Effects of aldosterone antagonism on microvascular function in obese individuals

Published: 02-09-2013
Last updated: 25-04-2024

Primary objectives:1. Is plasma aldosterone concentration associated with microvascular function, specifically insulin-mediated capillary recruitment, in obese subjects?2. Does mineralocorticoid receptor antagonism result in improvement of...

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

Summary

ID

NL-OMON45212

Source
ToetsingOnline

Brief title
Aldosterone antagonism and microvascular function

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Vascular hypertensive disorders

Synonym
hypertension/high blood pressure; insulin resistance/decreased sensitivity for insulin

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Aldosterone antagonism, Microcirculation, Obesity-related complications

Outcome measures

Primary outcome

Primary endpoints are capillary recruitment during hyperinsulinemia in skeletal muscle, and insulin sensitivity. They will be related to plasma aldosterone concentration and compared before and after treatment with a mineralocorticoid receptor antagonist.

Secondary outcome

Secondary endpoints are differences in other (micro)vascular measurements (baseline capillary density, skin capillary recruitment, skin vasomotion (basal and during local heating), endothelial glycocalyx thickness, carotid distensibility, augmentation index, carotid-femoral pulse wave velocity, and reactive hyperemia index), and biomarkers representing endothelial activation and low-grade inflammation, between fasting and hyperinsulinemic states. They will also be related to plasma aldosterone concentration, and compared before and after treatment with a mineralocorticoid receptor antagonist.

Study description

Background summary

The prevalence of obesity and obesity-related complications is currently taking epidemic proportions. These complications increase the risk of type 2 diabetes and cardiovascular disease, which are important causes of morbidity and mortality worldwide.
It is important to gain insight in the mechanisms underlying obesity-related complications, because this may lead to the development of directed therapeutic

strategies.
Currently, there is significant evidence that the cause of both insulin resistance and hypertension must be sought at the level of the microcirculation.
Over activity of the renin-angiotensin-aldosterone system is a potential cause of microvascular dysfunction. Angiotensin II was indeed found to be implicated in the pathogenesis of obesity-associated hypertension and insulin resistance, possibly through interference with the vascular effects of insulin.
Increased aldosterone levels have also been associated with resistant hypertension and insulin resistance, which is illustrated in patients with primary aldosteronism. Furthermore, aldosterone is known to exert several detrimental effects on the vasculature, some of which are offset by mineralocorticoid receptor antagonists.
In obese individuals, plasma aldosterone concentrations are increased as well. We hypothesize that increased aldosterone levels in adipose persons induce microvascular dysfunction, which contributes to the development of insulin resistance and hypertension, and mineralocorticoid receptor antagonism results in improved insulin sensitivity and decreased blood pressure by counteracting the adverse effects of aldosterone on the microvasculature.

Study objective

Primary objectives:
1. Is plasma aldosterone concentration associated with microvascular function, specifically insulin-mediated capillary recruitment, in obese subjects?
2. Does mineralocorticoid receptor antagonism result in improvement of microvascular function, specifically insulin-mediated capillary recruitment, and of insulin sensitivity, in obese subjects?

Secondary objectives:
1. Is plasma aldosterone concentration associated with vascular stiffness and endothelial function in obese subjects?
2. Does mineralocorticoid receptor antagonism result in reduction of vascular stiffness and improvement of endothelial function in obese subjects?

Study design

This is a randomized, double blind, placebo-controlled intervention study.

After screening for eligibility, participants will visite the study centre at two days.
During the first day, baseline measurements of vascular function (endothelial glycocalyx thickness, nailfold capillary microscopy, vasomotion analysis, contrast enhanced ultrasound, determination of pulse wave velocity and carotid distensibility, pulse wave analysis and peripheral arterial tonometry) will be performed before and during a hyperinsulinemic, euglycemic clamp test.

A total amount of 180 mL blood will be drawn for determination of electrolytes, renal and hepatic function, lipid profile, glucose, insulin, markers of endothelial activation and inflammation, adipokines and components of the RAAS system.
After the first study day, subjects will be randomized to treatment with either 50 mg Eplerenone during 4 weeks or placebo treatment.
At the end of the treatment period, all measurements of vascular function performed during the first day will be repeated before and during a hyperinsulinemic, euglycemic clamp, as well as the blood sampling.

Intervention

30 obese individuals will be randomized to treatment with the selective mineralocorticoid receptor antagonist Eplerenone, 50 mg once daily during 4 weeks. The remaining 30 obese individuals will be randomized to treatment with a matched placebo during 4 weeks.

Study burden and risks

Participants will visit the study center 3 times: once for a screening visit, and at two occasions for measurements of (micro)vascular function (baseline and follow-up) during a hyperinsulinemic, euglycemic clamp test. For screening purposes, 9 mL blood will be drawn to determine electrolytes, renal and hepatic function, lipid profile and glucose. At study days, measurements of (micro)vascular function will be performed in the fasting state, before and during a hyperinsulinemic, euglycemic clamp test for determination of insulin sensitivity. Participants will be requested to abstain from alcohol and not to smoke 12 hours prior to the measurements, and not to perform strenuous exercise 48 hours prior to the study days.
The most prevailing side effect of the hyperinsulinemic euglycemic clamp test is hypoglycemia. Measurements of (micro) vascular function include determination of endothelial glycocalyx thickness, skin capillary microscopy, skin vasomotion analysis (basal and during local heating), contrast-enhanced ultrasound of skeletal muscle, determination of carotid distensibility and carotid femoral pulse wave velocity, pulse wave analysis, and peripheral arterial tonometry, and are merely noninvase. The contrast agent administered during contrast-enhanced ultrasound of skeletal muscle has proven to be a safe imaging modality in previous investigations.
During both visits, a total amount of ~ 180 mL blood is drawn for determination of electrolytes, renal function, lipid profile, insulin, markers of endothelial activation and inflammation, RAAS components, and glucose values during the hyperinsulinemic, euglycemic clamp. This amount of blood carries no risks for the participants.
One week before baseline measurements, participants will be started on a moderately-low sodium diet, which is continued throughout the study (5 weeks total). Prior to baseline measurements, antihypertensive therapy (if

participants are receiving any) will be temporarily ceased. This is not expected to cause health concerns.
After baseline measurements of (micro)vascular function, participants will be randomized to treatment with either Eplerenone or a matched placebo during 4 weeks. Common side effects of Eplerenone include gastro-intestinal complaints, hypotension, hyperkalemia and impaired renal function. Blood pressure, potassium values, and renal and hepatic function will be monitored following the first week of treatment. After 4 weeks, all measurements of (micro)vascular function will be repeated.
Short-term treatment with Eplerenone will not be of sustained benefit for the participating subjects; subjects who are randomized to placebo treatment will obtain no health benefit at all. Furthermore, the sodium-restricted diet and the treatment with either Eplerenone or placebo demand a strict compliance from the participant. The amount of time invested is also considerable and a large amount of measurements will be performed (determination of (micro)vascular function, laboratory investigations, 24h blood pressure measurements).
This burden on the participants is justified, however, since we might elucidate mechanisms leading to obesity-related complications, which possess a major health risk. Participants will also gain insight into their own risk profile for the development of type 2 diabetes and cardiovascular disease.
All subjects will receive a compensation of ¤ 300,- after completion of the study.
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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 40-65 years
- Caucasian (because of ethnic differences in microvascular function, vascular stiffness, and the prevalence of cardiovascular disease and associated risk factors)
- Waist circumference > 102 cm (men)/> 88 cm (women)
- High-normal blood pressure (office blood pressure: 130/85 * 139/89 mm Hg) or stage I/II hypertension (office blood pressure: 140/90 mm Hg * 179/109 mm Hg; 24h ABPM: 125/80 * 169/99 mm Hg)

Exclusion criteria

- Cardiovascular disease (stroke, coronary artery disease, peripheral vascular disease, congestive heart failure, cardiac shunts, cardiac surgery, pulmonary hypertension, cardiac arrhythmias, family history of cardiac arrhythmias or sudden cardiac death)
- Diabetes mellitus/impaired fasting glucose (fasting glucose values > 6.1 mmol/L), because not only diabetes, but also intermediate hyperglycaemia has been associated with microvascular disease, which impedes the distinction between cause and consequence of disturbances in glucose metabolism in the concerning individuals
- Grade 3 hypertension (office blood pressure: > 180/110 mm Hg; ABPM > 170/100 mm Hg) in order not to expose these individuals to unnecessary risks by interrupting or postponing antihypertensive treatment
- Unstable or severe pulmonary disease
- Unstable or severe thyroid disorders
- Inflammatory diseases
- Alcohol use > 2 U/day (women)/> 3 U/day (men)
- Use of glucose-lowering medications, because of possible interference with microvascular function
- Use of corticosteroids (have also affinity for the mineralocorticoid receptor; can decrease the antihypertensive effect of Eplerenone), medication known to inhibit or induce CYP3A4 (possible interference with metabolism of Eplerenone), lithium (possible reduction of lithium excretion when used simultaneously with Eplerenone) , and tricyclic antidepressants or antipsychotic medication (risk of orthostatic hypotension when used simultaneously with

Eplerenone), and regular use (weekly or several times a week) of NSAIDs (risk of acute renal dysfunction and disturbance of electrolyte excretion when used simultaneously with Eplerenone)
- Plasma potassium levels < 3.2 mmol/L or > 5 mmol/L
- eGFR < 60 mL/min
- Impairment of hepatic function
- Pregnancy or lactation

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2014
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	02-09-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-05-2014
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT01887119
CCMO	NL44235.068.13