Effects of RAS inhibition on insulin sensitivity and IGF-I bioactivity

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

Summary

ID

NL-OMON35702

Source
ToetsingOnline

Brief title
RAS inhibition, insulin sensitivity and IGF-I bioactivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Ikazia Ziekenhuis
Source(s) of monetary or material Support: research fonds van het ziekenhuis

Intervention

Keyword: IGF-I bioactivity, IGF-I KIRA, Insulin sensitivity, RAS inhibition

Outcome measures

Primary outcome

The primary outcome will be the effect of short-term administration of the angiotensin-receptor antagonist losartan on insulin sensitivity, assessed by the baseline adjusted difference in the homeostasis model assessment of insulin resistance (HOMA) at eight weeks.

Secondary outcome

Secondary outcomes will be the effect of short-term losartan treatment on total IGF-I and IGF-I bioactivity, and the correlation between changes in insulin sensitivity and changes in IGF-I system.

Study description

Background summary

The prevalence of type 2 diabetes mellitus is rising rapidly worldwide, and interventions to prevent or delay its onset are becoming increasingly important. Previous studies have shown that the incidence of new-onset diabetes was reduced by inhibitors of the renin-angiotensin system (RAS), suggesting active positive effects of these drugs on long-term glucose metabolism. However, the exact mechanisms involved are still unclear.

The GH/IGF-I system is important in the maintenance of glucose homeostasis, and might thus play a protective role in the development of glucose intolerance. Improvement of the disturbed GH/IGF-I system (that is reduced levels of IGF-I and the GH hypersecretion) in patients with insulin resistance and type 2 diabetes mellitus might be one of the mechanisms through which RAS inhibitors could improve insulin sensitivity and thereby interfere in the development of type 2 diabetes. It was previously hypothesised that production of IGF-I is reduced by angiotensin II, which is reversed by the angiotensin-receptor antagonist losartan. Furthermore, in a former small study, we have observed

that short-term losartan treatment reduced insulin resistance in patients with impaired fasting glucose, which was close to significantly correlated to an increase in serum levels of free IGF-I.

Recently, an IGF-I kinase receptor activation assay (IGF-I KIRA) was developed and validated, now providing a highly sensitive and specific method for measuring IGF-I bioactivity in human serum. Also normative data for the IGF-I KIRA have become available. It has been suggested that the IGF-I KIRA method can provide information about the IGF-I system that in part differs from measures obtained from the classic immunoassays, and especially in the pathophysiology of insulin resistance.

Study objective

In this single centre pilot intervention study, we will investigate the effects of short-term administration of the angiotensin-receptor antagonist losartan on insulin sensitivity (assessed by using the homeostasis model assessment of insulin resistance (HOMA)), as well as on total IGF-I and IGF-I bioactivity in patients with impaired fasting glucose and/or impaired glucose tolerance.

Study design

In this randomised, controlled, open-label pilot study, 40 patients with impaired fasting glucose and/or impaired glucose tolerance will be included. 20 patientes will receive losartan tablets, 100 mg once daily, for 8 weeks, and the controlgroup of 20 patients will not receive medication. Before and after the treatment period, insulin sensitivity will be assessed using homeostasis model assessment of insulin resistance (HOMA). Also, the effects of short-term losartan treatment on the IGF-I system, including IGF-I bioactivity measured by IGF-I KIRA, will be investigated.

Intervention

Baseline: 3 fasting blood samples are taken at 5 minutes interval for measurement of:
- t=0: total IGF-I, IGF-I bioactivity, insulin, glucose
- t=5: insulin, glucose
- t=10: insulin, glucose
The three baseline samples are averaged for the mean levels of glucose and insulin for HOMA score calculations. HOMA uses mathematical modelling of fasting plasma glucose and insulin levels to estimate insulin resistance: fasting serum insulin (*U/ml) x fasting plasma glucose (mmol/l) / 22.57. -
After this, patients receive 8 weeks of treatment with the angiotensin-receptor antagonist losartan, 100mg orally, once daily.
During the first visit renal function and elektrolytes will be measured. The blood pressure, height and weight will also measured.

After 8 weeks of losartan treatment, again 3 fasting blood samples are taken at 5 minutes interval for measurement of:
- t=0: total IGF-I, IGF-I bioactivity, insulin, glucose
- t=5: insulin, glucose
- t=10: insulin, glucose
HOMA scores will again be calculated from these measurements.
Renal function, elektrolytes, weight and blood pressure will be measured again.

Study burden and risks

Burden:

- Patients have to come twice to the outpatient clinic. The visit will take about 30 minutes
- Patient will have a venipuncture at both visits, 15 cc of blood will be drawn
- Patients have tot take a tablet, once a day, for 8 weeks

Risks:

Losartan treatment can cause adverse events, which are extensively described in the patient information form

Benefits:

There is no expected direct benefit for the individual patient. Results from this study might be beneficial for patients with impaired fasting glucose and/or impaired glucose tolerance in the future.

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

- age 18 * 70 years
- impaired fasting glucose (IFG): fasting plasma glucose levels between 5,6 * 6,9 mmol/l (100 * 125 mg/dl) and/or impaired glucose tolerance (IGT): plasma glucose levels between 7,8 * 11,0 mmol/l (140 * 199 mg/dl) after 2 hours on the 75-g oral glucose tolerance test

Exclusion criteria

- use of RAS inhibitors within 6 weeks prior to inclusion
- use of oral glucose-lowering drugs or insulin
- use of statins
- use of betablockers
- use of steroids, hormone replacement therapy or other study medication
- contraindication for or intolerant to RAS inhibitors
- untreated hypothyroidism or hyperthyroidism
- negroid race
- pregnancy and breastfeeding
- severe renal insufficiency (GFR < 30mL/min) and/or known bilateral renal artery stenosis
- hyperpotassemia (potassium > 5,0mmol/L)

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-08-2012
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cozaar
Generic name:	Losartan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-10-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	03-07-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-003479-12-NL
CCMO	NL37656.101.11