Review

Uric Acid as a Causal Risk Factor for Cardiometabolic Syndrome: Insights from Recent Epidemiological and Experimental Evidence

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ABSTRACT

Background: Uric acid is the end product of purine metabolism and serves as a major antioxidant in human plasma. While physiological concentrations may be protective, elevated serum uric acid has been increasingly associated with insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidaemia, and non-alcoholic fatty liver disease. The role of uric acid as a causal factor in cardiometabolic syndrome remains controversial.

Methods: This narrative review examined evidence from epidemiological studies, experimental animal models, genetic analyses, and clinical trials that investigated the relationship between serum uric acid and cardiometabolic syndrome and its components. Emphasis was placed on mechanistic pathways and clinical implications of hyperuricemia.

Results: Most prospective and experimental studies indicate that elevated serum uric acid frequently precedes the development of insulin resistance and type 2 diabetes mellitus and is independently associated with cardiometabolic syndrome. Mechanistic evidence suggests that uric acid contributes to endothelial dysfunction through reduced nitric oxide bioavailability, increased oxidative stress, inflammation, and impaired insulin signaling. Hyperuricemia has also been linked to hypertension, renal dysfunction, and hepatic triglyceride accumulation via pathways involving mitochondrial dysfunction and inhibition of AMP-activated protein kinase. Pharmacological reduction of uric acid has been associated with improvement in cardiometabolic parameters in experimental models and selected clinical studies.

Conclusion: Current evidence supports a contributory role of elevated uric acid in the development of cardiometabolic syndrome. Uric acid may represent a modifiable risk factor and a potential therapeutic target in cardiometabolic disorders.

Keywords: Uric acid; cardiometabolic syndrome; insulin resistance; type 2 diabetes mellitus; non-alcoholic fatty liver disease.

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INTRODUCTION

Recent evidence further underscores the role of uric acid as a determinant of cardiometabolic syndrome.[1, 2] A 2025 NHANES-based analysis revealed that individuals in the highest serum uric acid (SUA) quartile had significantly higher odds of cardiometabolic syndrome (OR = 2.72), with notable variations by sex, education, and ethnicity.[3] Emerging genetic evidence also suggests a causal link between SUA and hypertension.[4] Mechanistically, elevated uric acid may drive insulin resistance, oxidative stress, and endothelial dysfunction—pathways central to metabolic syndrome and cardiovascular disease.[5,6] Notably, even adolescent populations with obesity show cardiometabolic risk elevations in the higher SUA tertiles (≥6.41 mg/dL).[7]

Uric acid is synthesized mainly in the liver, intestines and the vascular endothelium as the end product of an exogenous pool of purines, and endogenously from damaged, dying and dead cells, whereby nucleic acids, adenine and guanine, are degraded into uric acid. Mentioning uric acid generates dread because it is the established etiological agent of the severe, acute and chronic inflammatory arthritis, gout and is implicated in the initiation and progress of the metabolic syndrome,[8] yet uric acid is the predominant anti-oxidant molecule in plasma and is necessarily sufficient for induction of type 2 immune responses. These properties may explain its protective potential in neurological and infectious diseases, mainly schistosomiasis. The pivotal protective potential of uric acid against blood-borne pathogens and neurological and autoimmune diseases is yet to be established.[9] In the liver, uric acid is synthesized from xanthine via xanthine oxidase and contributes significantly to the antioxidant system which helps maintain oxidative stress particularly at concentrations that are in the range of low-to-normal human uremia.[10] However, higher uric acid level exerts nitric oxide inhibitory, pro-inflammatory, prooxidant and proliferative actions that frequently accompanies insulin resistance (IR)[11] and cardiometabolic syndrome (CMS).[12] An elevated serum uric acid is also one of the best independent predictors of diabetes and commonly precedes the development of both insulin resistance and diabetes type 2, as it was discovered that one quarter of diabetes cases can be attributed to a high serum uric acid level and elevated serum uric acid levels were found to be closely associated with insulin resistance and diabetes mellitus type 2. In response to controversial findings,[13] a meta-analysis of prospective cohort studies[14] and a recent critical review[11] concluded that serum uric acid is a strong and independent risk factor for diabetes in middle-aged and older people. Additionally, an increased serum uric acid level was significantly correlated with the severity of albuminuria and diabetic retinopathy in patients with type 2 diabetes mellitus.[15] Furthermore, studies have proposed that elevated uric acid termed hyperuricemia may be considered a true mediator of renal dysfunction and a causal risk factor for atherothrombotic CVD such as myocardial infarction, hypertension, preeclampsia, and stroke.[10,16] The aim of this review is to show that uric acid can be considered a causal risk factor of cardiometabolic syndrome.

Reports have suggested that uric acid promotes insulin resistance by inhibiting endothelial function because insulin depends on nitric oxide for stimulation of glucose uptake via vasodilation induced by nitric oxide in the skeletal muscle. Consequently, uric acid reduces glucose uptake in the skeletal muscle.[17] Therefore, excess uric acid reduces nitric oxide bioavailability and hyperuricemia plays an important role in the development or worsening of IR.[13] Therefore, elevated uric acid is suggested to be a relevant causal risk factor for the development of CMS and its complications.

METHODOLOGY

Relevant literature was identified through searches of major scientific databases including PubMed, Scopus, and Google Scholar. Key search terms included "uric acid," "hyperuricemia," "cardiometabolic syndrome," "insulin resistance," "hypertension," and "non-alcoholic fatty liver disease." Priority was given to peer-reviewed articles, meta-analyses, and prospective cohort studies published in English. Studies that explored mechanistic pathways, clinical associations, or therapeutic implications of uric acid in cardiometabolic disorders were included to provide a comprehensive overview of the current evidence.

DISCUSSION

Cardiometabolic Syndrome

Cardio Metabolic Syndrome (CMS), also known as IR syndrome or metabolic syndrome X, is a combination of metabolic disorders or risk factors that essentially includes a combination of diabetes mellitus, systemic arterial hypertension, central obesity and hyper-lipidemia. CMS has so far drawn global concern and interest.[18] This disease is easily justified because

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cardiovascular disease is the cause of death of 18 million people around the world with diabetes and hypertension being the major risk factors [19, 20, 21,22]. Diabetes mellitus, a key component of CMS, has been shown by many studies to create an increased relative risk (RR) for CVD events. Recent studies also show a higher prevalence of metabolic syndrome in people with hyperuricemia.[19,21,8] The results of some studies indicate a strong relationship between uric acid levels and metabolic syndrome in adults and children and have suggested various mechanisms to justify this relationship.[23,24] Also in a study, nicotine-induced cardiometabolic alteration was accompanied with elevated uric acid level through the adenosine deaminase/xanthine oxidase pathway (ADA/XO- pathway) and treatments that ameliorated cardiometabolic factors also suppressed uric acid level.[25] In other models of CMS as well, suppressing elevated uric acid attenuated CMS and its complications.[26,27] Furthermore, hyperuricemia promotes the occurrence and development of cardiovascular diseases by regulating molecular signals, such as inflammatory response, oxidative stress, insulin resistance/diabetes, endoplasmic reticulum stress, and endothelial dysfunction.[28]

Uric acid and insulin resistance: Insulin resistance (IR) is a pathological situation, in which there is a lack of physiological response to insulin acting on peripheral tissues [29,30,31]. IR reduces glucose utilization in the muscles and fats and increases gluconeogenesis in the liver, leading to metabolic and hemodynamic disturbances known as metabolic syndrome. Some studies have suggested that IR is the underlying cause of metabolic syndrome. Increased insulin secretion may increase blood uric acid levels due to its role in reducing renal excretion of uric acid and sodium, thereby affecting cardiovascular events [26,19,20,21] which contributes to increased incidence and mortality of cardiovascular disease compared to normal levels[32] Obesity, in particular visceral adiposity, is also positively associated with hyperuricemia, which can be reduced by body weight loss.[26,17,33,34] Hyperuricemia is also frequently observed in patients with cardiovascular diseases. The question of whether hyperuricemia is an independent risk factor for cardiovascular disease was raised more than five decades ago.[29,35,36,30] It has been reported so far, the association between hyperuricemia and IR which has contributed to high cardiovascular mortality. Also, studies suggest that hyperuricemia indeed may have a direct vascular effect [37,38]. In hypertensive children with normal renal function, there is a strong correlation between hyperuricemia and blood pressure,[39] and in a controlled trial, treatment of these subjects with the xanthine oxidase inhibitor allopurinol significantly lowered blood pressure in a short-term study.[37,40] In the last 20 years, over 10 studies have reported that hyperuricemia is an independent risk factor for the development of hypertension. Hyperuricemia has been reported to predict the onset of type 2 diabetes (T2DM) and have so far contributed to diabetes related mortality. Uric acid level is increased during the early stages of impaired glucose metabolism. [25,41,42,43] Furthermore, in diabetic patients, hyperuricemia has been linked to both micro- and macrovascular complications. Also, hyperuricemia has been traditionally related to nephrolithiasis and gout. However, it has also been associated with the development of T2DM, cardiometabolic and cardiovascular diseases.

On the basis of pathophysiological, elevated serum uric acid levels may be associated with abnormal lipid and glucose metabolism. The effects of antidiabetic drugs (e.g. metformin, pioglitazone, sulfonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors and insulin) on uric acid concentrations as have been reviewed[44] supports uric acid as a causal risk for CMS.

Chronically elevated circulating uric acid concentrations are associated with increased risk of hypertension, CV disease and chronic kidney disease (CKD). The extent to which uric acid contributes to these conditions, either as a cause or an aggravating factor, remains unclear, but interventions that reduce production or increase in uric acid excretion in hyperuricemic patients have consistently improved cardio-renal prognoses. Uric acid concentrations are often elevated in type 2 diabetes, which contributes to the metabolic syndrome of CV risk. Treatment of type 2 diabetes with a Sodium-glucose transport protein 2 (SGLT2) inhibitor increases uric acid excretion as a result, reduces circulating uric acid and improves parameters of CV alongside renal function. This raises the possibility that the lowering of uric acid by SGLT2 inhibition may assist in reducing adverse CV events and slowing progression of chronic kidney disease (CKD) in type 2 diabetes.[45,46]

***Uric acid and pathogenesis of hypertension*:** Over the years, the association between increased serum uric acid and hypertension has been controversial.[47] Hyperuricemia has been shown to increase the risk of

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sudden death associated with cardiac and diabetic vascular disease.[8]

Gout, kidney st0ones and vascular calcification are results of increased extracellular uric acid deposition [48,49]. According to the Mendelian randomization studies, serum urate is not likely a causal factor in hypertension and cardiometabolic syndrome, however, experimental reports strongly suggest that an increase in intracellular uric acid levels plays a significant role in the pathogenesis of primary hypertension. Also, reports from clinical trials reveal that lowering serum uric acid level is beneficial in hyperuricemic individuals who are young, hypertensive, and have preserved kidney function. Further evidence suggests that activation of the renin-angiotensin system (RAS) occurs in hyperuricemia and blocking the RAS may mimic the effects of xanthine oxidase inhibitors. Therefore, inhibition of adenosine deaminase/xanthine oxidase activities will possibly suppress uric acid production as well as concentration which will be of therapeutic advantage in cardiometabolic syndrome.[8]

Uric acid and non-alcoholic fatty liver disease: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease which is an independent determinant of the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). NAFLD is increasing rapidly worldwide due to widespread obesity and metabolic complications. Recently, the worldwide prevalence of NAFLD is currently estimated to be 24% [27,50]. Reports have suggested that NAFLD is the consequence of a complex interplay between dietary, environmental and metabolic factors. One of the pathophysiological mechanisms for the development of NAFLD is triglyceride (TG) accumulation which primes the liver for more forms of NAFLD especially in the presence of interrupted antioxidant capacity. Scientific evidence has shown that increased hepatic TG results in deterioration of the antioxidant barrier accompanied with mitochondrial dysfunction [25,51,52,53]. The major substrates for hepatic TG synthesis are free fatty acid (FFA) from hepatic de novo lipolysis, peripheral tissues, and dietary sources. It is worthy of note that growing interest exists in the attempt to decrypt the basis and importance of fatty liver as a result of its association with IR metabolic disease.[25,51] Certain factors are important to account for the global spread of metabolic derangement with NAFLD; western diet along with sedentary lifestyle,[54] and nicotine exposure.[31, 55]

Recently, nicotine-induced hepatic triglyceride (TG) accumulation through ADA/XO/UA-dependent pathway implicates uric acid production in the pathogenesis of NAFLD. This is in conformity with several experimental studies reports that increase prevalence of metabolic syndrome is closely related to intensified increases in hyperuricemia which strongly suggest elevated serum uric acid levels to be a predictor of metabolic syndrome, which also includes; impaired IR, lipid metabolism [56,57] and NAFLD.[58] It is noteworthy that uric acid, being capable of acting as a pro-oxidant, causes oxidative damage and may be involved in the pathogenesis of NAFLD.[59] Besides the mechanism involving increased oxidative stress, an elevated uric acid concentration may itself also contribute to hepatic lipid accumulation because a previous report showed uric acid to promote TG accumulation in hepatocytes through inhibition of AMP-activated protein kinase (AMPK).[60] AMPK and AMP deaminase (AMPD) within hepatocytes have been implicated in the development of hepatic steatosis. When AMPK activity is reduced excess fat infiltration occurs, while its stimulation can prevent steatosis through increased fat oxidation and inhibition of lipogenesis. AMPD possesses an opposing effect on fat deposition within the hepatocytes. AMPD activation increases intracellular uric acid synthesis.[61] Intracellular uric acid inhibits AMPK activity[61] thereby causing excess fat infiltration and endoplasmic reticulum stress in the hepatocytes leading fatty liver due to fat oxidation and inhibition of lipogenesis.

CONCLUSION

Uric acid acts as a strong antioxidant outside the cell and as a prooxidant inside the cell where it stimulates NADPH oxidase enzyme causing increased intracellular oxidative stress, mitochondrial injury, and ATP depletion. Elevated uric acid activates the enzyme arginase that reduces nitric oxide precursor leading to reduction in nitric oxide, resulting in increased production of superoxide molecules, reactive oxygen species and endothelial dysfunction. In line with this, TG accumulation in the liver is associated with decreased plasma and hepatic NO bioavailability. Studies have shown that impaired glucose regulation, hyperuricemia, hyperinsulinemia, increased endothelial dysfunction and oxidative stress mediate CMS. Furthermore, several reports have implicated the

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involvement of ADA/XO/UA-dependent pathway and/or uric acid production in metabolic syndrome in association with TG accumulation. Administration of products like allopurinol or febuxostat which prevents uric acid production has been reported to improve metabolic alterations/complications in animal models thereby giving uric acid a causal and unconventional role in cardiometabolic risk factors. Therefore, preventing excess uric acid production favors the constellation of several metabolic risk factors which includes; insulin resistance, hyperglycemia, obesity and lipid accumulation.

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