The role of the adrenergic system in hypoglycaemia induced inflammatory response in people with type 1 diabetes and people without type 1 diabetes-RAID-II

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To examine the effect of adrenergic inhibition on the hypoglycaemia induced inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by performing a hyperinsulinaemic hypoglycaemic glucose clamp alongside infusion of α-ARA...

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

Summary

ID

NL-OMON57053

Source
ToetsingOnline

Brief title
RAID-II

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Diabetes, inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adrenergic, Blockade, Diabetes, Inflammation

Outcome measures

Primary outcome

- The aim of the present study is to examine the effect of adrenergic inhibition on the hypoglycaemia induced inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by performing a hyperinsulinaemic hypoglycaemic glucose clamp alongside infusion of alpha and beta-receptor blockers.

Secondary outcome

- To study the change in inflammatory and anti-inflammatory proteins (e.g. hs-crp, Olink-proteomics AB inflammation panel (47) with but not limited to FGF-21, SLAMF-1)
- To study the ex vivo production of cytokines by isolated monocytes after exposure to hypoglycaemia and simultaneous adrenergic blockade.
- To study the duration of the inflammatory response to hypoglycaemia and simultaneous adrenergic blockade.
- To study the leukocyte phenotype changes after exposure to hypoglycaemia and simultaneous adrenergic blockade.
- To study the effects of glucose variability on the inflammatory response during hypoglycaemia and simultaneous adrenergic blockade.

- To study the effect of glucometric parameters such as amount of hypoglycaemia or time below range, on the inflammatory response during and after hypoglycaemia and simultaneous adrenergic blockade.

- To study the effect of hypoglycaemia and simultaneous adrenergic blockade on atherogenic plasma biomarkers .

- To study the effect of hypoglycaemia and simultaneous adrenergic blockade on adrenergic receptors present on the studies leukocytes.

- To study the effect of hypoglycaemia and simultaneous adrenergic blockade on leukocyte transcription factors (e.g. Egr-1).

- Markers of metabolic responses (e.g. glycerol, Non-esterified fatty acids (NEFAs), metabolomics profiling)

* Leukocyte transcription factors (e.g. Egr-1).

* Density and presence of adrenergic receptors on leukocytes

* Adrenergic symptoms assessed using the validated Edinburgh Hypoglycaemia Score (48)

* Hypoglycaemia awareness using the modified Clarke score (72)

Study description

Background summary

Hypoglycaemia has shown to cause a sustained pro-inflammatory response which could promote a pro-atherogenic state and explain the association between hypoglycaemia and cardiovascular events. This pro-inflammatory response has been linked to the adrenaline response to hypoglycaemia. Adrenergic blockade with α and β adrenergic receptor antagonists (ARA) has shown to blunt the leukocyte response after hypoglycaemia induction and adrenaline administration. Whether and to what degree a combined blockade blunts the hypoglycaemia induced

pro-inflammatory response is unknown.

Study objective

To examine the effect of adrenergic inhibition on the hypoglycaemia induced inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by performing a hyperinsulinaemic hypoglycaemic glucose clamp alongside infusion of α-ARA and β-ARA. Secondary objectives consist of the effect of adrenergic blockade during hypoglycaemia on atherogenic parameters and glucometrics.

Study design

Intervention study with a cross-over design

Intervention

Potentially eligible adult (16 - 75 years) participants will be recruited through social media, the Radboudumc outpatient clinic and other advertisements. We will recruit a total of 24 individuals, i.e. 12 healthy participants and 12 participants with type 1 diabetes. Participants with type 1 diabetes will be twice (as there are two investigational days) equipped with a blinded continuous glucose monitoring device (CGM) during the test, which will measure interstitial glucose levels for a total of 10 days.

Study burden and risks

The main burden of this study is the induction of experimental hypoglycaemia, the infusion of the adrenergic blockade and the time spent with frequent hospital visits (11 visits for people with type 1 diabetes and 9 visits for people without type 1 diabetes in total as it is a cross-over design). The hypoglycaemic clamps may produce typical symptoms (e.g. sweating, feeling hungry, palpitations), although these are generally mild and not harmful and resolve after restoration of euglycaemia. There is a possibility that the combination of phentolamine and propranolol can cause hypotension, orthostatic hypotension and bradycardia. The combination of these two drugs in a hypoglycaemic setting has been proven to be used safely in an identical setup (1, 2). In addition the participants will be in a supine position and their blood pressure and heart rate monitored every 15 minutes. Furthermore the intravenous administration ensures a short half-time for the drugs. The use of venous catheters may lead to hematomas or phlebitis, yet these are self-limiting and have in our hands never led to permanent damage.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

Overall inclusion criteria:
• Ability to provide written informed consent
• Body-Mass Index: 18,5-30 kg/m2
• Age >=16 years, <= 75 years
• Blood pressure: <140/90 mmHg
• Non-smoking
• Electrocardiogram not showing any serious arrythmias (PVCs and PACs accepted)
Diabetes group specific criteria:
• Insulin treatment according to basal-bolus insulin regimen (injections or insulin pump)
• Duration of diabetes > 1 year

• HbA1c < 100 mmol/mol,

Exclusion criteria

- Any event of cardiovascular disease in the past 5 years (e.g. myocardial infarction, stroke, symptomatic peripheral arterial disease)
- Pregnancy or breastfeeding or unwillingness to undertake measures for birth control
- Active epilepsy (with the need for treatment)
- Allergy for sulphite
- Active asthma with use of β2-bronchodilators or obstructive lung disease
- Current treatment with Alpha- or beta-blockers (e.g. doxazosin, propranolol)
- History of clinical significant Arrhythmias
- Use of immune-modifying drugs or antibiotics
- Use of antidepressants (Including MAO inhibitors, tricyclic antidepressants and serotonin-reuptake inhibitors)
- Use of antipsychotics
- Use of statins with the inability to stop statins >2 weeks before the investigational day.
- Proliferative retinopathy
- Nephropathy with an estimated glomerular filtration rate (by CKD-EPI) *60ml/min/1.73m2

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2024

Enrollment:	24
Type:	Anticipated

Ethics review

Approved WMO Date:	09-10-2024
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
CCMO	NL86961.091.24