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Uric Acid is a Key Ingredient in the Treatment Recipe for Cardiorenaal Metabolic Syndrome

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Abstract: Elevated serum uric acid levels are frequently observed in individuals with obesity, hypertension, cardiovascular diseases (CVD), kidney diseases, and cardiorenal metabolic syndrome (CRS). The increased consumption of fructose-rich Western diets has contributed to the growing prevalence of CVD, obesity, and diabetes, particularly in industrialized countries. Emerging evidence suggests that high dietary fructose intake plays a causal role in elevating uric acid levels, thereby contributing to CRS. Animal and epidemiological studies support the notion that elevated serum uric acid levels play a key role in the development of insulin resistance and arterial hypertension, suggesting potential pathophysiological mechanisms that drive CVD, associated cardiovascular disorders, and chronic kidney disease (CKD). Elevated serum uric acid levels appear to disrupt nitric oxide production, endothelial function, arterial stiffness, and activate the renin-angiotensin-aldosterone system (RAAS). Additionally, oxidative stress and maladaptive immune and inflammatory responses contribute to vascular, cardiac, and renal fibrosis, leading to associated functional impairments. Small clinical trials have shown that uric acid-lowering therapy may benefit such patients; however, there is no consensus on treating asymptomatic hyperuricemia. Larger randomized controlled trials are necessary to critically evaluate the benefits of serum uric acid reduction in patients with heart failure, diabetes, and/or hypertension.

Keywords: uric acid, fructose, cardiorenal metabolic syndrome, chronic kidney disease.

Introduction

The prevalence of obesity continues to rise globally, with childhood and adolescent obesity becoming a significant public health issue. Obesity is associated with an increased prevalence of cardiorenal metabolic syndrome (CRS), a collection of interrelated risk factors for cardiovascular diseases (CVD) and chronic kidney disease (CKD). These factors include obesity, insulin resistance, metabolic dyslipidemia, hypertension, diastolic cardiac dysfunction, and kidney dysfunction, such as proteinuria. Over the past three decades, the consumption of high-fructose corn syrup (HFCS) has significantly increased, exceeding the changes in the intake of any other food product. Accumulating evidence indicates that hyperuricemia is a critical factor contributing to the development and progression of CRS. In 1776, Swedish pharmacist Carl Wilhelm Scheele identified uric acid in bladder stones. Subsequent reports have linked elevated serum uric acid levels with gout, hypertension, and CKD. Hyperuricemia has been associated with inflammation, oxidative stress, insulin resistance, dysglycemia, endothelial dysfunction, vascular stiffness, cardiac and kidney abnormalities, diastolic cardiac dysfunction, hyperfiltration, and proteinuria—all components of CRS. The role of a high-fructose Western diet and hyperuricemia in CRS development is underscored by the relationship between excessive intake of sugar-sweetened beverages and elevated uric acid levels.

Methodology

The production and metabolism of uric acid are complex processes regulated by various factors, including hepatic synthesis and renal and intestinal excretion. Uric acid is the end product of both exogenous purine intake and endogenous purine metabolism. The amount of exogenous purines depends significantly on dietary habits, with animal proteins contributing substantially to the purine pool. Endogenous uric acid production mainly occurs in the liver, intestines, muscles, kidneys, and vascular endothelium. The formation of uric acid from purine catabolism involves enzymatic reactions, with xanthine oxidase playing a key role. Inosine serves as an intermediate in this process, which is converted to hypoxanthine by purine nucleoside phosphorylase. Xanthine oxidase then converts hypoxanthine to xanthine and, subsequently, to uric acid. Approximately two-thirds of uric acid is excreted through the kidneys, while one-third is eliminated via the gastrointestinal tract. Almost all uric acid is filtered at the glomeruli, with post-glomerular reabsorption and secretion regulating the excreted amount. Proximal tubules play a crucial role in uric acid reabsorption and secretion, with 90% reabsorbed into the bloodstream. The primary transporters in proximal tubules exchange intracellular anions for uric acid. Elevated serum uric acid levels observed in obese individuals and those with renal impairment result from multiple mechanisms. Obesity, particularly with high HFCS intake, leads to increased hepatic uric acid production. As glomerular filtration rate (GFR) decreases, serum uric acid levels rise, with 50% of renal failure patients experiencing hyperuricemia by the time dialysis begins. Hyperuricemia is closely linked to hyperinsulinemia and insulin resistance, although the underlying mechanisms remain unclear. Insulin signaling affects renal tubular function, and urinary uric acid clearance decreases with reduced insulin-mediated glucose excretion. Recent studies suggest that adipose tissue may serve as an endogenous source of uric acid, promoting macrophage infiltration and inflammatory responses. Uric acid is a byproduct of unregulated fructose metabolism, mediated by increased fructokinase activity. Fructokinase lacks a feedback inhibition system, utilizing ATP for phosphorylation, depleting intracellular phosphate, and accelerating uric acid production via AMP deaminase activation. Serum uric acid levels rise rapidly after fructose ingestion, increasing by up to 2 mg/dL within an hour.

Results

Epidemiological studies have confirmed a strong association between hyperuricemia and cardiorenal syndrome (CRS). A cross-sectional analysis of 1,370 adolescents aged 12–17 years using National Health and Nutrition Examination Survey (NHANES) data revealed that the prevalence of CRS was <1% in the lowest serum uric acid quartile, 3.7% in the second quartile, 10.3% in the third quartile, and 21.1% in the highest quartile. High-fructose diets were found to increase uric acid production and induce CRS components through mechanisms independent of energy intake or weight gain, effects not observed with glucose-rich diets. In a diabetes prevention study involving middle-aged individuals with impaired glucose tolerance, elevated baseline uric acid levels and their increase over time doubled the likelihood of developing type 2 diabetes (T2D). A meta-analysis of 154 studies reporting over 100 T2D cases with follow-up periods of 2–13.5 years demonstrated a positive correlation between serum uric acid levels and T2D development, independent of study characteristics. Hyperuricemia has also been linked to arterial hypertension, with early research reporting elevated uric acid levels in 25–40% of untreated hypertension patients and 75% of those with malignant hypertension. A study of over 100 participants in the Framingham Heart Study identified serum uric acid as an independent predictor of hypertension incidence and progression over four years. Among children referred for hypertension evaluation, serum uric acid levels correlated directly with both systolic and diastolic blood pressure. Dietary fructose-induced hyperuricemia was found to contribute to increased arterial pressure in randomized controlled trials. For instance, a placebo-controlled study involving 36 adolescents with untreated stage 1 hypertension and serum uric acid levels ≥6 mg/dL demonstrated that allopurinol therapy significantly reduced systolic and diastolic blood pressure compared to placebo. Similarly, in a study involving pregnant women, serum uric acid levels ≥5.5 mg/dL were predictive of preeclampsia risk. Meta-analyses have shown that hyperuricemia is associated with a higher risk of stroke incidence and mortality, highlighting its role in endothelial dysfunction, arterial stiffness, and cardiac

dysfunction. Randomized placebo-controlled trials have also demonstrated the efficacy of allopurinol in improving endothelial-mediated vasodilation and reducing cardiovascular disease incidence in patients with hypertensive nephropathy.

Discussion and Conclusion

It remains unclear whether uric acid is merely a marker or an independent risk factor for the onset and progression of chronic kidney disease (CKD). However, studies on animal models have shown that hyperuricemia accelerates kidney disease progression, including proteinuria and renal failure, accompanied by glomerulosclerosis and tubulointerstitial fibrosis. Epidemiological studies have linked hyperuricemia to declining renal function in the general population and among individuals with hypertension, diabetes, and CKD. Cardiorenal syndrome (CRS) is closely associated with CKD (defined as a glomerular filtration rate [GFR] <60 mL/min/1.73 m²) and microalbuminuria. The risk of CKD increases progressively with the number of CRS components. It has been hypothesized that excessive fructose consumption contributes to kidney disease through hyperuricemia, a hallmark of CRS. Recent studies have demonstrated that uric acid-lowering therapy can slow CKD progression. For instance, in a randomized trial involving patients with an estimated GFR <60 mL/min/1.73 m², allopurinol treatment significantly improved GFR compared to standard therapy. Additionally, in patients with hyperuricemic CKD, allopurinol reduced the incidence of renal failure and dialysis dependency compared to control groups. Hyperuricemia has been shown to induce endothelial dysfunction, vascular stiffness, and diastolic cardiac dysfunction. It exacerbates cardiovascular conditions through mechanisms such as nitric oxide depletion, oxidative stress, and maladaptive immune responses. These findings underscore the importance of uric acid as a therapeutic target in managing CRS and CKD.

Conclusion

Growing evidence suggests that uric acid plays a pivotal role in the pathogenesis of cardiovascular diseases (CVD), type 2 diabetes (T2D), CRS, and CKD. Potential mechanisms include inflammation driven by urate crystals, intracellular oxidative stress, RAAS activation, impaired nitric oxide availability, maladaptive immune responses, and insulin resistance. Although small-scale studies have demonstrated the benefits of uric acid-lowering therapy, there is currently no consensus on its routine use in hyperuricemic patients with asymptomatic conditions. Larger randomized controlled trials are required to determine whether lowering serum uric acid levels improves clinical outcomes, particularly in patients with CVD, T2D, or CKD.

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