

UCLA

UCLA Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/4wb2z5jd>

Journal

Diabetes Care, 36(7)

ISSN

1066-9442

Authors

Saisho, Yoshifumi
Butler, Alexandra E
Manesso, Erica
et al.

Publication Date

2013-07-01

DOI

10.2337/dc13-0486

Peer reviewed

 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 $\sim 50\%$ 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.

YOSHIFUMI SAISHO, MD^{1,2}
 ALEXANDRA E. BUTLER, MD¹
 ERICA MANESSO, PHD^{1,3}
 PETER C. BUTLER, MD¹

From the ¹Larry L. Hillblom Islet Research Center, University of California, Los Angeles, David

Geffen School of Medicine, Los Angeles, California; the ²Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; and the ³Department of Astronomy and Theoretical Physics, Lund University, Lund, Sweden.

Corresponding author: Peter C. Butler, pbutler@mednet.ucla.edu.

DOI: 10.2337/dc13-0486

© 2013 by the American Diabetes Association.

Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Acknowledgments—The work of this group is supported by funding from the National Institutes of Health (DK-059579 and DK-077967) and the Manpei Suzuki Diabetes Foundation.

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

.....

References

- Gargani SA, Pattou F, Kerr-Conte J. Comment on: β -Cell mass and turnover in humans: effects of obesity and aging. *Diabetes Care* 2013; 36:111-117 (Letter). *Diabetes Care* 2013;36:e111. DOI: 10.2337/dc13-0220
- Saisho Y, Butler AE, Manesso E, Elashoff D, Rizza RA, Butler PC. β -Cell mass and turnover in humans: effects of obesity and aging. *Diabetes Care* 2013;36:111-117
- Westermarck GT, Westermarck P, Berne C, Korsgren O; Nordic Network for Clinical Islet Transplantation. Widespread amyloid deposition in transplanted human pancreatic islets. *N Engl J Med* 2008;359:977-979
- Butler PC, Meier JJ, Butler AE, Bhushan A. The replication of beta cells in normal physiology, in disease and for therapy. *Nat Clin Pract Endocrinol Metab* 2007;3:758-768
- Meier JJ, Butler AE, Saisho Y, et al. Beta-cell replication is the primary mechanism subserving the postnatal expansion of beta-cell mass in humans. *Diabetes* 2008;57:1584-1594
- Dhawan S, Tschen SI, Bhushan A. Bmi-1 regulates the Ink4a/Arf locus to control pancreatic beta-cell proliferation. *Genes Dev* 2009;23:906-911