COMMENT ON PILEMANN-LYBERG ET AL.

Uric Acid Is an Independent Risk Factor for Decline in Kidney Function, Cardiovascular Events, and Mortality in Patients With Type 1 Diabetes. Diabetes Care 2019;42:1088–1094

Wenrong Chen,[1] Dan Lu,[2] Zuoming Huang,[1] and Lin Xiao[1]

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Type 1 diabetes (T1D) is an important risk factor for development of chronic kidney disease (CKD) and cardiovascular disease (CVD). Earlier detection of risk factors for diabetic complications can improve the risk stratification of the patients with diabetes and allow targeted treatment.

Recently, Pilemann-Lyberg et al. (1) reported that a higher uric acid (UA) level is associated with a higher risk of CKD and CVD. Importantly, adding UA to the adjusted model including conventional risk factors can significantly improve the relative integrated discrimination index. This study was interesting and provided further support that UA should be regarded as a risk factor of CKD and CVD in T1D.

Epidemiologic studies have shown inconsistent conclusions about the association between UA concentration and CKD in T1D. In observational studies, causal inference and confounding pose challenges to the accurate interpretation of the results. Although the study by Pilemann-Lyberg et al. adjusted for multiple confounders, undetected confounders may still exist. Furthermore, statistical significance may change in different analysis models, and results should be interpreted with caution. It is interesting that in another recently published article on the same cohort (2), no association was found between UA and decline in estimated glomerular filtration rate (eGFR). The research group considered that the difference in these results may be explained by the larger sample size (a rise from 476 patients to 510 patients with eGFR follow-up data) and increase in the follow-up period from 4.1 to 5.3 years (2). It should be noted that the statistical models are different in the two analyses of the same cohort. In the previous study, the data on annual decline in eGFR in the highest UA quartile were compared with the three lower quartiles (2). However, in the present study (1), hazard ratios were calculated per doubling of UA. It is interesting to ask whether the results would be consistent if the statistical models had been kept unchanged.

To overcome the shortcoming of observational studies, including residual confounders and reverse causality, Mendelian randomization can be used as an instrumental tool to mimic randomized controlled trials (3). Ahola et al. (4) included 3,895 participants with T1D in a Mendelian randomization analysis based on a single nucleotide polymorphsimm (SNP) score derived from 29 SNPs associated with UA (4). The results suggested that UA concentration is not causally related to diabetic nephropathy but is a downstream marker of kidney damage. However, it should be noted that because Mendelian randomization studies are susceptible to the effects of population stratification and ethnicity, these results could not exclude a causal relationship of UA to CKD in other ethnicities. We are performing a Mendelian randomization study in a Chinese population, which could help to clarify the associations between UA and CKD in a population with another genetic background.

Randomized controlled trials are the gold standard for assessing causality of risk factors and outcomes. The Preventing Early Renal Loss in Diabetes (PERL) study is a randomized placebo-controlled trial that will check whether UA reduction can preserve kidney function among patients with T1D (5). Until these results are documented, the question of whether UA is an independent risk factor for CKD is still unanswered.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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[1]*Department of Cardiology, Xingtan Hospital Affiliated to Shunde Hospital of Southern Medical University, Foshan, People's Republic of China*
[2]*Department of Scientific Research and Education, Xingtan Hospital Affiliated to Shunde Hospital of Southern Medical University, Foshan, People's Republic of China*
Corresponding author: Lin Xiao, shundexiaolin1979@126.com