COMMENTS AND RESPONSES

Comment on: Saisho et al. β-Cell Mass and Turnover in Humans: Effects of Obesity and Aging. Diabetes Care 2013;36:111–117

In the article by Saisho et al. (1), the effect of obesity on β-cell mass and turnover was addressed by indirectly estimating β-cell mass from human pancreatic specimens after death related to disease or trauma. Although these results are consistent with the direct measurement of islet volume after isolation from abruptly deceased healthy organ donors, the correlation between β-cell mass and BMI remains weak ($r \leq 0.5$) (2,3). The authors admit that cross-sectional studies provide limited information on the mechanisms that potentially link obesity with this increased (50%) β-cell mass. Rather unexpectedly, for example, no measurable difference in β-cell proliferation could be detected by Saisho et al. in pancreatic sections from obese individuals. Despite continued progress in clinical islet noninvasive imaging (4), the current lack of an efficient, quantitative method to assess β-cell mass in the native pancreas prohibits the direct and longitudinal study of islet adaptation to environment in humans.

To overcome this limitation, we studied the longitudinal adaptation of human islets to obesity in an immunodeficient mouse model (5). Briefly, after transplantation of a small human islet graft (400 islets), immunodeficient mice were placed on a control or high-fat diet (HFD) for 12 weeks, with 10% and 60% kcal from fat, respectively.

First, we observed a doubling of islet volume, corresponding to a 2.6-fold increase in β-cell volume in human islets grafted in mice on HFD compared with the same islets grafted in mice on the control diet. A functional compensation or doubling of fasting human c peptide levels at 12 weeks (HFD vs. controls) was also observed. Indeed, no difference in human β-cell proliferation determined with Ki67 and BrdU immunostaining was observed in obese mice (vs. controls), and proliferation levels in our model were strikingly similar to levels reported in the study by Saisho et al. Yet kinetic studies at 4, 6, 8, 10, and 12 weeks in this model suggest that both proliferation and neogenesis participate actively in islet mass expansion during obesity. Of note, diabetic human islets fail to adapt to this obese environment (5). Coupled with lineage-tracing technology, this surrogate model may accelerate and enable the long awaited longitudinal studies exploring the mechanism by which human islets adapt to obesity in vivo.

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

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