RESPONSE TO COMMENT ON RODRIGUEZ-CALVO ET AL.

Increase in Pancreatic Proinsulin and Preservation of β-Cell Mass in Autoantibody-Positive Donors Prior to Type 1 Diabetes Onset. Diabetes 2017;66:1334–1345

Teresa Rodriguez-Calvo,[1,2] Mark Atkinson,[3] and Matthias G. von Herrath[1,4]

Diabetes 2017;66:e10–e11 | https://doi.org/10.2337/dbi17-0029

We thank the editor for providing us the opportunity to respond to the comment by Drs. Skog and Korsgren (1) regarding our recent article (2).

Skog and Korsgren raise an issue regarding the use of the term "prediabetes," especially for cross-sectional studies in adults. We acknowledge that multiple studies support the notion that most single autoantibody-positive (Ab+) subjects would never develop type 1 diabetes (T1D). They also mention that "the risk for adults with one or two autoantibodies for developing T1D would be unknown" (1). However, data emerging from National Institutes of Health TrialNet demonstrate that the vast majority of relatives (1–45 years old) with two or more antibodies eventually develop clinical disease at a rate of 10–12% per year, although, of course, age is an important factor associated with the rate of progression (3). Therefore, we do not understand the point that progression to diabetes in double Ab+ individuals would be unknown. In addition, since T1D is evenly distributed within the first six decades of life as shown by the U.K. registry (4), we believe that it is critically important to study adults with diabetes in addition to children.

Our "risk index" was a proposal to estimate the possible correlation between the proinsulin-to-insulin area ratio and factors that influence disease progression such as age, HLA, and autoantibodies. We consider that it is in our own scientific freedom to propose this index based on the available data and that, if desired, authoritative bodies such as the American Diabetes Association as well as regulatory agencies have the option to take this information into account and seek further validation.

Last, Skog and Korsgren (1) raise the notion that the pathology seen in the Network for Pancreatic Organ Donors with Diabetes (nPOD) specimens and in this study may represent artifacts caused, for example, by the time spent in the intensive care unit. One particular argument against this notion is that we also studied cases from living individuals with pancreatic biopsies (Diabetes Virus Detection [DiViD] study), which would not exhibit such artifacts. Skog and Korsgren also argue that these particular individuals would be in poor metabolic control after T1D onset. However, most of these subjects were in very good metabolic control, as the biopsies (5) were taken months after diagnosis and likely the procedure would have been never allowed in individuals in bad metabolic control. Thus, we believe this argument is likely unfounded. Beyond this, there was no correlation between the time spent in the intensive care unit and β-cell mass (2). In addition, in a previous publication (6), we did not find significant differences between donors with and without pancreatitis and there was no correlation with the time of hospitalization for any of the parameters analyzed. Finally, we now know that immune or replicating cell frequencies are not affected by the length of hospitalization prior to donor's death in pancreata collected by nPOD (M.A., unpublished data).

Overall, we believe that our study is novel, that it provides potential new insights into the pathogenesis of the disease, and that the majority of issues raised by Skog and Korsgren (1) have no justifiable basis.

Duality of Interest. M.G.v.H. is an employee of Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

References

1. Skog O, Korsgren O. Comment on Rodriguez-Calvo et al. Increase in pancreatic proinsulin and preservation of β-cell mass in autoantibody-positive donors prior to

[1]Type 1 Diabetes Center, La Jolla Institute for Allergy and Immunology, La Jolla, CA
[2]Institute of Diabetes Research, Helmholtz Diabetes Center, Helmholtz Zentrum München, Neuherberg, Germany
[3]Department of Pathology, University of Florida, Gainesville, FL
[4]Novo Nordisk Diabetes Research & Development Center, Seattle, WA

Corresponding author: Matthias G. von Herrath, matthias@lji.org.

type 1 diabetes onset. Diabetes 2017;66:1334–1345 (Letter). Diabetes 2017;66:e8–e9. https://doi.org/10.2337/db17-0589

2. Rodriguez-Calvo T, Zapardiel-Gonzalo J, Amirian N, et al. Increase in pancreatic proinsulin and preservation of β-cell mass in autoantibody-positive donors prior to type 1 diabetes onset. Diabetes 2017;66:1334–1345

3. Wherrett DK, Chiang JL, Delamater AM, et al.; Type 1 Diabetes TrialNet Study Group. Defining pathways for development of disease-modifying therapies in children with type 1 diabetes: a consensus report. Diabetes Care 2015;38:1975–1985

4. Thomas NJS, Weedon M, Hattersley A, Oram R. Abstracts of 52nd EASD Annual Meeting. Diabetologia 2016;59(Suppl. 1):1–581

5. Krogvold L, Edwin B, Buanes T, et al. Pancreatic biopsy by minimal tail resection in live adult patients at the onset of type 1 diabetes: experiences from the DiViD study. Diabetologia 2014;57:841–843

6. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J, von Herrath MG. Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes 2014;63:3880–3890