GLP-1 receptor expression and beta-cell mass in patients with type 2 diabetes

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON55656

Source
ToetsingOnline

Brief title
GLP1R-T2D

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes Mellitus type 2, Diabetes type 2

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw,Diabetes Fonds

Intervention

Keyword: bèta-cell mass, exendin, GLP1 receptor, type 2 diabetes

Outcome measures

Primary outcome

- AIM 1: Establish the relation between exendin uptake and BCM under various levels of glycaemic control

- AIM2: Assess the specificity of exendin uptake during the progression of T2D

Secondary outcome

- AIM 3: Establish the relation between BCM and beta-cell function in patients with T2D

- AIM 4: Correlate ex vivo exendin uptake in GLP-1R positive tissues with GLP-1R gene expression profiles

Study description

Background summary

Reliable imaging biomarkers for non-invasive characterisation of beta cell mass are needed to aid our understanding regarding the relationship between beta-cell mass and function during the course of type 2 diabetes (T2D). This study will provide critical information necessary to validate the applicability of exendin-based imaging techniques in patients with T2D. The characterization of beta-cells is currently limited to pancreatic specimens available at autopsy, as in vivo pancreatic biopsy is associated with complications unacceptable in clinical studies [1]. To date, only measurements of circulating C-peptide and insulin levels can be obtained, but these measures do not reflect beta-cell mass, only total beta-cell function. Reliable imaging biomarkers for non-invasive characterisation of beta cell mass are therefore needed. These biomarkers could also be used to validate novel therapeutic strategies aimed to increase or preserve BCM or identify whether patients are eligible for a certain therapeutic strategy (e.g. when certain amount of beta-cells is required). One can also think of identifying responders to therapies early to

avoid unnecessary drug use and the accompanying costs.

Study objective

We aim to determine the specificity of radiolabelled exendin during the course of T2D and to examine the role of glycemic control on the correlation between pancreatic 111In-exendin uptake, BCM and GLP-1R expression in patients with T2D undergoing (partial) pancreatectomy. This will not only allow us to establish definite proof regarding the role of glycemic control on exendin uptake in humans, but also to establish clinical guidelines for the interpretation of clinical exendin-based scans in patients with T2D to avoid false interpretation of the scans.

Study design

After recruitment of the participating individuals, patients will undergo an enrollment check consisting of a medical interview and a physical examination performed by a qualified physician (in case this is not done during intake and surgical evaluation for pancreatectomy). Recent blood samples for standard laboratory checks (blood counts, electrolytes, liver enzymes, inflammation parameters) that have been taken in the preparation for pancreatectomy, will be used. To obtain information about glycemic control, patients will receive a glucose sensor subcutaneously (plaster with a small needle) to monitor glucose profiles continuously for maximally 7 days. If the physical status of the patient is good enough, an arginine stimulation test will be performed to assess beta-cell function. Prior to pancreatectomy, patients will be injected with either 111In-exendin (16h before before surgery) or 800CW-exendin (16h before surgery).
After pancreatectomy, samples for histology, autoradiography, and gene expression profiling, will be taken from the pancreatic head, body and tail and duodenum/pylorus if resected. If possible, subcutaneous and visceral adipose tissue samples will be obtained from the abdominal wall and the omentum), as the abdominal wall and omental bursa will already be opened during this surgery.

Study burden and risks

All individuals will undergo physical examination and blood sampling for standard laboratory parameters and they will receive a glucose sensor subcutaneously (small band-aid with a small needle) to monitor glucose profiles continuously. This will require a single and rapid placement of the sensor, which includes placing a small needle in the subcutis. The sensor will remain in place for a period of 7 days.
If the physical status of the patient is good, patients will undergo an arginine stimulation test. This test is performed in the morning and is preceded by an overnight 12-hour fast, during which water may be drunk. For

this test blood sampling is done via a venous catheter.
The injection of exendin may result in nausea and headache as has been reported for (much higher doses of) Byetta® in therapy studies. Also in our study monitoring beta-cell grafts in T1D patients (NL52630.091.15), two patients experienced nausea and had to vomit. These patients used Byetta in high doses in the past, which might explain their sensitivity to the compound.
In addition, single cases of low blood pressure and low blood glucose levels have been described previously after accidental heavy overdosing of Byetta®. However, in our previous studies with 111In-DTPA-[K40]-Exendin-4 (CPOP-EX and GLP1-EX-GELO) we did not observe any side effects.
The expected radiation exposure will not exceed 10 mSv and is therefore considered minimal to little. The envisaged clinical endpoint of this project is the full validation of GLP-1R imaging for BCM quantification in patients with T2D and to deliver protocols/guidelines regarding the interpretation of clinical exendin scans in patients with metabolic stress. As beta-cell dysfunction, dedifferentiation and death are presumed to be central events in the pathogenesis of both type 2 and type 1 diabetes, this imaging platform can help to elucidate the fate of beta-cells during the development and progression of type 2 and type 1 diabetes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Scheduled for partial or complete pancreatectomy at Radboudumc

Exclusion criteria

1.. Breast feeding, 2. Pregnancy or the wish to become pregnant within 6 months, 3. Creatinine clearance below 40ml/min, 4. Age > 18 years, 5. Liver disease defined as aspartate aminotransferase or alanine aminotransferase level of more than three times the upper limit of normal range, 6. Previous treatment with synthetic Exendin (Exenatide, Byetta®) or Dipeptidyl-Peptidase IV inhibitors in the past 3 months

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2021
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	111In-DTPA-AHX-Lys40-Exendin-4
Generic name:	111In-DTPA-AHX-Lys40-Exendin-4
Product type:	Medicine
Brand name:	800CW-Lys40-Exendin-4
Generic name:	800CW-Lys40-Exendin-4

Ethics review

Approved WMO Date:	12-07-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-09-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004615-40-NL
CCMO	NL63933.091.17