## COMMENTS AND RESPONSES

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

We thank Gargani et al. (1) for their interest in our article reporting β-cell mass in age-matched obese ($n = 61$) and lean ($n = 53$) human pancreas samples. In that study, we reported an ~50% greater β-cell mass (0.8 to 1.2 g) in obese humans compared with lean humans (2). We acknowledged that our study was cross-sectional and so we could provide no time course for the difference we reported. In the interesting report that Gargani et al. direct us to, we note their approach to the question of human islet adaptation to dietary insulin resistance. They implanted 400 human islet equivalents under the renal capsule in immunodeficient mice and then performed a cross-sectional study of the implants 12 weeks later after high fat ($n = 6$) versus a regular diet ($n = 7$). It is well known that the first week after implantation of human islets there is a substantial and variable β-cell loss, presumed to be in part due to anoxia after loss of islet vasculature and formation of islet amyloid (3).

Since there was no reported measure of β-cell apoptosis or necrosis in the report by Gargani et al., it is not clear to what extent the changes in graft β-cell volume 12 weeks later were due to differences in β-cell loss. The insulin and GLP-1 signaling pathways inhibit apoptosis, and levels of both would be predicted to be increased in the high-fat diet–fed mice, so it is perhaps plausible that engrafted β-cell loss may have benefited from the high-fat diet environment. Gargani et al. found no difference in β-cell replication at the 12-week evaluation by Ki67, although they concluded after repeated BRDU labeling early after transplantation that there was an increase in β-cell replication by this measure. However, BRDU labeling also occurs during DNA repair that might predictably be increased shortly following islet transplantation (4). It would be of interest if the β-cell Ki67 was increased at the same early time points, as this measure is less vulnerable to this problem.

In general, it seems at present that it might be premature to interpret the islet adaptation in the studies of Gargani et al. purely in terms of new β-cell formation or indeed the origins of such formation. If after decades of obesity β-cell mass has increased by ~0.5 fold, it would indeed be intriguing if human islets adaptively increase by 5 times that in just 12 weeks in the devascularized implant under the renal capsule.

Finally, we are less surprised than Gargani et al. that we did not see an increase in β-cell replication in human obesity (5,6). Expansion of β-cell mass occurs in the early postnatal phase by β-cell replication, and then the capacity for β-cell replication is silenced by epigenetic repression of cell-cycle regulators.

We congratulate Gargani et al. for their interesting studies and pursuit of the important but difficult question of β-cell turnover in human islets. We wish them well in their ongoing research.

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