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Review article

Hyperuricemia and endothelial function: From molecular background to clinical perspectives

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HIGHLIGHTS

- Uric acid is the end product of purine metabolism catalyzed by xanthine oxidase.
- Reactive oxygen species are concomitantly generated with uric acid production.
- Xanthine oxidase may be a therapeutic target of endothelial dysfunction.
- Experimental studies have shown that uric acid *per se* causes endothelial dysfunction.
- Biological effect of uric acid on endothelial function *in vivo* and in a clinical setting is not established.

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ABSTRACT

Uric acid is the end product of purine metabolism catalyzed by xanthine oxidase in humans. In the process of purine metabolism, reactive oxygen species, including superoxide, are generated concomitantly with uric acid production, which may deteriorate endothelial function through the reaction of superoxide with nitric oxide (NO), leading to decreased NO bioavailability and increased production of peroxynitrite, a reactive oxidant. Therefore, xanthine oxidase may be a therapeutic target in the treatment of endothelial dysfunction. Indeed, clinical studies have shown that endothelial dysfunction is restored by treatment with a xanthine oxidase inhibitor in patients with cardiovascular risk factors. However, it has not been fully determined whether uric acid *per se* is an independent causal risk factor of endothelial dysfunction in humans. Although experimental studies have indicated that uric acid absorbed into endothelial cells via the activation of uric acid transporters expressed in endothelial cells causes endothelial dysfunction through increased oxidative stress and inflammation, an actual biological effect of uric acid on endothelial function *in vivo* has not been fully elucidated, in part, because of the difficulty in investigating the effect of uric acid alone on endothelial function due to the close associations of uric acid with other conventional cardiovascular risk factors and the complicated relationship between uric acid and endothelial function attributed to the potent antioxidant properties of uric acid. In this review, we focus on the relationship between uric acid and endothelial function from molecular to clinical perspectives.

1. Introduction

Serum uric acid level is closely associated with established cardiovascular risk factors such as hypertension [1], chronic kidney disease [2], and metabolic syndrome [3]. Serum uric acid levels are higher in patients with these risk factors than in individuals without the risk factors. Recent epidemiological studies have also shown that the serum uric acid level is associated with the development of hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, and atrial fibrillation [4–8] as well as the occurrence of cardiovascular events [9–12]. Therefore, an increase in serum uric acid level is considered to be a marker of increased cardiovascular risk. Endothelial dysfunction is involved in the development and progression of atherosclerosis, leading to cardiovascular complications [13,14]. It is well known that

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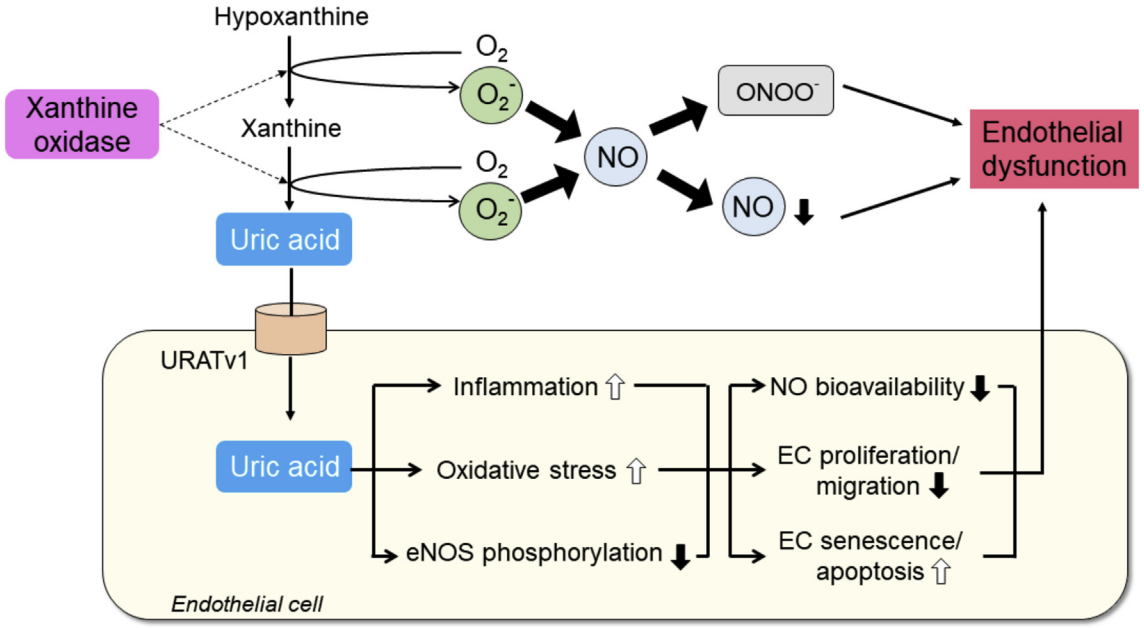

Fig. 1. Putative mechanisms underlying endothelial dysfunction induced by hyperuricemia.
NO, nitric oxide; $ONOO^-$, peroxynitrite; eNOS, endothelial NO synthase; URATv1, voltage-driven urate transporter 1; EC, endothelial cell.

traditional coronary risk factors, including hypertension, dyslipidemia, diabetes mellitus, smoking habit, obesity, and menopause, are associated with endothelial dysfunction. Experimental studies have demonstrated that hyperuricemia provokes endothelial dysfunction through increases in inflammation and oxidative stress. Recent clinical studies have also shown that hyperuricemia is associated with endothelial dysfunction in humans. Experimental and clinical studies have suggested that uric acid is not only a biomarker of cardiovascular risk but also a causal risk factor of endothelial dysfunction. However, it has not been fully determined whether uric acid *per se* is an independent causal risk factor of endothelial dysfunction, in part, because of the difficulty in investigating the role of uric acid alone in the pathogenesis of endothelial dysfunction due to the strong associations of uric acid with other risk factors such as hypertension, metabolic syndrome, chronic kidney disease, menopausal status, alcohol intake, and use of diuretics. In addition, uric acid is a potent antioxidant, making the relationship between uric acid and endothelial dysfunction more complicated. This review focuses on the underlying mechanisms of endothelial dysfunction associated with hyperuricemia and clinical data about the relationship between endothelial function and uric acid.

1.1. Endothelial function

The endothelium functions not only as a structural barrier separating the inside cavity and the blood vessel wall but also an endocrine organ secreting a wide range of vasoactive agents, including vasodilators such as nitric oxide (NO), prostaglandin I_2, and endothelium-derived hyperpolarizing factor and the vasoconstrictors such as endothelin-1, thromboxane A_2, and angiotensin II [15], among which NO plays a critical role in the prevention of atherosclerosis. A healthy endothelium plays a key role not only in the control of vascular tone but also in maintenance of vascular homeostasis by regulating the balances between vasoconstriction and vasodilation, growth promotion and growth inhibition, pro-thrombosis and anti-thrombosis, pro-inflammation and anti-inflammation, and pro-oxidation and anti-oxidation. Endothelial dysfunction refers to a condition in which vascular homeostasis is disturbed as a result of an imbalance between endothelium-derived vasodilating factors and vasoconstricting factors, leading to the progression of atherosclerosis. Considering the various anti-atherosclerotic effects of NO, such as vasodilation, suppression of vascular smooth muscle cell proliferation, inhibition of leukocyte adhesion, and inhibition of platelet aggregation and adhesion, reduced NO bioavailability (decreased NO production and/or increased NO inactivation) is generally referred to as endothelial dysfunction [16]. Although endothelial function is impaired in patients with hyperuricemia, it has not been fully determined whether hyperuricemia itself is a causal risk factor for endothelial dysfunction. Recent experimental and clinical studies have indicated the possibility that hyperuricemia is causally related to endothelial dysfunction.

1.2. Proposed mechanisms underlying endothelial dysfunction associated with hyperuricemia

1.2.1. Xanthine oxidase and endothelial NO synthase (eNOS) uncoupling

Xanthine oxidoreductase is a molybdoenzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to urate in the process of purine metabolism [17]. Xanthine oxidoreductase exists in two interconvertible but functionally distinct forms: xanthine dehydrogenase (XD) and xanthine oxidase (XO). XD is the constitutively expressed form *in vivo*, whereas XO is the post-transcriptionally modified form that is highly expressed under certain physiological and pathophysiological conditions, such as hypoxia and ischemia [18,19]. XD preferentially uses NAD^+ as an electron acceptor to catalyze the conversion of hypoxanthine to xanthine and xanthine to urate, resulting in the generation of the stable reaction product NADH, whereas XO preferentially uses molecular oxygen as an electron acceptor for the purine oxidation, leading to the generation of superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) [20,21]. Therefore, under a condition in which the activity of XO is enhanced for catalyzing the process of purine metabolism, not only uric acid but also reactive oxygen species (ROS) are generated concomitantly, which could have a deleterious effect on endothelial function (Fig. 1). Excessively generated O_2^- concomitant with increased uric acid production in the process of purine metabolism reacts directly with NO with high affinity, resulting not only in decreased NO bioavailability through degradation and inactivation of NO but also in increased formation of peroxynitrite ($ONOO^-$), a highly potent oxidant causing DNA damage, cell death, and lipid peroxidation. $ONOO^-$ can oxidize tetrahydrobiopterin, the essential eNOS cofactor,