A β vision on diagnosis

Beta cell imaging in people with type 1 diabetes and insulinoma

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Pancreatic beta cells have a crucial role in glucose homeostasis through their production and secretion of insulin. Tailor-made secretion of insulin is critical to keep blood glucose levels in the normal range and to prevent the body from exposure to (dangerously) high blood glucose levels. In the thesis, we describe two conditions that lead to dysregulated insulin production, each of which carries significant implications for people's health and quality of life. The first condition is type 1 diabetes, which is caused by a cell-mediated autoimmune attack on the pancreatic beta cell, resulting in a decline of both beta cell function and mass. When left untreated (with subcutaneous insulin), glucose levels can rise dangerously high leading to ketoacidosis and ultimately death. Second, we discuss hyperinsulinemic hypoglycaemia caused by either insulinomas or nesidioblastosis.

Here we focus on insulinomas, a rare type of neuroendocrine tumour that arises from beta cells, which can lead to uncontrolled insulin release and (severe) hypoglycaemia. To better understand the fate of the beta cell in type 1 diabetes and to improve insulinoma detection, the usefulness of a sensitive method to visualise beta cells is discussed. Non-invasive *in vivo* beta cell imaging with sufficient specificity and sensitivity has proven to be very challenging, but imaging with radiolabelled exendin has shown promising results. In this thesis, we describe various clinical studies using radiolabelled exendin, which provide novel insights in the field of beta cell imaging in diabetes and in insulinoma detection and treatment.

Exendin-based tracers

Radiolabelled exendin is an ideal imaging agent for detecting benign insulinomas, since it specifically targets the glucagon-like peptide-1 (GLP-1) receptor overexpressed in these tumours. We provide an overview of the development, clinical implementation and results of exendin-4-based tracers for the visualisation of insulinomas. We also discuss the development and utilisation of fluorescently labelled exendin for intraoperative optical insulinoma detection and targeted photodynamic therapy (tPDT). Furthermore, a view on peptide receptor radionuclide therapy (PRRT) with exendin is given together with current limitations and possible improvements.

Reduction of the renal accumulation of radiolabelled exendin

One of the limitations of radiolabelled exendin is addressed, which is the high renal accumulation of exendin-based tracers. The presence of the tracer in the kidneys can complicate insulinoma detection, especially when the tumour resides in the pancreatic tail, but it also influences the feasibility of PRRT. The high renal accumulation will lead to serious radiation-induced kidney damage, which renders PRRT impossible. Gelofusine has already shown to be effective in lowering the accumulation in a preclinical setting. In our cross-over study with healthy volunteers, we observed that when Gelofusine was co-infused, the renal accumulation of ^{111}In-labelled exendin-4 decreased by almost one-fifth. In certain participants, the use of Gelofusine resulted in an enhanced visibility of the pancreatic tail, which may be crucial in insulinoma detection. We next investigated the effect of Gelofusine on the dose that could potentially be administered in case of PRRT. Planar scintigraphy images of insulinoma patients who received injections with ^{111}In-labelled exendin were used for dosimetric calculations. Insulinoma absorbed doses that normally range from 30 to 128 Gy can in theory increase to the maximum allowed dose of 156 Gy with the use of Gelofusine. From this study, we conclude that co-injection of Gelofusine may improve insulinoma detection but also enhance the feasibility of PRRT with exendin-based tracers.

Beta cell imaging with radiolabelled exendin

An important milestone for beta cell imaging with radiolabelled exendin that comprises the histological validation of beta cell imaging in humans is discussed. Since the acquisition of tissue samples entails high risks that may be unethical for research purposes in study

participants, we obtained pancreas tissue from patients who underwent pancreas resection because of a pancreatic malignancy. Prior to surgery, ^{111}In-labelled exendin was administered and resected tissue slides of the pancreas were used for digital autoradiography and stained for insulin and the GLP-1 receptor. Analysis showed that tracer uptake was predominantly present in the islets of Langerhans (5-fold higher compared to the exocrine part), with substantiation of tracer specificity by the observed overlap between regions positive for insulin and the GLP-1 receptor. Together, these findings provide evidence for the potential of radiolabelled exendin to non-invasively quantify beta cell mass in humans.

Because the role of beta cell mass in glycaemic control is not completely clear in type 1 diabetes, we used radiolabelled exendin in an attempt to increase our understanding on this topic. In a clinical study, we imaged individuals with type 1 diabetes with either low or high glucose variability. With exendin PET, we were able to measure their beta cell mass that was represented by the mean standardised uptake value (see figure 1), and through a mixed-meal tolerance test we determined the beta cell function. Beta cell mass was considerably higher in individuals with low compared to high glucose variability (by approximately 75%). The beta cell function was numerically higher in this group, but the difference between the groups was statistically not significant. While for the whole group of participants beta cell mass correlated with beta cell function, on an individual basis there was no direct correlation between mass and function. Outcomes of our study point towards a beneficial role of residual beta cell mass on glycaemic control, and that it may be valuable to make efforts to protect remaining beta cells or enhance their function in future therapy choices.

Detection of intrahepatically transplanted islets of Langerhans

Lastly, we describe a study on individuals with type 1 diabetes and highly unstable glycaemic control who were eligible for intrahepatic islet transplantation (ITx). The therapeutic success of ITx is generally high with most patients becoming insulin-independent, although this usually

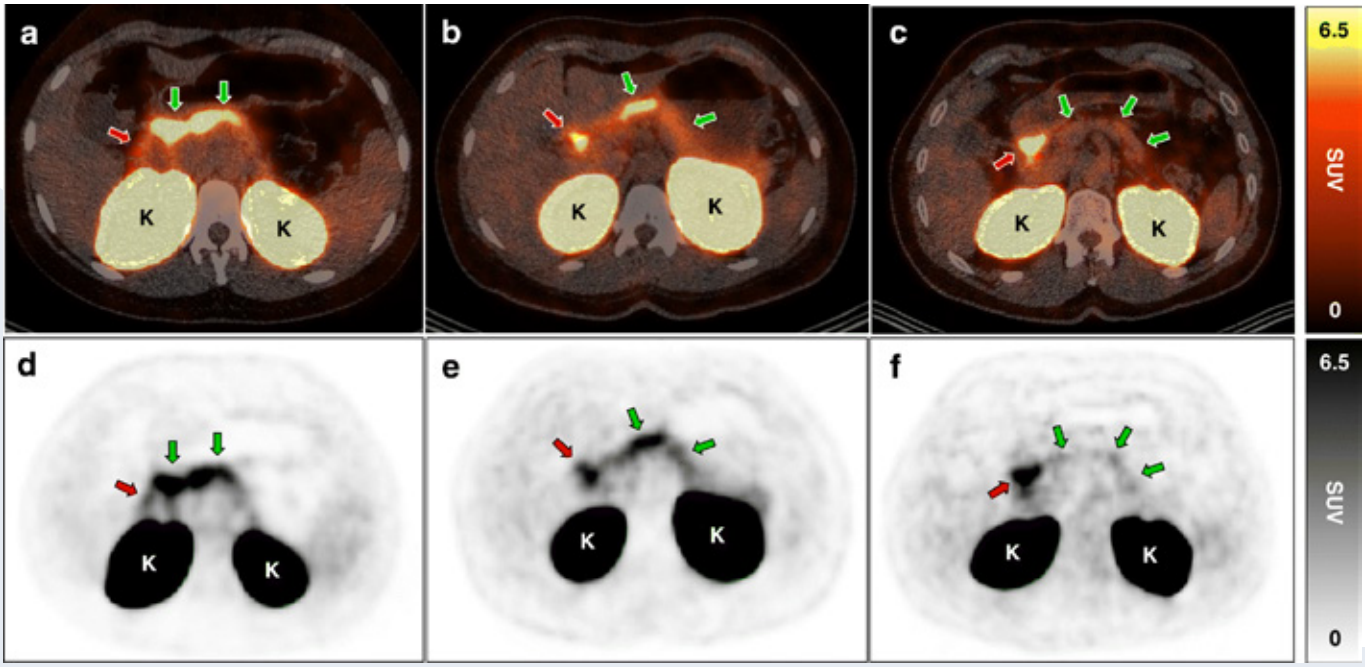

Figure 1. Abdominal PET/CT images with pancreatic uptake of radiolabelled exendin. Transversal fused PET/CT images (a-c) and PET images (d-f) of three individuals showing pancreatic uptake of [^{68}Ga]Ga-exendin as measure for beta cell mass (green arrows). Other regions with exendin uptake are the proximal duodenum (red arrows) and the kidneys (indicated with the letter 'K'). Pancreatic exendin uptake of individuals with low glucose variability were in the same range for individual 1 (a, d) (AUC for C-peptide 122 nmol min/l) and individual 2 (b, e) (no detectable C-peptide), despite differences in C-peptide response, and much greater than in individual 3 (c, f) (no detectable C-peptide)[1].

requires transplantation of islets from at least two donor organs. Unfortunately, transplant function declines over time and eventually most people require insulin therapy again. A method to monitor the fate and survival of pancreatic islet grafts in a noninvasive way would be highly relevant, and might contribute to the improvement of current ITx strategies. We tested the feasibility of dynamic exendin PET/CT imaging for islet graft detection in the liver, and found significantly higher tracer uptake in the identified hepatic hotspots in transplanted patients compared to non-transplanted patients. Interestingly, surgery on one of the transplanted patients (cholecystectomy) provided the opportunity to obtain tissue samples of the liver. Immunohistochemical analyses of the liver tissue showed insulin-positive cell clusters and GLP-1 receptor expression, demonstrating the presence of transplanted islet mass. No correlation was observed between tracer uptake and beta cell function. These findings underscore the additive value of beta cell imaging using radiolabelled exendin, on top of functional tests. Both measures provide complementary information that is relevant for evaluating strategies to enhance the engraftment, function and the survival of transplanted islet grafts. ♦

Reference

1. Jansen TJP, Brom M, Boss M et al. Importance of beta cell mass for glycaemic control in people with type 1 diabetes. Diabetologia. 2023;66:367-75 (https://doi.org/10.1007/s00125-022-05830-2)

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