

Review

Hyperuricemia and cardiometabolic disease: current evidence linking uric acid to obesity, insulin resistance and type 2 diabetes mellitus

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Received: 7 June 2026 / Accepted: 27 August 2026

Abstract

Hyperuricemia has long been regarded as the biochemical hallmark of gout; however, accumulating evidence indicates that its clinical relevance extends considerably beyond crystal-induced arthropathy. Elevated serum uric acid levels are increasingly encountered in individuals with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular disease, positioning hyperuricemia as a potentially integral component of the cardiometabolic continuum. This narrative review synthesizes current evidence linking serum uric acid to obesity, insulin resistance, T2DM, and cardiovascular risk. Epidemiological data consistently demonstrate robust associations between uric acid levels and adverse cardiometabolic profiles. Complementary experimental findings support plausible pathogenic mechanisms, including oxidative stress, mitochondrial dysfunction, endothelial injury, chronic low-grade inflammation, and activation of the renin-angiotensin-aldosterone system. Special emphasis is placed on the bidirectional relationship between obesity and hyperuricemia, the metabolic consequences of fructose overconsumption, and the emerging utility of uric acid as a predictor of incident metabolic disease. The question of whether hyperuricemia acts primarily as a marker or an active mediator of cardiometabolic dysfunction remains unresolved; current evidence, however, supports a contributory pathophysiological role. A deeper understanding of uric acid metabolism may enhance cardiometabolic risk stratification and inform the development of targeted preventive and therapeutic strategies.

Keywords: uric acid, obesity, insulin resistance, diabetes mellitus, cardiovascular risk

Introduction

Cardiometabolic diseases – encompassing obesity, insulin resistance, T2DM, hypertension, and cardiovascular disease – represent one of the most pressing challenges in contemporary global health, accounting for a substantial proportion of worldwide morbidity and mortality. Their rising prevalence has naturally directed research attention toward novel mechanistic pathways and potential biomarkers capable of refining cardiometabolic risk assessment and informing disease management [1, 2].

Serum uric acid has long been regarded primarily as the biochemical hallmark of gout. Yet this tradi-

tional view is increasingly difficult to sustain in light of mounting clinical and epidemiological evidence. Elevated uric acid levels are encountered with notable consistency in individuals with obesity, metabolic syndrome, insulin resistance, T2DM, and cardiovascular disease – a pattern that raises substantive questions about the role of uric acid in cardiometabolic pathophysiology [2–4].

Hyperuricemia, conventionally defined as serum uric acid exceeding 6.8 mg/dL, has been associated with multiple constituents of the metabolic syndrome, including central obesity, hypertension, dyslipidemia, impaired glucose metabolism, and non-alcoholic fatty liver disease [5–7]. Importantly, prospective data



suggest that elevated uric acid may precede the clinical emergence of obesity, insulin resistance, and T2DM – an observation difficult to reconcile with the notion of uric acid as a mere metabolic bystander [8–10].

Experimental evidence lends further biological plausibility to these associations. Uric acid has been mechanistically implicated in oxidative stress, endothelial dysfunction, chronic low-grade inflammation, mitochondrial impairment, and activation of the renin-angiotensin-aldosterone system (RAAS). Fructose metabolism and obesity-related adipose tissue dysfunction appear to amplify and reinforce these pathogenic interactions [4, 11–14].

Notwithstanding the breadth of available research, the precise pathophysiological role of hyperuricemia remains genuinely contested. Some investigators regard it as a downstream marker of underlying metabolic dysfunction, while others argue for a more active, causally relevant position – and consequently for its consideration as a legitimate therapeutic target [2, 15, 16].

The present narrative review synthesizes current evidence linking hyperuricemia to obesity, insulin resistance, T2DM, and cardiovascular risk, and examines its potential place within the broader cardiometabolic continuum.

Uric Acid and hyperuricemia: beyond gout

Physiology of uric acid metabolism

Uric acid is the final product of purine metabolism in humans. Unlike most mammals, humans lack the enzyme uricase, which converts uric acid into the more soluble compound allantoin. As a result, serum uric acid concentrations are naturally higher in humans than in other species [4].

Approximately two-thirds of uric acid is eliminated through the kidneys, while the remaining portion is excreted via the gastrointestinal tract. Serum uric acid levels are determined by the balance between production and excretion. Hyperuricemia may therefore result from increased uric acid synthesis, impaired renal clearance, or a combination of both mechanisms [2, 4].

Although uric acid has long been recognized for its role in gout, it also possesses important biological properties. Under physiological conditions, uric acid contributes substantially to plasma antioxidant capacity. However, when present in excessive concentrations, it may exert pro-oxidative and pro-inflammatory

effects, potentially contributing to vascular and metabolic dysfunction [4, 17].

Epidemiology and cardiometabolic relevance of hyperuricemia

Hyperuricemia has become increasingly prevalent worldwide, paralleling the global rise in obesity, metabolic syndrome, and T2DM. Its prevalence varies according to age, sex, ethnicity, dietary habits, and the presence of cardiometabolic risk factors, with men generally exhibiting higher serum uric acid concentrations than women until menopause [2, 18].

Elevated serum uric acid levels are particularly common among individuals with obesity, hypertension, insulin resistance, chronic kidney disease, and other components of the metabolic syndrome [2, 19, 20]. Population-based studies consistently demonstrate positive associations between serum uric acid levels and the clustering of metabolic abnormalities, supporting the close relationship between uric acid metabolism and cardiometabolic health [5, 21].

Beyond its traditional association with gout, hyperuricemia is increasingly recognized as a common feature of the cardiometabolic disease spectrum. Higher serum uric acid levels have been linked to obesity, T2DM, non-alcoholic fatty liver disease, hypertension, and cardiovascular disease, often independently of conventional risk factors [2, 11, 22–24].

Consequently, hyperuricemia is no longer viewed solely as a disorder of purine metabolism but as a clinically relevant marker of cardiometabolic risk. Whether it functions primarily as a biomarker, a mediator, or a potential therapeutic target remains under investigation, but its importance in contemporary cardiometabolic medicine is increasingly recognized [2, 10, 16].

Hyperuricemia and obesity

Epidemiological evidence

Obesity and hyperuricemia frequently coexist and are among the most prevalent metabolic abnormalities observed in contemporary populations. Numerous epidemiological studies have demonstrated a strong positive association between increasing body mass index (BMI) and serum uric acid levels across different age groups, ethnicities, and geographic regions [19, 20, 25].

Individuals with overweight and obesity consistently exhibit a higher prevalence of hyperuricemia

compared with normal-weight populations. Furthermore, the risk of elevated serum uric acid appears to increase progressively with the severity of obesity, suggesting a dose-dependent relationship between adiposity and uric acid metabolism [19, 20].

Recent large-scale population studies have also shown that hyperuricemia frequently clusters with other obesity-related metabolic abnormalities, including hypertension, dyslipidemia, insulin resistance, and metabolic syndrome, highlighting its close integration within the broader cardiometabolic risk profile [5, 18, 21].

Visceral adiposity and uric acid

Emerging evidence suggests that visceral adiposity may be more strongly associated with hyperuricemia than overall body weight alone. Visceral fat is metabolically active and contributes to systemic inflammation, oxidative stress, and metabolic dysregulation, all of which may influence uric acid homeostasis [1, 12].

Studies have demonstrated stronger correlations between serum uric acid concentrations and measures of central obesity, including waist circumference and abdominal fat accumulation, than with BMI itself [18, 25]. This observation is clinically important because visceral adiposity is recognized as a major determinant of cardiometabolic risk.

The relationship appears to be particularly relevant in individuals with metabolic syndrome and non-alcoholic fatty liver disease, where excess visceral fat and elevated uric acid levels frequently coexist and may act synergistically to worsen metabolic outcomes [7, 26].

The role of fructose consumption

Among dietary factors, fructose consumption has attracted considerable attention as a potential link between obesity and hyperuricemia. Unlike glucose metabolism, fructose metabolism rapidly consumes intracellular ATP, leading to increased purine degradation and enhanced uric acid production [4, 11].

Excessive intake of sugar-sweetened beverages and fructose-rich processed foods has been associated with both rising obesity rates and increasing prevalence of hyperuricemia worldwide. Experimental and clinical studies suggest that fructose-induced uric acid generation may contribute not only to elevated serum uric acid levels but also to the development of insulin resistance, hepatic steatosis, and cardiometabolic dysfunction [2, 4, 12]. These findings have strengthened the hy-

pothesis that dietary fructose may represent a common upstream driver of several interconnected metabolic disorders.

Bidirectional interactions between obesity and hyperuricemia

The relationship between obesity and hyperuricemia is increasingly recognized as bidirectional. On one hand, excess adiposity promotes uric acid accumulation through increased production, altered adipokine secretion, systemic inflammation, and reduced renal urate excretion. On the other hand, elevated uric acid may contribute to further metabolic deterioration by promoting oxidative stress, endothelial dysfunction, and insulin resistance [4, 11, 12].

Prospective studies have suggested that hyperuricemia may precede the development of obesity in some individuals, while obesity itself remains a major predictor of future hyperuricemia. These observations support the existence of a self-reinforcing cycle in which obesity and elevated uric acid levels mutually aggravate one another over time [7, 8, 13].

This bidirectional interaction may partly explain why hyperuricemia is so commonly encountered in patients with obesity and why both conditions frequently progress together toward a more adverse cardiometabolic phenotype.

Hyperuricemia and insulin resistance

Insulin resistance is a central feature of obesity, metabolic syndrome, T2DM, and cardiovascular disease. Increasing evidence suggests that hyperuricemia may contribute to its development through several interconnected mechanisms, although the exact causal relationship remains under investigation [10, 11, 14].

Experimental evidence

Experimental studies indicate that uric acid is an active biological molecule capable of influencing metabolic homeostasis. Elevated intracellular uric acid levels interfere with insulin signaling in adipocytes, hepatocytes, and vascular cells, resulting in impaired insulin responsiveness and glucose utilization [4, 14].

Animal models of hyperuricemia frequently develop insulin resistance, hypertension, visceral adiposity, and hepatic steatosis, while uric acid-lowering interventions have been shown to partially reverse

these abnormalities [4, 9, 11]. Consistent findings from human studies further demonstrate positive associations between serum uric acid levels and markers of insulin resistance, even before the onset of overt diabetes [10, 13].

Oxidative stress and mitochondrial dysfunction

Oxidative stress represents one of the principal mechanisms linking hyperuricemia to insulin resistance. Although uric acid acts as an antioxidant extracellularly, excessive intracellular accumulation may promote reactive oxygen species generation and disrupt cellular redox balance [4].

This oxidative environment impairs insulin signaling and contributes to mitochondrial dysfunction, reducing metabolic flexibility and cellular responsiveness to insulin. Experimental evidence suggests that elevated uric acid levels impair mitochondrial function and energy metabolism, thereby promoting insulin-resistant states [4, 14, 27].

Endothelial dysfunction

Endothelial dysfunction is an early event in both cardiovascular disease and insulin resistance. Hyperuricemia reduces nitric oxide bioavailability, impairing vasodilation, vascular homeostasis, and insulin-mediated glucose uptake in peripheral tissues [4, 17].

In addition, elevated uric acid levels promote vascular smooth muscle proliferation and oxidative injury within the vascular wall, contributing to hypertension and atherosclerotic processes [2, 15, 28]. These findings suggest that endothelial injury may represent an important pathway linking hyperuricemia with cardiometabolic disease.

Chronic low-grade inflammation

Chronic low-grade inflammation is another key mechanism connecting hyperuricemia and insulin resistance. Elevated uric acid concentrations stimulate inflammatory pathways and cytokine production, creating a metabolic environment that interferes with normal insulin signaling [4, 14].

This interaction appears particularly relevant in obesity, where dysfunctional adipose tissue already exhibits increased inflammatory activity. Hyperuricemia may further amplify this process, reinforcing the cycle linking adiposity, inflammation, and metabolic dysfunction [12, 13].

Renin-angiotensin-aldosterone system activation

Hyperuricemia may also contribute to insulin resistance through activation of RAAS. Experimental studies suggest that elevated uric acid levels stimulate RAAS activity, promoting vasoconstriction, oxidative stress, vascular remodeling, and sodium retention [2, 11]. Beyond blood pressure regulation, excessive RAAS activation contributes to inflammation, endothelial dysfunction, adipose tissue dysregulation, and impaired insulin signaling [2, 9]. Together, these observations support the concept that hyperuricemia participates in the complex pathophysiological network underlying insulin resistance and cardiometabolic disease.

Hyperuricemia and type 2 diabetes mellitus

The relationship between hyperuricemia and T2DM has attracted considerable scientific interest over the past decade. While insulin resistance represents an important mechanistic link between the two conditions, accumulating evidence suggests that elevated serum uric acid may be involved throughout the continuum of diabetes development, from early metabolic disturbances to established disease and its complications [10, 14, 27].

Hyperuricemia as a predictor of diabetes

A growing number of prospective studies have identified hyperuricemia as a significant predictor of future T2DM. Individuals with elevated serum uric acid levels appear to have a higher risk of developing diabetes compared with those with normal uric acid concentrations, even after adjustment for traditional risk factors such as obesity, hypertension, and dyslipidemia [9, 29, 30].

Several longitudinal investigations suggest that hyperuricemia may precede the onset of impaired glucose metabolism by many years, supporting the hypothesis that elevated uric acid is not simply a consequence of diabetes but may participate in its pathogenesis [10, 27].

Meta-analyses have further demonstrated a consistent association between higher serum uric acid levels and increased diabetes incidence across diverse populations. Although causality remains difficult to establish, the reproducibility of these findings has strengthened interest in hyperuricemia as a potential early marker of metabolic risk [11, 29, 30].

Effects on glucose metabolism

Several mechanisms may explain the relationship between hyperuricemia and impaired glucose homeostasis. Elevated uric acid levels have been associated with oxidative stress, endothelial dysfunction, inflammation, and impaired insulin signaling, all of which may adversely affect glucose metabolism [4, 14].

Reduced nitric oxide bioavailability may further impair insulin-mediated glucose uptake, while adipose tissue dysfunction and altered hepatic metabolism contribute to worsening insulin resistance and glucose dysregulation [4, 14, 17, 27]. Collectively, these observations suggest that uric acid may participate in multiple stages of the metabolic cascade leading to T2DM and should be viewed within the broader cardiometabolic network rather than as an isolated metabolic abnormality [10, 11].

Clinical implications in patients with diabetes

Hyperuricemia is highly prevalent in individuals with T2DM and is frequently associated with obesity, hypertension, dyslipidemia, metabolic syndrome, and an overall less favorable cardiometabolic profile [22, 27, 31].

Elevated serum uric acid levels have also been linked to diabetic complications, including chronic kidney disease, non-alcoholic fatty liver disease, and increased cardiovascular risk, supporting its role as a marker of adverse metabolic health [2, 16, 22].

From a clinical perspective, serum uric acid may provide additional information for cardiometabolic risk stratification in patients with T2DM. However, whether uric acid-lowering interventions can directly improve diabetic outcomes remains uncertain and requires further investigation [2, 14, 27].

Hyperuricemia and cardiovascular risk

Cardiovascular disease remains the leading cause of death worldwide and represents the ultimate clinical consequence of multiple interacting cardiometabolic abnormalities. In recent years, hyperuricemia has emerged as a potential contributor to cardiovascular risk, attracting growing attention from both researchers and clinicians. Numerous epidemiological studies have demonstrated associations between elevated serum uric acid levels and hypertension, atherosclerosis, coronary artery disease, heart failure, and cardiovascular mortality [2, 15, 17].

Although hyperuricemia frequently coexists with traditional cardiovascular risk factors, increasing evidence suggests that its relationship with cardiovascular disease extends beyond simple association. Experimental studies have identified several mechanisms through which elevated uric acid may contribute to vascular injury, including endothelial dysfunction, oxidative stress, inflammation, and activation of RAAS [4, 11, 32].

Hypertension, atherosclerosis and endothelial injury

The association between hyperuricemia and vascular disease is among the most extensively investigated aspects of cardiometabolic research. Elevated serum uric acid levels are frequently observed in individuals with hypertension and have been shown to predict the future development of elevated blood pressure in several population-based studies [2, 9, 11].

Experimental and clinical evidence suggests that hyperuricemia contributes to vascular injury through multiple interconnected mechanisms, including reduced nitric oxide bioavailability, oxidative stress, activation of RAAS, vascular smooth muscle proliferation, and chronic low-grade inflammation [2, 4, 15, 17]. These alterations impair endothelial function, promote vascular stiffness and remodeling, and create a pro-atherogenic environment.

Consequently, elevated serum uric acid levels have been associated not only with hypertension but also with markers of subclinical atherosclerosis, coronary artery disease, and adverse vascular outcomes [16, 23, 24, 28]. The relationship appears particularly relevant in individuals with coexisting cardiometabolic abnormalities, where multiple pathogenic pathways converge to amplify cardiovascular risk [23, 24, 28]. Collectively, these findings support the concept that hyperuricemia may participate in the early stages of vascular dysfunction and atherosclerotic disease rather than merely reflect established cardiovascular damage.

Cardiovascular morbidity and mortality

A growing body of epidemiological evidence supports an association between hyperuricemia and adverse cardiovascular outcomes. Elevated serum uric acid levels have been linked to increased risks of coronary artery disease, heart failure, stroke, and cardiovascular mortality across diverse populations [2, 16, 17].

Several large cohort studies have demonstrated that individuals with hyperuricemia experience a higher incidence of cardiovascular events compared

with those with normal uric acid concentrations. Importantly, these associations often persist after adjustment for conventional cardiovascular risk factors, including obesity, hypertension, diabetes mellitus, and renal dysfunction [23, 24, 28].

Recent prospective investigations have further identified hyperuricemia as an early indicator of cardiovascular risk in otherwise apparently healthy individuals, suggesting that elevated serum uric acid may provide additional prognostic information beyond traditional risk assessment tools [23, 24].

Nevertheless, an important question remains unresolved. While observational evidence strongly supports an association between hyperuricemia and cardiovascular morbidity and mortality, definitive proof that uric acid directly causes cardiovascular events is still lacking. This uncertainty has fueled ongoing debate regarding whether hyperuricemia should be regarded primarily as a causal risk factor, a marker of underlying cardiometabolic dysfunction, or both [2, 15, 16].

Despite these remaining questions, current evidence consistently places hyperuricemia within the broader network of cardiometabolic risk factors and highlights its potential clinical relevance in cardiovascular prevention and risk stratification [2, 11, 32].

Therapeutic implications

The close association between hyperuricemia and cardiometabolic disorders has raised important questions regarding the potential benefits of interventions aimed at reducing serum uric acid levels. Current therapeutic strategies primarily focus on lifestyle modification, dietary optimization, pharmacological urate-lowering therapy, and the use of antidiabetic agents that may favorably influence uric acid metabolism [2, 11, 27].

Lifestyle modification and weight reduction

Lifestyle modification remains the cornerstone of management in individuals with hyperuricemia and cardiometabolic disease. Weight reduction has consistently been associated with lower serum uric acid concentrations and improvements in insulin sensitivity, blood pressure, and overall metabolic health [1, 19].

Regular physical activity may further contribute to improved cardiometabolic outcomes and has been associated with a lower prevalence of hyperuricemia and gout-related complications in high-risk populations [1, 33].

Given the strong relationship between obesity and hyperuricemia, sustained weight management represents one of the most effective non-pharmacological strategies for reducing cardiometabolic risk [7, 12].

Dietary approaches

Dietary interventions play a central role in the management of hyperuricemia. Current recommendations emphasize limiting the consumption of fructose-rich beverages, ultra-processed foods, and excessive intake of purine-rich foods, while encouraging balanced dietary patterns rich in vegetables, fruits, whole grains, and unsaturated fats [4, 11].

Particular attention has been directed toward reducing fructose consumption because of its dual contribution to both uric acid production and metabolic dysfunction. Such dietary modifications may simultaneously improve serum uric acid levels, body weight, and cardiometabolic risk factors [4, 12].

Uric acid-lowering therapy

Pharmacological urate-lowering therapy is well established for the treatment of gout and symptomatic hyperuricemia. However, its role in asymptomatic hyperuricemia remains controversial [17, 34].

Although several studies suggest potential cardiovascular and metabolic benefits associated with uric acid reduction, current evidence remains insufficient to recommend routine urate-lowering therapy solely for cardiometabolic risk reduction in the absence of established gout or other approved indications [2, 11, 16].

Effects of modern antidiabetic therapies on uric acid levels

Recent advances in diabetes management have revealed important interactions between antidiabetic therapies and uric acid metabolism. Among contemporary glucose-lowering agents, sodium-glucose cotransporter 2 (SGLT2) inhibitors have consistently demonstrated uric acid-lowering effects in addition to their established glycemic, cardiovascular, and renal benefits [3, 27]. The reduction in serum uric acid observed with SGLT2 inhibitors may contribute, at least partially, to their favorable cardiometabolic profile. This observation further supports the concept that uric acid metabolism is closely integrated within broader metabolic and cardiovascular pathways [3, 14, 27].

As evidence continues to evolve, future therapeutic strategies may increasingly target both hyperglycemia and hyperuricemia as interconnected components of cardiometabolic disease.

Is hyperuricemia a marker or a mediator of cardiometabolic disease?

Whether hyperuricemia represents a marker of metabolic dysfunction or an active mediator of disease progression remains one of the key unresolved questions in cardiometabolic research [2, 32].

Elevated serum uric acid is strongly associated with obesity, insulin resistance, hypertension, type 2 diabetes mellitus, and chronic kidney disease, supporting its role as a marker of adverse metabolic health [2, 10, 11]. At the same time, experimental studies and prospective cohorts suggest that uric acid may contribute to disease development through mechanisms involving oxidative stress, endothelial dysfunction, inflammation, and impaired insulin signaling, and may precede the onset of obesity, hypertension, and diabetes in some individuals [4, 8, 9].

Recent epidemiological evidence further indicates that serum uric acid may provide prognostic information beyond traditional risk factors [5, 16, 24]. However, definitive evidence that uric acid-lowering interventions independently reduce cardiometabolic events remains limited [2, 16].

Taken together, current data suggest that hyperuricemia occupies an intermediate position within the cardiometabolic continuum, functioning both as a marker of metabolic disturbance and a potential mediator of disease progression. Clarifying its therapeutic significance remains an important objective for future research.

Future directions and research perspectives

Despite growing evidence linking hyperuricemia to cardiometabolic disease, important questions remain regarding its causal role and clinical significance. Although experimental and epidemiological studies support a pathogenic contribution of uric acid, definitive evidence from large randomized clinical trials is still lacking [2, 4, 16].

Future research should focus on identifying populations most susceptible to the adverse effects of hyperuricemia, particularly according to obesity phenotype,

visceral adiposity, liver function, sex, age, and associated metabolic disorders [7, 21, 25]. Further investigation is also needed into the complex interactions between hyperuricemia, T2DM, and non-alcoholic fatty liver disease, which appear to share common pathophysiological pathways and frequently coexist in high-risk individuals [22, 26, 27].

The growing use of SGLT2 inhibitors and other modern metabolic therapies offers new opportunities to explore whether modulation of uric acid metabolism contributes to cardiovascular and renal protection [3, 14, 27]. At the same time, integrated lifestyle approaches targeting obesity, fructose consumption, dietary inflammation, and insulin resistance, together with advances in precision medicine, may help refine future risk stratification and preventive strategies incorporating serum uric acid as a cardiometabolic marker [1, 12, 13, 30].

Conclusions

Hyperuricemia is increasingly recognized as an integral component of the cardiometabolic disease spectrum. Beyond its traditional association with gout, elevated serum uric acid levels are consistently linked to obesity, insulin resistance, T2DM, hypertension, and cardiovascular disease.

Current evidence suggests that hyperuricemia functions both as a marker of adverse metabolic health and as a potential contributor to disease progression. Although the causal nature of these relationships remains incompletely understood, serum uric acid appears to provide clinically relevant information regarding cardiometabolic risk.

Consequently, hyperuricemia should no longer be viewed solely as a disorder of purine metabolism. Rather, it represents an important element of the complex cardiometabolic continuum, warranting further investigation as a prognostic marker and potential therapeutic target.

Conflict of interest

The author declares no conflict of interest.

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