International Journal of Clinical and Experimental Medicine Research, 2024, 8(1), 187-190
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Research Progress on the Mechanism of Kidney Injury Associated with Hyperuricemia

Jianchun Chen, Xiaoying Yang, Caizhong Zhang, Wanping Lv*

Chengdu Rheumatology Hospital, Chengdu, Sichuan, China.

How to cite this paper: Jianchun Chen, Xiaoying Yang, Caizhong Zhang, Wanping Lv. (2024) Research Progress on the Mechanism of Kidney Injury Associated with Hyperuricemia. *International Journal of Clinical and Experimental Medicine Research*, 8(1), 187-190.
DOI: 10.26855/ijcemr.2024.01.032

Received: January 17, 2024
Accepted: February 14, 2024
Published: March 12, 2024

***Corresponding author:** Wanping Lv, Chengdu Rheumatology Hospital, Chengdu, Sichuan, China.

Abstract

Hyperuricemia (HUA) has become one of the global public health problems, and the mechanisms of renal injury caused by it have received increasing attention. This review focuses on the main mechanisms of hyperuricemia-associated renal injury, including the effects of three aspects: monosodium urate (MSU) crystal deposition, activated NLRP3 inflammasome, and mitochondrial dysfunction. We explored in detail how MSU crystals lead to kidney injury by inducing oxidative stress, inflammatory responses, and apoptosis. Second, we found that the activation of NLRP3 inflammatory vesicles plays a key role in hyperuricemia-induced renal injury by triggering a strong inflammatory response and further destroying renal tissues. Finally, we also discussed the importance of mitochondrial dysfunction in hyperuricemia-induced kidney injury, noting that mitochondrial dysfunction may exacerbate kidney injury by affecting cellular energy metabolism and modulating cell death pathways. Through a comprehensive understanding of these mechanisms, we hope to provide new ideas for the prevention and treatment of hyperuricemia-associated kidney disease.

Keywords

Hyperuricemia, kidney injury, MSU crystal, NLRP3 inflammasome

1. Introduction

Uric acid is the final metabolite of endogenous and exogenous purines and is synthesized primarily in the liver and produced in small amounts in the small intestine. In most mammals, uricase oxidatively degrades uric acid to the soluble compound allantoin [1]. During human evolution, inactivating mutations in the gene encoding uricase have occurred, resulting in uricase deficiency. Uric acid is one of the major antioxidant products in humans, responsible for up to 55% of the antioxidant scavenging capacity of free radicals. Average serum uric acid (serum urate) levels have tended to increase worldwide during this century, with hyperuricemia clinically defined as serum uric acid levels ≥7 mg/dL in men and postmenopausal women, and ≥6 mg/dL in premenopausal women. In recent years, due to changes in lifestyles and an increase in the elderly population, the overall prevalence of hyperuricemia in China has been 13.3%, with the number of patients reaching 177 million. The number of people with hyperuricemia has reached 177 million and is increasing at an annual rate of 9.7%. In fact, the prevalence of hyperuricemia in some coastal areas and developed cities in China has risen to 20 per cent, which is close to the level of developed countries [2].

Excessive uric acid levels can cause a variety of diseases such as gout and urinary tract stones and are also closely associated with diabetes, heart and kidney disease. An anthropometric and biochemical data from 625 patients with chronic kidney disease (CKD) from a nephrology department found that uric acid clearance (Cur) and glomerular uric acid filtration load (FLur) are more reliable indicators of high uric acid classification in CKD patients [3]. A long-term follow-up cohort study that included 13,338 volunteers with normal renal function in two communities showed a significant relationship between baseline uric acid levels and the risk of kidney disease, with an 11%

increase in the risk of kidney disease for every 7 mg/dL increase in serum uric acid. Traditionally, renal injury due to hyperuricemia is thought to be caused by the action of uric acid crystals. Specifically, uric acid crystals deposited in the lumen of the collecting ducts cause acute kidney damage. This, in turn, leads to tubular obstruction, the development of an inflammatory response, and progressive tubulointerstitial injury over time, which reduces the glomerular filtration rate (eGFR). However, there are inconsistent results reported regarding the role of uric acid in the progression of CKD. In a prospective analysis of 34,831 patients from a Taiwanese biobank, genetic risk scores and seven Mendelian randomization methods showed no significant association between serum urate levels and the risk of developing CKD [4]. Overall, with a large amount of experimental data, problems such as kidney disease associated with HUA still cannot be ignored, and an in-depth exploration of the mechanisms of uric acid-induced changes in renal pathology will contribute to the development of new therapeutic approaches for the prevention and treatment of kidney injury.

2. Synthesis and excretion of uric acid

Uric acid ($C_5H_4N_4O_3$) is a heterocyclic organic compound with a molecular weight of 168 Da [5]. Uric acid is synthesized primarily in the liver, with small amounts produced in the small intestine. It is the end product of purine metabolism in the body. Purine nucleotides generate adenosine, inosine, and guanosine under the action of adenosine deaminase; adenosine deamination generates inosine, inosine, and guanosine, are further converted to hypoxanthine, and guanine, hypoxanthine generates xanthine under the action of xanthine oxidase, and guanine deamination forms xanthine. Xanthine is again oxidized by xanthine oxidase to produce uric acid eventually [6]. In most mammals, uricase oxidizes uric acid to the soluble compound allantoin. During human evolution, inactivating mutations in the gene encoding the enzyme uricase have occurred, resulting in a deficiency of the enzyme. Studies have shown that two-thirds of the body's uric acid is excreted from the kidneys, one-third from the intestines and bile, and a tiny percentage of uric acid is excreted in the bile. Renal processing of uric acid includes glomerular filtration, tubular reabsorption, tubular secretion, and post-secretory reabsorption. The kidney regulates uric acid excretion by reabsorption and secretion from the proximal renal tubule, which is accomplished primarily through uric acid transporter proteins. Uric acid transporter proteins are necessary for the renal processing of uric acid and can be broadly categorized into reabsorption-related proteins and secretion-related proteins. Reabsorption-associated proteins include urate anion transporter protein 1 (URAT1), organic anion transporter protein 4 (OAT4), and glucose transporter protein 9 (GLUT9); secretion-associated transporter proteins include OAT1, OAT3, multidrug-resistant protein 4 (MRP4/ABCC4), and breast cancer resistance protein (BCRP/ABCG2).

3. Mechanisms associated with hyperuricemia-induced renal impairment

3.1 MSU crystal deposition

Urate crystals may form MSU crystals when the urate level is >6.8 mg/dL (405 μmol/l), the solubility limit under physiologic conditions. Several factors have been found to influence the formation of MSU crystals, including temperature, sodium and cation concentrations, pH, mechanical stress, cartilage composition, uric acid-binding antibodies, and cartilage and synovial fluid composition. The process of MSU crystallization is similar to the formation of other crystals and is thought to depend on urate concentration and other factors. It is thought that MSU remains in solution until there is a change in solubility (e.g., an increase in concentration and a decrease in temperature). This causes MSU molecules to aggregate in solution. These clusters aggregate into nuclei, which provide the basis for additional crystal formation and growth. Nucleation and crystal growth can be facilitated by local factors, e.g., low pH, elevated calcium levels, organic molecules originating from cartilage or synovium, albumin, antibodies, sodium ions) [7]. Although the presence of hyperuricemia is critical for MSU crystal formation, only a tiny percentage (2-6%) of hyperuricemic patients develop clinical gout. This may be due to different biological responses to elevated urate or inadequate disease detection. In contrast, some patients have normal serum urate (≤6.0 mg/dL) during an acute gouty attack, suggesting a complex relationship between serum urate levels and acute MSU crystallization. Decreased urate levels during an acute attack may be secondary to the uric acid excretory effects of inflammatory mediators and hormone production (IL-6 and adrenocorticotropic hormone, respectively).

MSU crystals are recognized as a damage-associated molecular pattern (DAMP) that stimulates the innate and adaptive immune system [8]. An in vitro study found that oxidative stress generated by MSU crystals promotes renal cell apoptosis through the mitochondrial cysteine asparaginase-dependent apoptotic pathway. Another in vitro study showed that MSU crystals are cytotoxic to renal cells and that this cytotoxicity involves necrotic apoptosis, a form

of regulated cell death in vitro and in vivo. An in vitro study in human embryonic kidney cells showed that MSU crystals promoted the expression of reactive oxygen species, inducible nitric oxide synthase, and cyclooxygenase 2. In addition, MSU crystal-stimulated enhancement of cysteinyl asparaginase expression led to apoptosis in renal cells. It was also shown that MSU incubation with human renal mesangial cells (HRMC) increased the expression of intercellular adhesion molecule 1 and subsequent intercellular adhesion between HRMC and monocytes. Infiltration of monocytes into the glomerular mesangium contributes to the development of glomerulonephritis.

3.2 Activation of the NLRP3 inflammasome

Inflammasome are a component of the innate immune system and have been implicated in the pathogenesis of cold and heat protein-associated periodic fever syndrome (CAPS) [9]. In recent years, abnormal inflammasomes have been associated with a range of more common and complex diseases, including metabolic disorders, crystal-associated diseases, and autoimmune disorders. NLRP3, an inflammasome sensor protein in the innate immune system, detects invasion by exogenous pathogens and endogenous cellular damage and responds by forming NLRP3 inflammasomes. The three main components of the NLRP3 inflammasome are NLRP3, caspase-1, and ASC (apoptosis-associated speck-like protein) [10]. Aberrant activation of NLRP3 drives the chronic inflammatory state in vivo and thus regulates the pathogenesis of inflammation-related diseases.

On the one hand, activation of NLRP3 inflammatory vesicles can lead to cellular damage and even death through endoplasmic reticulum stress, lysosomal disruption, mitochondrial dysfunction, and interactions between the Golgi apparatus and extracellular vesicles. On the other hand, NLRP3 inflammasome acts as a molecular platform that triggers the activation of caspase-1 and cleavage of IL-1β, IL-18, and Gasdermin D through different molecular mechanisms. The cleaved NT-GSDMD forms pores in the cell membrane and triggers pyrophosphorylation, which induces cell death and releases intracellular pro-inflammatory molecules.

Studies have found a close relationship between uric acid and NLRP3 inflammatory vesicles in recent years. Uric acid can affect the morphology and function of renal parenchymal cells by activating NLRP3 inflammatory vesicles and secreting related inflammatory factors. Upon cellular stress, various intracellular organelles become dysfunctional and are involved in the NLRP3 inflammatory vesicle activation process, thus affecting the occurrence and development of CKD in hyperuricemia. An increasing number of studies have focused on the significant impact of gut flora on the kidney. The pathogenic interconnection between the gut microbiome and renal disease is known as the "gut-kidney axis." In addition to the kidneys, the gut is thought to be an organ that excretes uric acid, and the GI tract heavily expresses genes related to uric acid synthesis and transport; the gut excretes more than 30-40% of uric acid and defects in intestinal clearance contribute to HUA. Uric acid drives intestinal barrier dysfunction via TSPO-mediated activation of NLRP3 inflammatory vesicles. Pharmacological studies analyzing palmatine from the cortex of Phellodendron Bark found that its uric acid-lowering and nephroprotective effects were attributed to targeting the Keap1-Nrf2/NLRP3 axis [11]. Ma et al. found that soluble uric acid alone increased the release of ROS, depolarized the mitochondrial membrane potential, up-regulated TSPO, and increased the expression of TLR4 and NLRP3, which in turn activated the NLRP3 inflammatory vesicles and NF-κB signaling [12].

3.3 Mitochondrial dysfunction

It was found that hyperuricemia leads to mitochondrial dysfunction, affecting ATP synthesis and energy metabolism. Using RNA sequencing and biochemical analyses, the researchers found that the expression and nuclear localization levels of nuclear factor E2-related factor 2 (NRF2) increased early in hyperuricemic nephropathy (HN) progression and gradually declined below baseline levels. Specifically, activation of NRF2 signaling reduces oxidative stress by restoring mitochondrial homeostasis and decreasing the expression of NADPH oxidase 4 (NOX4) in vivo or in vitro. NRF2 is a crucial regulator for improving mitochondrial homeostasis and fibrosis in renal tubular cells, and activation of NRF2 represents a promising strategy for restoring redox homeostasis and combating HN. Serum- and glucocorticoid-induced kinase 1 (SGK1) is a serine/threonine kinase that can be transcriptionally regulated by glucocorticoids, serum, and a variety of cellular stress stimuli, including oxidative stress, and it functions as a potent anti-apoptotic kinase under these circumstances. Increased SGK1 expression and activity have been reported to protect endothelial cells from oxidative stress, whereas inhibition of SGK1 leads to increased stress injury in neuronal cells. In addition, recent studies have shown that SGK1 is dynamically overexpressed and activated during ischemia/reperfusion injury in rat kidneys, and SGK21 protects renal cells from hypoxia/reoxygenation injury by promoting autophagy. Most importantly, SGK1 attenuates oxidative stress-induced renal tubular epithelial cell injury by regulating mitochondrial function [13].

Several studies have demonstrated that the onset and development of HN can occur through a variety of

mechanisms, such as the promotion of autophagy and NLRP3-mediated inflammation, inhibition of transforming growth factor (TGF)-β, extracellular signal-regulated kinase 1/2 (ERK1/2), and nuclear factor (NF)-κB signaling pathways. On the one hand, hyperuricemia can cause oxidative stress, which induces the overproduction of reactive oxygen species (ROS) in the mitochondria of renal tubular epithelial cells, and ROS play an essential role in the pathogenesis of renal tubulointerstitial fibrosis in HN. On the other hand, oxidative stress generated by MSU crystallization promotes renal cell apoptosis, which is induced through the mitochondrial cysteine asparaginase-dependent apoptotic pathway. Further, rats with hyperuricemia due to inhibition of uricase with PO develop endothelial dysfunction, hypertension, and renal injury. Numerous studies have linked uric acid to endothelial dysfunction in humans, and many reports suggest that lowering uric acid with allopurinol ameliorates endothelial dysfunction. Recent studies have found that uric acid-induced endothelial dysfunction is associated with reduced mitochondrial mass and ATP production [14].

4. Conclusion

In summary, as the prevalence of HUA increases, the development of CKD is also affected. The mechanisms of HUA-associated kidney injury mainly include MSU crystal deposition, activated NLRP3 inflammatory vesicles, and mitochondrial dysfunction. Lowering blood uric acid levels is the key to treating HUA, and xanthine oxidase inhibitors and uric acid-lowering agents are considered reasonable candidates for lowering serum uric acid levels; however, strong evidence is lacking to support that lowering uric acid may slow the progression of kidney disease. Furthermore, the key to exploring the disease's pathomechanisms and drug development is the selection of an appropriate research model, especially in such a complex disease. However, with the research boom initiated by 16S rRNA gene sequencing and untargeted metabolomics, genes, metabolic pathways, and other novel medical approaches, this may become a new way of thinking to study the mechanism of HUA-associated renal injury and pave the way for targeted therapies for HUA-associated renal injury. Overall, future work will require synergistic advances in all disciplines to address the renal problems and challenges associated with HUA.

References

[1] Zhang W. Uric acid en route to gout [M]. Elsevier. 2023: 209-275.

[2] Ko J, Kang H, Kim D, et al. Uric acid induced the phenotype transition of vascular endothelial cells via induction of oxidative stress and glycocalyx shedding [J]. The FASEB Journal, 2019, 33(12): 13334-13345.

[3] Guan H, Zheng Y, Zhou X, et al. Efficacy of different urinary uric acid indicators in patients with chronic kidney disease [J]. BMC Nephrology, 2020, 21(1).

[4] Tsao H-M, Lai T-S, Chang Y-C, et al. Serum Urate and Risk of Chronic Kidney Disease [J]. Mayo Clinic Proceedings, 2023, 98(4): 513-521.

[5] Chen C, Lü J-M, Yao Q. Hyperuricemia-Related Diseases and Xanthine Oxidoreductase (XOR) Inhibitors: An Overview[J]. Medical Science Monitor, 2016, 22: 2501-2512.

[6] Mandal A K, Mount D B. The Molecular Physiology of Uric Acid Homeostasis [J]. Annual Review of Physiology, 2015, 77(1): 323-345.

[7] Keenan R T. The biology of urate [J]. Seminars in Arthritis and Rheumatism, 2020, 50(3): S2-S10.

[8] Mei Y, Dong B, Geng Z, et al. Excess Uric Acid Induces Gouty Nephropathy Through Crystal Formation: A Review of Recent Insights [J]. Frontiers in Endocrinology, 2022, 13.

[9] He Y, Zeng M Y, Yang D, et al. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux [J]. Nature, 2016, 530(7590): 354-357.

[10] Fu J, Wu H. Structural Mechanisms of NLRP3 Inflammasome Assembly and Activation [J]. Annual Review of Immunology, 2023, 41(1): 301-316.

[11] Ai G, Huang R, Xie J, et al. Hypouricemic and nephroprotective effects of palmatine from Cortex Phellodendri Amurensis: A uric acid modulator targeting Keap1-Nrf2/NLRP3 axis [J]. Journal of Ethnopharmacology, 2023, 301: 115775.

[12] Ma C, Yang X, Lv Q, et al. Soluble uric acid induces inflammation via TLR4/NLRP3 pathway in intestinal epithelial cells [J]. Iranian Journal of Basic Medical Sciences, 2020.

[13] Jiang D, Fu C, Xiao J, et al. SGK1 Attenuates Oxidative Stress-Induced Renal Tubular Epithelial Cell Injury by Regulating Mitochondrial Function [J]. Oxidative Medicine and Cellular Longevity, 2019: 1-12.

[14] Sánchez-Lozada L G, Lanaspa M A, Cristóbal-García M, et al. Uric Acid-Induced Endothelial Dysfunction Is Associated with Mitochondrial Alterations and Decreased Intracellular ATP Concentrations [J]. Nephron Experimental Nephrology, 2012, 121(3-4): e71-e78.