O
ne of the recent topics of interest to suppress the progression of atherosclerosis is residual risks such as high levels of triglycerides, postprandial blood glucose, and diurnal variation of blood pressure. Serum uric acid (SUA) is also considered to be one candidate of residual risks, although whether lowering elevated SUA in hyperuricemic patients could have beneficial effects on cardiovascular morbidity and mortality still remains unknown. Indeed, xanthine oxidase (XO) is known to catalyze the process to generate uric acid (UA) from xanthine. In the process, superoxide anion is also generated concomitantly, which leads to cardiovascular damage. On the other hand, UA is also known to have an antioxidative effect (Figure 1). Indeed, febuxostat, a novel xanthine oxidase inhibitor, has been reported to decrease not only oxidative stress levels (derivatives of reactive oxygen metabolites) but also antioxidant potential (biological antioxidant potential) in hyperuricemia patients. Furthermore, previous studies have revealed the J-shaped associations of SUA with stroke incidence and cardiovascular mortality. Therefore, not only high SUA but also excess low SUA might be harmful, and thus, it is very important to control SUA within the range of appropriate concentration in clinical practice.

Of note, a novel finding was released on this topic, viz. there is a substantial association between SUA and left ventricular hypertrophy (LVH) in both genders. In fact, there is increasing evidence that SUA is a useful biomarker to predict heart failure, renal dysfunction, LVH, stroke, and cardiovascular events. We have also revealed that hyperuricemia is independently associated with endothelial dysfunction in postmenopausal women but not in premenopausal women. Previously, Yamauchi, et al have demonstrated that SUA was substantially associated with LVH independent of fibroblast growth factor 23, a bone-secreted phosphaturic hormone, in male patients with cardiac disease. In the present study, they have shown that SUA is associated with left ventricular mass index in females, independent of confounding factors even after adding the use of diuretic agents as a potential covariate in multivariate analysis, which is similar to the results in males. However, in their multivariate analysis when diuretic use was added as a potential covariate, there was no significant association between SUA and left ventricular ejection fraction (LVEF) in males and no statistical associations of SUA with LVEF and brain natriuretic peptide (BNP) in females. Taken together, these results may indicate that SUA is a suitable biomarker in patients with LVH, but not in patients with heart failure taking diuretic agents.

Considering the usefulness of SUA as a biomarker of cardiovascular disease, gender differences need to be adequately discussed. Nevertheless, the gender difference of the association between SUA and LVH still remains controversial. This study showed a significant association of SUA with LVH in both genders, which is consistent with a previous study. Meanwhile, other studies reported opposite findings in which the association of SUA with LVH was found to be apparent only in female subjects or only in male subjects. In addition, Yamauchi, et al, demonstrated an inverse J-shaped association between SUA and LVH, viz. female patients with the third, but not the 4th highest, quartile of SUA having the highest odds ratio for LVH which is different from the previous studies in which a J-shaped association between SUA and cardiovascular risk was reported (Figure 2). In male patients, such an inverse J-shaped association was not reported, namely, the 4th highest quartile was significantly associated with LVH. Although previous studies have postulated several mechanisms concerning the J-shaped associations of SUA with cerebro- and cardiovascular diseases, including the gender difference, the precise mechanisms are still unknown. Further investigations are needed in the future.

Whether elevated SUA is a cause or effect of LVH is quite pivotal in order to fully understand UA kinetics in humans. Considering the inverse J-shaped association in this study, the authors suggested that not SUA per se, but other related factors such as XO activity, might be the mechanisms of the association between SUA and LVH. If so, SUA might be a useful biomarker, but not a mediator for aggravation of LVH. Indeed, if SUA is a mediator of LVH progression, SUA-lowering agents may have beneficial effects on cardiovascular disease including LVH. Nonetheless, previous studies have failed to show the beneficial effects on renal dysfunction and cardiovascular risk. As for endothelial function, few studies have reported...
an improvement of endothelial function by oral administration of xanthine oxidase inhibitors, but other studies showed the opposite. Furthermore, XO inhibitors per se could directly reduce superoxide anions. Therefore, lowering SUA by XO inhibitors may have a beneficial effect on cardiovascular protection, while investigation with oral administration of XO inhibitors may not be suitable for investigating and identifying the direct harmful effect of SUA. Similarly, lifestyle modification is quite important to improve cardiovascular morbidity and mortality. However, lifestyle modification is not also appropriate for the investigation of any direct SUA-mediated harmful effect because lifestyle modification could coincidentally improve blood pressure, lipid profile, blood glucose, metabolic disorder, and other parameters. Further investigations using other SUA lowering agents such as uricosuric agents are necessary.

There is accumulating evidence that SUA is one of the useful biomarkers of cardiovascular disease. Nonetheless, the ultimate goal is whether lowering SUA could improve future cardiovascular injury, morbidity, and mortality in patients with hyperuricemia. To determine the ultimate goal, the investigation of 1) precise biokinetics of SUA, 2) harmful and/or beneficial effects of SUA per se, and 3) reliable evidence of the beneficial effects on cardiovascular damage by lowering SUA in each of the pathophysiological conditions is definitely needed. Indeed, the extent of the beneficial effect by lowering SUA may be different in each pathophysiological condition, for example, depositing kidney calculi could evoke renal inflammation and subsequent exacerbation of renal dysfunction in patients with chronic kidney disease (CKD) so that SUA is an established therapeutic target in such patients. Further studies to determine whether SUA is a therapeutic target and one of the pivotal residual risks in patients without CKD are warranted.

DISCLOSURE

Conflict of interest: There is no conflict of interest to report.

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