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Reponse to Comments 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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We would begin by thanking both Dr. Engel (1) and Dr. Heine (2), as well as their colleagues, for their interest in our recent publication (3). Both collectives of authors raise issues regarding the number of individuals studied and the age-matching of the incretin-treated versus non-incretin-treated groups of individuals with type 2 diabetes. We acknowledge that the study of pancreata from brain-dead organ donors with type 2 diabetes subject to either incretin (sitagliptin, $n = 7$; exenatide, $n = 1$) or no incretin therapy ($n = 12$) is small compared with the large clinical studies undertaken by drug sponsors. We also accept the critique that the matching of the two diabetic groups does not meet the standards expected for a randomized clinical study. However, to the best of our knowledge, with the exception of a single case report (4), we believe our effort represents the first evaluation of human pancreata following antecedent glucagon-like peptide 1 (GLP-1)-based therapy. We would also portend that the *very* random nature of obtaining human pancreata under the circumstances of brain-dead organ donors is limiting, both in terms of which individuals become obtainable and the quantity of available clinical information related to their diabetes. We fully agree that priority should be given to evaluating a larger number of pancreata, particularly given the widespread use of this class of drugs and the uncertainties with regard to their unintended actions on the pancreas.

Having mentioned the relatively small sample size, we are surprised that Heine et al. (2) would propose the use of covariate analysis to address potential confounders. To the best of our understanding, the use of covariate analysis is a statistical approach suited to large population studies

rather than hypothesis testing in smaller cohorts such as the present one. With each additional covariate analyzed, a degree of freedom is lost; so when the analysis was adjusted by Heine et al. for the four covariates of BMI, duration of diabetes, sex, and age, statistical power was negligible. Hence, a lack of significance in the absence of statistical power is not informative. These authors also propose removing four individuals for potentially having type 1 diabetes in the analysis of α -cell mass and pancreatic weight; yet, as noted below, the available data support these individuals as having type 2 diabetes. Heine et al. also question the relevance of cited studies that report α -cell hyperplasia with decreased glucagon signaling as a potential explanation of the α -cell hyperplasia that we report following incretin therapy. We proposed that this might potentially occur as a consequence of GLP-1-mediated suppression of glucagon secretion. In terms of our response, Xu et al. (5) have, in fact, independently reported increased α -cells in diabetic rats (post-partial pancreatectomy) treated with exenatide. Also of note, scientists from Lilly noted α -cell hyperplasia, even with partial suppression of hepatic α -cell signaling in rats, implying complete suppression of glucagon signaling is not required (6). Moreover, the lack of findings in mostly short-term studies in nondiabetic models in preclinical studies does not necessarily contradict findings in humans with type 2 diabetes treated for a year or more with incretin therapy. In this context, the finding of a glucagon-expressing neuroendocrine tumor in one of eight subjects as well as glucagon-expressing microadenomas in three of eight individuals with prior incretin therapy is surely not to be simply dismissed as a chance finding. Beyond this, to further address the questions noted regarding age and pancreatic intra-epithelial neoplasia (PanIN) lesions, herein we show the frequency of PanINs detected in each subject plotted as a function of age (Fig. 1). Our own interpretation of this data is that this information does not offer assurance that the increase noted in patients previously subjected to incretin therapy can be accounted for by the function of age.

To address questions raised as to whether some individuals in the study (3) had type 1 rather than type 2 diabetes, we have, with the notion of even more transparent and complete disclosure, assembled relevant information regarding these cases in a table (Table 1). Of note, only one patient with diabetes in the study was glutamic acid

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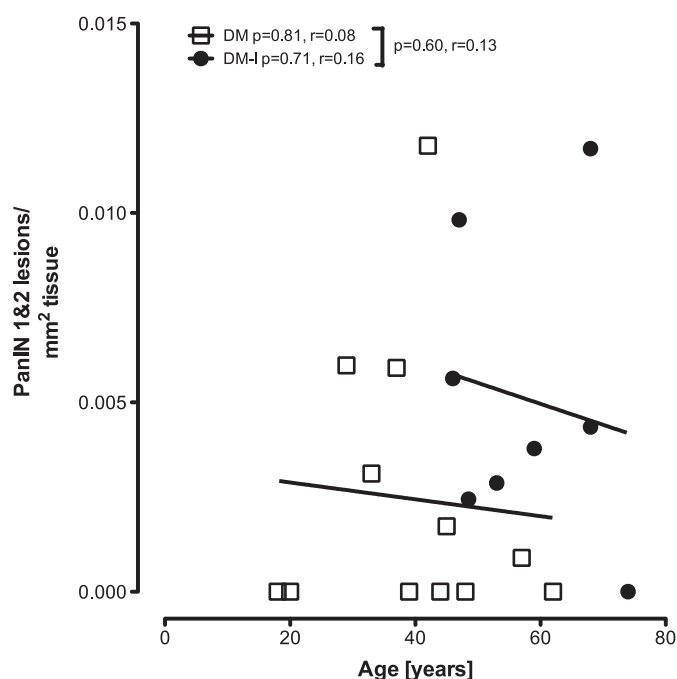


FIG. 1. Correlation between number of PanIN 1 and 2 lesions per mm² of pancreas vs. age in years of the brain-dead organ donors. DM, did not receive GLP-1 drugs; DM-I, received incretin therapy.

decarboxylase (GAD) autoantibody-positive; that individual being a single autoantibody-positive individual, yielding a percentage that is equivalent to that common to clinical studies of subjects with type 2 diabetes where positivity ranges of 5–15% are often observed (7). Beyond this, we would note that the presence of insulin antibodies in individuals who have been treated with insulin is common and not predictive of autoimmunity. This is in distinction from the Network for Pancreatic Organ Donors with Diabetes (nPOD) study cited by Engel et al. (1) that reported pancreas weights were decreased in *nondiabetic* individuals never exposed to insulin (8). The comparison of concern in the current report (3) is that the pancreas mass was increased in individuals with type 2 diabetes treated with incretin therapy even though they were, as pointed out, on average older than individuals with said disease without incretin therapy. An ever-expanding list of literature suggests that pancreas mass is decreased in persons with type 2 diabetes and furthermore, it also decreases with age (9). With this, we would suggest that the increased pancreas mass in older individuals with incretin therapy, in fact, represents a conservative estimate. Our finding is also consistent with some preclinical studies reporting an increase in pancreas mass with incretin therapy (10). To address the specific concerns raised by Heine et al. (2) with regard to individuals with prior diabetic ketoacidosis (DKA), we again refer the correspondents to Table 1. We are confident that the two control patients with diabetes referred to who had a history of DKA (cases 6109, 6110) had type 2 diabetes. One of these patients was Hispanic (case 6109) and the other African American (case 6110), and both had typical endocrine pathology of type 2 diabetes with islet amyloid in addition to the absence of insulinitis. DKA in type 2 diabetes is well recognized, particularly in African American and Hispanic individuals with >30 BMI (11). We are also confident that the two individuals who required insulin before age 20 years

(cases 6149, 6028) also had type 2 diabetes, again based on African American ethnicity, C-peptide levels, and pancreas pathology with islet amyloid. There is an increasing incidence of type 2 diabetes in youth, individuals who frequently require insulin before age 20 years (12).

Another issue raised by Heine et al. (2) is an intriguing one, this being the question of whether the period of brain death on ventilator support preceding organ harvesting may have been the cause of endocrine proliferation. In order to address this issue, we examined the relationship between the duration in the intensive care unit (ICU) and either α -cell or β -cell fractional area. Despite donors having a wide range of ICU duration, there was no relationship between ICU duration and fractional pancreatic endocrine area in either of the two groups with diabetes or non-diabetic control subjects.

Heine et al. also raised the issue of pancreatic inflammation in relation to GLP-1 therapy with a critique offered that numerous preclinical animal studies and recent studies of incretin therapy in diabetic Zucker Fatty rats did not find evidence of pancreatitis. Patients with type 2 diabetes have an increased incidence of chronic pancreatitis, and this is not always appreciated in life. We cited the study of Gier et al. (13) because, to our knowledge, it remains the only study of incretin therapy in a model of chronic pancreatitis, with this study demonstrating an acceleration of PanIN lesions with increased blood lipase levels with exenatide therapy. The recent revelation that lipase levels were also increased, but not reported, in a clinical trial of exenatide further underscores the concern that GLP-1 mimetic therapy may have unintended proinflammatory effects on the exocrine pancreas in humans and thereby warrants further investigation (14).

To summarize, we acknowledge that securing the precious resource of human pancreas under the circumstances of brain death has limitations that differ from large clinical trials. With this line of thought, we would portend rather than one form of study negating the other that *both* lines of investigation are vitally important and should be evaluated in terms of the potential safety of incretin therapy. Indeed, each study type can shed unique insights into this vitally important question. Heine et al. (2) propose that data from long-term clinical randomized trials are required to evaluate the balance of the benefits to safety of the incretin therapies. We wholeheartedly agree that such studies are needed and should be open to the same scrutiny that has permitted more than 300 registered scientists to directly view the pancreas sections from all nPOD cases. This would permit independent investigators to monitor important caveats to these studies, including how individuals with events such as pancreatitis or pancreatic tumors are adjudicated with regard to the timing of incretin therapy and how pancreatitis is defined and/or excluded. Indeed, we are proud that both the open nature of the nPOD program and our article permitted the correspondents the opportunity to directly evaluate our findings. This form of free and open research allows everyone the opportunity to provide constructive comments, which presently is not the case for much of the safety data previously generated by companies investigating both incretin and other newly available therapies for individuals with diabetes (14). With this, we support the recent suggestion by the American Diabetes Association that ongoing post-marketing studies of the incretin class of therapies should also be opened for independent scrutiny. Likewise, it has also been suggested that the pancreas sections of the

TABLE 1
Autoantibody-positive cases

| Case | Age (years) | Duration of T2D (years) | Sex | BMI (kg/m ²) | Ethnicity | AutoAbs | C-peptide (ng/mL) | Diabetes meds | History | Pathology |
|---|-------------|-------------------------|-----|--------------------------|------------------|----------|-------------------|-----------------------------------|---|---|
| 6109 | 48 | ? | F | 32.5 | Hispanic | mIAA+ | <0.05 | None | Cause of death: ICH/stroke DKA; HbA _{1c} = 8.0; hypertension, hyperlipidemia | Plentiful insulin + islets; amyloid in numerous islets |
| 6127 | 44 | 10 | F | 30.4 | Caucasian | mIAA+ | 0.08 | Insulin pump, Novolog | History of gestational diabetes mellitus with 2 pregnancies 17 and 21 years prior; hypercholesterolemia | Plentiful insulin + islets; amyloid in numerous islets |
| 6142 | 29 | 14 | F | 34.4 | Hispanic | mIAA+ | 0.19 | Previous insulin but noncompliant | Strong family history of T2D; insulin dependent but noncompliant | Plentiful insulin + islets; amyloid in numerous islets |
| 6149 | 39 | 16 | F | 29.1 | African American | GAD+ | 11.55 | Insulin | History of gestational diabetes mellitus 14 years prior and treated with regular insulin; hypertension for 20 years; renal dialysis for 2 years | Plentiful insulin + islets; amyloid in numerous islets |
| Prior history of DKA | | | | | | | | | | |
| 6109 | 48 | ? | F | 32.5 | Hispanic | mIAA+ | <0.05 | ? | HbA _{1c} = 8; cause of death: ICH/stroke DKA, hypertension, hyperlipidemia | Plentiful insulin + islets; amyloid in numerous islets |
| 6110 | 20 | 0.2 | F | 40.0 | African American | Negative | 0.58 | ? | DKA; acute onset T2D; history of gestational diabetes mellitus; father had diabetes (unknown type) | Plentiful insulin + islets; amyloid in occasional islet |
| Onset of diabetes before age 20 years requiring insulin | | | | | | | | | | |
| 6028 | 33 | 17 | M | 30.0 | African American | Negative | 22.4 | Insulin | Gunshot wound to head | Plentiful insulin + islets; amyloid in several islets |
| 6149 | 39 | 20 | F | 29.1 | African American | GAD+ | 11.55 | Insulin | History of gestational diabetes mellitus with 2 pregnancies 17 and 23 years previously; hypercholesterolemia | Plentiful insulin + islets; amyloid in numerous islets |

AutoAbs, autoantibodies; ICH, intracerebral hemorrhage; mIAA+, micro-insulin autoantibody–positive; T2D, type 2 diabetes.

nonhuman primates exposed to incretin drugs should be made comparably openly available (14). The credibility of the arguments raised about our studies by the correspondents would surely be advanced by such actions. In the end, our only desire (albeit clearly controversial) is to stimulate open exchange regarding this class of drugs for the purpose of positioning, to be best means possible, issues of patient safety.

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