Prospective single-center case-control *proof of principle* study to determine the association of glucagon-mediated activation of the calcineurin-pathway with left ventricular hypertrophy in insulin-resistant diabetic patients

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The primary objective of this study is to determine whether glucagon-mediated activation of the calcineurin-pathway is associated with LVH in severely insulin-resistant diabetic subjects.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON36906

Source
ToetsingOnline

Brief title
LVH-DM

Condition

- Myocardial disorders
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
left ventricular hypertrophy, thickening of the muscle of the heart

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: - calcineurin, - diabetes mellitus, - glucagon, - left ventricular hypertrophy

Outcome measures

Primary outcome

Primary endpoint of this investigation will be a significant (P < 0.05)

difference in glucagon levels and calcineurin activation between the two groups

(LVH vs. no LVH).

Secondary outcome

Secondary endpoint will be a significant (P < 0.05) difference in NT-proBNP and

galectin-3 levels between the two groups (left ventricular hypertrophy vs. no

left ventricular hypertrophy).

Study description

Background summary

Diabetes mellitus is a complex, multifactorial syndrome characterized by defective insulin secretion and insulin resistance. Fasting and postprandial hyperglycemia are the result of dysregulated hepatic glucose production and reduced glucose uptake, which is generally attributed to reduced activity of insulin.
Wang et al. recently demonstrated that glucagon promotes CRTC2 dephosphorylation during fasting by triggering increases in cytoplasmatic calcium via phosphorylation of the inositol-1,4,5-triphosphate receptors (InsP3Rs) that lead to calcineurin activation and consequently an increase in gluconeogenic gene expression. They found that, in diabetes, InsP3Rs and calcineurin activity was increased, leading to upregulation of the

gluconeogenic programme. Knockdown of either calcineurin or InsP3Rs in db/db mice reduced gluconeogenetic gene expression and hepatic gluconeogenesis.(1) This suggests that agents that can selectively block the activity of the InsP3Rs and calcineurin might lower CRTC2 dephosphorylation and hepatic gluconeogenesis in diabetic subjects.
Interestingly, besides its involvement in diabetes, increased calcineurin activity is also associated with induction of LVH.(2) In this study, we aim to investigate whether glucagon-mediated activation of calcineurin is associated with LVH in severely insulin-resistant diabetic subjects.

Study objective

The primary objective of this study is to determine whether glucagon-mediated activation of the calcineurin-pathway is associated with LVH in severely insulin-resistant diabetic subjects.

Study design

Prospective single-center case-control proof of principle study.

Study burden and risks

Echocardiography: no risk and low burden
MRI of the heart: Side-effects of gadolinium contrast are very rare (0.066% in all investigations with gadolinium) but can cause headache, nausea, rash and pruritus. In severe cases, an allergic reaction or shock is seen. MRI of the heart has a low burden.
Blood drawing: low risk and low burden

Participating in this trial encompasses no burden or risk associated with being either in the LVH or no LVH group.

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

1. Patient is * 18 years-old.
2. Insulin-resistance requiring insulin injection of more than 1,5 IU/kg/day
3. Written informed consent to participate in this study prior to any study procedures

Exclusion criteria

1. Any (known) cardiac history
2. Patients treated with any dose of glucagon-lowering medication as DPP-4 inhibitors (Saxagliptin, Sitagliptin and Vildagliptin) and incretin-mimetics (Exenatide and Liraglutide).
3. Patients treated with immunosuppressive medication as cyclosporine A, tacrolimus or pimecrolimus.
4. Patients with current uncontrolled hypertension or uncontrolled hypertension in the past two years (Office measurement of systolic blood pressure >165 mmHg or office diastolic blood pressure >105 mmHg at any moment in the past two years)
5. Presence of any cardiac abnormalities on study-related echocardiographic examination (clinically relevant valvular disease, severe congenital abnormalities, asymmetric hypertrophy with one wall exceeding 15mm while other areas are below 10mm thickness, dilated cardiomyopathies)
6. Patients with contraindications for MRI or gadolinium contrast (claustrophobia, implanted electronic devices, creatinine > 200 µmol/L determined within 3 months prior to inclusion, proven gadolinium contrast allergy)
7. Presence of a glucagonoma

Study design

Design

Study type:	Observational invasive
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):	07-05-2013
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	10-12-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL41800.018.12