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COMMENT

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Uric acid, xanthine oxidase, and vascular damage: potential of xanthine oxidoreductase inhibitors to prevent cardiovascular diseases

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Hyperuricemia, defined as a serum uric acid (UA) level >7.0 mg/dL in Japan [1], may be a risk factor for the development of cerebrocardiovascular disease, and various intervention studies have been conducted for it. However, hyperuricemia is not a clear risk factor for cerebrocardiovascular diseases at this time. The guidelines of the American Rheumatology Society also do not recommend drug therapy for asymptomatic hyperuricemia patients [2], whereas Japanese guidelines do consider drug therapy for asymptomatic hyperuricemia patients who meet certain criteria [1]. Under such circumstances, the paper by Shiina et al. [3] shows that the administration of febuxostat, which is a xanthine oxidoreductase (XOR) inhibitor, is effective for improving early arteriosclerosis in patients with asymptomatic hyperuricemia without altering blood pressure or renal function. As a result, this important report suggests that febuxostat may have a preventive effect on the onset of cardiovascular diseases (CVDs). The relationship between UA and arteriosclerosis is close, and a variety of mechanisms are thought to underlie their relationship. In this paper, I focus on XOR, which is the only enzyme in the purine-degrading system that produces UA, and UA.

Xanthine oxidoreductase and vascular damage

UA is synthesized via hypoxanthine and xanthine through the purine synthesis pathway starting with the breakdown of purines. XOR is an enzyme that catalyzes the final two steps of the purine degradation system and hydroxylates hypoxanthine to produce xanthine and xanthine to produce UA. XOR has only been found to act as xanthine dehydrogenase (XDH) in non-mammalian organisms. On the other hand, XOR can be reversibly converted into XDH and xanthine oxidase (XO) in mammals. XDH reduces NAD^+ to NADH, whereas XO uses oxygen to produce hydrogen peroxide and superoxide [4]. Therefore, inadequate activation of XOR and XO can increase reactive oxygen species (ROS), resulting in oxidative stress-induced injury in the vascular endothelium and cardiovascular tissues [4].

An increase in plasma XOR activity is associated with obesity, smoking, liver dysfunction, hyperuricemia, dyslipidemia, insulin resistance, and adipokines [5]. A general population-based cohort study including 1631 Japanese demonstrated that plasma XOR activity level was independently associated with body mass index, diabetes mellitus, dyslipidemia, and UA level. Furthermore, subjects in the top quartile of XOR activity were associated with a high risk of CVDs calculated using the Framingham Risk Score after adjustment for baseline characteristics. The results of this cross-sectional study suggested that high XOR activity is a marker of cardiovascular risk in the general population [6].

Uric acid and vascular damage

UA has both an antioxidant function and a pro-oxidant function in vivo [7]. At serum UA levels above 6 mg/dL, UA is taken up by vascular endothelial cells via the UA transporters present on them and induces the production of ROS by nicotinamide adenine dinucleotide phosphate oxidase. Furthermore, at 9 mg/dL and above, UA induces apoptosis of vascular endothelial cells [8]. That is, an excessively large increase in the serum UA level can upset the balance between oxidation and antioxidants, induce

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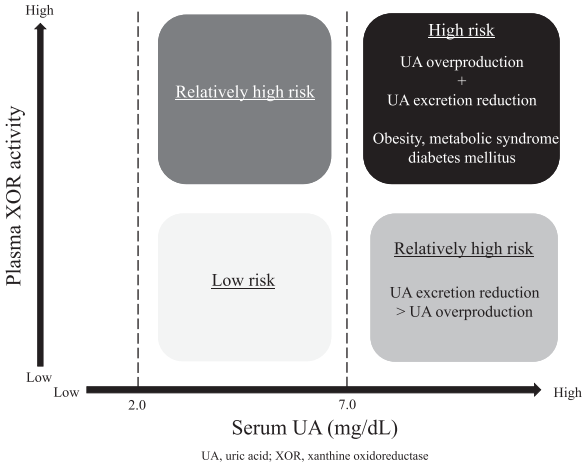

Fig. 1 Conceptual diagram of the risk of cardiovascular diseases for serum uric acid level and plasma xanthine oxidoreductase activity

oxidative stress, and lead to vascular endothelial cell damage, arteriosclerosis, and CVDs. On the other hand, hypouricemia is defined as a serum UA concentration ≤2 mg/dL [9]. Hypouricemia is well known to be a high-risk factor for exercise-induced acute kidney injury (EIAKI) and urolithiasis. Renal hypouricemia is considered to cause EIAKI through an oxidative stress-induced spasm of the renal artery, since UA acts as an antioxidant that protects endothelial function.

Hyperuricemia is closely related to life-related diseases and metabolic syndrome [1, 2]. The serum UA level shows a positive correlation with the visceral fat area and increased number of components of metabolic syndrome. The mechanisms by which UA increases are thought to include increased UA production due to visceral fat accumulation and decreased UA excretion in the kidney due to increased insulin resistance. This leads to the question of whether or not there is any correlation between the UA level produced by XOR as the final metabolite of purines and plasma XOR activity. Plasma XOR activity and serum UA level do not necessarily appear to be correlated [10]. There are several reasons for this. One reason for this is that there are many more hyperuricemic patients in Japan with the under-excretion of UA type than the overproduction of UA type of hyperuricemia [1], so the serum UA level does not accurately determine the amount of UA produced. That is, patients with obesity, metabolic syndrome, and diabetes mellitus have conditions in which both serum UA and plasma XOR activity are elevated. Recently, inhibition of XOR activity is thought to be more promising than just control of the uricemia level for preventing cardiovascular events because XOR inhibition also reduces the intracellular accumulation of urate and the production of ROS [4]. Figure 1 represents a conceptual diagram of the risk of developing CVDs for UA level and XOR activity from the viewpoint of the purine degradation system.

Effects of xanthine oxidoreductase inhibitors on arterial stiffness

In humans, XOR is a target enzyme for hyperuricemia drugs, as it is the only enzyme that produces UA. There are reports indicating that the serum UA level was associated with carotid plaque and arterial stiffness [1]. However, currently available data on the effects of XOR inhibitors on arterial properties are inconsistent. In the report of Shiina et al. [3], the brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI) were measured as surrogate markers for the onset of CVDs. The baPWV and CAVI are physiological tests that evaluate arterial stiffness, including vascular smooth muscle and connective tissue. Both the baPWV and CAVI can predict the onset of cardiovascular events, and subjects with increased baPWV values and increased CAVI values are more likely to develop CVDs [11]. The results of improved baPWV value and CAVI value in the report by Shiina et al. [3] suggested that febuxostat improved arterial stiffness. As a result, they indicated that febuxostat appeared to improve the prognosis of CVDs in patients with asymptomatic hyperuricemia.

In this report, I speculate on the reasons for the improvement in arterial stiffness from two clinical perspectives. Regarding the first one, Shiina et al. administered febuxostat for a long term, 24 months, and strictly controlled the serum UA level to an average UA value of 4.46 mg/dL at 24 months. Two studies have compared the effects of febuxostat and allopurinol treatment on cardio-femoral pulse wave velocity (cfPWV), which mainly assesses elastic arteries, in patients with gout. In Desideri's study [12], patients with gout and serum UA levels ≥8 mg/dL were evaluated for changes in cfPWV, and the results showed that about 70% of the patients in their febuxostat group had serum UA levels ≤6 mg/dL after 36 weeks of urate-lowering therapy. However, there were no significant changes in cfPWV from baseline to 36 weeks in both their febuxostat group and allopurinol group [12]. In the study of Tausche et al. [13], the authors administered a urate-lowering therapy for 12 months with a target serum UA level ≤6.05 mg/dL for a very small number of patients with chronic tophaceous gout. They then evaluated oxidative stress and arterial stiffness in the patients. The results showed no significant changes in oxidative stress or arterial stiffness in both their febuxostat group and allopurinol group after 12 months of treatment. Interestingly, after 12 months of therapy, they observed that febuxostat appeared to be more beneficial compared with allopurinol for preventing further arterial stiffening. Kario et al. [14] conducted a study in hypertensive patients with hyperuricemia. They observed the effects of febuxostat and topiroxostat treatment on CAVI for a short period of 24 weeks. In their febuxostat group and topiroxostat group, there were no significant changes in CAVI from baseline to 24 weeks [14]. The results of these studies [12–14] suggest that the effect of febuxostat on arterial stiffness was

different depending on the duration of febuxostat administration and the control level of UA. This suggests the question of whether it is necessary to administer febuxostat for at least 1 year.

The second clinical perspective is related to the different patient backgrounds in the research. In the febuxostat group in the study of Shiina et al. [3], there were not many subjects with obesity, smoking habits and diabetes mellitus, and it is possible that an XOR inhibitor more efficiently affects arterial stiffness (Fig. 1). In another study, some hyperuricemic patients who were being treated with an XOR inhibitor maintained high plasma XOR activities that were independent of their serum UA levels [5]. Those subjects were being treated for diabetes mellitus and/or were obese and had liver dysfunction. Compared with the subjects in the studies of Desideri et al. [12] and Kario et al. [14], the proportion of subjects with high XOR activity was relatively low due to the lower BMI and lower frequencies of smoking and diabetes mellitus in the study of Shiina et al. [3], and this may have made the influence of febuxostat clearer.

Kario et al. [14] newly reported that topiroxostat, but not febuxostat, significantly decreased plasma XOR activity versus baseline and decreased urinary albumin from baseline to 24 weeks. Topiroxostat, which is thought to have the effects of both febuxostat and allopurinol [15], also needs to be investigated, and this may lead to the discovery of new effects beyond the UA level-lowering effects of XOR inhibitors. Finally, the relationship between hyperuricemia and the development of CVDs still needs to be discussed.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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