[^{11}C]5-hydroxy-tryptophan PET for Assessment of Islet Mass During Progression of Type 2 Diabetes

Lina Carlbom,[1] Daniel Espes,[2,3] Mark Lubberink,[1] Mats Martinell,[4] Lars Johansson,[1,5] Håkan Ahlström,[1] Per-Ola Carlsson,[2,3] Olle Korsgren,[6] and Olof Eriksson[7]

Diabetes 2017;66:1286–1292 | DOI: 10.2337/db16-1449

ISLET STUDIES

[^{11}C]5-hydroxy-tryptophan ([^{11}C]5-HTP) positron emission tomography of the pancreas has been shown to be a surrogate imaging biomarker of pancreatic islet mass. The change in islet mass in different stages of type 2 diabetes (T2D) as measured by noninvasive imaging is currently unknown. Here, we describe a cross-sectional study where subjects at different stages of T2D development with expected stratification of pancreatic islet mass were examined in relation to individuals without diabetes. The primary outcome was the [^{11}C]5-HTP uptake and retention in pancreas, as a surrogate marker for the endogenous islet mass. We found that metabolic testing indicated a progressive loss of β-cell function, but this was not mirrored by a decrease in [^{11}C]5-HTP tracer accumulation in the pancreas. This provides evidence of retained islet mass despite decreased β-cell function. The results herein indicate that β-cell dedifferentiation, and not necessarily endocrine cell loss, constitutes a major cause of β-cell failure in T2D.

Pancreatic uptake and utilization of the radiolabeled serotonin precursor [^{11}C]5-hydroxy-tryptophan ([^{11}C]5-HTP) has previously been shown by us to provide a seemingly accurate measurement of the total endogenous islet mass in individuals without diabetes and individuals with type 1 diabetes (T1D) (1,2). Recently, we also showed that hepatic [^{11}C]5-HTP uptake could be used as a quantitative measurement of intraportally transplanted islet mass (3). In a retrospective study, we earlier investigated the pancreatic uptake in individuals with type 2 diabetes (T2D), who were previously examined up to four times by [^{11}C]5-HTP due to a suspected neuroendocrine tumor (2). In this small population, we found a gradual decrease in pancreatic uptake of [^{11}C]5-HTP, paralleling the progression of diabetes.

In order to obtain further understanding for the potential of [^{11}C]5-HTP as a surrogate marker for pancreatic islet mass, we designed a cross-sectional study where we examined four groups of subjects at different stages of T2D development with expected stratification of pancreatic islet mass in relation to one group of individuals without diabetes. The primary outcome was the [^{11}C]5-HTP uptake in pancreas, which was hypothesized to correlate with remaining functional capacity of the β-cells. Exploratory end points were pancreatic perfusion (radiowater positron emission tomography [PET]), pancreatic volume (MRI), pancreatic fat content (MRI), and hepatic fat content (MRI) and changes in these parameters during progression of T2D.

RESEARCH DESIGN AND METHODS

Study Population and Metabolic Characterization

Individuals with T2D were recruited from daily clinical routine at Uppsala University Hospital and from the diabetes registry ANDiU (All New Diabetics in Uppsala). Healthy control individuals without diabetes (HC) were recruited by advertising. All individuals in the study were given written and oral information and signed a consent form prior to participation. The study was approved by the regional ethical board in Uppsala (EPN 2012/302). The studies were conducted according to the principles expressed in the Declaration of Helsinki.

[1]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[2]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden
[3]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[4]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
[5]Antaros Medical AB, Mölndal, Sweden
[6]Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, Sweden
[7]Department of Medicinal Chemistry, Uppsala University, Uppsala, Sweden
Corresponding author: Olof Eriksson, olof.eriksson@pet.medchem.uu.se.

Received 25 November 2016 and accepted 16 February 2017.
Clinical trial reg. no. NCT02967354, clinicaltrials.gov.
L.C. and D.E. contributed equally to this study.
P.-O.C., O.K., and O.E. share senior authorship.

Individuals with T2D were divided into four groups based on their BMI and current diabetes treatment regimen: group A, BMI >30 kg/m^2 (obese) treated with oral antidiabetes drugs (OAD); group B, BMI 20–26 kg/m^2 (lean) treated with OAD; group C, BMI >30 kg/m^2 (obese) treated with OAD and insulin; and group D BMI 20–26 kg/m^2 (lean) treated with OAD and insulin.

The metabolic control of study participants was evaluated under fasting conditions based on HbA_{1c} levels, plasma glucose, and plasma C-peptide levels. Based on that, HOMA indexes were calculated using the HOMA2 calculator. HOMA2-B is an estimate of the β-cell steady-state function and HOMA2-S is an estimate of insulin sensitivity; values are given as a percentage and the model has previously been calibrated so that 100% represents values obtained from young healthy adults. HOMA2-IR is an estimate of insulin resistance.

In addition to estimations of metabolic control and β-cell function based on fasting parameters, we conducted an intravenous arginine test and a glucose-potentiated arginine test, which are considered the gold standard to assess the functional β-cell mass (4,5). In brief, the tests were conducted as follows. After overnight fasting and sampling of baseline blood samples, arginine (5 g) was administered intravenously. Blood samples were drawn from the opposite arm after 2, 3, 4, 5, 7, 10, and 40 min. C-peptide and glucose levels were analyzed in plasma, and the maximum C-peptide secretion was calculated by subtracting the fasting levels from the average value of the three highest recordings during the first 5 min. During the glucose-potentiated arginine test, glucose was infused (50 mg/mL, 18 mL/min), and after 60 min, blood samples were collected and arginine (5 g) was administered intravenously. Repeated blood samples were then collected after 2, 4, 5, 7, and 10 min. By subtracting the C-peptide level recorded just prior to arginine administration from the average C-peptide levels during the following 5 min, the maximum β-cell secretion capacity was calculated.

PET/Computed Tomography Examinations

All individuals were fasting >4 h prior to the PET examinations. Two intravenous catheters were placed, one in each arm. The individual was placed in supine position in a Discovery ST PET/computed tomography (CT) (GE Healthcare) scanner, and a scout CT examination was performed to position the abdomen including the pancreas in the scanner field of view. A low-dose abdominal CT examination was performed in order to provide anatomical coregistration and for attenuation correction for the PET images.

First, a 10-min dynamic PET examination (time frames: 1 × 10 s, 8 × 5 s, 4 × 10 s, 2 × 15 s, 3 × 20 s, 2 × 30 s, and 6 × 60 s) was performed after intravenous administration of 400 MBq [^{15}O]H_2O (radiowater) in order to assess the pancreatic blood perfusion at the basal state. Next, 4 MBq/kg [^{11}C]5-HTP was administered intravenously. Each individual was examined with [^{11}C]5-HTP for 60 min, and this PET image data set was temporally divided into 33 time frames (1 × 10 s, 8 × 5 s, 4 × 10 s, 2 × 15 s, 6 × 30 s, 5 × 120 s, 5 × 300 s, and 2 × 600 s). During the [^{11}C]5-HTP examination, discrete venous blood samples were acquired after 5, 20, and 40 min to assess the percentage of native [^{11}C]5-HTP in the blood plasma.

The software VOIager (GE Healthcare) was used to manually delineate the pancreas and to analyze PET tracer uptake. The pancreatic perfusion (in mL/min/mL tissue) was calculated by using the radiowater 1 tissue compartment model (1TC). [^{15}O]H_2O content in pancreas was obtained by delineating only PET voxels fully inside the pancreatic parenchyma, in order to avoid partial volume effects. The [^{15}O]H_2O content in aorta was used as input in the 1TC model, and >10 voxels fully inside the aortic lumen was delineated to achieve this without partial volume effects.

[^{11}C]5-HTP uptake was measured by delineating the pancreas using the same method as for [^{15}O]H_2O described above. Pancreatic uptake of [^{11}C]5-HTP was normalized to the percentage of injected dose taken up per gram of pancreas (%ID/g). The total percentage of injected dose taken up by the pancreas (%ID) was calculated by multiplying %ID/g by the pancreatic volume (mL) as separately assessed by MRI. In order to correlate [^{11}C]5-HTP uptake in pancreas with age, data from a previous study in a younger cohort were included (2).

MRI Examinations

MRI examinations were performed using a 1.5T clinical scanner (Philips). Pancreas and liver fat content were measured using a dedicated Dixon scan, using a spoiled 3D multigradient echo sequence. An in house–developed method was used to reconstruct water and fat data correcting for T2* decay (6). The pancreas and liver were delineated manually from the images using the software ImageJ.

RESULTS

Study Population and Metabolic Characterization

In total, 39 individuals were enrolled in the study. Descriptive data are given in Table 1.

One individual in the group of HC did not participate in any imaging studies and was not included in the reporting of the imaging results. One individual in the HC group exhibited markedly high [^{11}C]5-HTP pancreas uptake and retention (1.2%ID) in addition to having an unusually large pancreas (148 g) despite having smaller than average body size. Since an anatomical abnormality of the pancreas could not be ruled out, this individual was excluded from the report. One individual in group A (BMI >30 kg/m^2 [obese] treated with OAD) did not undergo a [^{15}O]H_2O PET scan and is therefore not included in the reporting of pancreas perfusion and pancreatic blood flow (PBF). One individual in group D (BMI 20–26 kg/m^2 [lean] treated with OAD and insulin) did not undergo an MRI scan and is therefore not included in reporting of pancreas volume, pancreas perfusion, [^{11}C]5-HTP pancreas uptake, and pancreas and liver fat percentage.

Table 1—Descriptive data of all study participants.

	HC	Group A	Group B	Group C	Group D
Total *n*	8	7	7	9	8
Antidiabetes treatment	NA	OAD	OAD	OAD + insulin	OAD + insulin
Sex (*n* male)	4	5	5	7	4
Age (years)	63.3 ± 2.2	56.7 ± 3.8	60.3 ± 4.1	61.8 ± 2.4	66.3 ± 1.9
Diabetes duration (years)	NA	1.6 ± 0.3	3.4 ± 2.0	11.4 ± 2.0††#	15.7 ± 1.8††††###
BMI (kg/m^2)	28.1 ± 1.2	33.3 ± 1.0**	25.1 ± 0.9	33.2 ± 1.2**	25.8 ± 0.5
P-glucose (mmol/L)	5.9 ± 0.1	9.6 ± 0.7	8.3 ± 0.6	10.4 ± 1.6*	10.2 ± 2.1
P-C-peptide (nmol/L)	0.86 ± 0.09	1.36 ± 0.21	0.78 ± 0.05	1.2 ± 0.24	0.56 ± 0.08
HbA_{1c} (mmol/mol)	37.6 ± 0.9	53.3 ± 4.0*	49.6 ± 2.2	71.3 ± 5.8****	61.4 ± 2.4***
HOMA2-B (%)	107 ± 8	69 ± 9*	56 ± 4**	65 ± 14*	40 ± 6***
HOMA2-S (%)	56 ± 8	32 ± 5	52 ± 4	60 ± 23	68 ± 14
HOMA2-IR	2 ± 0.2	4 ± 0.6	2 ± 0.2	4 ± 1	2 ± 0.4
P-cholesterol (mmol/L)	5.9 ± 0.4	4.4 ± 0.3*	4.6 ± 0.2	3.7 ± 0.3***	5.1 ± 0.5
P-triglycerides (mmol/L)	2.0 ± 0.5	1.4 ± 0.2	1.2 ± 0.2	2.2 ± 0.6	1.5 ± 0.2
P-HDL cholesterol (mmol/L)	1.3 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.9 ± 0.1**	1.3 ± 0.1
P-LDL cholesterol (mmol/L)	3.7 ± 0.3	3.0 ± 0.2	2.9 ± 0.2	2.1 ± 0.2***	3.2 ± 0.4

HOMA indexes were calculated using the HOMA2 calculator based on fasting glucose and C-peptide levels. HOMA2-B is an estimate of the β-cell steady-state function and HOMA2-S is an estimate of insulin sensitivity; 100% corresponds to young healthy adults. HOMA2-IR is an estimate of insulin resistance. Data are given as means ± SEM, unless stated otherwise. A one-way ANOVA using Dunnett post hoc test with comparison with HC was applied for statistical analysis when values were compared with HC. A one-way ANOVA using Tukey post hoc test was applied for statistical analysis when data were compared between the groups of patients with diabetes. Group A, BMI >30 kg/m^2 treated with OAD; group B, BMI 20–26 kg/m^2 treated with OAD; group C, BMI >30 kg/m^2 treated with OAD and insulin; group D, BMI 20–26 kg/m^2 treated with OAD and insulin; NA, not applicable; P, plasma. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$; ††$P < 0.01$, when compared with group C; ††††$P < 0.0001$, when compared with group C; #$P < 0.05$, when compared with group E; ###$P < 0.001$, when compared with group E.

The acute C-peptide secretion in response to arginine was decreased in lean subjects with T2D when compared with obese subjects. Subjects treated with exogenous insulin showed a more marked decrease in stimulated C-peptide secretion when compared with subjects on OAD (Fig. 1*A*). During the glucose-potentiated arginine test, a decreased C-peptide response was observed in all groups with T2D when compared with HC (Fig. 1*B*).

Pancreatic Perfusion

Perfusion was increased in obese subjects on OAD compared with HC ($P = 0.02$). Otherwise there were no clear differences between the groups. The pancreatic size accounts to a large extent for this difference, as seen by the lack of difference in PBF per gram of tissue in the same group (Fig. 2*B*).

[11C]5-HTP Uptake and Utilization in Pancreas

It has previously been reported that the [11C]5-HTP uptake at the 55-min time point yields optimal contrast between islets and remaining exocrine pancreas (2). All reported values here are therefore at the 55-min mark. There were no differences in pancreatic uptake of [11C]5-HTP in any of the groups (Fig. 3). There was a greater variation in each of the groups consisting of individuals with T2D (a factor of three or more), whereas the variation in the individuals without diabetes was smaller (factor of two). There was a tendency of decreased uptake in lean subjects requiring exogenous insulin (the group with highest decrease in β-cell function) (Fig. 1), but one outlier exhibited strong uptake almost six times higher than the majority of the individuals in this group.

Pancreatic Volume

Pancreatic volume was increased in obese individuals requiring exogenous insulin (group *C*) (Fig. 4). There was a tendency of increase in pancreatic size also in obese individuals on OAD, except for one outlier with a small pancreas.

Fat Content in Pancreas and Liver

The fat content in pancreas varied markedly between the individuals in each group, with no significant difference between groups (Fig. 5*A*, *C*, and *D*). Obese individuals, both on OAD as well as those on exogenous insulin, exhibited a higher hepatic fat content as compared with individuals without diabetes (Fig. 5*B*).

DISCUSSION

We report data on the relationship between pancreatic uptake of the serotonin biosynthesis PET marker [11C]5-HTP in groups of subjects stratified to correspond with the progression of T2D. In summary, metabolic testing indicated a progressive loss of β-cell function, but this was not mirrored by a clear decrease in [11C]5-HTP tracer accumulation in the pancreas.

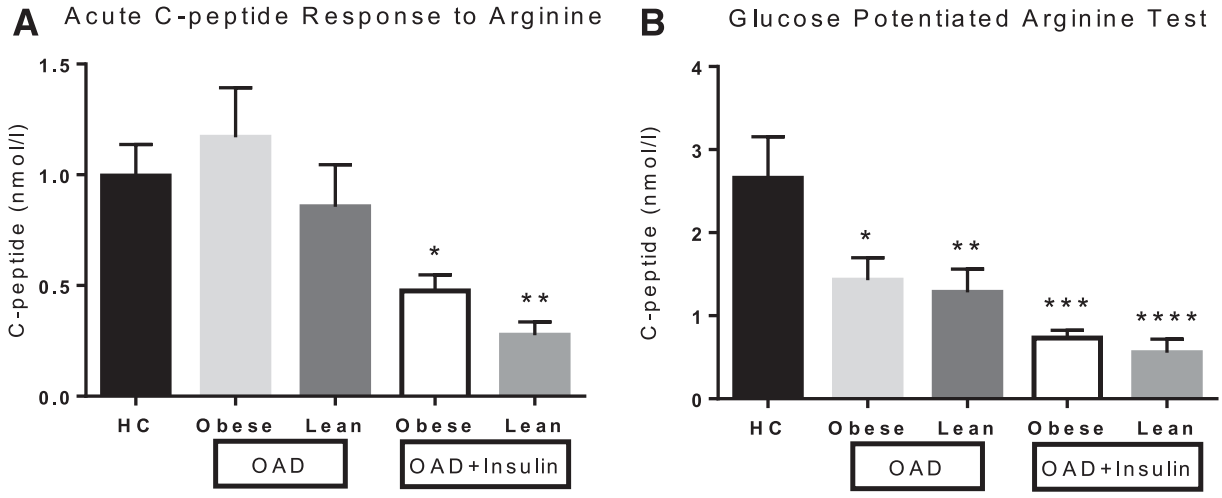

Figure 1—Estimates of functional β-cell mass. The functional β-cell mass was estimated by conducting an intravenous arginine stimulation (*A*) and a glucose-potentiated arginine stimulation (*B*). *A*: The response to intravenous arginine stimulation is comparable to that of HC in patients with OAD (groups A and B), whereas a decreased C-peptide response was observed in patients with OAD and insulin treatment (groups C and D). *B*: The C-peptide response to a glucose-potentiated arginine test was decreased in all patients with T2D when compared with HC. All values are given as means ± SEM. A one-way ANOVA using Dunnett post hoc test with comparison with HC was applied for statistical analysis. **P* < 0.05; ***P* < 0.01; ****P* < 0.001; *****P* < 0.0001.

Intuitively, this indicates that the primary study outcome was negative and questions the [^{11}*C*]5-HTP tracer as an endocrine biomarker, as opposed to a previously reported study where [^{11}C]5-HTP uptake was reduced by two-thirds in β-cell–deficient individuals with longstanding T1D. However, in morphological investigation of subjects with T2D, a decrease in β-cell mass could only be observed in subjects examined >20 years after diagnosis (7). The authors concluded that loss of β-cell mass most likely could not be the primary cause for T2D and that "alterations of β-cell function are quite important for the onset and progression of T2D." Notably, the duration of T2D for the subjects in the current study was only 16 years or less on average. Hence, our imaging results are in accord with previous morphological examinations of a retained β-cell mass during the initial period after diagnosis of T2D.

[^{11}C]5-HTP labels both α- and β-cells in the pancreas (1,2,8). The importance of glucagon in the control of glucose metabolism in T2D was recently elegantly reviewed by Holst and colleagues (9), and presented findings highlight the importance of an imbalance in the ratio of insulin to glucagon secretion in T2D. Also, dedifferentiation of β-cells into immature endocrine cells with reduced functional capacity for insulin secretion, or *trans*-differentiation into α-cells, as recently described in the human pancreas during T2D, would provide a tentative explanation for the retained capacity for 5-HTP uptake and retention in the present report (10–12). This is in contrast with the situation in T1D where acute β-cell loss occurs through direct cell destruction, which corresponds to a loss in [^{11}C]5-HTP uptake and retention capacity (2). Importantly, even if the regulation of serotonin biosynthesis in β-cells is

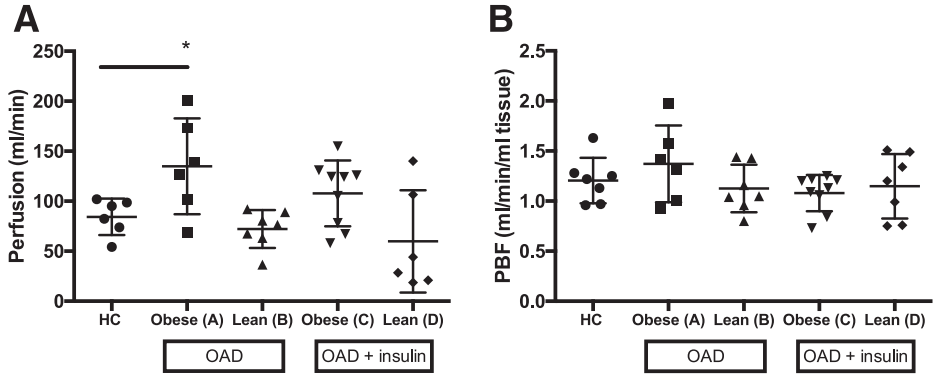

Figure 2—Pancreatic perfusion. Total pancreatic perfusion was increased in obese individuals on OAD compared with HC, but otherwise unchanged (*A*). The PBF per gram of pancreas did not differ between the groups (*B*). **P* < 0.05.

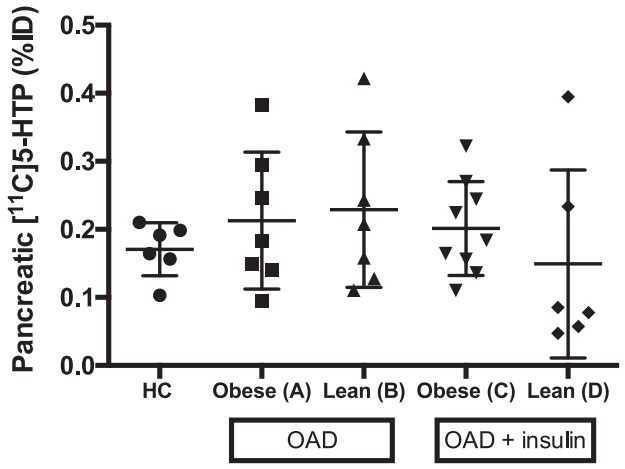

Figure 3—Pancreatic uptake of [^{11}C]5-HTP. The uptake and retention of [^{11}C]5-HTP in pancreas was assessed at the 55-min time point after intravenous administration. There was no clear change in [^{11}C]5-HTP uptake between the groups, although there was a tendency of decrease in lean individuals requiring exogenous insulin, with exception for one outlier.

poorly understood, the limited literature on the matter indicates that the serotonin biosynthesis (dopa decarboxylase [DDC] activity) is unchanged also in dysfunctional β-cells (13). These phenomena would explain the results seen in both the current study in individuals with T2D and the previous study in individuals with T1D.

In support of this hypothesis, studies in mice suggest that β-cell dedifferentiation and conversion into other endocrine cells due to failure of expression of FoxO1 constitute an important mechanism for β-cell failure in T2D (12).

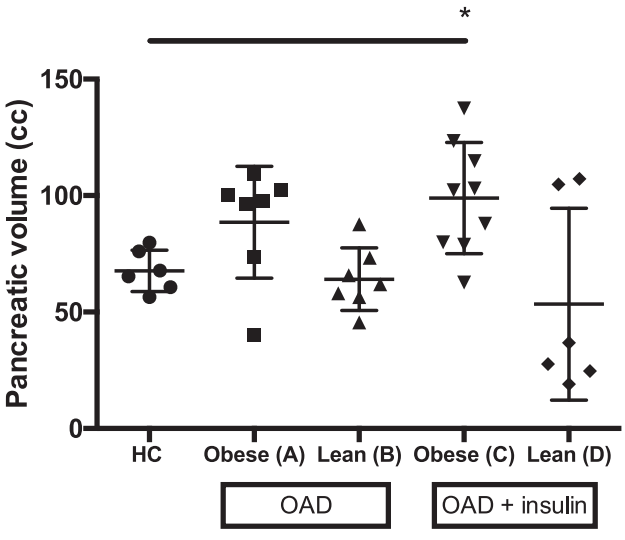

Figure 4—Pancreas volume in HC and patients with T2D. Pancreatic size was increased in obese subjects requiring exogenous insulin, as well as a tendency for increase in size in obese individuals on OAD only. *$P < 0.05$.

This postulation was further corroborated by findings that mature human β-cells can lose their identity and convert to α-cells ex vivo (14) and in vivo in subjects with T2D (10). The transition from β-cells into α-cells may explain the frequently reported increase in the ratio of α-cells to β-cells (15–17) and the rare finding of bihormonal cells and expression of mesenchymal markers in subjects with T2D or insulin resistance (18–21). Importantly, recent reports on single-cell transcriptome in islet cells from subjects without diabetes and subjects with T2D revealed that α- and β-cells in subjects with diabetes exhibited marked similarities with those found in endocrine cells from pediatric donors, again indicating a transition to a more immature state (11). The authors interpret their results to support the notion that T2D could in part result from dedifferentiation and failure of specific β-cell function. Our imaging findings with similar [^{11}C]5-HTP uptake in all groups of subjects with T2D are in accord with the hypothesis presented in these reports and suggest that the total endocrine pancreas mass remains in most subjects with T2D, but that a substantial fraction of the β-cells has dedifferentiated and therefore shows impaired functional capacity.

We hypothesize that a dual-tracer approach, using [^{11}C]5-HTP combined with a more β-cell–selective PET tracer (22), e.g., GPR44 targeting tracers (23), could be used to quantify total islet as well as β-cell mass, respectively. The α-cell mass during the progress of T2D could then be approximated.

The retention of the radioactive label in pancreatic endocrine tissues can potentially be modulated in several ways by different pharmaceuticals. Inhibition of the monoamine oxidase A (MAO-A)–mediated intracellular degradation of [^{11}C]5-HT by peroral moclobemid could increase islet cell retention several-fold (1,24). Additionally, peroral 100–200 mg carbidopa has been shown to increase the [^{11}C]5-HTP lesion-to-background contrast in subjects with neuroendocrine tumors by slowing down the peripheral metabolism of [^{11}C]5-HTP and thereby leaving more unmetabolized [^{11}C]5-HTP in the blood for uptake in endocrine cells (25).

However, neither of these approaches was used in this study for a couple of reasons. First, it is unknown if these interventions change the preference of retention in α- versus β-cells. MAO-A inhibition has, for example, been shown to have a larger effect in α-cells in mouse (8). This uncertainty would add another variable to the data.

Second, peroral preadministration of a pharmaceutical would add individual variability in degree of inhibition as well as the time between preadministration and intravenous administration of [^{11}C]5-HTP. Again, this intervention would yield additional variations in the data, with uncertain benefits.

The secondary outcomes demonstrated a tendency for decreased perfusion of the T2D pancreas in lean individuals, which is in agreement with previously reported results (26) and as also seen in subjects with T1D (27). We found increased pancreatic size, as well as increased hepatic fat

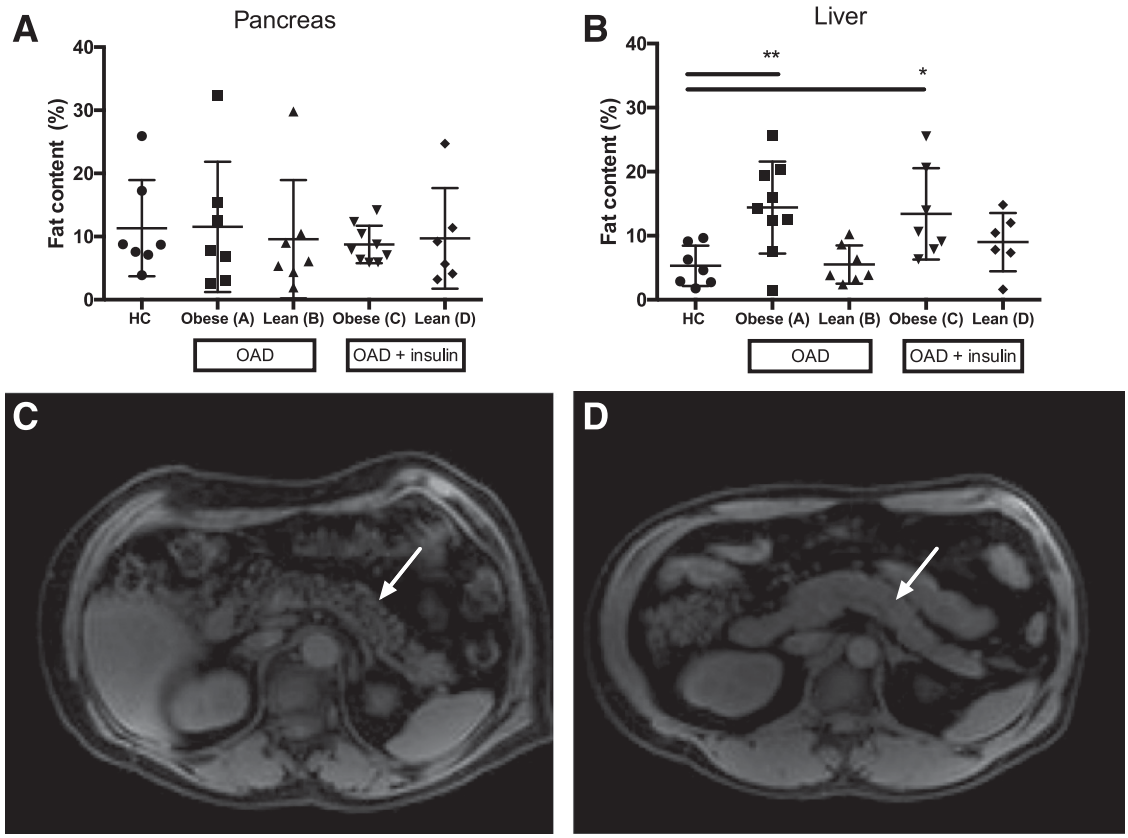

Figure 5—Fat content in abdominal organs. Fat content in the pancreas (*A*) and liver (*B*). The individual in panel *C* has a markedly increased fat content in the pancreas (white arrows) compared with the individual in panel *D*. *$P < 0.05$; **$P < 0.01$.

content, in both groups of obese individuals with T2D, which is also in agreement with previous studies.

Notably, the pancreatic uptake of [^{11}C]5-HTP in elderly (>50 years of age) HC in this study was markedly reduced when compared with that in younger (<26 years) subjects without diabetes reported previously (2), i.e., 0.17 ± 0.02%ID for subjects with an average age of 63 years vs. 0.40 ± 0.05%ID for subjects <26 years old (Fig. 6). This is a striking and unexpected difference, which may primarily be due to two reasons: *1*) reduced capacity for 5-HTP uptake and retention (serotonin biosynthesis) in islet cells in older subjects without diabetes, or *2*) reduced pancreatic endocrine cell mass in older subjects without diabetes.

In aging subjects without diabetes, there is a gradual decline in β-cell function (28). The selectivity of [^{11}C]5-HTP for the endocrine human pancreas is dependent not only on the expression of the enzyme DDC, which converts 5-HTP into serotonin, but also on the significantly higher blood perfusion in islets (about 10 times that of acinar pancreas), resulting in proportionally higher tracer delivery. In mice, a similar uptake of tritiated HTP was found in both α- and β-cells, but the retention in β-cells was markedly higher, resulting in an increased relative accumulation in β-cells 60 min after intravenous administration with 75% of the tracer found within the β-cells. These findings in mice have been corroborated by us in nonhuman primates and humans by the observations that the pancreatic [^{11}C]5-HTP uptake is almost exclusively

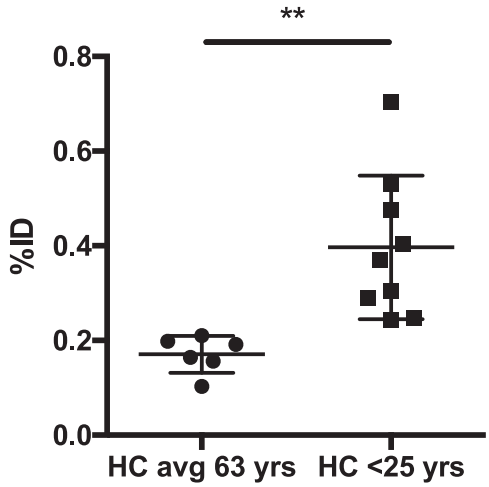

Figure 6—Pancreatic uptake and retention of [^{11}C]5-HTP is decreased with age. In a comparison with a previous study of [^{11}C]5-HTP in young adults without diabetes (2), a greater uptake in the pancreas was observed compared with that observed in older individuals without diabetes enrolled in the current study. **$P < 0.01$.

through serotonergic biosynthesis mediated by DDC (1). Our finding with a higher [11C]5-HTP uptake in the pancreas in young subjects without diabetes when compared with that herein found in aging subjects is in accord with the notion of a reduction in β-cell mass with increased age (7). With these facts in mind, we hypothesize that the reduction in [11C]5-HTP uptake and retention in pancreas with age corresponds to a loss in islet cell mass also in individuals without diabetes, albeit not to the extent to induce clinically important dysregulation of glucose metabolism.

Conclusion

Our finding of an unchanged accumulation of islet marker [11C]5-HTP in subjects with different stages of T2D is in accord with recent findings using single-cell transcriptome and morphological analysis, indicating that β-cell dedifferentiation, and not necessarily endocrine cell loss, constitutes a major cause of β-cell failure in T2D. A dual-tracer approach separately measuring islet cell and β-cell mass as described above may shed further light on this important issue.

Acknowledgments. The authors thank Martin Gotthardt (Radboud University) for valuable discussions.

Funding. This study was funded by the European Foundation for the Study of Diabetes/Novo Nordisk Programme, the Swedish Medical Research Council (K2015-54X-12219-19-4, K2013-64X-08268-26-3, K2013-55X-15043, and 921-2014-7054), Diabetes Wellness, the Ernfors Family Fund, the Novo Nordisk Foundation, Barndiabetesfonden, Diabetesfonden, EXODIAB (Excellence Of Diabetes Research in Sweden), the Helmsley Charitable Trust, and JDRF.

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

Author Contributions. L.C. performed and analyzed the imaging study and contributed to writing the manuscript. D.E. performed and analyzed the metabolic study and contributed to writing the manuscript. M.L. analyzed the imaging study and contributed to writing the manuscript. M.M. performed and analyzed the metabolic study and contributed to writing the manuscript. L.J., H.A., and P.-O.C. designed and analyzed the study and contributed to writing the manuscript. O.K. and O.E. designed, analyzed, and interpreted the studies and wrote the manuscript. O.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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