Aldosterone-induced microvascular dysfunction as a cause of salt-sensitivity in obesity?

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To investigate whether increased aldosterone levels in obese individuals lead to impairment of microvascular function through reduction of NO-availability, and to establish the role of microvasculaire dysfunction in the pathogenesis of salt-...

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

Summary

ID

NL-OMON40283

Source
ToetsingOnline

Brief title
Aldosterone, microvascular function and salt-sensitivity

Condition

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

Synonym
insulin resistance/decreased sensitivity for insulin, salt-sensitivity of blood pressure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Aldosterone, Microcirculation, Obesity, Salt-sensitivity

Outcome measures

Primary outcome

Primary endpoints are skin capillary recruitment during reactive hyperemia, both basally and during hyperinsulinemia, skeletal muscle microvascular recruitment during hyperinsulinemia, aldosterone levels and salt-sensitivity. They will be compared between obese and lean individuals, under circumstances of low and high salt intake.

Secondary outcome

Secondary endpoints are results of other microvascular measurements (baseline capillary density, skin vasomotion (basal and during local heating), endothelial glycocalyx thickness), both basally and during hyperinsulinemia, insulin sensitivity, blood pressure, other RAAS components, biomarkers representing endothelial activation and low-grade inflammation, and urinary excretion of albumin and products of NO metabolism. They will be compared as well between obese and lean individuals under circumstances of low and high salt intake.

Study description

Background summary

Currently, the incidence of obesity and obesity-related disorders is reaching epidemic proportions, which entails an increasing burden for health care systems. The association of obesity with other risk factors for type 2 diabetes mellitus and cardiovascular disease, such as insulin resistance and

hypertension, is often referred to as the metabolic syndrome. During recent years, salt-sensitivity of blood pressure has emerged as an additional cardiovascular risk factor that is related to obesity and other key components of the metabolic syndrome. The underlying pathophysiological mechanisms of these interrelationships are complex and incompletely elucidated. A more detailed insight, however, is essential to identify and treat persons at risk for cardiovascular disease at an early stage. Recently, microvascular dysfunction has been proposed as a link between insulin resistance and hypertension in obese individuals. In addition, impairment of microvascular function was found to be associated with salt-sensitivity of blood pressure. Loss of NO-mediated vasodilation is an important feature of microvascular dysfunction and may contribute to the pathogenesis of salt-sensitivity. Furthermore, an impaired insulin-mediated microvascular NO production has been suggested to underlie the reduction in insulin-stimulated glucose disposal that is characteristic of insulin-resistant states. Increased aldosterone levels, as observed in obese individuals, might be a cause of microvascular dysfunction-induced salt-sensitivity and insulin resistance. Aldosterone not only gives rise to sodium-retention in the distal tubule of the kidney, but was also found to impair endothelial function and thus lower NO-availability. In addition, elevated aldosterone levels are associated with both hypertension and insulin resistance, which is illustrated in patients with primary aldosteronism, but also in the general population. Whether and how microvascular dysfunction is involved in the pathogenesis of salt-sensitivity, has never been directly investigated in humans or more specifically, obese individuals. The role of aldosterone in the pathogenesis of microvascular dysfunction-induced salt-sensitivity has never been established as well.

Study objective

To investigate whether increased aldosterone levels in obese individuals lead to impairment of microvascular function through reduction of NO-availability, and to establish the role of microvasculaire dysfunction in the pathogenesis of salt-sensitive hypertension.

Study design

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

Intervention

After recruitment, participants will be either started on a low salt diet of 50 mmol NaCl/24h or a high-salt diet of 250 mmol NaCl/24h during one week. Thereafter, measurements of microvascular function will be performed. This is followed by a 2-week wash-out period of ad-libitum salt intake. Subsequently, participants who initially used a low salt diet will now be placed on a high salt diet and vice versa, for another week, where after

measurements of microvascular function will be repeated.
The sequence of variation in salt intake for each individual participant will be determined by means of block randomization.

Study burden and risks

Participants will visit the study center 3 times: once for a screening visit and at two occasions for measurements of microvascular function before and during a hyperinsulinaemic, euglycaemic clamp test.
For screening purposes, 9 mL blood will be drawn to determine electrolytes, renal function, lipid profile and glucose. After recruitment, participants will be randomized to a period of 7 days of either low (50 mmol NaCl/24h) or high (250 mmol NaCl/24h) salt intake. This might induce a slight decrease or increase in blood pressure, which will most probably not be noticed by the participants and carries no health risks.
Possible side effects of the high salt diet are mild gastro-intestinal complaints, although not reported by all studies applying this intervention. Since we use slow-release capsules, we expect that these side effects will be reduced to a minimum or do not occur at all. Prior to the initial measurements, antihypertensive therapy (if participants are receiving any) will be temporarily ceased. This is not expected to cause health concerns.
At the end of the week of either low or high sodium ingestion, 24h urine will be collected to verify compliance to the diet, and 24h blood pressure measurements are performed.
This is followed by a first study day, during which microvascular function will be assessed in the fasting state, before and during a hyperinsulinaemic, euglycaemic clamp test for determination of insulin sensitivity.
Participants will be requested to abstain from alcohol 12 hours prior to the study days, and not to perform strenuous exercise 48 hours beforehand.
Measurements of microvascular function include contrast-enhanced ultrasound of skeletal muscle (CEUS), skin capillary microscopy, skin vasomotion analysis, registration of heating-induced microvascular dilatation and determination of endothelial glycocalyx thickness, and are merely noninvasive. The contrast agent administered during the CEUS procedure has been proven to be a safe imaging modality in previous investigations. The most prevailing side effect of the hyperinsulinaemic euglycaemic clamp test is hypoglycaemia. A total amount of ~ 140 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 hyperinsulinaemic, euglycaemic clamp. This amount carries no risk for the participants.
The first study day is followed by a 2-week washout period of ad-libitum salt-intake. Thereafter, participants who initially used a low salt diet will now be placed on a high salt diet and vice versa, for another week. At the end of this week, 24h urine collection and 24h blood pressure measurements will be iterated, for verification of compliance to the diet and salt-sensitivity of blood pressure.
Subsequently, all procedures performed during the first study day will be

repeated, to establish the effect of variation in sodium intake on microvascular function and insulin sensitivity.
Participants will obtain no specific health benefits. The periods of low and high sodium intake demand a strict compliance, but since the diet is adapted to the individual caloric intake of the participants, and due to the relative short-time interventions and the intervening wash-out period of ad-libitum salt intake, the burden for the participants is somewhat reduced. Nevertheless, the amount of time invested is considerable and a large amount of measurements will be performed (determination of microvascular function, laboratory investigations, 24h blood pressure measurements).This 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 individual risk profile for the development of type 2 diabetes and cardiovascular disease. All subjects will receive a compensation of ¤ 250,- after completion of the study.

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

Obese individuals
- Age 18-65 years
- Caucasian (because of ethnic differences in microvascular function and in the prevalence of cardiovascular disease and associated risk factors)
- Waist circumference > 102 cm (men)/> 88 cm (women) ;Lean individuals
- Age 18-65 years
- Caucasian (because of ethnic differences in microvascular function and in the prevalence of cardiovascular disease and associated risk factors)
- Waist circumference < 94 cm (men)/< 80 cm (women)

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 glucose metabolism (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
- Stage 3 hypertension (blood pressure > 180/110 mm Hg) in order not to expose these persons to unnecessary risks
- Unstable or severe pulmonary disease
- Unstable or severe thyroid disorders
- Inflammatory diseases
- Smoking (due to impairment of microvascular function)
- Alcohol use > 2 U/day (women)/> 3 U/day (men)
- Use of glucose-lowering medications, because of interference with microvascular function
- Use of corticosteroids (might cause hypertension and interfere with electrolyte homeostasis and glucose metabolism) and regular use (weekly or several times a week) of NSAIDs (might cause disturbance of microvascular function and electrolyte excretion)
- eGFR < 60 mL/min
- Impairment of hepatic function
- Pregnancy or lactation

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2014
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	21-05-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2014
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	NCT02068781
CCMO	NL47438.068.14