RESPONSE TO 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

Sascha Pilemann-Lyberg,[1] Tine Willum Hansen,[1] and Peter Rossing[1,2]

Diabetes Care 2019;42:e188 | https://doi.org/10.2337/dci19-0037

We appreciate the comments by Chen et al. (1) regarding our investigation of the association between serum uric acid (UA) and the risk of developing complications in patients with type 1 diabetes (2). We found that increased levels of UA, expressed as hazard ratio per doubling of UA, was a significant and independent risk factor for loss of renal function, cardiovascular events, and mortality. However, in a previous study investigating UA in the same cohort with shorter follow-up time and no data on hard end points, we were not able to show any association between UA and loss of renal function (3). Chen et al. correctly point out that this could be due to different statistical models. We originally found UA related to progression to macroalbuminuria in a study with a nonlinear association between UA and events (4), and we applied the same method in our initial glomerular filtration rate (GFR) study (3). In the most recent article with longer follow-up and more individuals, we were able to confirm a linear association between log-transformed UA and decline in estimated GFR, as described in the article (2). As a model using continuous variables is considered stronger in this situation than one using quartiles, we were able to apply that in the analysis (2). Had we used the same approach with quartiles as in the previous study, we would not have found a significant association, illustrating that when the requirements are met a continuous analysis is stronger. So, the difference in the two results for annual decline in estimated GFR is partly attributed to the choice of statistical model and not only a result of increase in follow-up time.

Our study supports that UA may be regarded as a risk marker for the development of diabetic kidney disease, cardiovascular events, and mortality in patients with type 1 diabetes, but other observational studies have shown inconclusive results, as pointed out by Chen et al. (1). We fully agree that we need intervention studies to demonstrate the role of UA as a potential risk factor. This is why we, along with our collaborators, are currently investigating the long-term (3 years) effect of lowering UA with allopurinol in people with type 1 diabetes as part of a multicenter trial using a randomized, placebo-controlled study design, the Preventing Early Renal Loss in Diabetes (PERL) study (5).

Duality of Interest. P.R. reports having given lectures for AstraZeneca, Novo Nordisk, Eli Lilly, Bayer, and Boehringer Ingelheim and has served as a consultant for AbbVie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Boehringer Ingelheim, Astellas, Janssen, and Novo Nordisk outside the current work, with all fees given to Steno Diabetes Center Copenhagen. P.R. also reports equity interest in Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Reference

1. Chen W, Lu D, Huang Z, Xiao L. 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 (Letter). Diabetes Care 2019;42:e187. DOI: 10.2337/dc19-1321
2. Pilemann-Lyberg S, Hansen TW, Tofte N, 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
3. Pilemann-Lyberg S, Hansen TW, Persson F, et al. Uric acid is not associated with diabetic nephropathy and other complications in type 1 diabetes. Nephrol Dial Transplant 2019;34:659–666
4. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes 2009;58:1668–1671
5. Afkarian M, Polsky S, Parsa A, et al.; PERL Study Group. Preventing Early Renal Loss in Diabetes (PERL) study: a randomized double-blinded trial of allopurinol—rationale, design, and baseline data. Diabetes Care 2019;42:1454–1463

[1]*Steno Diabetes Center Copenhagen, Gentofte, Denmark*
[2]*University of Copenhagen, Copenhagen, Denmark*

Corresponding author: Sascha Pilemann-Lyberg, sply@novonordisk.com