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COMMENT

Tips and pitfalls in uric acid clinical research

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The number of patients with hyperuricemia and gout is increasing worldwide, and the number of studies on uric acid is also increasing [1]. However, many pitfalls exist when conducting uric acid research. Uric acid is known to be affected not only by diet (high purine diet) and beverages (alcohol and fructose) but also by sex, obesity, diabetes, and medications. Moreover, hyperuricemia often accompanies hypertension, metabolic syndrome, diabetes, dyslipidemia, chronic kidney disease, and cardiovascular disease, including heart failure [1]. Therefore, it is difficult to show the causality between hyperuricemia and other diseases [2], and it is crucial to consider the influence of these confounding factors when conducting uric acid studies (Fig. 1).

One way to remove confounding factors related to uric acid is to include patients with no complications other than hyperuricemia. Studies of young patients with hyperuricemia would make much sense because adolescents have few comorbidities. Feig et al. showed that allopurinol decreased blood pressure in adolescents with newly diagnosed hypertension in a short-term, crossover study [3]. Moreover, their group showed that uric-acid-lowering therapy, even allopurinol or probenecid, reduced systemic vascular resistance and blood pressure in prehypertensive, obese adolescents aged 11–17 years in a randomized, double-blinded, placebo-controlled trial [4]. We also have shown a positive relationship between uric acid levels and cardiometabolic diseases in patients without comorbidities such as hypertension, diabetes, dyslipidemia, and chronic kidney disease in a generally healthy population using annual health check-up data from a 5-year cohort study [5].

Serum uric acid levels and the risks for cardiometabolic diseases are largely different between males and females, so conducting uric acid research requires conducting every analysis according to sex. In general, serum uric acid levels are higher in males than in females because female hormones decrease serum uric acid levels. Female hormones, such as estrogen and progestogen, decrease with age, especially after menopause, and serum uric acid levels increase after menopause [6]. Many studies have shown that uric acid affects cardiometabolic diseases more strongly in females than in males. Nevertheless, we should consider the effects of age on serum uric acid levels, especially in females. Generally, uric acid becomes crystallized in the human body when the serum uric acid level exceeds 7.0 mg/dL owing to the presence of uric acid-binding proteins, even though the physiological solubility of uric acid occurs at 6.4 mg/dL [1]. From the viewpoint of the uric acid crystal mechanism, the definition of hyperuricemia as serum uric acid concentrations >7 mg/dL appears reasonable. Nevertheless, most of the previous studies showed that the effects of hyperuricemia on hypertension or cardiovascular diseases in females were stronger than those in males [5, 7]. We should account for the difference in serum uric acid levels between sexes.

Some diseases and medications affect serum uric acid levels. In general, hyperuricemia is a predictor of or a risk factor for the development of diabetes [8]. However, severe diabetic conditions cause decreased serum uric acid levels by increasing urinary excretion of glucose and uric acid. Therefore, when including diabetic patients in uric acid studies, the severity of diabetes in the study population needs to be accounted for. Among medications, losartan, fibrate, or sodium-glucose cotransporter-2 (SGLT-2) inhibitors are drugs that are well known to decrease serum uric acid levels. Mainly, SGLT-2 inhibitors induce a rapid and sustained reduction in serum uric acid levels and clinical

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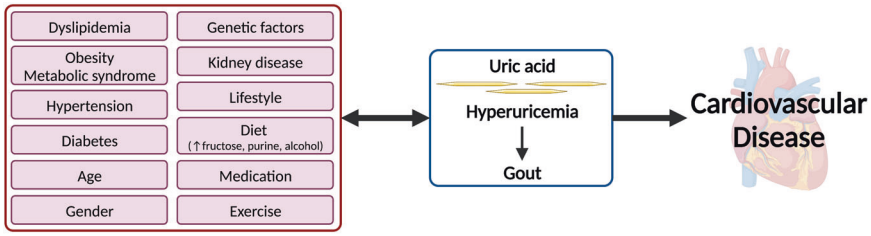

Fig. 1 The difficultly in showing the causality between hyperuricemia and each disease

Tips and pit-falls in uric acid clinical research

- Gender difference (Female hormones decrease uric acid)
- Uric acid is affected by lifestyle, including food (purine body), beverage(fructose), alcohol, and exercise
- Uric acid is affected many comorbidities, like obesity, metabolic disease, hypertension, dyslipidemia, diabetes, chronic kidney disease, cardiovascular disease, and so on
- Severe diabetic condition decreases serum uric acid levels
- Many medication affects serum uric acid levels
- Gout flare affects cardiovascular diseases
- J curve phenomenon (hypouricemia may be a risk for cardiometabolic diseases)
- Not to mix hypouricemia and normo-uricemia in the lowest levels of uric acid category when conducting the quantile analysis

Fig. 2 Summary of tips and pitfalls in uric acid clinical research

events related to hyperuricemia [9]. In contrast, diuretics (loop or thiazide) and beta-blockers increase serum uric acid levels. In uric acid studies, we should consider these medications when including patients with hypertension, dyslipidemia, or diabetes.

Uric acid has antioxidant effects. Some studies have shown that low uric acid levels could be a risk factor for cardiometabolic diseases. In the Syst-Eur trial [10], the CASTEL study [11], and the PIUMA study [12], a J-shaped relationship between serum uric acid levels and cardiovascular events was observed in hypertensive patients. The findings of these studies suggested that serum uric acid levels <4.5 mg/dl in males and <3.2 mg/dl in females were associated with an increased risk of cardiovascular diseases in patients with hypertension. However, most studies have shown that hyperuricemia is associated with a greater risk for cardiometabolic diseases than low serum uric acid levels [13]. A recent study showed that only hypouricemia less than 2 mg/dL in males and 1 mg/dL in females was related to an increased cardiometabolic risk [14]. We also showed that extreme hypouricemia (≤0.8 mg/dL) was associated with endothelial dysfunction, but normal hypouricemia (0.8 mg/dL<) was not associated with endothelial dysfunction [15]. Therefore, when dividing patients into groups according to serum uric acid level tertiles or quantiles, it is preferable not to mix patients with hypouricemia and patients with normouricemia in the lowest serum uric acid level category.

Optimal serum uric acid levels may vary depending on the disease. We indicated that the optimal serum uric acid range associated with the lowest development of cardiometabolic diseases was less than 5 mg/dL for males and 2–4 mg/dL for females in a generally healthy population. However, the optimal serum uric acid level for chronic heart failure patients with hyperuricemia treated with xanthine oxidase inhibitors has never been reported [13]. Naganuma et al. published an article that showed the relationship between uric acid reduction and endothelial function improvements in patients with chronic heart failure and hyperuricemia [16]. The study was a post hoc analysis of the Excited-UA study using data from 133 patients with chronic heart failure and comorbid hyperuricemia. The study divided the study patients into tertiles based on their serum uric acid level 24 weeks after initiating xanthine oxidase inhibitor treatment with topiroxostat or allopurinol on the basis of flow-mediated dilation (FMD) and the reactive hyperemia index (RHI) measured by reactive hyperemia peripheral arterial tonometry (RH-PAT). The results showed that the change in FMD from baseline to 24 weeks after treatment was comparable among the three groups. In contrast, the change in the RHI from baseline to 24 weeks after treatment significantly differed among the three groups. After multiple adjustments, the difference in the RHI in the moderate uric acid level group, in the range of 5.1–6.4 mg/dL, tended to be higher than that in the high uric acid level group and was significantly higher than that in the low uric acid level group. The authors concluded that it might be less beneficial to target excessively low uric acid levels by treatment with xanthine oxidase inhibitors to improve microvascular endothelial function in patients with chronic heart failure.

Although this study concept appears to be good, the backgrounds of the three groups vastly differed. Nevertheless, the study did not adjust for sex differences or medications, including the kinds of xanthine oxidase inhibitors used, diet, alcohol intake, diabetes, and so on. As we mentioned above, many factors influence serum uric acid levels, and careful adjustments of the confounders of uric acid are needed. In particular, sex differences in serum uric acid need to be accounted for. It is good to conduct the study by including only males if performing sensitivity analyses by sex is challenging. The adjustment for sex differences is required even though there was no difference in the percentage of males among the three groups.

Naganuma et al. assessed the change from baseline in endothelial function, but the tertiles were based on their serum uric acid level 24 weeks after initiating xanthine oxidase inhibitor treatment. It is difficult to assess and predict serum uric acid levels 24 weeks after treatment. Moreover, tertiles of serum uric acid were not used to assess hypouricemia, as we mentioned above. In the study, the 3rd tertile of serum uric acid levels (5.1>mg/dL) might include both patients with hypouricemia and patients with normouricemia. Therefore, it could be challenging to assess the risk or benefit. There are many tips and pitfalls in uric acid clinical research (Fig. 2). Thus, well-designed uric acid studies are needed.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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