Uric Acid and Hypertension Because of Arterial Stiffness

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Hyperuricemia is strongly associated with hypertension, but we cannot conclude whether these relationships are causal or not.[1] A meta-analysis of observational studies showed that hyperuricemia is an independent risk factor for the development of hypertension,[1] and experimental studies on hyperuricemia also had suggested that uric acid (UA) may have an independent modulatory or causal role in hypertension.[2] Furthermore, some experimental and clinical studies demonstrated that lowering serum UA level significantly improves systolic and diastolic blood pressure.[1] Another meta-analysis showed that hyperuricemia was associated with an increased risk of coronary heart disease incidence and mortality, independent of traditional coronary heart disease risk factors.[3] However, because many of the subjects with hyperuricemia have comorbidities such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, metabolic syndrome, and obesity, it is difficult to rule out the role of UA from coexistence with other comorbid conditions.[4] Moreover, the serum UA level is known to vary significantly depending on meals (including soft drink and alcohol), lifestyle, and medications like diuretics.[4] When discussing the causal relationship between UA and hypertension, we have to account for many cofactors accompany with hyperuricemia. A recent study revealed that asymptomatic hyperuricemia without comorbidities showed an independent risk for the development of hypertension even after adjusting for well-known traditional risk factors.[5] Moreover, hyperuricemia becomes an independent risk for developing hypertension from prehypertension state both in men and women after adjusting for traditional risk factors.[6] From the recent evidence, we can elicit this causality between hyperuricemia and hypertension. However, the mechanism how serum UA causes hypertension is still unclear. The intriguing and timely article by Tomiyama et al[7] in the present article of *Hypertension* provides a new evidence that hyperuricemia in men without hypertension may have a longitudinal association with the development of hypertension, and increased arterial stiffness and inflammation may be involved in the risk of development of hypertension associated with hyperuricemia. This clinical study added an important mechanism why/how hyperuricemia is a risk factor for hypertension.

The potential mechanisms by which serum UA may cause arterial stiffness or hypertension have been previously published.[1] We showed the 2 main mechanisms how hyperuricemia causes arterial stiffness: urate crystal mechanism and crystal-independent mechanism (Figure). In urate crystal mechanism, serum UA itself directly causes arteriosclerosis. Macrophages can engulf urate crystal, which causes the activation of the NLRP3 (Nod-like receptor family protein 3) inflammasome.[8] The NLRP3 inflammasome pathway is involved in the secretion of interleukin-1β from monosodium urate-stimulated human macrophages in a post-translational modification-dependent manner, and it causes inflammation and collagen production, leading to the development of arteriosclerosis. Atherosclerosis is strongly associated with arterial stiffness at various sites in the vascular tree. In crystal-independent mechanism, UA induces intracellular and mitochondrial oxidative stress and reduces endothelial nitric oxide (NO) bioavailability and stimulates the intracellular renin-angiotensin system.[9]

Hyperuricemia is well known as a biomarker for the activation of xanthine oxidase, which releases oxidants during the generation of UA.[10] An increase in oxidant production, primarily the superoxide, promotes endothelial dysfunction.[11] Moreover, human blood vessels express urate transporter GLUT 9 (glucose transporter 9)/URATv1 (voltage-driven urate efflux transporter 1), and it plays an important role in the absorption of UA into blood vessels, causing inflammation, oxidative stress, and dephosphorylation of eNOS (endothelial nitric oxide synthase) in vasculature.[12] NO has an important role in regulation of vascular tone and arterial stiffness. Either a decrease in NO bioavailability or an imbalance of reduced production of NO promotes endothelial dysfunction, which leads to elevation of blood pressure.[11] UA in blood vessels causes arteriosclerosis and arterial stiffness by the inflammation pathway. Tomiyama et al[7] showed these mechanisms by this clinical study. However, the result was only positive in men, but not in women. Tomiyama et al[7] mentioned the limitation of the small number of women subjects and discussed about this sex difference. Most of the previous clinical studies used a definition of hyperuricemia as serum UA concentrations >7.0 mg/dL in men and ≥6.0 mg/dL or >6.0 mg/dL in women because female hormones decrease serum UA level by increasing UA excretion from the kidneys.[1,5,6] However, Tomiyama et al[7] used the definition of hyperuricemia as serum UA concentrations >7.0 mg/dL both in men and women as the Japanese guideline for the management of hyperuricemia

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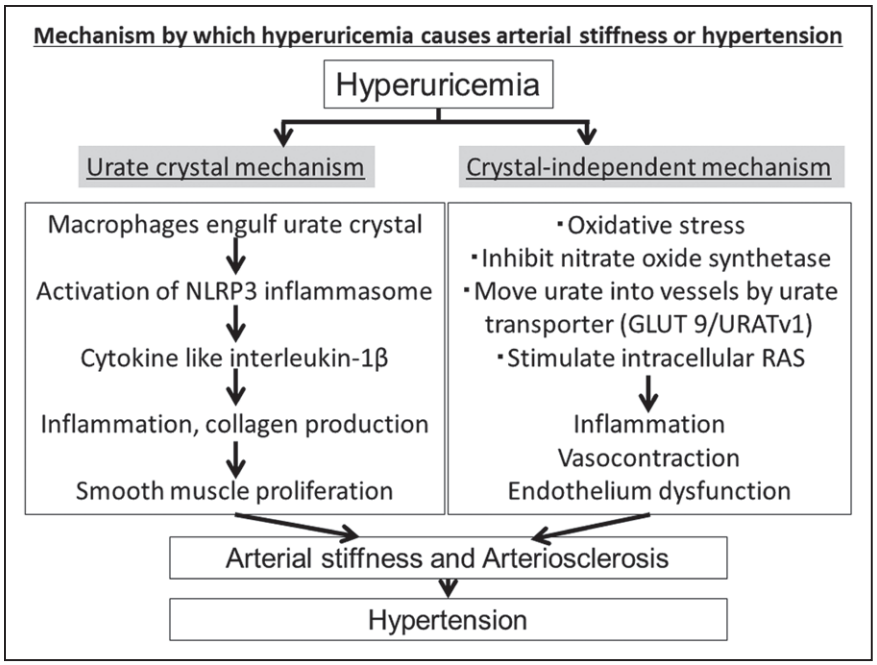

Figure. Mechanism by which hyperuricemia causes arterial stiffness or hypertension. GLUT 9 indicates glucose transporter 9; NLRP3, nod-like receptor family protein 3; RAS, renin-angiotensin system; and URATv1, voltage-driven urate efflux transporter 1.

and gout. Generally speaking, UA starts to crystallize within the human body when the serum UA level exceeds 7.0 mg/dL by the presence of UA-binding proteins, even though the physiological solubility of UA occurs at 6.4 mg/dL.[4] From the viewpoint of urate crystal mechanism, it is reasonable to use the definition of hyperuricemia as serum UA concentrations >7 mg/dL. However, most of the previous studies showed that the effects of hyperuricemia on hypertension in women were higher than those in men.[5,6] We should account for the difference of serum UA levels between these genders.

The Brisighella Heart Study showed that serum UA was significantly correlated with hypertension and intima-media thickness, but not with pulse wave velocity (aortic stiffness).[13] However, when they analyzed only in subjects with normal or mildly reduced kidney function, serum UA independently predicts pulse wave velocity.[14] These results were similar with the results from Tomiyama study. Tomiyama et al[7] showed that increased arterial stiffness and inflammation, but not kidney dysfunction, may be involved in the risk of development of hypertension associated with hyperuricemia.[7] These findings suggest that hyperuricemia not caused by chronic kidney disease is the main cause of arteriosclerosis and hypertension.

Most of the Mendelian randomized studies have not been able to show a relationship between serum UA and hypertension. However, Mendelian studies did not account for acquired cofactors, like lifestyle, diet, exercise, or medication, and it causes a significant limitation because lifestyle and diet (including fructose) are primary factors for hyperuricemia.[4] Most hyperuricemia are acquired in human life, except for some rare hereditary diseases like Lesch-Nyhan syndrome (deficiency of hypoxanthine-guanine phosphoribosyltransferase) and adenine phosphoribosyltransferase deficiency. It is time to conduct further well-designed studies to clarify the relationship between serum UA and hypertension and relationship between serum UA and cardiovascular diseases. Last but not least, multi-center prospective randomized controlled studies with large sample sizes and long-term follow-up should be planned to answer what should be the target serum UA level and lowering serum UA prevents/delays the development of hypertension.

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Disclosures

None.

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