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COMMENT

# Serum uric acid level mirrors arterial stiffness in women: a window for her cardiovascular risk assessment?

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Sex differences in serum uric acid (SUA) levels and their varying effects on cardiovascular and non-cardiovascular properties often complicate interpretation in relevant clinical and research areas. There is a consensus that SUA-lowering therapy should be implemented in cases of very high SUA levels in accordance with the relevant guidelines, regardless of sex. In contrast, an incidence of hyperuricemia, defined as SUA 7.0 mg/dL, is less common in women because their SUA levels are lower than those of men. In typical clinical practice settings, SUA levels in most women, especially those without defined hyperuricemia, may not be the subject of clinical attention. This may be partially because the clinical reflection of SUA levels is not fully understood. If a normal SUA level has little clinical significance and merely reflects individual differences, then it would make sense to assume that there is little need for intervention in SUA. However, if these values reflect some significance or value, clinicians will look at SUA differently, even if they are not at the level of hyperuricemia, and we will see SUA as a novel biomarker.

Accordingly, numerous studies have shown that an increased SUA level could be a causal risk factor for atherosclerotic progression, including endothelial dysfunction, arterial stiffening, and plaque formation in a wide range of cohort populations, possibly contributing to the increased risk of cardiovascular events [1, 2]. Through these findings, clinicians have become increasingly aware of the need to manage hyperuricemia to reduce the risk of not only gout but also atherosclerosis and cardiovascular events. However, whether SUA levels that do not meet the criteria for hyperuricemia need to be clinically addressed is rarely discussed, and the clinical significance of such SUA levels in terms of sex differences is not yet fully understood.

To address such an evidence gap, Maruhashi et al. recently published a report in the current issue of *Hypertension Research* which states that SUA in women, but not in men, was independently associated with impaired nitroglycerine-induced vasodilation (NID) of the brachial artery [3]. Authors cross-sectionally measured NID, which is indicative of endothelium-independent arterial medial layer (vascular smooth muscle) function, for cardiovascular risk assessment and collected clinical and laboratory information in subjects (598 women and 1008 men) with a wide spectrum of cardiovascular risk status at Hiroshima University Hospital. The key findings of their study were as follows; (i) SUA levels were weekly negatively associated with NID in women, but not in men, (ii) an impaired arterial medial layer (vascular smooth muscle) function, defined as a NID of <8.4% for women and <9.9% for men, was more common with increased levels of SUA even after adjusting for multiple cofounders in women, but not in men, (iii) this association in women was not affected by age (<50 or ≥50 years), and (iv) the optimal cutoff value of SUA for the arterial medial layer (vascular smooth muscle) dysfunction in women was 4.8 mg/dL. Their findings highlight the clinical importance of recognizing that increased SUA levels, even those outside the range of hyperuricemia, can mirror the degree of arterial stiffness in women.

This study is the first to assess the detailed association between SUA levels and arterial stiffness marker as assessed by NID while considering differences based on sex. In a previous issue of *Hypertension Research*, Lina et al. reported that a higher SUA level was longitudinally associated with an increased arterial stiffness as assessed by brachial-ankle pulse wave velocity, another physiological vascular functional test to evaluate arterial stiffness, in a Chinese hypertensive population [4]. Their study suggested

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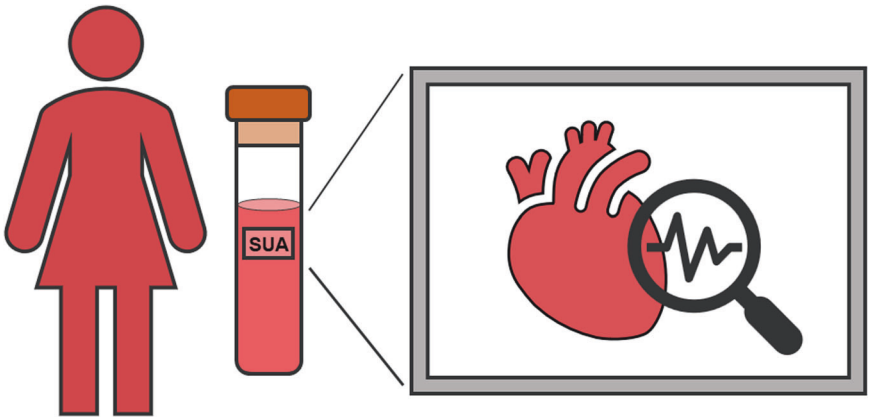


**Fig. 1** SUA level in women could be a window for her cardiovascular risk assessment. SUA serum uric acid

that an increased SUA level could be a causal risk factor for arterial stiffening in patients with hypertension [5]. The current findings by Maruhashi et al. potentially expand the previous knowledge to a wider population and underscore the sex difference in this association.

We also previously reported that lower SUA levels, especially those below the normal range, were associated with better vascular properties, such as better endothelial and medial layer functions and plaque formation, in female subjects being treated for hypertension, but not in male subjects [6]. The research topic on the sex difference in the association between SUA levels and vascular functional status is still active, and accumulated findings appear to be generally consistent in individual studies [7, 8]. Given the stronger association between SUA levels and cardiovascular risk status in women than in men [9], the SUA levels in women may play a role in mirroring not only vascular function but also comprehensive cardiovascular risk status. Although the precise reasons explaining the sex differences in these associations are still uncertain, SUA levels in women could be a useful marker for implementing sex-based risk stratification and precision medicine of cardiovascular diseases. Importantly, such a role may not necessarily be limited to higher SUA levels, as in hyperuricemia, as demonstrated in a study by Maruhashi et al. [3].

Thus, Maruhashi et al. suggested the possibility that SUA levels may mirror arterial stiffness and subsequent cardiovascular risk beyond the dynamics of uric acid itself. Even when SUA levels are below normal, SUA-guided clinical management of vascular failure and cardiovascular risk may be meaningful, especially in women. However, whether the use of SUA-lowering medications can lead to better management and improvement of vascular function and outcomes remains inconclusive. In the study by Maruhashi et al. [3], the effects of background medications on the endpoint were not considered, and longitudinal outcomes were not assessed, owing to their study design. Therefore, readers and clinicians should be eager to know the ways to better manage SUA levels in women. Although observational studies examining this association could generally provide an important clinical question to be addressed, prospective interventions or implementation studies are also often needed to explore and establish better clinical strategies. These complementary study complexes will satisfy the evidence gap and are expected to further advance the relevant clinical performance. SUA levels are generally affected by several confounding factors. Therefore, further cross-disciplinary studies are required to assess how to better manage SUA levels in clinical practice.

Finally, we would like to congratulate the authors of the study conducted by Maruhashi et al. [3]. on the publication of their work in *Hypertension Research*. Their study provided a major impetus to reconsider the clinical significance of SUA levels, especially in women, in terms of the prevention of vascular failure and cardiovascular diseases, even if they are not significantly elevated. We hope that readers and clinicians will consider SUA levels in women differently ever. Why? SUA levels could serve as a window for her cardiovascular risk assessment (Fig. 1).

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## Compliance with ethical standards

**Conflict of interest** AT has received honoraria from Boehringer Ingelheim Japan, Mochida, and Amgen; research funding from Bristol-Myers Squibb. KN has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, and Otsuka; research grant from Astellas, Bayer, Boehringer Ingelheim Japan, Fuji, Mochida, and Novartis; scholarship from Abbott, Boehringer Ingelheim Japan, Daiichi Sankyo Healthcare, Mitsubishi Tanabe, and Teijin.

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