^{111}In-exendin SPECT imaging suggests presence of residual beta cells in patients with longstanding type 1 diabetes

M. Boss[1], I Kusmartseva[2], W. Woliner - van der Weg[1], L Joosten[1], M. Brom[1], M. Béhe[3], C.J. Tack[4], O.C. Boerman[1], M.J.R. Janssen[1], M. Atkinson[5], M. Gotthardt[1]

[1]Department of Radiology, Nuclear Medicine and Anatomy, Radboud University Medical Center, Nijmegen, Netherlands,
[2]Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Florida, United States
[3]Paul Scherrer institute, Center for Radiopharmaceutical Sciences, Villingen-PSI, Switzerland,
[4]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands.
[5]UF Diabetes Institute, University of Florida, Florida, United States

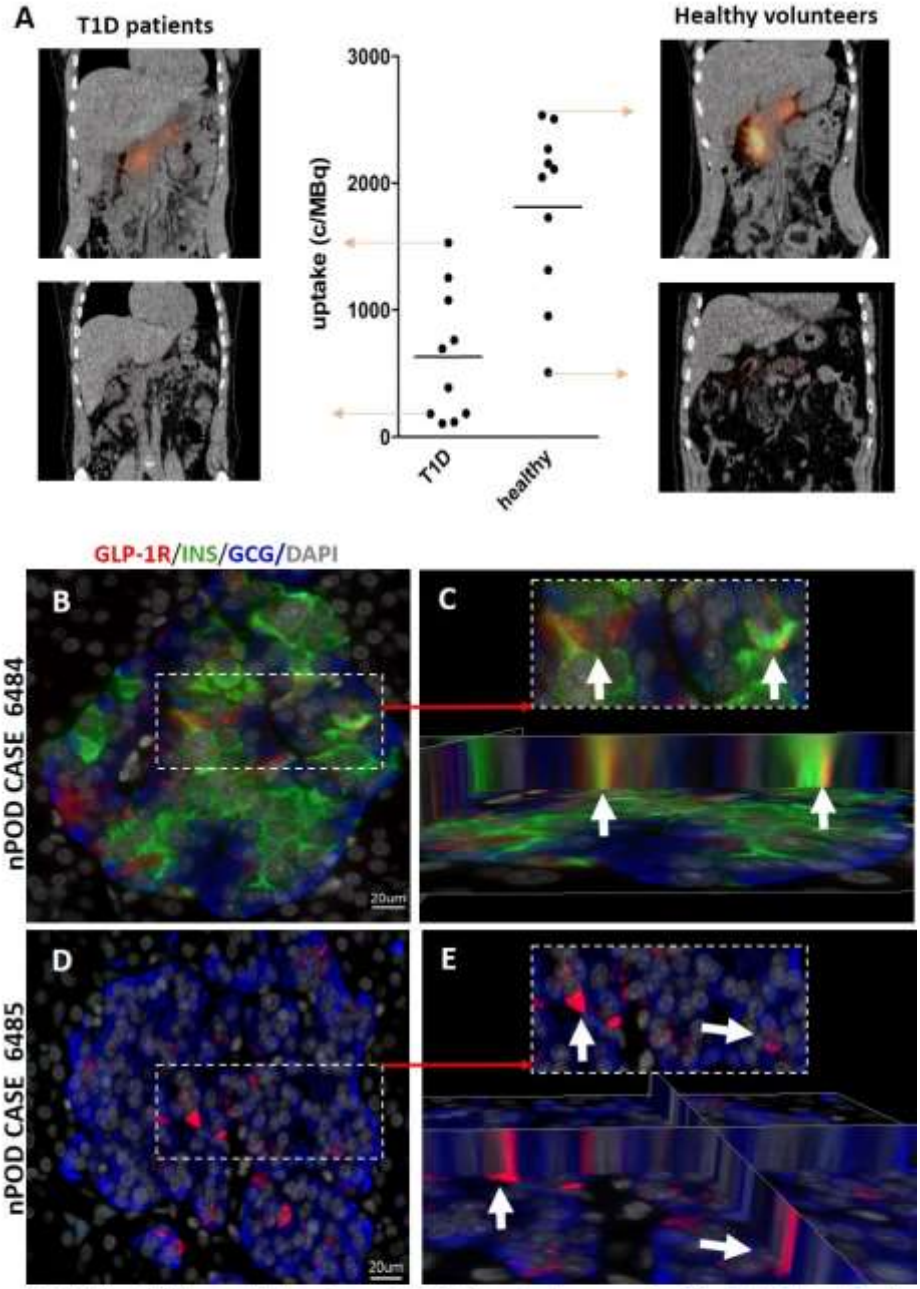
Background and aims
There is increasing evidence for the presence of residual, dysfunctional beta cells in patients with type 1 diabetes (T1D), but research is hampered by the lack of methods to quantify beta cell mass (BCM) in vivo in humans. Image-based quantification of pancreatic BCM using radiolabeled exendin-4 might provide such a method. We hypothesized that T1D patients have considerable remaining BCM and therefore, should have detectable ^{111}In-exendin-4 uptake in the pancreas.

Materials and methods
Ten T1D patients and ten matched healthy controls underwent quantitative SPECT following injection of 150 MBq ^{111}In-exendin-4 after which pancreatic tracer uptake was determined. In addition, immunohistochemical analysis of human pancreatic sections from organ donors with longstanding T1D (C-peptide negative) was performed to assess GLP-1R expression, insulin, glucagon and somatostatin.

Results
Uptake of ^{111}In-exendin-4 was above background levels in 6/10 individuals with T1D and even comparable to levels in healthy controls in 5/10 patients. In all remaining patients, only background uptake (~30% of the mean uptake in T1D patients) was observed. Uptake was independent of stimulated C-peptide levels (<0.03 nmol/L in 8/10 patients).
Immunohistochemistry demonstrated the presence of insulin/GLP-1R positive cells in 12/19 cases, explaining the high radiotracer uptake found in a subgroup of T1D patients. Furthermore, insulin-negative /GLP-1R positive cells were found, which proved to be somatostatin-positive, showing GLP-1R expression on delta cells and explaining the background tracer uptake in patients without remaining beta cells.

Conclusion
Quantitative exendin imaging was able to show differences in beta cell mass between patients

and uncover the presence of residual beta cells in a subgroup of patients with T1D with low and stable background uptake levels. This demonstrates the value of this technique for in vivo determination of human pancreatic BCM and its potential use as a tool to further elucidate the complex pathophysiology of diabetes or study the effect of various interventions on BCM.



(A) Uptake of ^{111}In-exendin (counts per MBq) in the whole pancreata of the individual subjects 24 h post injection. On the left side coronal cross sections of the SPECT-CT of the T1D patients with the highest and lowest uptake. On the right side the images of the healthy volunteers with the highest and lowest uptake. **(B,C,D,E) Immunofluorescence staining of GLP-1R positive cells in pancreata of organ donors from the Network for Pancreatic Donors with Diabetes (nPOD) with long duration of T1D and undetectable C-peptide.** Representative image of insulin-containing islet with GLP-1R$^+$/Insulin$^+$ cells are shown for nPOD donor 6484 (28 years old male, 10 years with T1D (B, C). Representative image of insulin negative islet with GLP-1R$^+$/Insulin$^-$ /Glucagon$^-$ cells are shown for nPOD donor 6485 (10 years old male, 7 years with T1D (D,E).