Mechanisms of Albuminuria in Diabetes: Reversal of Injury to the Glycocalyx by the Ace-inhibitor Lisinopril

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Ethical review	Approved WMO
Status	Pending
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON32380

Source
ToetsingOnline

Brief title
MADRIGAL

Condition

- Diabetic complications
- Nephropathies
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
diabetes mellitus, Type 1 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Stichting Asklepios

Intervention

Keyword: Glycocalyx, Lisinopril, Microalbuminuria, Type 1 diabetes

Outcome measures

Primary outcome

The primary parameter of the study is the change in microvascular glycocalyx

thickness before and after treatment with lisinopril and placebo.

Secondary outcome

The secondary parameters of the study are change in blood pressure,

microalbuminuria, glomerular charge selectivity, plasmalevels of hyaluronan,

hyaluronidase,vWf and prothrombin fragment 1+2, VCAM-1 and ICAM-1 and change in

15(S)-8-iso-prostaglandin levels in 24 hours urine samples.

Study description

Background summary

Microalbuminuria in diabetes mellitus is not only associated with progression to renal disease, it is also a potent predictor of cardiovascular disease and thus may reflect widespread vascular damage. Endothelial dysfunction is one of the first steps in the development of vascular damage, and is commonly found in patients with microalbuminuria. The endothelium is covered by the endothelial glycocalyx. In patients with type 1 diabetes a significant reduction of its systemic volume and microvascular thickness was found. This reduction was even more profound in patients with microalbuminuria.
Ace-inhibitors have a positive effect on microalbuminuria in diabetic patients and on endothalial function. This might be caused by a direct effect on the glycocalyx.

Study objective

The primary objective of this study is to determine whether ACE inhibition results in an improvement of microvascular glycocalyx-thickness in patients

with type 1 diabetes. The secondary objectives are to investigate whether this (hypothesized) improvement correlates with a decrease in microalbuminuria as well as glomerular charge selectivity and whether the improvement can be explained by an amelioration of the oxidative or inflammatory state in these patients.

Study design

Double-blind, randomized placebo-controlled crossover study.

Intervention

All included subjects will be randomly treated with either placebo or lisinopril 20 mg for two weeks, followed by a two week washout period. After the washout period, the subjects who received placebo in the first treatment period will receive lisinopril for two weeks and vice versa. The total study period will amount to six weeks for all included subjects.

Study burden and risks

Included subjects will visit the AMC hospital five times:
Visit 1: Screening visit, informed consent, medical history and vital signs.
Visit 2: Orthogonal polarization spectral (OPS) imaging of the sublingual microcirculation, laboratory measurements and collect urine, start study medication A.
Visit 3: OPS imaging of the sublingual microcirculation, laboratory measurements and collect urine, start washout period.
Visit 4: OPS imaging of the sublingual microcirculation, laboratory measurements and collect urine, start study medication B.
Visit 5: OPS imaging of the sublingual microcirculation laboratory measurements and collect urine, end of study.
Burden for the patient: At all visits approximately 20 ml of blood will be drawn, OPS imaging is non-invasive and painless.

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

Caucasian
Male
Diagnosis of type 1 diabetes according to ADA criteria
Urinary albumin/creatinin ratio <3,5 mg/mmol, without antiproteinuric treatment

Exclusion criteria

Hypertension as defined by systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or use of antihypertensive drugs
Previous use of RAS inhibitors
Smoking
Primary dyslipidemia*s
Use of statins during the six weeks before visit 1
Use of antioxidants in the two weeks prior to visit 1
Angioedema in medical history
Hypersensitivity to Ace inhibitors

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	26-05-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Lisinopril
Generic name:	Lisinopril
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	04-06-2008
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
EudraCT	EUCTR2008-002610-21-NL
CCMO	NL23244.018.08