Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl. Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Review Articles

Hyperuricemia as a Risk Factor for Cardiovascular Diseases

Ichiro Hisatome[1*], Peili Li[1], Fikri Taufiq[2], Nani Maharani[3], Masanari Kuwabara[4], Haruaki Ninomiya[5], and Udin Bahrudin[6]

[1]Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, Yonago, Japan
[2]Department of Physiology, Faculty of Medicine Sultan Agung Islamic University, Semarang, Indonesia
[3]Department of Pharmacology and Therapy, Faculty of Medicine Diponegoro University, Semarang, Indonesia
[4]Intensive Care Unit and Department of Cardiology, Toranomon Hospital, Tokyo, Japan
[5]Department of Biological Regulation, Tottori University Faculty of Medicine
[6]Dept. of Cardiology and Vascular Medicine, Faculty of Medicine, Diponegoro Universitys – Dr Kariadi Hospital, Semarang, Indonesia

Article Info
History
Received: 13 Nov 2020
Accepted: 23 Dec 2020
Available: 31 Dec 2020

Abstract
Serum uric acid level above 7 mg/dl is defined as hyperuricemia, which gives rise to the monosodium urate (MSU), causing gout and urolithiasis. Hyperuricemia is an independent risk factor as well as a marker for hypertension, heart failure, atherosclerosis, atrial fibrillation and chronic kidney disease. MSU crystals, soluble uric acid (UA) or oxidative stress derived from xanthine oxidoreductase (XOR) might be plausible explanations for the association of cardio-renovascular diseases with hyperuricemia. In macrophages, MSU activates the Nod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and proteolytic processing mediated by caspase-1 with enhanced interleukin (IL)-1β and IL-18 secretion. Soluble UA accumulates intracellularly through UA transporters (UAT) in vascular and atrial myocytes, causing endothelial dysfunction ad atrial electrical remodeling. XOR generates reactive oxygen species (ROS) that lead to cardiovascular diseases. Since it remains unclear whether asymptomatic hyperuricemia could be a risk factor for cardiovascular and kidney diseases, European and American guidelines do not recommend pharmacological treatment for asymptomatic patients with cardio-renovascular diseases. The Japanese guideline, on the contrary, recommends pharmacological treatment for hyperuricemia with CKD to protect renal function, and it attaches importance of the cardio-renal interaction for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure. In this review, the authors report the associations of hyperuricemia with cardiovascular diseases, and discuss its underlying mechanisms and the clinical implication of Japanese guideline 3rd edition of management for hyperuricemia and gout.

Keywords: hyperuricemia; cardiovascular disease; uric acid transporter; xanthine oxidase; inflammasome; guideline
Permalink/ DOI: https://doi.org/10.14710/jbtr.v6i3.9383

INTRODUCTION

Hyperuricemia occurs in 20 % of men and in 5 % of women in the entire Japanese population.[1] Gene mutations may accelerate uric acid production or reduce either renal or extrarenal excretion of uric acid.[1] In addition, a diverse range of environmental factors causes hyperuricemia. Hyperuricemia is defined as the serum urate level above 7.0 mg/dl.[1] Hyperuricemia increases the uric acid pool to give rise to MSU crystals, which causes gouty arthritis and ureteral calculus and kidney failure.

*Corresponding author:
Email: hisatome@tottori-u.ac.jp
(Ichiro Hisatome)

While clinical studies suggested that asymptomatic hyperuricemia frequently associates with cardiovascular diseases, it remains unclear whether hyperuricemia could be a risk factor for cardiovascular diseases (CVD), hypertension, stroke, atrial fibrillation (AF), metabolic syndrome (Mets), nonalcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD) and diabetes mellitus (DM) (Table 1). The underlying mechanisms on the associations of hyperuricemia with cardiovascular diseases and the clinical implication of Japanese guideline 3rd edition of management for hyperuricemia and gout[1] have been discussed.

Formation and physical properties of uric acid and the definition of hyperuricemia

1) Formation of uric acid

Since evolutionally loss of uricase activity, uric acid has been the end product of purine metabolism in the human body. Uric acid is synthesized from xanthine by xanthine oxidoreductase as well as from guanosine. The free purine bases, yielded by nucleoside cleavage are adenine, guanine, hypoxanthine and xanthine. Since purine nucleoside phosphorylase acts with relatively higher affinity on inosine and guanosine, the major bases generated are hypoxanthine and guanine. Hypoxanthine is oxidized to xanthine by xanthine oxidoreductase (XOR) and then further oxidized to uric acid by the same enzyme, while guanine is oxidized to xanthine. Uric acid synthesis happens mainly in the liver, where XOR is richly expressed.[2]

2) Solubility of uric acid in plasma

The weak acidity of uric acid is due to ionization of hydrogen atoms at positions 9 (pKa=5.75) and 3 (pKa=10.3). The ionized forms of uric acid easily form monosodium urate (MSU), and at pH7.4, approximately 98% of uric acid takes this form. When the concentration of MSU exceeds the solubility limit of body fluid, the crystals as monosodium urate monohydrate are formed in the synovial fluid or the tophi. Based on the MSU solubility product is 4.9×10^{-5}, aqueous solution with the sodium concentration under physiological conditions is saturated with MSU at 6.4 mg/dl at 37℃. MSU solubility in the presence of 140 mM Na^+ depends on temperature and is saturated with 6.8mg/dl at 37℃. Solubility of uric acid and MSU also depends on pH: with increasing pH uric acid is more soluble, whereas MSU is less. Seegmiller et al reported that when MSU crystal was incubated with serum obtained from gouty or nongouty subjects at 38℃, actual determination MSU in human plasma indicated that saturation occurs at about 7mg/dl. Considerably higher concentrations of MSU in plasma above 7 mg/dl can be achieved in a supersaturated solution, since serum contains factors that enhance urate solubility such as proteins. However, these solutions are unstable and MSU readily precipitates out. Thus, based on the solubility of MSU in plasma, hyperuricemia is defined as the serum urate level above 7mg/dl.[1]

3) Crystalline Forms

Hyperuricemia was previously categorized to three types; the urate over-production type, the urate underexcretion type and the mixed types. Recently, the reduced urate extrarenal excretion type due to impaired uric acid secretion transporter, ABCG2 has been added.[1] SUA level above 7mg/dl increases the frequency of gout arthritis. MSU occurs as monohydrate and forms crystals that are needle- or bar-shaped in a monoclinic or triclinic system. When rapidly crystalized in a pure solution, crystals are very fine and appear amorphous. Tissue deposits are composed of MSU monohydrate, while urinary stones are composed largely of uric acid. Both urate and uric acid crystals show strong negative birefringence when viewed under polarized light.[3] MSU crystals are taken up by macrophages in the joint. In these cells, the assembly of the NLRP3 inflammasome activates caspase-1, leading to production of IL-1□ and IL-18.

Evidence for the role of hyperuricemia and gout as a risk factor for cardio-renovascular diseases

1) Uric Acid and Hypertension

Hyperuricemia is a common complication of hypertension. 17 to 25% of hypertensive patients have hyperuricemia and this ratio increases to 65–75% in those with untreated hypertension.4 Decreased renal blood flow5 and tubular secretion of uric acid6 have been reported to cause hyperuricemia in hypertension. Hyperinsulinemia secondary to insulin resistance has also been reported to contribute to its association with hypertension via enhancing renal reabsorption of uric acid through URAT1. Enhanced myogenic production of uric acid precursor hypxanthine is associated with elevation of SUA level in untreated hypertension.7

Uric acid could be a risk factor for hypertension. Kuwabara et al[8] reported that the occurrence of hypertension in hyperuricemic patients was 1.5 times higher than that in normouricemic patients. A meta-analysis on 18 cohort studies revealed the relative risk for hypertension of 1.41 (Table 1). Uric acid lowering agents might reduce blood pressure in certain hypertensive patients. Administration of allopurinol or probenecid reduced the SUA and this decrease was accompanied by reduction of blood pressure in adolescent male prehypertension subjects. A meta-analysis using interventional studies indicated that allopurinol reduced systolic blood pressure by 3.3 mmHg and diastolic blood pressure by 1.3 mmHg.[9] Taken together, hyperuricemia could not only be a marker but also a risk factor for hypertension.

2) Uric Acid and Heart Failure

Hyperuricemia is often accompanied by heart failure (HF), since 47-56% of patietns with heart failure has been reported to associate with hyperuricemia[10,11]. In patients with HF, the prevalence of hyperuricemia ranges from 30 to 60%.[12] Incidence of heart failure was ≈6-fold higher in patients with the highest quartile of serum uric acid (>6.3 mg/dL) than incidence in those with the lowest quartile (<3.4 mg/dL). Adjusted hazard ratio for the highest quartile of serum uric acid compared with the lowest was 2.1 (1.04 to 4.22). Ogino et al[11] reported that the prevalence of hyperuricemia increased in line with the NYHA classification and that the level of serum uric acid correlated to insulin resistance and renal function.

Table 1. Relative risk of uric acid for cardiovascular diseases

	Number of Reports	Number of Patients	Relative Risk	Reports
Onset on CKD	15	99205	1.22	PLoS One 9:3100801,2014
Onset on hypertension	18	55607	1.41	Arthritis Care Res 63:102-110, 2011
Coronary events	13	69898	1.09	Arthritis Care Res 62:170-180, 2010
Coronary death	13	333099	1.16	Arthritis Care Res 62:170-180, 2010
Onset on stroke	16	222099	1.47	Arthritis Reum 61:885-891, 2009
Stroke death	16	238449	1.26	Arthritis Reum 61:885-891, 2009
Onset on AF	7	146792	1.8	Int J cardiol 184: 699-702, 2015
Onset on Mets	9	51249	1.3	J Clin Endocrinol Metab 100: 4198-4207, 2015
Onset on NAFLD	9	51249	1.21	J Clin Endocrinol Metab 100: 4198-4207, 2015
Onset on DM	7	32016	1.56	PLoS One 8:e56864,2013

CKD: chronic kidney disease, AF: atrial fibrillation, Mets: metabolic syndrome, NAFLD: nonalcoholic fatty liver disease, DM: diabetes mellites

Mortality of patients with HF depends on the level of SUA. Hyperuricemia was also an indicator of poor prognosis in HF.[13] A meta-analysis of observational studies showed that hyperuricemia was associated with an increased risk of HF and the risk of all-cause mortality and the composite endpoint, respectively.[14]

Several studies asked whether uric acid lowering agents could influence the prognosis of HF. In meta-analysis of 5 case-controlled studies, uric acid lowering agents reduced cardiovascular mortality in patients with heart failure. There were two reports of randomized control trials in patients with chronic HF treated with xanthine oxidase inhibitors. In OPT-CHF study,[15] oxipurinolol did not influence the composite primary endo points in patients with HF. In EACT-HF study,[16] which examined whether allopurinol suppresses the cardiovascular mortality of patients with HF whose SUA >9.5mg/dl, there was no difference either in cardiovascular mortality or re-hospitalization between allopurinol and placebo group. Taken together, hyperuricemia is a marker of HF, but it remains unelucidated whether hyperuricemia is a risk factor for HF.

3) Uric acid and renal disease

Hyperuricemina is recognized as a risk of CKD as shown in meta-analysis (Table 1). A meta-analysis,[1] with 255 patients in the drug intervention group and 239 subjects in the control group, showed a statistically significant difference in the amount of change determined as 4.12 mL/min/1.73 m2. A meta-analysis, with 134 patients in the drug intervention group and 106 subjects in the control group,[1] revealed a risk ratio on the onset of renal events of 0.51, indicating a statistically significant difference between groups. Taken together, hyperuricemia is an independent risk factor for CKD.

4) Uric acid and atherosclerosis

Because of oxidative stress induced by SUA, hyperuricemia is associated with endothelial dysfunction and atherosclerosis. Flow-mediated vasodilation (FMD), an index of endothelial function, was impaired in patients with hyperuricemia.[17] Since activation of XOR would increase both SUA and ROS, XOR inhibitors could be beneficial to prevent endothelial dysfunction. According to a double-blind study, allopurinol improved endothelial function measured by the forearm blood flow response to acetylcholine, in subjects with chronic HF.[18]

Incidence of hyperuricemia in patients with myocardial infarction is 48%.[19] Three meta-analyses indicated that high SUA increased the risk of MI (RR: 1.20) and mortality (RR: 1.22).[20] A meta-analysis enrolling 8776 patients with acute coronary syndrome (ACS) showed that higher SUA level increased the risk of MACE (RR: 1.86), all-cause mortality (RR: 1.86) and cardiovascular mortality (RR: 1.74).[21] As shown in Table 1, the relative risks of morbidity and mortality of ischemic heart disease were reported to be 1.09 and 1.16, respectively, in patients with hyperuricemia. Urate-lowering have been shown to reduce the risk of MI.[22] Taken together, hyperuricemia is a predictor of atherosclerosis and may be a risk factor for ischemic heart disease.

5) Uric acid and atrial fibrillation

Prevalence of hyperuricemia in patients with atrial fibrillation (AF) was higher (2.1%) than in those without hyperuricemia (1.7%). Incidence of AF in patients with gout increased with hazard ratio of 1.61 and the estimated prevalence was 7.42%.[23] A follow up for 9 years of SUA in 107,360 Chinese patients revealed that the highest quartile of SUA had 1.91 times higher risk of AF in comparison to the lowest quartile.[24] Incidence of AF with elevated SUA correlates linearly with age (OR: 2.08).[25] A cohort study in Korea enrolling 282,473 patients indicated that the risk of AF in woman was 6.93-fold higher in the highest quartile of SUA than the lowest quartile, although in the men it was higher in the third and the highest quartile with hazard ratio 1.53 and 1.60 respectively.[26] In Japanese patients with hyperuricemia had an increased risk to develop AF (OR: 3.187).[27] Similarly (Table 1), SUA ≥6.5 mg/dl in men and SUA ≥ 4.9 mg/dl in women induced AF with hazard ratio of 1.60 and 1.64, respectively.[28] Meta-analysis revealed that the relative risk of AF in patients with high SUA was 1.67.[29] Data from another meta-analysis indicated that in hyperuricemia patients the risk of new onset or recurrence of AF was 1.66 and 2.07, respectively.[30] Reduction of SUA with a use of urate-lowering therapy reduced incidence of AF (HR: 0.65).[31] Taken together,

Table 2. Clinical questions and recommendations for hyperuricemia with CKD, hypertension and heart failure

CQ (A): Can urate lowering agents be recommended in patients with hyperuricemia and kidney injury over non-medication?
Recommendation
The use of urate lowering agents to retard the decline in kidney function is conditionally recommended in patients with hyperuricemia and kidney injury.
CQ (B):Can urate lowering agents be recommended for hypertensive patients with hyperuricemia over non-medication treatment?
Recommendation
The use of urate lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be conditionally recommended for hypertensive patients with hyperuricemia
CQ (C): Can urate lowering agents be recommended for patients with heart failure and hyperuricemia over non-medication treatment?
Recommendation
The use of urate lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be conditionally recommended for patients with heart failure and hyperuricemia.

hyperuricemia could be an independent risk factor for AF.

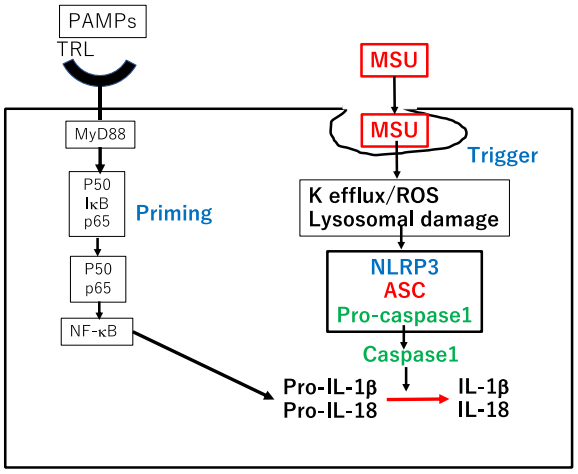

Figure 1. Activation of NLRP3-inflammasome by MSU crystal
After priming through activation of toll-like receptor (TRL), which produces pro-IL-1beta and pro-IL-18, MSU crystal absorbed in macrophage activates NLRP3-inflammasome via either K^+ efflux, ROS or lysosomal damage, leading to process caspase1, which cleavages pro-IL-1beta and pro-IL-18 to produce IL-1beta and IL-18

Mechanisms Underlying Cardiovascular Risk Due to MSU Crystals, Soluble Uric Acid and Xanthine Oxidase

1) Monosodium Urate and Cardiovascular Diseases

Inflammation underlies various diseases such as rheumatic, gout and cardiovascular diseases. Hyperuricemia causes nucleation of monosodium urate (MSU) crystals, causing gout. The inflammatory response due to MSU crystals is affected by their size, electrostatic charge, state of aggregation and the presence and nature of coating proteins.[2] MSU crystals are taken up by macrophages. In these cells, assembly of the NLRP3 inflammasome activates caspase-1 (Figure 1). Caspase-1 cleaves pro-IL-1β leading to secretion of active IL-1β.[32,33] NLRP3 inflammasome may play a pivotal role in the onset of not only gout but also various diseases such as chronic kidney disease, cardiovascular disease, atrial fibrillation, metabolic syndrome and diabetic complications.[34]

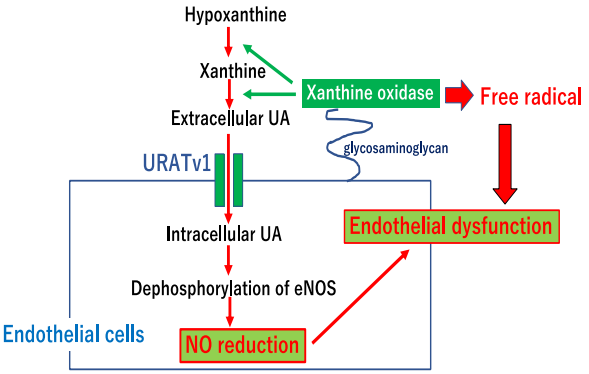

Figure 2. Intracellular uric acid and xanthine oxidase induces endothelial dysfunction
Through converting from hypoxanthine to xanthine and uric acid, XOR (xanthine oxidoreductase) generate free radical, causing endothelial dysfunction. Soluble uric acid via a uric acid transporter URATv1 reduces NO production via dephosphorylation of eNOS, causing endothelial dysfunction.

2) Soluble uric acid and cardiovascular diseases.

In humans, 90% of uric acid filtered at the glomeruli is reabsorbed in the renal tubules. Uric acid is reabsorbed

by the urate transporter 1 (URAT1) localized on the apical side of proximal tubular cells,[1] whereas it exits the cells via voltage-driven urate transporter 1 (URATv1) located at the basolateral side.[1] Recent experimental studies [35] have shown that uric acid transporters are expressed not only in renal tubular cells but also in other types of cells, and that four uric acid transporters URATv1, MCT9, ABCG2 and MRP4 are commonly expressed in various organs. URATv1 and MCT9 belong to the influx transporter that reabsorb uric acid, whereas ABCG2 and MRP4 belong to the efflux transporter that secrete uric acid.

Mishima et al. demonstrated that in HUVECs, uric acid reduced NO production through eNOS dephosphorylation and that NO production were restored by urate transporter inhibitors,[36] suggesting that uric acid absorbed into endothelial cells causes inflammation, oxidative stress and dephosphorylation of eNOS [Figure 2].

Mouse atrial myocytes express at least four UATs: URATv1/GLUT9, ABCG2, MRP4 and MCT9.[37] Uric acid could stabilize Kv1.5 channel proteins in mouse atrial myocytes (HL-1 cells) (Figure 3), resulting in an increase of ultra-rapid delayed-rectifier current (I_{Kur}) and shortening of the atrial action potential through UATs. Inhibition of uric acid-influx UATs by benzbromarone attenuated UA-induced enhancement of Kv1.5 protein expression. Inhibition of uric acid-efflux transporter ABCG2 accelerated UA-induced enhancement of Kv1.5 protein expression. Intracellular uric acid damaged the cells via an increase of oxidative stress and activation of the ERK1/2/Akt pathway together with phosphorylation of HSF-1 and HSP70.[37,38] This effect was oxidative stress-dependent, since the enhancement of Kv1.5 protein expression by uric acid was reversed by the antioxidant N-acetylcysteine and the NADPH-oxidase inhibitor apocynin. This process involved the ERK1/2 pathway as part of the downstream signaling of urate-derived ROS, which was in consistent with the findings of other studies[39]. An antioxidant may be a novel therapeutic approach against AF in hyperuricemic patients.

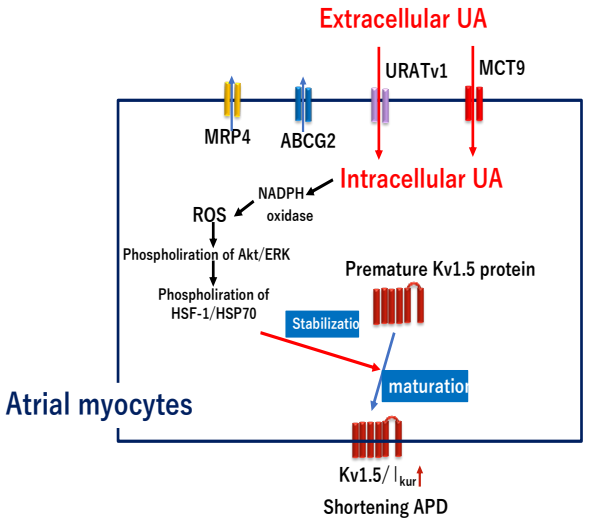

Figure 3. Intracellular uric acid causes the electrical remodeling of atrial myocytes

Accumulation of intracellular uric acid through UAT (URATv1/MCT9) induces nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase-dependent reactive oxygen species (ROS) production to increase Kv1.5 through Akt/ERK/HSF-1/HSP70 pathway. AKT, protein kinase B; HSF-1-S326, Ser 326 at heat shock factor 1; Hsp70, heat shock protein 70; URATv1/MCT9, influx uric acid transporters. ABCG2/MRP4, efflux uric acid transporters

3) Xanthine oxidase and cardiovascular diseases

XOR is a central player in the formation of uric acid. XOR is composed of XDH and XO. XO is generated from XDH by its protein modification and catalyses the last few steps of the reactions that convert hypoxanthine to xanthine, and xanthine to uric acid. These reactions yield hydrogen peroxide and reactive oxygen species (ROS).[40] A high activity of XO creates pro-oxidative condition by generating O_2^- which results in a decrease in nitric oxide expression, and endothelial dysfunction. Although XOR is highly active in the liver and small intestine, it also exists both in the cytoplasm and on the surface of endothelial cells. Recently, XOR was found to exist in human plasma. This circulating XOR is believed to be released from XO-rich organs such as liver. It binds glycosaminoglycans on the surface of endothelial cells and may be subsequently endocytosed [Figure 3].[41] The endothelial dysfunction has further consequences including reduced vascular elasticity, platelet aggregation, increased proliferation of smooth muscle cells, and fibrotic remodelling.[42]

A study using mice fed with Western diet showed the high SUA level was followed by an increase in XO activity. The mice developed cardiac hypertrophy, oxidative stress in myocardium, interstitial fibrosis and impaired diastolic relaxation, which were improved after allopurinol therapy.[43] An in-vivo study in dogs assessed the effect of allopurinol on the progression of atrial vulnerability. Allopurinol was able to suppress AF by inhibiting both electrical and structural remodelling of the atrium, suggesting the role of XO in enhancement of atrial vulnerability.[44]

Uric Acid-Induced Modification of Neurohumoral Factors in The Cardiovascular System

1) Uric Acid and Insulin Resistance

Insulin resistance is the core of pathophysiology in metabolic syndrome and is linked to several diseases including diabetes mellitus, stroke, and coronary artery disease.[45] The increase of SUA is accompanied by increased prevalence of the metabolic syndrome.[46] Choi et al [47] reported that elevation of fasting plasma insulin level correlates with elevation of SUA. Hyperinsulinemia due to insulin resistance enhanced both renal reabsorption of uric acid via activation of URAT1 and hepatic production of uric acid.

Hyperuricemia may in turn, cause insulin resistance. Insulin stimulates release of NO from endothelial cells, which causes vasodilation and aids delivery of glucose to the skeletal muscle. Uric acid reduces endothelial NO via several mechanisms, including inhibition of L-arginine uptake,[48] stimulation of L-arginine degradation[49] and chelating NO,[50] leading to suppression of vasodilation and glucose delivery.

Uric acid may also induce insulin resistance via its effects on adipocytes. Uric acid enters adipocytes via URAT-1 and increases oxidative stress in these cells via

activation of NADPH oxidase, generating oxidized lipids and inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1)[51,52] These events lead to inflammation, insulin resistance, and a decrease in adiponectin synthesis.[51] In the hyperuricemic mouse, allopurinol attenuates the inflammatory response in the visceral fat, reduces the expression of inflammatory cytokines, and enhances circulating levels of adiponectin.[52] Likewise, administration of allopurinol or benzbromarone in the fructose-fed rat resulted in less insulin resistance and decreases the leptin level in the visceral fat.[53]

2) Uric Acid and the Renin-Angiotensin System (RAS)

Hyperuricemia has been reported to activate the systemic RAS in the kidney. Uric acid increases renin expression, and studies in adult patients with essential hypertension[54] and hyperuricemic children [55] have also found an association of the plasma renin activity (PRA) and SUA. SUA level also correlated with urinary excretion of aldosterone in healthy men. Renal biopsy from rats demonstrated a correlation between SUA and the number of renin positive juxtaglomerular cells.[56] Hyperuricemic rats exhibited increased juxtaglomerular renin and decreased macular densa neuronal NOS.[57]

Uric acid stimulates formation of angiotensin II in vascular endothelial cells via activation of the inflammatory pathway. Cellular uptake of uric acid into cells via URAT1, induces oxidative stress, activation of mitogen activated protein kinases, and the nuclear factor kappa b and APO-1.[58] These processes lead to release of vasoconstrictors, including thromboxane, endothelin-1 and angiotensin II.[59] Uric acid is an antioxidant in the extracellular environment, but it has direct prooxidative effects once it gains entry into cells such as endothelial cells, adipocytes and vascular smooth muscle cells. This is followed by activation of the local RAS, angiotensin II type 1 and type 2 receptor expression, and the induction of senescence and apoptosis of endothelial cells.[59]

Rationality of Pharmacological Treatment of Asymptomatic Hyperuricemia

Is asymptomatic hyperuricemia should be treated in patients with cardio-renovascular disease? There are different recommendations for pharmacological treatment of asymptomatic hyperuricemic patients between Western countries and Asian country Japan. The European and American guidelines[60] do not recommend use of uric acid lowering agents (ULAs) for asymptomatic hyperuricemia to prevent gout, renal dysfunction and cardiovascular events. In contrast, Japanese guideline recommend use of ULAs for asymptomatic hyperuricemia. Medicare system in Japan cover the medical expense in treatment with ULAs of asymptomatic hyperuricemia. Therefore, it is easy to conduct the clinical trials to examine whether pharmacological treatment of hyperuricemia could be reasonable have been conducted. FEATHER study[61] reported that the treatment with xanthine oxidase inhibitor febuxostat significantly reduce the newly onset of gout in asymptomatic hyperuricemia with CKD compared to placebo, demonstrating the rationality of their pharmacological treatment of asymptomatic hyperuricemia in order to prevent gout.

Japanese guideline 2nd edition[62] states that ULAs may be considered when patients have renal dysfunction, lifestyle related diseases or cardiovascular diseases and their SUA is > 8 mg/dl. The Japanese Guideline for the Treatment of Hyperuricemia and Gout 3rd edition[1] was developed to clarify the rationality of pharmacological treatment in asymptomatic hyperuricemia in order to protect kidney disease or CVD according to GRADE approach. In order to make a recommendation to clinical questions (CQs) in this guideline, after setting the key clinical issues on hyperuricemia and gout, CQs together with advantage and disadvantage outcomes have been selected. Using systematic reviews on reports related to outcome of each CQs, the bias risk of each evidence has been estimated.

Taken together with the certainty in body of evidence, patients' opinions and medical economics, the recommendation for each clinical question has been determined. As shown in Table 2, the recommendations have 3 elements: direction of recommendation, strength of the recommendation and strength (certainty) of evidence, and recommendations were expressed using combinations of these. The direction of recommendation refers to whether the recommendation will be implemented. Strength of recommendation refers to whether the recommendation is strong or weak, while the strength of evidence corresponds to one of A (strong), B (moderate), C (weak/low), or D (very weak/low) according to the GRADE approach. As referred to CQ (A) in Table 2, ULAs improved the renal function and suppressed the end-stage renal failure in CKD patients, although there was not any significant difference in adverse effects between ULAs treatment and placebo groups, indicating that the benefit of treatment with ULAs is much greater than the harm. Thus, in order to prevent renal failure, ULAs are partially recommended for use in hyperuricemic patients with CKD. There is not enough evidence that ULAs improve the total mortality or cardiovascular mortality in patients with both hypertension (CQ (B)) and chronic heart failure (CQ (C)), although there was no difference in adverse effects between ULAs treatment and placebo groups. Thus, in order to prevent CVD or improve prognosis, ULAs are not partially recommended for use in either hyperuricemic patients with hypertension or hyperuricemic patients with heart failure. Recently, FREED study[63] reported that febuxostat significantly improved the primary composite endpoint of cardio-renovascular events in hypertension, diabetes and cerebro-cardiovascular disease in patients with hyperuricemia. This improvement was attributable to improvement of renal function indicating that improvement in renal function restores cardiac function (cardio-renal continuum). Thus, in order to reduce mortality in cardio-renovascular disease patients, ULAs could be used, when patients agree.

Japanese Medicare system covers the medical expense for treatment with ULAs in patients with asymptomatic hyperuricemia with being different from western countries. Taken together with the evidences reported in CQ (A), (B) and (C), treatment with ULAs

could not only reduce the onset of gout and CKD, but also decrease the onset of CVDs through improvement of cardio-renal continuum, thus, it is strongly recommended that like Japan, Asian and western country may consider the rationality of pharmacological treatment of asymptomatic hyperuricemia to reduce both gout and reno-cardiovascular diseases.

CONCLUSION

Hyperuricemia together with XO can induce inflammation, endothelial dysfunction and remodeling of the cardiovascular systems through UATs, free radical or crystal induced NLRP3 inflammasome, which play a pivotal role in development of CVDs as a risk. Several lines of evidence report in the Japanese guideline attaches importance of the cardio-renal interaction for treatment of asymptomatic hyperuricemia patients. Thus, this review demonstrates the rationality of pharmacological treatment of asymptomatic hyperuricemia in order to reduce mortality in these patients.

REFERENCES

1. Hisatome I, Ichida K, Mineo I, Ohtahara A, Ogino K, Kuwabara M, et al. Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout 3rd edition Gout and Uric & Nucleic Acids. Supplement, 2020; Vol.44, 1-40. https://doi.org/10.14867/gnamtsunyo.44.Supplement_sp-1
2. Watts RW, Watts JE, Seegmiller JE. Xanthine oxidase activity in human tissues and its inhibition by allopurinol 4-hydroxypyrazolo [3,4-d] pyrimidine). J Lab Clin Med. 1965 Oct;66(4):688-97.
3. Huskisson EC, Balme HW. Pseudopodagra. Differential diagnosis of gout. Lancet. 1972 Aug 5;2(7771):69-71.
4. Feig DI, Kang D-H, Johnson RJ. Uric Acid and Cardiovascular Risk. N Engl J Med. 2008; 359:1811-1821. doi: 10.1056/NEJMra0800885
5. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Annals of Internal medicine 1980; 93:817-821. doi: 10.7326/0003-4819-93-6-817
6. Tykarski A. Evaluation of renal handling of uric acid in essential hypertension: hyperuricemia related to decreased urate secretion. Nephron 1991; 59:364-368. doi: 10.1159/000186593
7. Ohtahara A, Hisatome I, Yamamoto Y, Furuse M, Sonoyama K, Furuse Y, et al. The release of the substrate for xanthine oxidase in hypertensive patients was suppressed by angiotensin converting enzyme inhibitors and alpha1-blockers. J Hypertens 2001;19 :575-582. doi: 10.1097/00004872-200103001-00009
8. Kuwabara M, Niwa K, Nishi Y, Mizuno A, Asano T, Masuda K, et al. Relationship between serum uric acid levels and hypertension among Japanese individuals not treated for hyperuricemia and hypertension. Hypertens Res 2014;37:785-789. doi: 10.1038/hr.2014.75
9. Agarwal V1, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2013;15:435-442. doi: 10.1111/j.1751-7176.2012.00701.x
10. Hamaguchi S, Furumoto T, Tsuchihashi-Makaya M et al (2011) Hyperuricemia predicts adverse outcomes in patients with heart failure. Int J Cardiol 151:143–147. https://doi.org/10.1016/j.ijcard. 2010.05.002 45
11. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. Circ Heart fail 2010; 3:73-81. doi: 10.1161/CIRCHEARTFAILURE.109.868604
12. Roger VL. Epidemiology of heart failure. Circ Res 2013; 113:646-659. doi: 10.1161/CIRCRESAHA.113.300268
13. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003; 107:1991-1997. doi: 10.1161/01.CIR.0000065637.10517.AD
14. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart fail 2014; 16:15-24. doi: 10.1093/eurjhf/hft132
15. Hare JM, Mangal B, Brown J, Fisher C Jr, Freudenberger R, Colucci WS, et al. : Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol 2008; 51: 2301-2309. doi: 10.1016/j.jacc.2008.01.068
16. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients : The xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. Circulation 2015; 131 : 1763-1771. doi: 10.1161/CIRCULATIONAHA.114.014536
17. Kato M, Hisatome I, Tomikura Y, Kotani K, Kinugawa T, Ogino K, et al. Status of endothelial dependent vasodilation in patients with hyperuricemia. Am. J. Cardiol 2005: 96:1576-1578. doi: 10.1016/j.amjcard.2005.07.068
18. J. George, E. Carr, J. Davies, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006 ; 114 :2508-2516. doi : 10.1161/CIRCULATIONAHA.106.651117
19. Wang R, Song Y, Yan Y, Ding Z. Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease : A meta-analysis. Atherosclerosis 2016;254:193-199. doi: 10.1016/j.atherosclerosis.2016.10.006
20. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general

population : a systematic review and. Clin Chem Lab Med 2016;54:7-15. doi: 10.1515/cclm-2015.0523
21. He C, Lin P, Liu W, Fang K. Prognostic value of hyperuricemia in patients with acute coronary syndrome : A meta-analysis. Eur J Clin Invest 2019;49:e13074. doi: 10.1111/eci.13074
22. Gupta MK, Singh JA. Cardiovascular Disease in Gout and the Protective Effect of Treatments Including Urate-Lowering Therapy. Drugs 2019;79:531-541. doi: 10.1007/s40265-019-01081-5
23. Kuo C, Grainge MJ, Mallen C, Zhang W, Doherty M. Impact of gout on the risk of atrial fibrillation. Rheumatology 2016; 55:721-728. doi: 10.1093/rheumatology/kev418
24. Li S, Cheng J, Cui L, Gurol ME, Bhatt DL, Fonarow GC, et al. Cohort Study of Repeated Measurements of Serum Urate and Risk of Incident Atrial Fibrillation. J Am Hear Assoc. 2019; 8:e012020. doi: 10.1161/JAHA.119.012020
25. Huang G, Xu R, Xu J, Liu Z, Xie X, Zhang T. Hyperuricemia is associated with atrial fibrillation prevalence in very elderly-a community based study in Chengdu , China. Sci Rep. 2018; 8:12403. doi: 10.1038/s41598-018-30321-z
26. Kwon CH, Lee SH, Lee J, Ryu S, Sung K. Uric Acid and Risk of Atrial Fibrillation in the Korean General Population. Circ J 2018; 82:2728-2735. doi: 10.1253/circj.CJ-18-0748
27. Kawasoe S, Kubozono T, Yoshifuku S, Ojima S, Miyata M, Miyahara H, et al. Uric Acid Level and New-Onset Atrial Fibrillation in the Japanese General Population. Circ J 2019; 83:156-163. doi: 10.1253/circj.CJ-18-0508
28. Kuwabara M, Niwa K, Nishihara S, Nishi Y, Takahashi O, Kario K, et al. Hyperuricemia is an independent competing risk factor for atrial fibrillation. Int J Cardiol 2017; 231:137-142. doi: 10.1016/j.ijcard.2016.11.268
29. Tamariz L, Hernandez F, Bush A, Palacio A, Hare JM. Association between serum uric acid and atrial fibrillation : A systematic review and meta-analysis. Hear Rhythm 2020; 11:1102-1108. doi: 10.1016/j.hrthm.2014.04.003
30. Xu X, Du N, Wang R, Wang Y, Cai S. Hyperuricemia is independently associated with increased risk of atrial fibrillation : A meta-analysis of cohort studies. Int J Cardiol 2015; 184:699-702. doi: 10.1016/j.ijcard.2015.02.038
31. Gupta MK, Singh JA. Cardiovascular Disease in Gout and the Protective Effect of Treatments Including Urate-Lowering Therapy. Drugs 2019;79:531-541. doi: 10.1007/s40265-019-01081-5
32. Busso N, So A. Mechanisms of inflammation in gout. Arthritis Res Ther 2010;12:206. doi: 10.1186/ar2952
33. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237-241. doi: 10.1038/nature04516
34. Taufiq Fikri, Peili Li, Masanari Kuwabara, Yasutaka Kurata, Toshihiro Hamada, Aiko Takami, et al. Novel inhibitory effects of dotinurad, a selective urate reabsorption inhibitor, on urate crystal-induced activation of NLRP3 inflammasomes in macrophages. Vascular Failure 2019; 3:59-67. doi: 10.30548/vascfail.3.2_59
35. Maharani N, Kuwabara M, Hisatome I. Hyperuricemia and Atrial Fibrillation. Int Heart J 2016; 57:395-399. doi: 10.1536/ihj.16-192
36. Mishima M, Hamada T, Maharani N, Ikeda N, Onohara T, Notsu T, et al. Effects of uric acid on the NO production of HUVECs and its restoration by urate lowering agents. Drug Res 2016; 66: 270-274. doi: 10.1055/s-0035-1569405
37. Maharani N, Ting YK, Cheng J, Hasegawa A, Kurata Y, Li P, et al. Molecular Mechanisms Underlying Urate-Induced Enhancement of Kv1.5 Channel Expression in HL-1 Atrial Myocytes. Circ J 2015; 79:2659-2668. doi: 10.1253/circj.CJ-15-0416
38. Taufiq F, Maharani N, Li P, Kurata Y, Ikeda N, Kuwabara M, et al. Uric Acid-Induced Enhancements of Kv1.5 Protein Expression and Channel Activity via the Akt-HSF1-Hsp70 Pathway in HL-1 Atrial Myocytes. Circ J 2019; 83:718-726. doi: 10.1253/circj.CJ-18-1088
39. Zhang Y, Yamamoto T, Hisatome I, et al. Uric acid induces oxidative stress and growth inhibition by activating adenosine monophosphate-activated protein kinase and extracellular signal-regulated kinase signal pathways in pancreatic β cells. Mol Cell Endocrinol 2013; 375: 89-96.
40. Berry CE, Hare JM. Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. J Physiol 2004;555 :589-606. doi: 10.1113/jphysiol.2003.055913
41. Houston M, Estevez A, Chumley P, Asian M, Marklund S, Parks DA,et al. Binding of xanthine oxidase to vascular endothelium. Kinetic characterization and oxidative impairment of nitric oxide-dependent signaling. J. Biol. Chem 1999;274: 4985-4994. doi: 10.1074/jbc.274.8.4985
42. Bove M, Cicero AFG, Borghi C. The Effect of Xanthine Oxidase Inhibitors on Blood Pressure and Renal Function. Curr Hypertens Rep 2017;19:95. doi: 10.1007/s11906-017-0793-3
43. Jia G, Habibi J, Bostick BP, Ma L, DeMarco VG, Aroor AR, et al. Uric acid promotes left ventricular diastolic dysfunction in mice fed a Western diet. Hypertension 2015;65:531-539. doi: 10.1161/HYPERTENSIONAHA.114.04737
44. Sakabe M, Fujiki A, Sakamoto T, Nakatani Y, Mizumaki K, Inoue H. Xanthine oxidase inhibition prevents atrial fibrillation in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Electrophysiol 2012;23:1130-1135. doi: 10.1111/j.1540-8167.2012.02356.x
45. Boden G. Obesity, insulin resistance and free fatty acids. Curr Opin Endocrinol Diabetes Obes 2011; 18:139-143. doi: 10.1097/MED.0b013e3283444b09
46. Bahrudin U, Dayana B, Amalia V, Sholeh I, Surastri B, Herry Y, et al. Circulating uric acid links to metabolic syndrome: a population study in urban area of Indonesia. Eur Heart J 2016; 18 (Supplement B), B1–B15.

47. Choi HK, Ford ES. Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels--the Third National Health and Nutrition Examination Survey. Rheumatology (Oxford) 2008; 47:713-717. doi: 10.1093/rheumatology/ken066
48. Schwartz IF, Grupper A, Chernichovski T, Grupper A, Hillel O, Engel A, et al. Hyperuricemia attenuates aortic nitric oxide generation, through inhibition of arginine transport, in rats. J Vasc Res 2011; 48:252-260. doi: 10.1159/000320356
49. Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER, et al. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. Am J Physiol Cell Physiol 2008; 295: 1183-1190. doi: 10.1152/ajpcell.00075.2008
50. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 2005; 16: 3553-3562. doi: 10.1681/ASN.2005050572
51. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol 2007; 293: 584-596. doi: 10.1152/ajpcell.00600.2006
52. Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes 2011; 60: 1258-1269. doi: 10.2337/db10-0916
53. Lanaspa MA, Sautin YY, Ejaz AA, Madero M, Le MP, Manitius J, et al. Uric acid and metabolic syndrome: what is the relationship? Curr Rheum Rev 2011; 7: 162-169. doi: 10.2174/157339711795305004
54. Saito I, Saruta T, Kondo K, Nakamura R, Oguro T, Yamagami K, et al. Serum uric acid and the renin-angiotensin system in hypertension. J Am Geriatr Soc 1978; 26: 241-247. doi: 10.1111/j.1532-5415.1978.tb02396.x
55. Gruskin AB. The adolescent with essential hypertension. Am J Kidney Dis 1985; 6: 86-90. doi: 10.1016/s0272-6386(85)80146-3
56. Kang DH, Hughes J, Mazzali M, Schreiner GF, Johnson RJ. Impaired angiogenesis in the remnant kidney model: II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. J Am Soc Nephrol 2001; 12: 1448-1457.
57. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001; 38: 1101-1106. doi: 10.1161/hy1101.092839
58. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte hemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003; 41: 1287-1293. doi: 10.1161/01.HYP.0000072820.07472.3B
59. Yu MA, Sanches-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. J Hypertens 2010; 28: 1234-1242. doi: 10.1097/HJH.0b013e328337da1d
60. Sivera F, Andrés M, Carmona L, Kydd AS, Moi J, Seth R, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2014; 73:328-335. doi: 10.1136/annrheumdis-2013-203325
61. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial. Am J Kidney Dis 2018; 72: 798-810. doi: 10.1053/j.ajkd.2018.06.028
62. Yamanaka H. The Guideline for the Treatment of Hyperuricemia and Gout 2nd edition. Gout and Nucleic Acid Metabolism 2010; 34 110-144. doi: 10.1080/15257770.2011.596496
63. Kojima S, Matsui K, Hiramitsu S, Hisatome I, Waki M, Uchiyama K, et al. Febuxostat for Cerebral and Cardiorenovascular Events Prevention Study. Eur Heart J 2019; 40:1778-1786. doi: 10.1093/eurheartj/ehz119