Hypertension Research
https://doi.org/10.1038/s41440-024-01637-3

COMMENT

Is uric acid a causal risk factor of arterial stiffness in patients with hypertension?

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Received: 2 February 2024 / Revised: 20 February 2024 / Accepted: 24 February 2024

Keyword Arterial stiffness · Uric acid · Brachial-ankle pulse wave velocity · Hypertension

In humans, uric acid (UA) is the end product of purine metabolism catalyzed by xanthine oxidase. Serum UA levels tend to be elevated in the presence of several established cardiovascular risk factors including metabolic syndrome, chronic kidney disease, and hypertension. Therefore, patients with hyperuricemia are often complicated by these risk factors, which may lead to the use of serum UA levels as a biomarker of atherosclerosis as well as a prognostic marker for cardiovascular events. However, whether UA is a causal risk factor of atherosclerosis and cardiovascular events remains controversial.

Arterial stiffness increases with the progression of atherosclerosis. In addition, increased arterial stiffness may contribute to the progression of end-organ damage and the development of cardiovascular events due to the attenuated buffering effect on the pulsatile flow generated by cardiac contraction. Therefore, indices of arterial stiffness can be used not only to assess the severity of atherosclerosis but also to predict future cardiovascular events. Among several indices of arterial stiffness, brachial-ankle pulse wave velocity (baPWV) is widely used in clinical practice because of its simplicity and high reproducibility. Meta-analyses have shown that baPWV is associated with future cardiovascular events in subjects with and those without a history of cardiovascular disease independent of traditional cardiovascular risk factors, indicating that baPWV can be used as a prognostic marker of cardiovascular events [1, 2]. Therefore, maintaining baPWV at low levels through appropriate interventions may prevent end-organ damage and cardiovascular events in patients with cardiovascular risk factors.

Hypertension is strongly associated with arterial stiffness. Increased arterial stiffness contributes to the development of hypertension, and hypertension contributes to the progression of arterial stiffening, which may form a vicious cycle and consequently lead to cardiovascular events. Indeed, baPWV has been shown to be independently associated with future cardiovascular events in patients with hypertension [3]. Lowering blood pressure may be the most effective intervention for lowering baPWV in patients with hypertension. In addition to lowering blood pressure, identifying other risk factors and preventing the progression of baPWV through appropriate interventions may be important to improve cardiovascular prognosis in patients with hypertension.

Hypertension is often accompanied by hyperuricemia. The association between serum UA levels and PWV has been investigated in several cross-sectional and longitudinal studies to determine whether UA is a causal risk factor for arterial stiffness in patients with hypertension, although conflicting results have been reported [4–11]. In the current issue of *Hypertension Research*, Lina et al. reported the results of a study on the association between serum UA levels at baseline and the progression of baPWV in a Chinese hypertensive population with baPWV ≤1800 cm/s at baseline, with a mean follow-up period of 4.6 ± 2.8 years [12]. Subjects with a bilateral low ankle-brachial index (ABI) (<0.9) were carefully excluded from the study, and baPWV of the normal ABI side was used for analyses in subjects with a unilateral low ABI because arterial stiffness is not correctly assessed by baPWV in the leg with a low ABI value due to stenotic or occlusive lesions in lower limb arteries [13]. Participants were divided into three groups according to serum UA tertiles at baseline. The authors

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Published online: 14 March 2024

Graphical Opinion

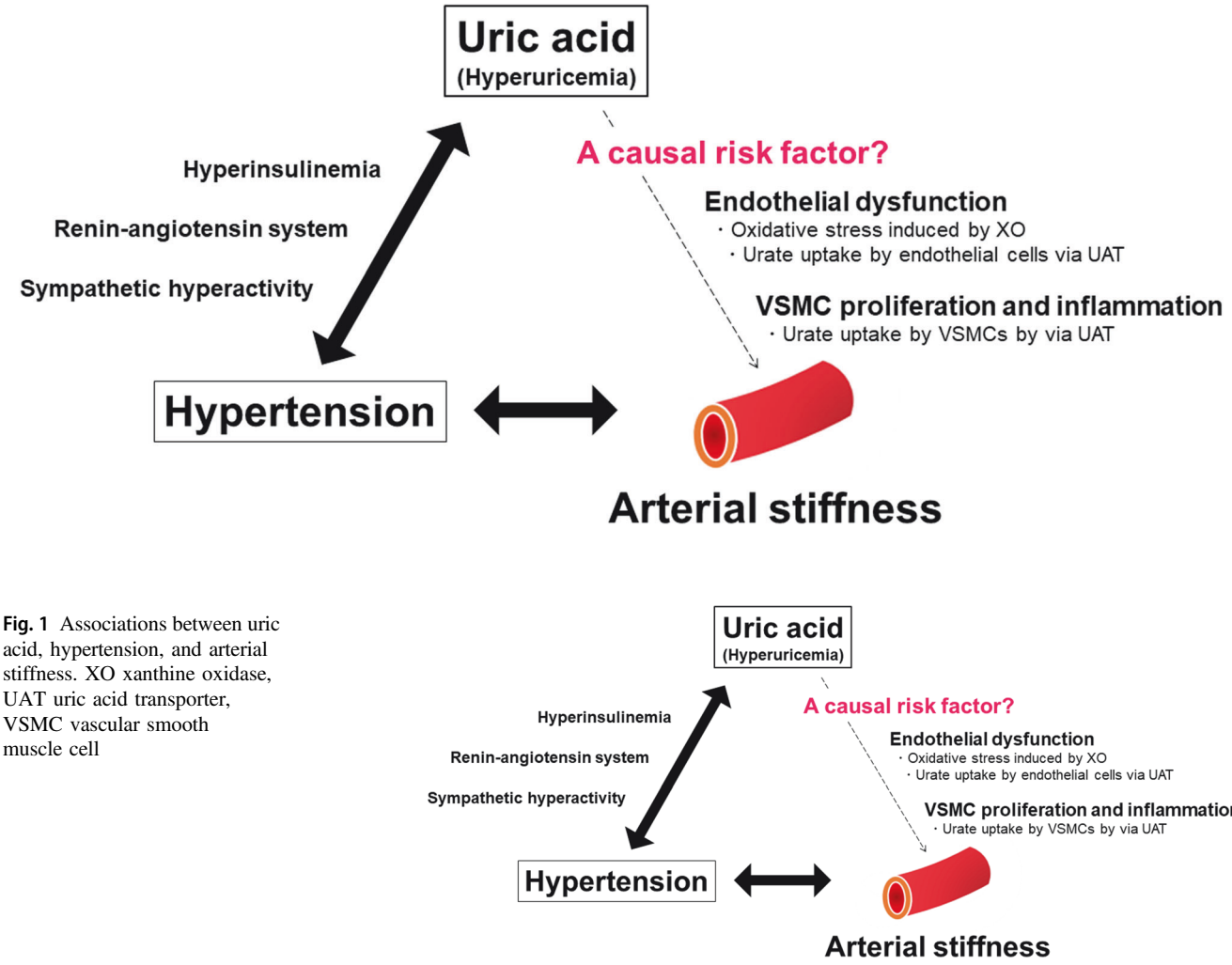

Fig. 1 Associations between uric acid, hypertension, and arterial stiffness. XO xanthine oxidase, UAT uric acid transporter, VSMC vascular smooth muscle cell

reported that the highest serum UA group (serum UA > 6.09 mg/dL) had a significantly higher risk of increased arterial stiffness defined as baPWV ≥1800 cm/s than that in the lowest serum UA group (serum UA < 4.72 mg/dL) even after adjustment for several confounders including age, sex, mean arterial pressure and heart rate at baPWV measurement, alcohol use, physical activity, education level, estimated glomerular filtration rate, and use of diuretic use. These findings suggest that UA is causally related to the progression of arterial stiffness and that UA is a therapeutic target for inhibiting the progression of arterial stiffness in patients with hypertension. Several mechanisms underlying the association between UA and arterial stiffness have been postulated. Endothelial dysfunction caused by reactive oxygen species generated by the activation of xanthine oxidase and the uptake of UA by endothelial cells via UA transporters may be involved in hyperuricemia-induced vascular injury [14]. In addition, experimental studies have shown that inflammation and proliferation of vascular smooth muscle cells (VSMC) are caused by the uptake of UA by VSMC via UA transporters, which may contribute to the progression of arterial stiffness (Fig. 1) [15, 16].

However, serum UA levels are affected by various environmental factors. In addition, hyperuricemia is strongly associated with other cardiovascular risk factors. Therefore, it is difficult to investigate the effects of hyperuricemia alone on atherosclerosis in observational studies. Thus, clinical intervention studies on the inhibitory effects of UA-lowering drugs on the progression of atherosclerosis in patients with hyperuricemia are needed to determine whether UA is a causal risk factor for atherosclerosis and whether uric acid is a therapeutic target for inhibiting the progression of atherosclerosis. Recent clinical studies have shown that UA-lowering therapy improves markers of arterial stiffness. Shina et al. reported that 24 months of treatment with febuxostat inhibited the progression of arterial stiffness assessed by baPWV or cardio-ankle vascular index (CAVI) in patients with asymptomatic hyperuricemia [17]. Tanaka

et al. reported that 24 weeks of treatment with dotinurad improved CAVI in patients with asymptomatic hyperuricemia and hypertension [18]. These findings suggest that UA is causally related to the progression of arterial stiffness and that UA-lowering therapy inhibits the progression of arterial stiffness. However, the former study was a subanalysis and the latter study was a single-arm study, which limited these studies. Further randomized controlled intervention studies are needed to determine whether UA is a causal risk factor for arterial stiffness and whether UA-lowering therapy inhibits the progression of arterial stiffness in patients with asymptomatic hyperuricemia.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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