Consequences of (recurrent) hypoglycaemia on cardiovascular and inflammatory responses in patients with diabetes mellictus type 1, type 2 and healthy volunteers

Published: 27-05-2019
Last updated: 12-04-2024

Primary objective:* To investigate the consequences of (recurrent) hypoglycaemia on inflammatory responsesSecondary objectives:* To study the atherogenic consequences of (recurrent) hypoglycaemia* To study the molecular mechanisms involved in the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49321

Source
ToetsingOnline

Brief title
HCIR

Condition

- Endocrine disorders congenital
- Diabetic complications
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
sugar disease

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: HYPO-Resolve Consortium

Intervention

Keyword: Diabetes type 1, Hypoglycemia, inflammatoire response

Outcome measures

Primary outcome

The main study endpoint is the ex vivo production of pro- and anti-inflammatory cytokines and chemokines after ex vivo stimulation of isolated monocytes.

Secondary outcome

Furthermore we will measure the following parameters in circulating monocytes isolated from the blood:

* Monocyte foam cell formation

* Distribution of pro- and anti-inflammatory monocyte subsets using FACS (Fluorescence-activated Cell Sorting).

* Gene expression of circulating monocytes using mRNA-sequencing assays.

* Chromatin accessibility of circulating monocytes using ATAC-seq. (Assay for Transposase-Accessible Chromatin sequencing)

* Epigenetic signature of circulating monocytes using DNA-methylation.

* Characterization of intracellular metabolism of isolated innate immune cells by ex vivo Sea HorseTM respirometer

* Metabolomics

* Oxidative stress measured in urine

* MicroRNA using PCR on plasma

* Examine the changes in cardiac function with echocardiography

Study description

Background summary

Hypoglycaemia is the most common complication in people with type 1 or type 2 diabetes treated with insulin. Hypoglycaemia is associated with an increased risk of cardiovascular events and mortality. The underlying pathophysiological mechanism explaining this association still needs to be revealed. Several studies have shown elevated pro-atherogenic biomarkers and inflammatory cytokines during hypoglycaemia. A more detailed characterization of changes in composition and inflammatory status of leukocytes, underlying pathways, upstream and downstream effects, duration of changes and epigenetic profiling is needed to provide deeper insights. Furthermore, the explanation might be found in oxidative stress, or by changes in the cardiac function during hypoglycaemia. We would also like to investigate the possibility of using miRNA as a biomarker for cardiovascular damage due to hypoglycaemia. Finally, there are virtually no data on the durability of such pro-atherogenic effects of acute hypoglycaemia. Therefore we want to investigate the consequences of hypoglycaemia on epigenetic profiles and inflammatory responses in healthy humans and in humans with diabetes type 1.

Study objective

Primary objective:
* To investigate the consequences of (recurrent) hypoglycaemia on inflammatory responses

Secondary objectives:
* To study the atherogenic consequences of (recurrent) hypoglycaemia
* To study the molecular mechanisms involved in the inflammatory responses to (recurrent) hypoglycaemia
* To study the consequences of (recurrent) hypoglycaemia on epigenetic profiles
* To study the consequences of (recurrent) hypoglycaemia on oxidative stress
* To study the cardiac function using the echocardiography during hypoglycaemia
* To study the consequences of (recurrent) hypoglycaemia on cognitive function
* To study the potential of the use of miRNA as a diagnostic biomarker for future cardiovascular damage of hypoglycaemia

Study design

Intervention study

Intervention

The subjects will undergo a modified hyperinsulinemic normoglycaemic-hypoglycaemic glucose clamp (nadir 2.8 mmol/L).

Study burden and risks

The subjects will not benefit directly from participation to the study.

In order to investigate the inflammatory effects of hypoglycaemia subjects will have to undergo a hypoglycaemic clamp. As a consequence, subjects may experience hypoglycaemic symptoms, such as sweating, shaking, palpitations, hunger and concentration problems. However, this condition is generally well tolerated by subjects. Consequent to the clamp conditions, the risk of developing more severe hypoglycaemia leading to loss of consciousness or worse is negligible, because plasma glucose levels are frequently monitored and glucose 20% will be infused when glucose levels tend to fall too much. The investigators have ample experience with the use of hyperinsulinemic hypoglycaemic normoglycaemic clamps.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Overall inclusion criteria
* Ability to provide written informed consent
* Must be able to speak and read Danish (for Hillerød-site) and Dutch (for Nijmegen-site)
* Insulin treatment according to basal-bolus insulin regimen (injections or insulin pump) (except for group 5)
* Body-Mass Index: 19-40 kg/m2
* Age *18 years, * 75 years
* Blood pressure: <140/90 mmHg
* Duration of diabetes > 1 year (except for group 5)
* HbA1c < 100 mmol/mol, Group specific
* Group 1: HbA1c >64 mmol/mol
* Group 2: IAH as assessed by a score of *3 on the modified Clarke questionnaire, *4 on the Gold questionnaires and a positive score on the Pedersen-Bjergaard questionnaire.
* Group 3: NAH as assessed by a score of <3 on the modified Clarke questionnaire, <4 on the Gold questionnaire and a negative score on the Pedersen-Bjergaard.
* Group 4: Insulin treatment for at least 1 year and age*18 years, * 80 years
* Group 5: HbA1c <42 mmol/mol and age*18 years, * 80 years
Recurrent hypoglycaemia study
Healthy participants
- Ability to provide written informed consent
- Body-Mass Index: 19-40 kg/m2
- Age *16 years, * 75 years
- Blood pressure: <140/90 mmHg

Exclusion criteria

- Severe medical or psychological conditions interfering with the perception of hypoglycaemia other than IAH such as brain injuries, epilepsy, a major cardiovascular disease event or anxiety disorders
- Use of immune-modifying drugs or antibiotics
- Treatment with glucose-modifying (other than insulin, SGLT-2 inhibitors and methformin) agents (e.g. prednisolon)

- Use of anti-depressive drugs
- Pregnancy or breastfeeding or unwillingness to undertake measures for birth control
- Use of statins (e.g. stop statins >2 weeks before performing blood sampling. This can be safely done in the context of primary prevention)
- Any event of cardiovascular disease in the past 5 years (e.g. myocardial infarction, stroke, heart failure, symptomatic peripheral arterial disease)
- Auto-inflammatory or auto-immune diseases
- Any infection in past three months
- Previous vaccination in the past three months
- Laser coagulation for proliferative retinopathy in the past six months
- Proliferative retinopathy
- Diabetic nephropathy as reflected by an albumin-creatinine ratio * 30 mg/gor an estimated glomerular filtration rate (by MDRD) *60ml/min/1.73m2
- History of pancreatitis (acute or chronic) or pancreatic cancer

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-08-2019
Enrollment:	56
Type:	Actual

Ethics review

Approved WMO

Date:	27-05-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-04-2020
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
ClinicalTrials.gov	NCT03976271
CCMO	NL67229.091.18