Pancreatic islet cell response to multiple stimuli in long standing diabetes mellitus type 1

Published: 30-09-2016
Last updated: 17-04-2024

Primary objective:- To determine the residual *-cell function by measuring thedifferential response of *-cells measured by C-peptide and proinsulin secretion to various stimuli in patients with long-standing type 1 diabetes mellitus.Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON46034

Source
ToetsingOnline

Brief title
Islet cell response in longterm diabetes mellitus type1

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes mellitus type 1, juvenile Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: afdeling researchbudget uit verschillend onderzoeksfondsen

Intervention

Keyword: □-cells, Diabetes mellitus type 1

Outcome measures

Primary outcome

- the delta maximum concentration of the C-peptide concentration in response to the individual stimuli

Secondary outcome

- delta maximum concentration of the other biomarkers in response to the individual stimuli

- Ratios of the C-peptide concentration at the clamp day and the C-peptide concentration at the meal test day after certain stimuli

Study description

Background summary

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which pancreatic *-cells are destroyed and endogenous insulin production is lost. Moreover in the period around diagnosis there is a clear functional *-cell function deficit including disturbed proinsulin cleavage.1 There is mounting evidence that some *-cells still survive in a significant portion of patients with long standing T1D. In patients with the diagnosis of T1D for 4-67 years, *-cells are detected in 88% of subjects histologically and stimulated C-peptide concentrations could be detected with an ultrasensitive assay in 73% of patients with T1D and a median disease duration of thirty years.2;3 Studies have shown that this residual *-cell function is associated with improved glycaemic regulation, lower risk of complications and fewer hypoglycaemic events.4;5 There is little known about the function of these residual *-cells in regard to the secretion insulin to various stimuli and the efficiency of proinsulin cleavage in long-standing T1D. Furthermore, cumulative *-cell stimulation might be a useful clinical marker for *-cell mass, which now can only be assessed post-mortem. Elucidating this differential and cumulative *-cell response to various stimuli can lead to better pathophysiological understanding and novel treatment insights.

Besides the obvious *-cell deficit in type 1 diabetes, hyperglucagonaemia after meals and lack of glucagon secretion during hypoglycaemia are observed.6;7 Since little is known about the *-cell function regarding the response to the various *-cell stimuli and the precise role of the *-cells in the pathophysiology of T1D remains unclear, glucagon concentration will also be assessed.

Study objective

Primary objective:
- To determine the residual *-cell function by measuring thedifferential response of *-cells measured by C-peptide and proinsulin secretion to various stimuli in patients with long-standing type 1 diabetes mellitus.

Secondary objectives:
- To determine the residual *-cell function by measuring the response of alpha cells measured by glucagon to various stimuli in patients with long-standing type 1 diabetes mellitus.
- To determine how the various stimuli relate to the more commonly used mixed meal tolerance test (MMTT)

Study design

This is a prospective, single-centre, non-therapeutic intervention study

Intervention

The patients will visit our research unit twice. The first visit consists of a mixed meal test with a standardised liquid meal followed by an 5g arginine bolus. On the second visit they will receive a euglycaemic clamp set at 5 mmol/L after which a 5g arginine bolus is given. This is followed by a hyperglycaemic clamp set at 14 mmol/L after which another bolus of arginine is given. For the last step patients receive a continuous infusion of glucagon-like peptide 1 (GLP-1) followed again by a bolus of arginine.

Study burden and risks

Burden:
The study participants are asked to visit twice after an overnight fast and remain recumbent each visit for 2-5 hours. Two venous catheters will be placed to draw a total of 150 ml blood . Arginine was well-tolerated in previous studies with flushing and oral paraesthesia as most common complaints, and some patients experienced mild nausea.8 The most reported adverse effect of GLP-1 are gastro-intestinal symptoms,9;10 although this is uncommon with the dose that is administered intravenously in this study.11-13 In a previous study some mild hypoglycaemic symptoms occurred after the GLP-1 infusion was stopped but

this could be abolished by a meal and by infusing glucose thirty minutes longer.14

Risks:
An anaphylactic reaction to arginine has been described once.15 Since GLP-1 is a physiological peptide it is tolerated well, some gastro-intestinal symptoms have been described although this is uncommon after intravenous administration.9;10

Benefit:
More insight in the pathophysiology of type 1 diabetes, possible therapeutic approaches to stimulate remaining *-cells and a clinically applicable marker of total *-cell mass.

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

Diagnosis of diabetes according to the ADA criteria for diagnosis of diabetes mellitus
At least 5 years after the first insulin injection
History and clinical course consistent with diabetes mellitus type 1

Exclusion criteria

Having had an allergic reaction to arginine and/or GLP-1 (agonists)
Use of *-cell stimulants (e.g. sulphonylureas), GLP 1 agonist, dipeptidyl peptidase- IV inhibitors, insulin sensitizers (e.g. metformin, thiazolidinediones) in the 3 months before inclusion
Use of medication know to induce insulin resistance (e.g. corticosteroids) in the 3 months before inclusion
History of cardiovascular disease (cerebral, coronary or peripheral artery disease), kidney disease (eGFR <60 ml/min/1.73m-2 in the last year), liver disease or disease of the central nervous system

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-08-2017
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	30-09-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-01-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
CCMO	NL55988.058.16