Extremely Low Levels of Serum Uric Acid Are Associated With Endothelial Dysfunction in Humans

Tatsuya Iso, MD, PhD; Masahiko Kurabayashi, MD, PhD

Uric acid (UA) is the endproduct of purine metabolism in humans. Most serum UA (SUA) is freely filtered in the glomerulus, and approximately 90% of the filtered SUA is reabsorbed, implying that SUA is likely to have a physiological role, rather than simply being a waste of purine metabolism. Furthermore, the SUA level in humans is almost 10-fold higher than those in the majority of other mammals, which supports the hypothesis that the SUA level increased during human evolution as an advantage to humans.1

Many epidemiological studies have demonstrated that increased SUA is associated with cardiovascular (CV) events in high-risk groups, such as patients with hypertension, heart failure, diabetes, and metabolic syndrome.2,3 A potential causative role of UA in CV risk is primarily supported by in vitro study results demonstrating that exposure of cultured endothelial cells to UA induces NADPH oxidase activity and the production of reactive oxygen species.4

Conversely, the association between hyperuricemia and CV disease is only marginal or may be cofounded by other risk factors, such as hypertension, gout, and male sex. Likewise, hyperuricemia could be a consequence of impaired kidney function, diuretic therapy or oxidative stress, and as such, the role of SUA in conditions associated with oxidative stress is not entirely clear.5

Increasing experimental and clinical evidence shows that SUA has an antioxidant role in vivo that protects the CV system. Studies have shown a J-shaped relationship of SUA with CV events.5,6 For instance, the rate of CV events tended to be higher in SUA quartile 1 than in SUA quartile 2 in the PIUMA study.

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received February 26, 2015; accepted February 27, 2015; released online March 19, 2015

Department of Medicine and Biological Science (T.I., M.K.), Education and Research Support Center (T.I.), Gunma University Graduate School of Medicine, Maebashi, Japan

Mailing address: Tatsuya Iso, MD, PhD, Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi 371-8511, Japan. E-mail: isot@gunma-u.ac.jp


All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
that all patients with severe hypouricemia (SUA <0.8 mg/dl) had homozygous or compound heterozygous mutations in SLC22A12/URAT1, but not in SLC2A9A/GLUT9. Furthermore, the maximum SUA in patients with homozygous or compound heterozygous mutations in SLC22A12/URAT1 (functionally null mutations) was 0.9 mg/dl, which was lower than the minimum SUA in patients with heterozygous mutations or no mutations in SLC22A12/URAT1 (Figure 2A). Finally, patients with functionally null mutations in SLC22A12/URAT1 showed reduced FMD compared with the control group. Thus, patients with renal hypouricemia can be divided into 2 groups, very low and moderately low levels of SUA (Figure 2B), and only the group with very low SUA showed endothelial dysfunction and functionally null mutations in SLC22A12/URAT1. Mutations in SLC2A9/GLUT9 are also possible candidates for severe hypouricemia.

(Hypouricemia is arbitrarily defined as a SUA concentration <2–3 mg/dl.1,10,11 Renal hypouricemia, which is caused by a defect in renal tubular UA transport, appears to be more common in Japanese and non-Ashkenazi Jews.1,10,11 The underlying defect in the great majority of patients is a mutation in SLC22A12 (solute carrier family 22, member 12), which encodes URAT1 (urate transporter 1).1 Renal hypouricemia has also been described in patients with mutations in the SLC2A9 gene, which encodes GLUT9.1,10 URAT1 expressed in the luminal membranes of proximal tubular cells is responsible for a large portion of proximal UA reabsorption.1 Patients homozygous for URAT1 mutations typically have SUA concentrations <1.0 mg/dl and a partial UA reabsorption defect with fractional excretion of UA (FEUA) that ranges between 30% and 90% (normal FEUA =10%).1

In this issue of the Journal, Sugihara et al reported for the first time that extremely low levels of SUA caused by SLC22A12/URAT1 loss-of-function mutations cause endothelial dysfunction in vivo,12 as exhibited by flow-mediated dilation (FMD).13 They initially found a positive correlation between SUA and FMD only in the hypouricemia group (SUA <2.5 mg/dl). Sequence analysis of genomic DNA revealed

![Figure 2.](image-url)
the clear differences in SUA levels between those groups. Genotypes rather than low SUA levels may be important for endothelial dysfunction.

In summary, Sugihara et al suggest that extremely low levels of SUA (approximately <1.0 mg/dl), which are mostly caused by null mutations in SLC22A12/URAT1, cause endothelial dysfunction in humans. Given that severe hypouricemia is highly rare, it is difficult to perform a randomized controlled trial with adequate power to determine whether severe hypouricemia is a CV risk. In this regard, follow-up studies of these patients will provide a better understanding of the biological role of UA in humans.

References