Comment on: Butler et al. Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors. Diabetes 2013;62:2595–2604

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In the study by Butler et al. (1) in the July issue of *Diabetes*, we noted several issues in study design and data interpretation that substantially limit the ability to form conclusions from this small autopsy series. The study was designed with a nondiabetic control group (n = 14) that was age-, sex-, and BMI-matched to a group of 20 subjects with diabetes, 8 of whom had received incretin-based therapy and 12 of whom had not. However, the authors conducted a series of comparisons between the two subsets of subjects with diabetes who were not matched and who differed in important ways that were not adjusted for with respect to key characteristics. For example, compared with the non-incretin-treated subset, incretin-treated subjects were older (mean age 58 vs. 40 years), disproportionately male (75 vs. 33%), had a longer duration of diabetes (12 vs. 8 years), and had more often been treated with antihyperglycemic therapy (100 vs. 58%).

The lack of comparability between these two subsets is additionally supported by further review of their clinical characteristics available in the Network for Pancreatic Organ Donors with Diabetes (nPOD) database (2). Among the non-incretin-treated subjects, four had positive anti-GAD or anti-insulin antibodies (one with a history of diabetic ketoacidosis [DKA]), and two additional subjects had a history of DKA; in contrast, among the incretin-treated subjects, only one was antibody-positive and none had a history of DKA. Taken together, these data suggest important differences in the underlying pathobiology of disease, indicating that the study was not designed to make valid comparisons between the two subsets of subjects with diabetes, and no clear conclusions can be drawn. For example, the imbalances in sex between the two diabetes subsets may have influenced some of these findings, as the male sex is associated with greater pancreatic volume (3). Further, it has been reported from the nPOD database that pancreas organ weight in nondiabetic individuals with diabetes-associated autoantibodies is significantly lower than that in control subjects (4). Additionally, given the observation that the incidence of pancreatic intraepithelial neoplasia (PanIN) lesions increases with age (5), the authors' observation of differences in PanIN scores between the two diabetes subsets should be interpreted with caution given the differences in age between the two subsets. We also noted that pancreatic weight data were missing for 50% of the nondiabetic subjects; for those with data, which included one subject 14 years of age and another subject 24 years of age, the mean age was markedly lower than for those without data (35 vs. 56 years). Because pancreatic volume is known to increase with age from childhood to early adulthood (3,6), analysis of differences in pancreatic weight that included comparison with the nondiabetic control group was likely affected by these missing data.

In summary, there are substantial methodological issues with the design of this study that limit the interpretation of the authors' observations and the ability to draw conclusions from this work.

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