# Mechanisms of albuminuria in diabetes: reversal of injury to the glycocalyx by the ace-inhibitor lisinopril

No registrations found.

| | |
|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Pending |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON23821

**Source**
Nationaal Trial Register

**Brief title**
MADRIGAL

**Health condition**

Diabetes Mellitus, microalbuminuria, glycocalyx, ACE-inhibitor

### Sponsors and support

**Primary sponsor:** Academic Medical Center (AMC), Department of Internal Medicine
**Source(s) of monetary or material Support:** Stickting Asklepios

### Intervention

### Outcome measures

**Primary outcome**

The primary outcome of this study is the change in microvascular glycocalyx thickness after treatment.

### Secondary outcome

Secondary outcomes are changes in oxidative stress, inflammation, coagulation microalbuminuria and glomerular charge selectivity.

## 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, a negatively charged mesh that plays an important role in vascular homeostasis, regulating the adhesion of blood cells to the vascular endothelium and vascular permeability. Acute hyperglycaemia has been shown to damage the endothelial glycocalyx and in patients with type 1 diabetes and micraolbuminuria a significant reduction of its systemic volume and microvascular thickness was found.

Angiotensin converting enzyme (ACE) inhibitors are first line therapy for patients with microalbuminuria. Their antiproteinuric effect in diabetes cannot fully be explained by the lowering of blood pressure and is believed to result from a beneficial effect on the vascular endothelium. The mechanism by which this antiproteinuric effect occurs is not clear, but may lie in the preservation of the glomerular charge barrier. As the endothelial glycocalyx is an important charge barrier in the glomerular membrane, we hypothesize that the antiproteinuric effect of ACE inhibitors results from a preservative effect on the endothelial glycocalyx. 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.

To this end 20 patients with type 1 diabetes will first recieve lisinopril and then a placebo or vice versa. Before and after each treatment assessment of the thickness of the glycocalyx and laboratory measurements will be performed.

### Study objective

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, a negatively charged mesh that plays an important role in vascular homeostasis, regulating the adhesion of blood cells to the vascular endothelium and vascular permeability. Acute hyperglycaemia has been shown to damage the endothelial glycocalyx and in patients with type 1 diabetes and micraolbuminuria a significant reduction of its systemic volume and microvascular thickness was found.
Angiotensin converting enzyme (ACE) inhibitors are first line therapy for patients with microalbuminuria. Their antiproteinuric effect in diabetes cannot fully be explained by the lowering of blood pressure and is believed to result from a beneficial effect on the vascular endothelium. The mechanism by which this antiproteinuric effect occurs is not clear, but may lie in the preservation of the glomerular charge barrier. As the endothelial glycocalyx is an important charge barrier in the glomerular membrane, we hypothesize that the antiproteinuric effect of ACE inhibitors results from a preservative effect on the endothelial glycocalyx. 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**

T=0: OPS imaging + venipuncture + collect urine + randomisation + start study medication A.

T=14: OPS imaging + venipuncture + collect urine + start washout period.

T=28: OPS imaging + venipuncture + collect urine + start study medication B.

T=42: OPS imaging + venipuncture + collect urine_End of 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.

# Contacts

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# Eligibility criteria

## Inclusion criteria

1. Caucasian males

2. Diagnosis of type 1 diabetes according to ADA criteria

3. Urinary albumin/creatinin ratio <3,5 mg/mmol, without antiproteinuric treatment

## Exclusion criteria

1. Hypertension as defined by systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or use of antihypertensive drugs

2. Previous use of RAS inhibitor2

3. Smoking

4. Primary dyslipidemia’s

5. Use of statins during the six weeks before visit 1

6. Use of antioxidants in the two weeks prior to visit 1

7. Angioedema in medical history

8. Hypersensitivity to ACE inhibitors

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-06-2008 |
| Enrollment: | 20 |
| Type: | Anticipated |

# Ethics review

Positive opinion

| | |
|---|---|
| Date: | 29-05-2008 |
| Application type: | First submission |

# 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 |
|---|---|
| NTR-new | NL1286 |
| NTR-old | NTR1332 |
| Other | METC : 08/138 |
| ISRCTN | ISRCTN wordt niet meer aangevraagd |

# Study results

**Summary results**
N/A