Pancreatic islet cell response to hypoglycaemia in long standing type 1 diabetes

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- To determine whether the remaining *-cell in long standing type 1 diabetes are capable of decreasing their insulin secretion upon hypoglycaemia- To determine how much delay there is between plasma glucose and interstitial glucose measured by a...

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

Summary

ID

NL-OMON49391

Source
ToetsingOnline

Brief title
Hypo T1D

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes mellitus type 1, Type 1 diabetes

Research involving
Human

Sponsors and support

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

Intervention

Keyword: beta cells, Hypoglycemia, Machine learning, Type 1 diabetes

Outcome measures

Primary outcome

- Change in serum C-peptide concentration

- Time delay between plasma glucose and interstitial glucose measured by a FGM and/or implantable CGM during the emergence and the resolution of a hypoglycaemia

- Difference in facial expression as determined by a deep learning module of Microsoft before, during and after hypoglycaemia

- Difference in heart rate variability before, during and after hypoglycaemia

Secondary outcome

- Association of differences in facial expression and heart rate variability with counterregulatory mechanisms (norepinephrine, epinephrine, heart rate), hypoglycaemic symptoms (semiquantitive symptom questionnaire and simple cognitive testing)

- Change in other products of the islets (for instance glucagon and proinsulin)

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. The long term detrimental effects of the ensuing chronic hyperglycaemia can be partially prevented by intensive insulin therapy. However, only 15% of the patients with

T1D reaches the target HbA1c of 53 mmol/mol, with hypoglycaemia being the most important limiting factor. The high burden of hypoglycaemia in patients with T1D can be explained by exogenous insulin therapy combined with dysfunction of the counter regulatory mechanisms against hypoglycaemia.

Failure of the *-cell undermines two out of the three known counter regulatory mechanisms, namely the ability to lower the insulin secretion and increase the glucagon release in response to hypoglycaemia. This is illustrated by the finding that higher levels of remaining endogenous insulin secretion in the first few years after diagnosis are associated with fewer hypoglycaemic events in combination with a lower risk of long term complications. 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 median disease duration of thirty years.2;3 It is not known whether this small population of surviving *-cells can still contribute to hypoglycaemia counter regulation by decreasing insulin secretion in reaction to hypoglycaemia.

Continuous glucose monitoring and flash glucose monitoring can help reduce the burden of hypoglycemia, however it is also known that these devices are less accurate in hypoglycemia, and there is a time delay for interstitial measurements when compared to capillary measurements. It is not known how much this influence the utility of these devices during the emergence and resolution of hypoglycaemia.

People living close with diabetes patients frequently mention that they can see from the facial expression whether that person is experiencing a hypoglycaemia, often before the patient notices him or herself. Our goal is to explore if during hypoglycaemia with machine learning techniques a hypoglycaemia face or *hypo-face* could be identified. This tool might help patients in the future to recognize personal hypoglycaemic symptoms and might be used as an education tool in gaining hypoglycaemia awareness.

Moreover a pilot study was performed in type 1 diabetes in which was found that heart rate variability could be used in detecting occurrence of hypoglycaemia. We would like to investigate how this method perform both in accuracy and timing against the glucose measurement devices and the *hypo-face*.

Study objective

- To determine whether the remaining *-cell in long standing type 1 diabetes are capable of decreasing their insulin secretion upon hypoglycaemia
- To determine how much delay there is between plasma glucose and interstitial glucose measured by a Flash glucose monitor and an implantable continuous glucose monitor during the emergence and the resolution of a hypoglycaemia

- To explore if specific changes in the face during hypoglycaemia in type 1 DM could be recognized by machine learning techniques and thereby creating a tool that can identify a *hypo *face*.
- To determine how the predicting value of the *hypo-face* is in comparison to predicting hypoglycaemia with heart rate variability
- To determine whether the *hypo-face* and change in heart rate variability are associated with the different counter regulatory mechanisms of hypoglycaemia

Study design

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

Intervention

The participants will visit our research unit after an overnight fast, where they will receive a fixed insulin infusion and a variable glucose infusion at t=0 to bring the participant in an euglycemic state (5 mmol/L) (t=0-60min). For this purpose, frequent plasma glucose concentrations will be measured. At t=105 minutes the glucose infusion is decreased to allow the glucose concentration to drop to 2.5 mmol/L and then at t=210 min 30 grams of oral dextrose is ingested.

Study burden and risks

Burden:
The participants are asked to visit once after an overnight fast and will remain recumbent for approximately 5.5 hours. Two venous catheters will be placed to infuse at average 450ml and to draw at maximum 100 mL blood. The participants will probably experience some symptoms related to sympathetic neural activation by hypoglycaemia including palpitation, tremor, sweating and paresthesia.

Risks:
By inducing the hypoglycaemia in a very controlled setting with very frequent glucose measurements, the risk of severe hypoglycaemic symptoms is very low. In the unlikely event that a severe hypoglycaemic event does occur, intravenous glucose can immediately be administered to counter the hypoglycaemia.

Benefits:
The study will give more insight in how novel devices perform in detecting hypoglycaemia and looks into possible future approaches of detecting hypoglycaemia. It will also create more knowledge in the pathophysiology of hypoglycaemia in patients with diabetes mellitus type 1 and thereby possible future therapeutic approaches.

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

Type 1 diabetes
HbA1c <75 mmol/mol
BMI < 30kg/m2

Exclusion criteria

History of epilepsy
Use of medicationknow to induce insulin resistance
Use of medication for diabetes other than insulin (analogs)
History of cardiovascular disease, kidney disease, 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):	26-09-2019
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	11-05-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-01-2019

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL60321.058.17