Comparison of the beta cell mass during and shortly after the honeymoon phase of type 1 diabetes using Ga-68-exendin PET

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

Summary

ID

NL-OMON47470

Source
ToetsingOnline

Brief title
GLP1-honeymoon

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes mellitus type 1, diabetes type 1

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Diabetesfonds en IMI (EU/EFPIA),EFPIA

Intervention

Keyword: Beta cell mass, Exendin, Honeymoon phase, Type 1 diabetes

Outcome measures

Primary outcome

The primary study objective is to determine the beta cell mass in subjects with type 1 diabetes during and shortly after the honeymoon phase, to examine possible differences in beta cell mass and to improve understanding of the change in metabolic control after the honeymoon phase.

Secondary outcome

The secondary aim is to correlate the beta cell mass to the beta cell function from the measurements that will be performed during and shortly after the honeymoon phase.

Study description

Background summary

The exact role of beta cell mass during the development and course of diabetes is still poorly understood. Initially, the belief was that practically all beta cells would die after the previously described autoimmune attack in type 1 diabetes (T1D). However, recent literature suggests that a considerable number of beta cells can survive this autoimmune attack, even when their function gradually dissipates. This could mean that the function of the surviving beta cells is partially or completely lost. The contradiction between the initial belief and recent literature indicates the still consisting lack of knowledge concerning beta cell mass, function and their relation. Therefore, further research on beta cell mass is essential to obtain more insights that might aid in the development of novel therapies for diabetes.
We want to focus on a specific phase of T1D that is called the 'honeymoon phase' or period of partial remission. Once insulin treatment has started, the honeymoon phase will arise in most patients. In this period, T1D patients

become temporarily less insulin-dependent due to an increase of endogenous insulin secretion and improvement of peripheral insulin sensitivity. The occurrence and duration of the honeymoon phase might differ depending on factors such as the age at onset and manifestation of T1D. Unfortunately, the honeymoon phase is only temporary, in which a decline in blood glucose regulation will be seen afterwards, leading to an increasing demand for insulin. During the honeymoon phase, the decrease in insulin dependence suggests the presence of beta cells, indicating that this change in metabolic control depends on the cell function. However, after the honeymoon phase, it is not completely clear whether the ongoing deterioration of glycemic control can be attributed to the loss of beta cell function or to a decreasing number of beta cells (beta cell mass). To increase understanding of this change in metabolic control after the honeymoon phase, we want to perform repeated measurements of the beta cell mass and function, during and shortly after the honeymoon phase.
The aim of this study is to compare beta cell mass and function during and shortly after the honeymoon phase. Beta cell mass will be determined using Ga-68-exendin positron emission tomography (PET), which allows visualization and absolute quantification of tracer uptake, providing a non-invasive method to measure pancreatic beta cell mass. In addition, the beta cell function will be determined by a mixed-meal tolerance test. The comparison of both measurements can lead to an increased understanding whether changes in insulin demand after the honeymoon phase is mainly dependent on a decline in the beta cell mass, or because of a decrease in functional beta cells (ratio functional and non-functional beta cells and insulin secretory capacity per beta cell).
The outcome of this study can provide new insights, which can contribute to the development of novel treatment options, aimed at preservation and stimulation of residual beta cells to eventually lower the impact of diabetes on the life of patients.

Study objective

The study objective is to measure beta cell mass and function in subjects with type 1 diabetes during and shortly after the honeymoon phase, to determine whether the change in metabolic control is mainly caused by a decrease in the total number of beta cells or more dependent on the function of the beta cells.

Study design

Subjects in the honeymoon phase of T1D will be recruited from the outpatient clinic of the Department of Paediatrics and Internal Medicine of the Radboudumc and from Diabeter in Rotterdam (centre for paediatric and adolescent diabetes care and research). The subjects must have a minimum age of 16 years and will be asked by their physician for participation, at least 3 weeks after diagnosis. In case patients agree to participation, the researcher will approach them to provide further information regarding the study.

After recruitment, subjects will visit the Department of Radiology and Nuclear Medicine in the Radboud University Medical Center (Radboudumc) in Nijmegen or Diabeter in Rotterdam. During this first visit, a glucose sensor will be placed to obtain glucose profiles via continuous glucose monitoring (CGM), providing valuable insights into their metabolic control. CGM requires the placement of a blinded sensor that measures glucose subcutaneously.
During the second visit, a medical check will be performed by a qualified physician. This medical check will include a medical interview and a physical examination. Blood samples will be taken to obtain laboratory values of the pancreas, kidney and liver function (C-peptide, insulin, glucose, HbA1c, creatinine, ALAT, ASAT). The beta cell function will be determined by a mixed-meal tolerance test.
During the third visit, which will take place at the Department of Radiology and Nuclear Medicine, a PET/CT scan will be made. For this, 0.75 MBq/kg of Ga-68-NODAGA-exendin-4 will be administered to the study participant, which is preceded by a fasting period of 4 hours. The PET/CT scan will take place at the start of the tracer injection.
Once the honeymoon phase has passed, the subjects will visit the Department of Radiology and Nuclear Medicine or Diabeter again for a fourth visit, to perform CGM for a second time. A fifth visit is needed to perform a second mixed-meal tolerance test. Lastly, the sixth and last visit is required at the Department of Radiology and Nuclear Medicine to repeat the PET/CT scan.
Image analysis and statistical analysis will be performed at the Department of Radiology and Nuclear Medicine.

Study burden and risks

The study requires 6 visits in total. The participants will need to visit the Department of Radiology and Nuclear Medicine of the Radboudumc in Nijmegen or Diabeter in Rotterdam twice for the placement of the glucose sensor for CGM. This will require a single and rapid placement of the blinded sensor, which includes placing a small needle in the subcutis. The advantages of CGM are the reduction in fingerpricks in comparison to 7-points curves and the increased number of glucose measurements that can be performed.
A mixed-meal tolerance test will be performed . For the PET/CT scans, two additional visits at the Department of Radiology and Nuclear Medicine in the Radboudumc are required. During all visits blood sampling will be performed. Blood sampling will be done via an intravenous catheter, which reduces the number of required venipunctures. Due to the placement of intravenous catheters, there is a small chance of bruising, pain and inflammation at the site of catheter placement.
For the PET/CT scan, 0.75 MBq/kg Ga-68-NODAGA-exendin-4 will be administered. Injection of this radiopharmaceutical may theoretically result in nausea and headache as has been reported for (much higher doses) of Byetta® in therapy studies. In imaging studies this has only been observed in 2 cases so far (see section 5.4). In addition, single cases of low blood pressure and low blood glucose levels have been described after application of therapeutic or higher

doses of Byetta®. Although low blood glucose levels only occurred after accidental heavy overdosing of Byetta®, patients will be closely monitored. In this study, we will only administer 0.75 MBq/kg Ga-68-NODAGA-exendin-4. Therefore, no (serious) adverse events will be expected. In case of administering Ga-68-NODAGA-exendin-4, the expected radiation exposure will be 0.023 mSv/MBq. In addition, 1.25 to 2 mSv will be received due to the low-dose CT. The expected radiation doses will vary for each subject, noting that the injected dose is based on the body weight of the participant. The comparison of the beta cell mass during and shortly after the honeymoon phase is possible, requiring 2 PET/CT scans per subject. The total expected radiation exposures are listed in section 5.9 (table 2 and 3). The level of radiation exposure can therefore be considered minor to intermediate according to the ICRP.
Despite the radiation exposure, Ga-68-exendin PET can be used to provide in vivo visualization and quantification of the beta cell mass in a longitudinal manner. Beta cell mass measurements in humans are needed, especially considering the lack of knowledge regarding the changing aspect of beta cell mass. The added clinical value of this study is to improve understanding of the decline in beta cell function after the honeymoon phase and might provide new insights in the field of diabetes.
The participants will not benefit directly from this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria: honeymoon phase
- Age >=16 years
- Subject is diagnosed with type 1 diabetes (T1D)
- Presence of anti-GAD (glutamic acid decarboxylase)
- Subject is in the honeymoon phase of T1D: IDAA1c <9
- 17<= BMI <=30 kg/m^2 at the moment of the first visit
- Ability to sign informed consent

Exclusion criteria

Exclusion criteria:
- Previous treatment (within 6 months) with synthetic Exendin (Exenatide, Byetta®) or Dipeptidyl-Peptidase IV inhibitors
- Liver disease defined as aspartate aminotransferase or alanine aminotransferase level of more than 3 times the upper limit of normal range
- Renal disease defined as MDRD <40 ml/min/1.73m^2
- Pregnancy or the wish to become pregnant within 6 months after the study
- Breastfeeding
- BMI <17 kg/m^2 or BMI >30 kg/m^2
- Age <16 years
- When the end of the honeymoon phase (IDAA1c >=9) is not observed within 11 to 13 months after the inclusion of the subject
- Inability to sign informed consent

Study design

Design

Study phase: 2

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-10-2019
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	68Ga-NODAGA-[K40]-Exendin-4
Generic name:	68Ga-NODAGA-[K40]-Exendin-4

Ethics review

Approved WMO Date:	13-11-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-10-2018
Application type:	First submission
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	EUCTR2017-002959-29-NL
CCMO	NL61915.091.17