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

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We read with interest the article by Rodriguez-Calvo et al. (1). The main finding of the report is that a larger area of the pancreata retrieved from subjects without diabetes contained insulin-positive cells than pancreata from subjects diagnosed with type 1 diabetes (T1D). Moreover, the pancreatic proinsulin-to-insulin ratio was increased in autoantibody-positive (Ab+) organ donors without diabetes and in subjects with T1D. The authors concluded that their data "indicate that β-cell mass (and function) is maintained until shortly before diagnosis and declines rapidly at the time of clinical onset of disease," and throughout the text they refer to Ab+ donors as having "prediabetes." As pointed out previously (2), the term "prediabetes" should be used with caution, especially in cross-sectional studies without knowledge of whether the subjects would have developed T1D. In this study, 5 of the 13 Ab+ cadaveric organ donors were 40 years or older. Notably, 3 of these 5 donors had only one autoantibody. The risk for adults with one or two autoantibodies to develop T1D is unknown. Moreover, 8 of the 13 Ab+ donors had pancreatitis or ongoing inflammation in the exocrine pancreas as compared with only 2 out of 9 in the control group. Exocrine inflammation and fibrosis are common findings in adult Ab+ organ donors without T1D (3), and induction of autoantibodies by processes not related to T1D cannot be excluded in this age-group.

Rodriguez-Calvo et al. (1) defined a novel risk index to correlate obtained immune histological findings to the risk of developing T1D. The rational for the algorithm should be further elaborated; remarkably, being below the age of 30 years conferred the same risk as having two islet autoantibodies. Before a more general application, the proposed risk index needs to be validated.

When interpreting the data, one must also consider that most subjects display a huge release of cortisol during the development of brain edema and herniation. Also during this phase, high doses of steroids are usually given at the intensive care units. Because of this, severe insulin resistance develops that often cannot be controlled by the native β-cells; the resulting hyperglycemia usually requires substantial amounts of exogenous insulin. Tentatively, this is more pronounced in subjects with exocrine inflammation and ongoing pancreatitis. Even though subjects with recent-onset T1D are usually metabolically well controlled during the first 2 months after diagnosis, they seldom achieve metabolic control similar to that in subjects without diabetes. The proinsulin-to-insulin ratio is influenced by the workload of the native islets (1), and without detailed information on dosages of insulin and metabolic control, observed findings could equally well be due to an increase in islet workload.

Given these considerations, one should refrain from speculations on defects in insulin processing and maturation as part of the T1D pathology, and the conclusion that β-cell mass remains intact until shortly before diagnosis must be viewed with caution. The study is cross-sectional, and currently we have no solid information that the Ab+ subjects have prediabetes or even increased risk of developing T1D.

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## References

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