RESPONSE TO COMMENT ON NIEWCZAS ET AL.

Circulating Modified Metabolites and a Risk of ESRD in Patients With Type 1 Diabetes and Chronic Kidney Disease. Diabetes Care 2017;40:383–390

Monika A. Niewczas[1,2] and Andrzej S. Krolewski[1,2]

Diabetes Care 2017;40:e109–e110 | https://doi.org/10.2337/dci17-0009

We appreciate the invitation to respond to comments by Luo et al. (1) on our article (2). The clinical ascertainment of exposures and the outcome is crucial for epidemiological studies and we appreciate the given attention.

The goal of our study was to evaluate metabolomic determinants predicting development of end-stage renal disease (ESRD) 10 years in advance. Apparently, we were not explicit in explaining that our study design was prospective and not cross-sectional.

Luo et al. (1) mentioned limitations regarding the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to estimate glomerular filtration rate in the elderly and in subjects with certain CKD stages or to define ESRD. These might be valid diagnostic concerns relevant in the cross-sectional setting, but they are not applicable to our prospective study. We chose development of ESRD within 8–12 years, an ultimate and clearly defined outcome of diabetic nephropathy (DN), as the end point. As we described (2), the prospective status was based on queries against nationwide registries: the United States Renal Data System and the National Death Index. ESRD was defined by date of initiation of renal replacement therapy (based on United States Renal Data System records) or a listing of renal failure as cause of death (based on National Death Index records). The CKD-EPI formula was not used to define our ESRD cases. This formula, however, has been extensively evaluated, and its use remains recommended by current guidelines (3,4). In the experience of our group, it is the most optimal measure of renal function that allows tracking of renal function decline over time (5). Therefore, we used it to estimate renal function at baseline and the respective longitudinal slopes.

In addition to renal function (as indicated by estimated glomerular filtration rate), increased albumin excretion is another key feature defining DN. Measurements of the albumin-creatinine ratio are characterized by high intraindividual variation, so multiple measurements are required. Contrary to the suggestion by Luo et al. (1), proteinuria was based on multiple measurements in our study. As described, baseline status was derived from a geometric mean of multiple albumin-creatinine ratio measurements during 2 years preceding sampling for metabolomic profiling.

We also recognize the importance of other clinical measures of DN, so we have put our most stringent efforts into meticulously ascertaining clinical characteristics of Joslin Kidney Study participants over the years. The clinical data that Luo et al. (1) believed to be incomplete in our study were provided in abbreviated form because that article (2) focused on novel metabolomic determinants independent of clinical legacy measures. However, our previously published studies (5,6) that focused on the natural history of the disease considered clinical characteristics of this study population in greater detail, as referenced in our article.

Unfortunately, we disagree with the commenters' statement that kidney biopsy is the gold standard in patients with DN. The 2017 guidelines from the American Diabetes Association (3) and the Kidney Disease: Improving Global Outcomes 2012 guidelines (4) recommend biopsy only in patients with an unusual nephropathy course. We argue further that noninvasive circulating (metabolomic) biomarkers that robustly predict ESRD independently of current clinical measures have advantages.

The relevance of metabolomic determinants of early renal function decline in diabetes may differ in later stages of the disease process. We focused our study on a highly relevant group of individuals with an advanced disease who are at the highest risk of developing ESRD. Improvements in patient care for this particular group are desperately needed. Metabolomic studies evaluating nonalbuminuric pathways or other chronic complications (retinopathy or cardiovascular disease) are certainly of value and, when conducted, will advance our understanding of the disease course in the future.

Funding. This study was supported by grants from JDRF to M.A.N. (Career Development

[1]*Research Division, Joslin Diabetes Center, Boston, MA*
[2]*Department of Medicine, Harvard Medical School, Boston, MA*

Corresponding author: Monika A. Niewczas, monika.niewczas@joslin.harvard.edu.

Award 5-CDA-2015-89-A-B) and to A.S.K. (17-2013-311) and from the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases to A.S.K. (DK-41526).

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

References

1. Luo K, Fang W, Xu G. Comment on Niewczas et al. Circulating modified metabolites and a risk of ESRD in patients with type 1 diabetes and chronic kidney disease. Diabetes Care 2017;40:383–390 (Letter). Diabetes Care 2017;40:e108. https://doi.org/10.2337/dc17-0157

2. Niewczas MA, Mathew AV, Croall S, et al. Circulating modified metabolites and a risk of ESRD in patients with type 1 diabetes and chronic kidney disease. Diabetes Care 2017;40:383–390

3. American Diabetes Association. Microvascular complications and foot care. Sec. 10. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S88–S98

4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. Kidney Int Suppl 2013;3:1–150

5. Skupien J, Warram JH, Smiles AM, Stanton RC, Krolewski AS. Patterns of estimated glomerular filtration rate decline leading to end-stage renal disease in type 1 diabetes. Diabetes Care 2016;39:2262–2269

6. Rosolowsky ET, Skupien J, Smiles AM, et al. Risk for ESRD in type 1 diabetes remains high despite renoprotection. J Am Soc Nephrol 2011;22:545–553