The Key Role of Hyperuricemia in Oxidative Stress, Inflammatory Response, and Endothelial Dysfunction

Huan Yi[1], Fachun Zhou[2*], Shijing Tian[2], Sanle Jiang[1]

1. Chongqing Medical University, Chongqing 400016, China.

2. The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

Abstract: Uric acid is the end product of purine metabolism in humans. A growing body of experimental and clinical evidence suggests that hyperuricemia has pathogenic effects in vivo such as inducing oxidative stress, promoting inflammatory responses, and causing endothelial dysfunction, and is involved in affecting systemic inflammatory responses and hemodynamics by a variety of mechanisms. This review will provide an overview of the role of hyperuricemia in oxidative stress, inflammatory response, and endothelial dysfunction.

Keywords: Hyperuricemia; Oxidative Stress; Inflammation; Endothelial Dysfunction

Introduction

Uric acid is an end product of purine metabolism and is produced by 80% of the body's cellular metabolism and 20% is obtained from food. Most uric acid is excreted by the kidneys (65-75%) and the intestine (25-35%)[1] . Uric acid in body fluids is a potent antioxidant, scavenging monomorphic oxygen and free radicals, and is estimated to account for approximately 50% of the total antioxidant capacity of human biological fluids [2]. Intracellular uric acid, on the other hand, is pro-oxidant and can lead to oxidative stress, induce inflammatory responses with causing endothelial dysfunction, which can lead to cardiovascular disease and kidney disease [3, 4]. In addition, due to the low solubility of uric acid in water, once the concentration of uric acid exceeds 6.5 mg/dL , urate crystals are precipitated and may be deposited in joints, kidneys and other tissues, which can lead to tissue damage [5].

Hyperuricemia is clinically defined as blood uric acid levels of ≥7 mg/dL (420 umol/L) in men and postmenopausal women and ≥6 mg/dL (360 umol/L) in premenopausal women [6].

1. Pathogenesis of hyperuricemia

Hyperuricemia is caused by an imbalance in the production and excretion of uric acid. High purine diet, increased purine metabolism and excessive alcohol consumption contribute to increased uric acid production. Massive cellular damage in tumor lysis syndrome, which promotes nucleic acid metabolism, is also responsible for increased uric acid production [7]. Other rare causes of acute hyperuricemia include seizures, rhabdomyolysis, and excessive exercise. Considering that purine intake and its excretion in the gastrointestinal tract are fairly constant in most individuals, serum uric acid concentration depends to a large extent on endogenous purine production and its renal excretion, while the renal excretion of uric acid depends on glomerular filtration and subsequent tubular reabsorption, influenced by renal function and intrarenal hemodynamics [8].

2. Oxidative stress induced by hyperuricemia

Once transported into cells, uric acid becomes a pro-oxidant, which increases the production of reactive oxygen species (ROS), including superoxide anion (O2-), H2O2, and 8-isoprostane [9, 10]. Many studies have shown that oxidative stress

caused by hyperuricemia affects several organs and systems, including the heart and kidneys [11]. Pathologically, oxidative stress associated with hyperuricemia leads to DNA damage, oxidation and inactivation of enzymes, production of inflammatory cytokines, and apoptosis [12]. Mitochondria in renal tubular epithelial cells (TEC) may be severely damaged by oxidative stress, and antioxidants are beneficial for the recovery of endothelial function, such as reduced glutathione [13].Another important source of ROS is NADPH oxidase. It has been found that uric acid stimulates ROS synthesis via NADPH oxidase in various cells, such as adipocytes, vascular smooth muscle cells and vascular endothelial cells [14] .

In conclusion, hyperuricemia-mediated oxidative stress directly damages multiple organs and systems, especially the kidney, and is therefore a biotherapeutic target for uric acid-induced kidney injury.

3. Hyperuricemia promotes inflammatory response

Recent in vivo and in vitro studies have shown that UA stimulates the release of early inflammatory response factors IL-1, IL-6, and IL-8 by binding to cellular NF-kB (nuclear factor) receptors, which subsequently causes a systemic cascade of inflammatory responses leading to systemic multi-organ failure [15]. In addition, basic studies have found that soluble UA activates the secretion of IL-1β from NLRP3 inflammatory vesicles in macrophages and stimulates the release of CXCL12 and HMGB1 from renal tubular epithelial cells [16, 17]. HMGB1 amplifies the inflammatory response through multiple pathways, including promoting the secretion of pro-inflammatory cytokines by monocytes, the expression of adhesion molecules, and inflammatory cell infiltration [18]. When uric acid levels exceed 6.8 mg/dl, urate crystals can form, which can be deposited in the joint cavity to stimulate the expression of inflammatory factor TNF-α by joint cavity monocytes and synovial cells [16], and also directly in the vascular wall leading to inflammatory responses and endothelial damage, which in turn cause activation of neutrophils and platelets and release of inflammatory cytokines, chemokines, and adhesion molecules, which contribute to the The development of cardiovascular diseases [19].

4. Endothelial cell dysfunction due to hyperuricemia

Endothelial cells can secrete a variety of vasoactive substances involved in the regulation of blood vessels and blood circulation, which can be classified according to their function as vasodilators, vasoconstrictors and other vasoactive factors. Examples include nitric oxide (NO), prostacyclin, endothelin, angiotensin, antithrombin III and fibrinogen activator [20]. Also endothelial cells can sense changes in blood flow signals through membrane receptors and regulate blood flow dynamics. There is growing evidence that uric acid affects endothelial function by downregulating NO production and endothelial-type nitric oxide synthase (eNOS) activity, thereby decreasing NO bioavailability [21]. Serum endothelin-1 (ET-1) mainly acts in the cardiovascular system, and studies have shown that hyperuricemia elevates ET-1 levels and decreases NO levels, leading to vascular endothelial dysfunction, which is closely associated with cardiovascular diseases such as atherosclerosis and hypertension [22].

Uric acid induces endothelial dysfunction through multiple pathways, and targeted therapy can improve endothelial dysfunction [23].

Summary and Outlook

Hyperuricemia can stimulate intracellular reactive oxygen species synthesis and induce oxidative stress through multiple mechanisms, promote the development of local or systemic inflammation through multiple pathways, and affect vascular endothelial function primarily through downregulation of NO production and eNOS activity. In contrast, the role of elevated blood uric acid in other inflammation-related diseases and whether uric acid-lowering therapy improves clinical outcomes require rigorous clinical studies to be designed to verify.

References

[1] Chinese Medical Association, Chinese Medical Journals Publishing House, Chinese Society of General Practice,

Chinese Association of Gout Study, et al.Guideline for primary care of gout and hyperuricemia(2019) [J] Chinese Journal of General Practitioners, 2020, 19(4): 293-303.

[2] Alvarez-Lario B, Maccaron-Vicente J: Is there anything good in uric acid? QJ Med 2011; 104: 1015–1024.

[3] Nakagawa T, Kang DH, Feig D, et al. Un- earthing uric acid: an ancient factor with re-cently found significance in renal and cardio- vascular disease [J]. Kidney Int, 2006, 69 (10): 1722-1725.

[4] Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hyper- tension and cardiovascular and renal disease? [J]. Hypertension, 2003, 41 (6): 1183-1190.

[5] Wang H., Zhang H., Sun L., Guo W. Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases. American Journal of Translational Research. 2018, 10(9): 2749–2763.

[6] Komori H., Yamada K., Tamai I. Hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2018;1860(5):973–980.

[7] Ngo JS., Ho MHM. Evaluation of rasburicase use in the Fraser Health Authority: a retrospective review. The Canadian Journal of Hospital Pharmacy. 2019; 72(4): 311–319.

[8] Zhou X, Matavelli L, Frohlich ED, Uric acid: its relationship to renal hemodynamics and the renal renin-angiotensin system. Curr Hypert Rep 2006; 8: 120-124.

[9] Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. Journal of Hypertension. 2010;28(6):1234-1242.

[10] Roumeliotis S., Roumeliotis A., Dounousi E., Eleftheriadis T., Liakopoulos V. Dietary antioxidant supplements and uric acid in chronic kidney disease: a review. Nutrients. 2019;11(8):p. 1911.

[11] Doehner W., Schoene N., Rauchhaus M., et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation. 2002; 105(22): 2619–2624.

[12] Yang L., Chang B., Guo Y., Wu X., Liu L. The role of oxidative stress-mediated apoptosis in the pathogenesis of uric acid nephropathy. Renal Failure. 2019; 41(1): 616-622.

[13] Sánchez-Lozada LG., Lanaspa MA., Cristóbal-García M., et al. Uric acid- induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Experimental Nephrology. 2013; 121(3-4): e71-e78.

[14] Kadowaki D., Sakaguchi S., Miyamoto Y., et al. Direct radical scavenging activity of benzbromarone provides beneficial antioxidant properties for hyperuricemia treatment. Biological & Pharmaceutical Bulletin. 2015; 38(3): 487– 492.

[15] Lu WJ et al. “Uric Acid Produces an Inflammatory Response through Activation of NF-κB in the Hypothalamus: Implications for the Pathogenesis of Metabolic Disorders.” Scientific reports vol. 5 12144. 16 Jul. 2015.

[16] Kim S. M., Lee S. H., Kim Y. G., et al. Hyperuricemia-induced NLRP3 activation of macrophages contributes to the progression of diabetic nephropathy. American Journal of Physiology-Renal Physiology. 2015;308(9):F993–F1003.

[17] Rabadi MM., Kuo MC., Ghaly T., et al. Interaction between uric acid and HMGB1 translocation and release from endothelial cells. American Journal of Physiology-Renal Physiology. 2012;302(6):F730–F741.

[18] Choe JY., Choi CH., Park KY., Kim SK. High-mobility group box 1 is responsible for mono- sodium urate crystal-induced inflammation in human U937 macrophages. Biochemical and Biophysical Research Communications. 2018; 503(4): 3248-3255.

[19] Iribarren C, Folsom AR, Eckfeldt JH, McGovern PG, Nieto FJ. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: the ARIC Study.

[20] WANG Y,BAO X. Effects of uric acid on endothelial dysfunction in early chronic kidney dis ease and its mechanisms [J]. Eur J Med Res,2013,18:26.

[21] Li P., Zhang L., Zhang M., Zhou C., Lin N. Uric acid enhances PKC-dependent eNOS phosphorylation and mediates cellular ER stress: a mechanism for uric acid-induced endothelial dysfunction. International Journal of Molecular Medicine. 2016; 37(4): 989–997.

[22] Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension. 2003 Jun; 41(6):1287-93.

[23] Long CL., Qin XC., Pan ZY., et al. Activation of ATP-sensitive potassium channels protects vascular endothelial cells from hypertension and renal injury induced by hyperuricemia. Journal of Hypertension. 2008; 26(12):2326-2338.

*Corresponding author:Sanle Jiang[1],The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.