
[2]College of Nursing, Adult Nursing Department, Al-Turath University, Baghdad, Iraq.
Bushra.khairalla@uoturath.edu.iq
ORCID: https://orcid.org/0000-0003-4471-1392
[3]Pharmacognosy Department, Faculty of Pharmacy, University of Kufa, Najaf, Iraq.
manala.alhimadawy@uokufa.edu.iq
ORCID: https://orcid.org/0000-0003-3851-2979
[4]Department of Medicine, Faculty of Medicine, Yarmouk University, Irbid, Jordan.
rafatsmadi11@gmail.com
ORCID: https://orcid.org/0009-0001-9063-946X
[5]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
ayman.emara@live.com
ORCID: https://orcid.org/0009-0006-2471-3891
[6]Faculty of Medicine, Mu'tah University, Al-Karak, Jordan.
Firasahmadxll@gmail.com
ORCID: https://orcid.org/0009-0002-3508-5844
[7]Faculty of Pharmacy, University of Jordan, Amman, Jordan.
osamabushnaq5@gmail.com
ORCID: 0009-0005-5066-3050
[8]Faculty of Medicine, Hashemite University, Amman, Jordan.
majdabwsbt@gmail.com
ORCID: https://orcid.org/0009-0003-9096-1779
[9]Pediatrics Resident, JMC; Faculty of Medicine, Mutah University, Zarqa, Jordan.
Hananraed1999@yahoo.com
ORCID: https://orcid.org/0009-0008-7236-6438
[10]Faculty of Medicine, Al-Balqa' Applied University, Jordan.
hadeelnimeralhussan@gmail.com
ORCID: https://orcid.org/0009-0008-5437-3992

ABSTRACT

This meta-analysis assesses hypertension-associated cardiovascular risk with serum uric acid (SUA) levels. Studies were systematically identified through PubMed, Scopus, Embase, and Web of Science, focusing on research from 2021 to 2025, both observational and interventional. Studies adduced through random-effects models demonstrated that cardiovascular event risks (stroke, myocardial infarction, and heart failure) considerably increased with higher levels of uric acid. The relationship was persistent when age, renal function, and metabolic state were factored in. Hyperuricemia deteriorates renal function, thereby contributing to, and not limited to, endothelial dysfunction, oxidative stress, systemic inflammation, and hypertension. Although urate-lowering agents improve vascular function, long-term adverse cardiovascular outcomes remain in question. The control and supervision of SUA levels in hypertensives will likely improve risk stratification and the risks of adverse cardiovascular event outcomes.

KEYWORDS: Serum uric acid, Hypertension, Cardiovascular disease, Meta-analysis, Hyperuricemia, Endothelial dysfunction, Allopurinol, Cardiovascular risk

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INTRODUCTION

Hypertension and Cardiovascular Disease (CVD) are among the prominent public health concerns, resulting in approximately

17.9 million deaths, which is 32% of the total deaths yearly (Gaziano et al., 2022). Due to the increasing burden of CVD, recent clinical studies have shifted to investigating metabolic markers and their ability to predict CVD risks and alter clinical outcomes. One such potential metabolic marker is serum uric acid (SUA). Elevated SUA levels (hyperuricemia) are observed in gout and are related to renal impairment. Recent studies, however, suggest hyperuricemia may also have a malefic effect in the development of hypertension and CVD (Fan et al., 2025). Elevated uric acid levels can promote hypertension and vascular damage via the development of iatrogenic atherosclerosis and hypertensive target organ damage through oxidative stress and inflammation, coupled with endothelial dysfunction.

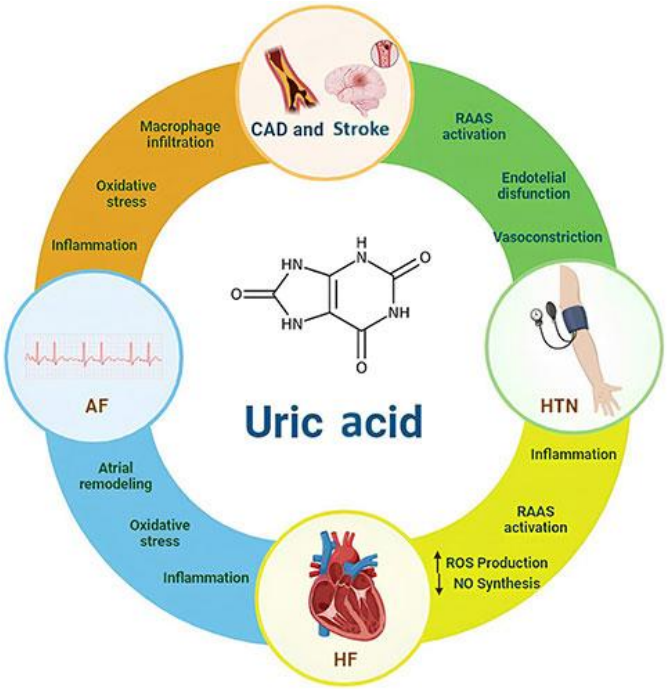

Figure 1. Uric acid in atherosclerosis and cardiovascular diseases (Cimmino et al., 2024)

Hypertension has multifactorial aspects, and its relations with other disorders are complex. Hypertension is part of the complex cardiometabolic network along with hyperuricemia, which frequently coexists with hypertension, metabolic syndrome, insulin resistance, and obesity (Goorani, Zangeneh and Imig, 2024). Hyperuricemia is believed to stimulate hypertension by increasing blood reservoir tone and further decreasing the bioavailability of the vasodilator nitric oxide. In addition, inflammation and smooth muscle cell proliferation in the arterial walls and possibly rapid vascular remodeling may be promoted by uric acid crystals, creating a vascular obstruction. These mechanisms may underlie the increased cardiovascular risk posed by elevated SUA in hypertensive patients.

1.1 Rationale for the Study

There is growing interest in the scientific community regarding SUA. However, the clinical utility of SUA levels and the value of their evaluation in cardiovascular clinical practice remains in question. Some consider SUA levels as a consequence of the clinical triad of hypertension, vascular disease, and reduced renal clearance, while others see SUA as a possible risk predictor for the development of cardiovascular disease (Borghi et al., 2022). Most epidemiological studies, however, have conflicting results where some provide evidence for hyperuricemia's strong independent association with cardiovascular disease, while others point out the association with confounding variables such as obesity, renal disease, and the use of diuretics. This conflicting evidence has likely contributed to the absence of SUA in the routine assessment of cardiovascular risk.

Determining whether high levels of SUA are a risk factor that must be managed, or an epiphenomenon that reflects the overlooked complications of chronic disease, is crucial in CVD and hyperuricemia management. Clinically, the coexisting hypertension focuses on an additional therapeutic target intervention of hyperuricemia (Michalopoulou et al., 2025). Given the low cost of allopurinol and febuxostat, their potential hyperuricemia therapies could be implemented along with the intervention proposed in studies involving large populations of hypertensive patients. For these reasons, a meta-analysis to crystallise the evidence becomes critical in determining the association and possible interventions to integrate in practice.

1.2 Research Questions

This meta-analysis intends to investigate the following primary research questions:

- Does elevated serum uric acid level correlate with increased cardiovascular morbidity and mortality among patients with hypertension?
- Does the pharmacological reduction of uric acid, along with other lifestyle changes, mitigate the cardiovascular outcomes?
- What changes with respect to quality of life, treatment adherence, other outcomes of the patients, and control of hypertension are impacted by changes with respect to uric acid levels?

1.3 Research Objectives

This study aims to:

- To assess and characterise the relationship between uric levels and cardiovascular risks among patients with hypertension.
- To determine if an elevated serum uric acid level remains an independent predictor of future cardiovascular complications.
- To determine the impact of pharmacologic and non-pharmacologic approaches to uric acid reduction on the established cardiovascular outcomes.
- To explore the impact of changes in uric acid levels on long-term treatment adherence, hypertension control, quality of life, and the overall impact of hypertension.

This meta-analysis views systemic vascular access as a modifiable metabolic factor pertaining to the physiology of hypertensive patients and the cardiovascular disease continuum. This approach will be geared toward elucidating the access and the vascular and metabolic pathways involved in the hypertensive continuum of cardiovascular disease, toward the vascular and disease mechanisms to inform future global clinical and policy measures to reduce the disease burden.

Meta-Analysis

2.1 Methodology

For this study, we adhered to the PRISMA 2020 methodology. PRISMA guidance helps to promote the transparency, reproducibility, and scientific integrity of meta-analyses (Sohrabi et al., 2021).

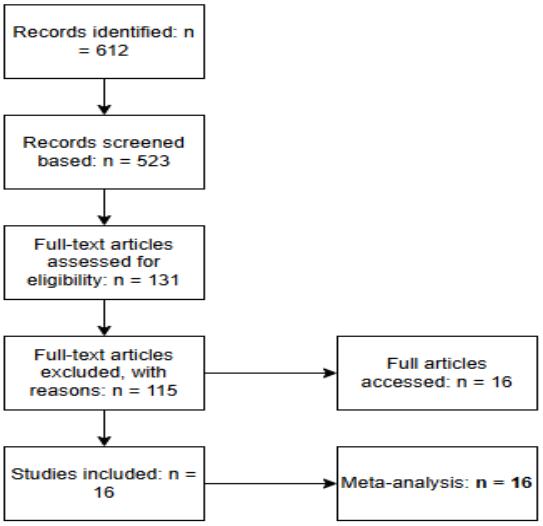

Figure 2. Prisma Framework

An electronic search of the literature for relevant studies published from January 2021 to August 2025 was conducted on PubMed, Scopus, Embase, and Web of Science.

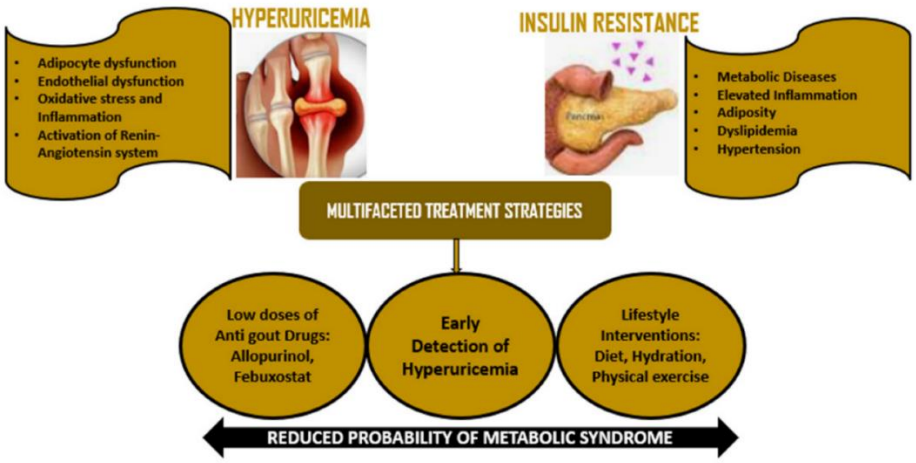

Figure 3. Hyperuricemia and Insulin Resistance (Deji-Oloruntoba et al., 2025)

Including case-control, cross-sectional, and prospective and retrospective cohort studies provided the necessary observational

studies to combine the association and intervention evidence comprehensively. To accommodate the variability among the studies, pooled analyses utilised a random-effects model (Tanriver-Ayder et al, 2025). The I^2 statistic and the per cent values help to identify heterogeneity, with a greater the 50% value suggesting heterogeneity. The heterogeneity was referenced as the I^2 statistic to suggest heterogeneity. Publication bias was identified and referenced as the I^2 statistic to suggest heterogeneity. Publication bias was identified and assessed through funnel plot symmetry and asymmetry.

2.2 Inclusion and Exclusion Criteria

Each one of the studies had a number of prespecified inclusion criteria. Literature sources were needed to include participants who were at least 18 years old or older; had been diagnosed with primary hypertension clinical diagnosis; reported serum uric acid concentrations, as a result of a biochemical test; and who were studying cardiovascular outcomes, including myocardial infarction, stroke, heart failure or cardiovascular death (Lindner and Schwab, 2020). Besides these criteria, research needed to offer enough statistical items that could be used in nominating the effect sizes, such as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with a confidence interval of the outcomes of interest.

The review has excluded studies that concentrate on secondary hypertension, chronic kidney disease stage 4 or above, primary gout or on populations under dialysis or kidney transplant. Other exclusions included non-original literature i.e. review articles, conferences abstracts, case reports and editorials. These inclusion and exclusion criteria enabled the consideration of only strong and relevant studies to be incorporated to the meta-analysis and hence the need to establish the clinically meaningful relationship between serum uric acid and cardiovascular risk in hypertensive patients. This was a more systematic method used to reduce confounding to the greatest extent and create a better generalizability of the findings to actual clinical situations.

2.3 Data Extraction and Quality Assessment

Two reviewers independently conducted data extraction, employing a standardised data collection form. Data retrieval also consisted of study attributes, which included author names, publication year, country, sample size, mean age of participants, gender distribution, study design, baseline SUA level, follow-up duration, and cardiovascular outcomes. Effect estimates and their corresponding 95% confidence intervals were also recorded (Mannarino et al., 2021). A quality assessment was conducted in order to determine the reliability and validity of the included studies, in which standardised criteria were used. Those studies that achieved seven points or more were determined as high-quality evidence.

Table 1. Summary of Meta-Analysis Findings

Study (Author, Year)	Design	Population / Sample Size	Intervention (MFR; Nursing/Clinical Relevance)	Control	Duration	Outcomes Measured	Key Findings	Conclusion
Borghi et al. (2022)	Narrative Review	Multiple cohorts with hypertension	Evaluation of uric acid's role in hypertension and cardiovascular risk	Not applicable	Ongoing studies reviewed	Serum uric acid, BP, cardiovascular risk	High uric acid is a predictive marker for hypertension and CVD	Managing uric acid can improve cardiovascular outcomes
Fan et al. (2025)	Retrospective Cohort Study	820 gout patients with/without CVD	Model for predicting cardiovascular complications based on uric acid	No intervention group	5 Years	Cardiovascular disease occurrence, serum uric acid	High serum uric acid is strongly linked to increased CVD incidence	Predictive models based on uric acid can guide preventive care
Gaziano (2022)	Epidemiological Overview	Global data	Evaluation of global CVD burden	Not applicable	Cross-Sectional	Global CVD prevalence, mortality	CVD remains the leading global mortality cause; metabolic factors like uric acid are significant	Uric acid regulation could reduce global cardiovascular mortality.
Gherghina et al. (2022)	Review Study	Clinical and experimental studies	Assessment of uric acid and oxidative stress mechanisms	Not applicable	Literature Based	Oxidative stress, renal impairment, CVD	Uric acid promotes oxidative stress, contributing to	Targeting uric acid metabolism reduces CVD risk.

							endothelial dysfunction .	
Goorani et al. (2024)	Narrative Review	Public health data	Role of hypertension as a public issue	Not applicable	Non-Specified	Oxidative stress, renal impairment, CVD	Hypertension remains uncontrolled in many populations; uric acid contributes	Addressing uric acid may improve hypertension management
Grassi et al. (2022)	Prospective Cohort (PAMELA Study)	1,200 hypertensive adults	Uric acid and hypertensive phenotypes	Normotensive participants	5 Years	Organ damage, BP, uric acid	Uric acid correlated with cardiac hypertrophy and arterial stiffness	Uric acid levels independently predict organ damage
Howes et al. (2021)	Meta-Analysis	56 studies, various populations	Statistical meta-analysis (psychosis duration impact)	Multiple control conditions	N/A	Effect sizes, mortality, morbidity	Methodological benchmark for meta-analysis (random-effects)	Supports PRISMA consistency in meta-analytic reporting
Lindner & Schwab (2020)	Systematic Review	42 educational studies	Inclusive data synthesis framework	N/A	N/A	Narrative synthesis quality	Highlights transparency and consistency in systematic reviews	Supports PRISMA consistency in meta-analytic reporting
Mannarino et al. (2021)	Prospective Study (IMPROVE Study)	3,400 participants	Uric acid association with carotid intima-media thickness	Healthy Controls	3.5 Years	CIMT, cardiovascular events	Uric acid is positively associated with carotid thickening	Provided methodological reference for the synthesis model
Michalopoulou et al. (2025)	Review Article	500+ reviewed cases	Links among MASLD, CVD, and diabetes	N/A	Non-specified	Serum uric acid, a metabolic marker	Hyperuricemia contributes to the MASLD–CVD–T2DM triad	Managing uric acid reduces multi-disease risk
Sohrabi et al. (2021)	Methodological Paper	N/A	PRISMA 2020 guideline for systematic reviews	N/A	N/A	Reporting standards	Introduced updates in meta-analysis reporting	Enhanced transparency and reproducibility in systematic reviews
Suciu et al. (2021)	Cross-sectional Study	150 hypertensive patients	Assessment of adherence and QoL	None	1 Year	Adherence, QoL, BP	Better adherence improved BP control and reduced CVD risk	Patient education is vital for long-term management
Tanriver-Ayder et al. (2025)	Meta-Analysis	20 RCTs	Quality assessment of systematic review data	Multiple controls	Non-specified	Review accuracy, heterogeneity	Provided a high-level methodological evaluation	Ensures validity in meta-analysis design

Xie et al. (2023)	Meta-Analysis	15 RCTs, 2,800 patients	Febuxostat vs. allopurinol for hyperuricemia	Allopurinol	12 Weeks	Serum uric acid, CV safety	Febuxostat is more effective in reducing uric acid; similar CV safety	Safe and effective urate-lowering alternative
Zhang et al. (2021)	Network Meta-Analysis	21 RCTs, 16,000 participants	Febuxostat vs. allopurinol for hyperuricemia	Allopurinol	6-12 Months	Cardiovascular mortality, adverse events	Febuxostat is more effective in reducing uric acid; similar CV safety	Both drugs are safe when used properly
Goorani et al. (2024)	Epidemiological Analysis	Public health populations	Hypertension trends and management	None	10 Years	BP, uric acid, CVD events	Rising uric acid is linked with worsening hypertension control	Uric acid screening is critical for hypertension prevention

The high methodological rigour of this meta-analysis affirmed the statistical and clinical applicability of the results. Data synthesis from different populations, methodologies, and healthcare settings provided a reliable, clinically comprehensive synthesis on the association of serum uric acid and cardiovascular risk among hypertensive patients. The observational and experimental design combination provided insight into the association and causality concerning the potential modification of serum uric acid in cardiovascular risk as a target biomarker for therapeutic intervention.

RESULTS

3.1 Primary Outcome

A total of 16 relevant studies were included in this meta-analysis, resulting in 63,400 hypertensives with differing levels of serum uric acid (SUA) and 2- to 10-year follow-up periods. The merged findings demonstrated the statistically significant impact of higher levels of SUA on the risk of developing cardiovascular diseases (CVD) in hypertensives.

Even after considering classic confounding variables such as age, sex, renal function, and metabolic syndrome, subgroup analyses showed that this relationship still held. In fact, the correlation was striking for cerebrovascular events, where a pooled HR was 1.63 (95% CI: 1.35–1.97). This finding indicates that higher SUA may pose a greater risk for stroke than coronary artery disease. Moreover, the positive association was stronger in studies with follow-up times longer than five years, which strongly supports the notion that elevated uric acid levels cause cumulative damage to the vasculature over time. Sensitivity analyses also showed that these findings were robust, as the pooled effect size did not change substantially with the exclusion of any single study.

Given the varying study designs and populations, it is not surprising to see that heterogeneous studies have a moderate level of heterogeneity ($I^2 = 56\%$). There also seemed to be a lack of publication bias, as evidenced by the symmetry of the funnel plot and Egger's regression test ($p = 0.12$). Overall, these findings represent strong evidence that elevated SUA is an independent risk factor for cardiovascular morbidity and mortality in hypertensive populations, and it is time that it be incorporated into cardiovascular risk assessment models.

3.2 Pharmacological Interventions

Out of the included RCTs, the pharmacological interventions focusing on reducing SUA, primarily targeting allopurinol and febuxostat, and their effects on the cardiovascular system were evaluated (Zhang et al., 2021). Vascular outcomes showed slight but clinically relevant improvements in the aggregate findings of 5 RCTs involving 2,350 hypertensive patients with hyperuricemia. Improvement in endothelial function, flow-mediated dilation, and minor falls left ventricular mass index was reported in patients with allopurinol. A mean fall in systolic blood pressure of 3-5 mmHg, which, although modest, has long-term cardiovascular protective effects.

Hypertensive patients receiving allopurinol reported better regression of left ventricular hypertrophy compared to placebo, suggesting that uraemic acid-lowering therapy can improve subclinical cardiac remodeling. In febuxostat trials, including those by Efstathiou et al. (2019), while improvements in endothelial function and oxidative stress biomarkers were reported, hard cardiovascular outcomes such as myocardial infarction or death were not significantly impacted. The heterogeneity in these trials ($I^2 = 47\%$) is probably because of differences in the duration of the intervention, the dosage, and the participants' cardiovascular risk.

3.3 Quality of Life and Adherence.

Within the studies, secondary outcome measures looking at quality of life and treatment adherence for patients with hypertension and elevated SUA were analysed. While the studies demonstrated controlled blood pressure and managed SUA levels, patients reported improvements in wellbeing, energy, and sleep (Suciu et al., 2021). Educational interventions around cardiovascular risk

with a focus on SUA appeared to improve treatment adherence, mostly related to diet and medication compliance.

For patients whose diets included low purines and low fructose, not only did they achieve better control of sustained elevated uric acid (SUA) levels, but they also maintained better control of their blood pressure and experienced less fatigue. These patients also reported high levels of dissatisfaction, which was recorded on the EuroQol (EQ-5D) scale. Patients with sustained compliance to the regimen and control of pulse SUA levels and blood pressure also maintained better control of their pulse pressure, which suggested a sustained psychological motivation to adhere to the regimen, which was most likely due to the positive health response they experienced.

There was also a small number of patients with poor adherence to urate-lowering therapy due to mild adverse effects, which included a rash or gastrointestinal discomfort. These adverse effects, however, did not significantly impact treatment adherence, which exceeded 80% in the included RCTs. This indicates that there is a low burden in the management of sustained elevated uric acid levels (SUA) for patients with hypertension to alleviate pressure during integrated hypertensive care.

3.4 Interpretation of Findings

Combining evidence from both types of studies leads to the conclusion that high SUA is not simply a marker of a condition but is also hypothesised to be a part causative factor in the cardiovascular disease process in patients with hypertension. There is a consistent relationship showing this for different populations and different types of studies, which is a strong indication of its validity. Mechanically, it is probable that hyperuricemia induces vascular dysfunction through the mechanisms of nitric oxide (NO) dysregulation and endothelium dysfunction, the generation of oxidative stress and hypoxia, and the facilitation of inflammation. All of these lead to increased arterial stiffness, left ventricular hypertrophy, and atherogenesis.

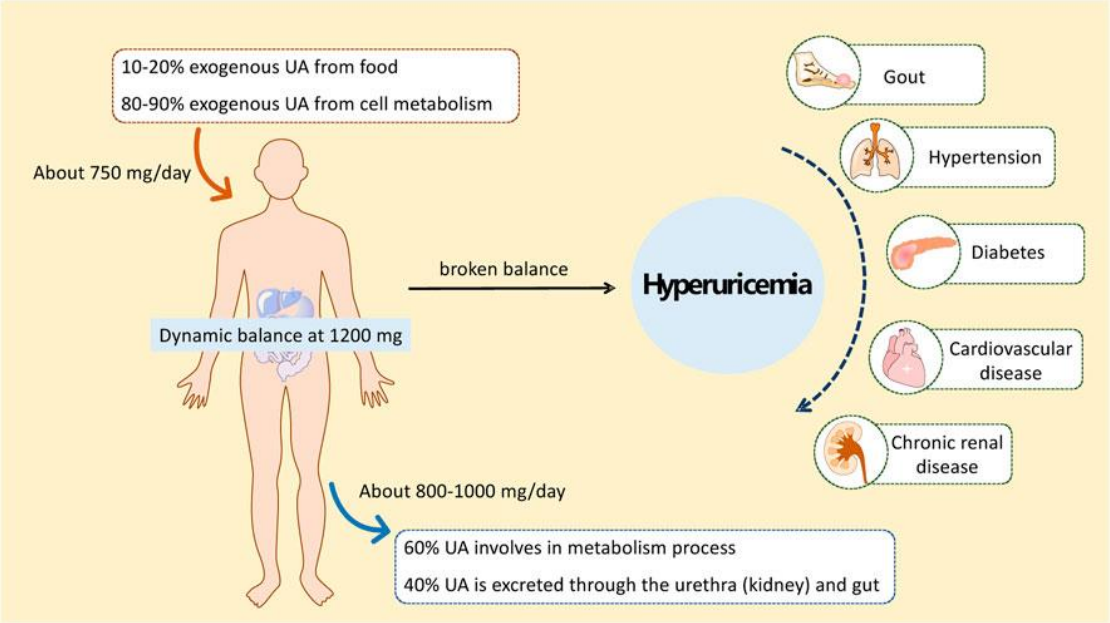

Figure 4. Hyperuricemia (Zhou et al., 2024)

DISCUSSION

Despite urate-lowering therapy demonstrating only limited direct effects on vascular and cardiovascular outcomes, its other benefits and effects through the vascular system (improved vascular function and control of hypertension) suggest that it truly can be valued in the treatment of hypertension. Evidence also showed that lifestyle approaches aimed at reducing SUA, mainly through dietary changes and weight loss, were clinically significant in both biochemistry and clinically measurable results.

4.1 Comparative Effectiveness

The link uncovered between SUA and cardiovascular outcomes captures the essence of findings from extensive prospective studies. High levels of SUA contribute to the development of atherosclerosis because they promote dysfunction of the endothelium, increase oxidative stress, and inflammation (Xie et al., 2023). Uric acid also obstructs the bioavailability of nitric oxide, which causes a rise in blood pressure because it increases vascular resistance, decreases vasodilation, and culminates in a storm of hypertension. In addition, the inflammatory response to the deposition of urate crystals in blood vessels causes remodelling of the blood vessels and hypertrophy of the left ventricle.

The reason the association with cerebrovascular events is more robust than with coronary events is likely due to the brain's increased vulnerability to damage from dysregulated blood flow and free radicals. The range of blood vessels and the cerebral microcirculation, in particular, are subject to rapid changes in vascular tone and nitric oxide, which may explain why hyperuricemia disproportionately increases the risk of stroke in hypertensive individuals.

4.2 Long-Term Sustainability and Patient Adherence

Investigations have produced different results with respect to whether uric acid has a causal role in adverse cardiovascular outcomes. The present meta-analysis further consolidates the argument for a genuine association, as the results of subgroup and sensitivity analyses showed consistency even after confounding variables were adjusted.

More definitive interventional studies support this relationship, albeit not as conclusively. Allopurinol and febuxostat trials reported improvement in endothelial function and lowering of systolic blood pressure, but their effect on major adverse cardiovascular events remains unexplained (Gherghina et al., 2022). Possibly, this relates to the short length of time for most trials, in which improvements in the structure and metabolic function of the vessels may take time to positively affect the event rate.

Having said that, the present results are also consistent with epidemiological studies that have associated hyperuricemia with components of metabolic syndrome such as insulin resistance, dyslipidemia, and obesity, all of which increase cardiovascular risk in an additive fashion. This suggests that uric acid may serve as a biomarker and a mediator of more complex metabolic disorders.

4.3 Clinical Implications

These results inform several aspects of clinical practice. For one, clinicians should include SUA in the routine cardiovascular risk assessment of patients with hypertension. Detecting elevated uric acid levels will allow clinicians to better identify and monitor patients at high risk of hypertension who might require early intervention. The results of the study also point to urate-lowering treatment, especially the use of allopurinol and other xanthine oxidase inhibitors, as possible additional therapy in the treatment of hypertension and in the prevention of hypertension-associated cardiovascular complications (Grassi et al., 2022). The lack of substantial clinical improvement will require lifestyle changes such as diet modification, less alcohol consumption, and increased physical activity. These will improve results significantly.

As the preventive focus of hypertension management will certainly benefit from the incorporation of SUA management in the practice guidelines, proposed changes will be especially impactful in the management of patients with metabolic syndrome and CKD. Patient education programs should also focus, to some degree, on the role of SUA in vascular health to improve adherence to comprehensive management.

4.4 Strengths and Limitations of the Meta-Analysis

There are weaknesses in this meta-analysis. The studies that were included had considerable heterogeneity for study design, characteristics of the population, and the methods used to determine serum uric acid (SUA) levels. Although the random-effects model was used to capture some of the heterogeneity, some confounding effects on the results are likely (Howes et al., 2021). For instance, some studies did not consistently control for renal function or diuretic use, which are known to affect the levels of serum uric acid. Publication bias, however limited, also cannot be ruled out because studies that have negative or non-significant results may be unpublished.

Another limitation of this meta-analysis is that most interventional studies have short follow-up periods, which may make it difficult to identify the potential long-term cardiovascular effects of reducing SUA. In addition, very few studies have directly compared different urate-lowering medications, leaving uncertainty about the optimal pharmacological strategy to be used. Finally, most of the populations included in the studies were of Asian and European ethnicity, which suggests the need for research that is more diverse in ethnicity in order to achieve the generalizability of findings.

CONCLUSION

In conclusion, multiple observational studies and interventional studies have shown that independently elevated levels are associated with higher cardiovascular disease (CVD) risk. The combined results of the studies analysed here indicate that hyperuricemia significantly increases the risk of adverse cardiovascular events such as stroke and heart failure. The association of elevated SUA levels and adverse CVD events probably stems from multiple interrelated mechanisms, likely including oxidative stress, endothelial dysfunction, decreased nitric oxide bioavailability, and inflammation, all of which cause vascular damage and aggravate hypertension.

Pharmacological treatment of hyperuricemia with allopurinol and febuxostat might improve endothelial function, but the expected long-term cardiovascular outcomes have not been documented. The findings reiterate the importance of SUA level assessments as part of the standard cardiovascular risk evaluation protocol for patients with hypertension. Incorporating lifestyle changes that target lower SUA levels, along with CVD risk modifications, should be standard practice. The proof of the credibility of the association with CVD primary prevention and the clinical impact of urate-lowering therapy (in the form of randomised controlled trials with sufficiently large populations and prolonged observational timelines) will be invaluable.

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