The effect of pyridoxamine supplementation on vascular function and insulin sensitivity; a double-blind randomized placebo controlled trial in abdominally obese subjects.

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The objective is to study the possible effects of AGE/ALE reduction on vascular function as primary endpoint, insulin sensitivity, and adipokine levels in abdominally obese subjects. We will investigate the following parameters:1) Micro- and...

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

Summary

ID

NL-OMON50192

Source
ToetsingOnline

Brief title
Pyridoxamine supplementation, vascular function and insulin sensitivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Insulin resistance, obesity

Research involving

Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: TIFN;CTMM

Intervention

Keyword: Clinical trial, Insulin sensitivity, Pyridoxamine, Vascular function

Outcome measures

Primary outcome

Measurements at baseline and during the follow-up study day (after the intervention) will be compared to analyse the effect between the study groups. The main study parameters are the evaluation of vascular (dys)function, insulin sensitivity, and adipokine levels. These parameters will be investigated by a series of predominant micro- and macrovascular measurements, a hyperinsulinemic euglycemic clamp, an OGTT, AGE skin readings and blood plasma analysis for several inflammation, endothelial, and adipokine markers, as well as AGE levels.
Microvascular tests include skin capillary videomicroscopy, skin flowmotion and heating-response (LDF), sublingual imaging of the endothelial glycocalyx, and contrast-enhanced ultrasound of the skeletal muscle microcirculation. All microcirculation measurements will be performed before and during the hyperinsulinemic euglycemic clamp to study insulin-induced microvascular function. Macrovascular tests include carotid distensibility, pulse wave analysis, pulse wave velocity, brachial artery flow mediated dilatation (FMD).

Primary parameters:

1) Micro- and macrovascular function by means of skeletal muscle

contrast-enhanced ultrasound (CEUS) measurements and flow mediated dilation

(FMD)

2) Whole body insulin sensitivity using a hyperinsulinemic, euglycemic clamp

Secondary outcome

1) Micro- and macrovascular function by means of skin capillary

videomicroscopy, skin laser doppler flowmetry (LDF), and arterial stiffness

(pulse wave velocity and local stiffness).

2) Glucose metabolism and B-cell function using an OGTT

3) AGE measurements in blood plasma and skin (skin autofluorescence (SAF)).

4) Adipokine, endothelial function marker, and inflammation marker measurements

in plasma.

Study description

Background summary

A growing body of evidence demonstrates that increased adipose mass, especially visceral adipose tissue, contributes directly towards an increase in systemic inflammation, vascular dysfunction and the burden of CVD, insulin resistance and type 2 diabetes. The induced expression and secretion of adipokines most likely plays a causal role in this process.
Advanced glycation/lipoxidation endproducts (AGEs/ALEs) are a heterogeneous family of unavoidable by-products, which are formed by reactive metabolic intermediates derived from glucose and lipid oxidation. In addition to the overwhelming amount of data demonstrating the role of AGEs/ALEs in the development of vascular disease, AGEs/ALEs are also implicated in the development of insulin resistance. We recently investigated the accumulation of AGEs/ALEs in the expanding adipose tissue and found that the activation of the AGE-RAGE axis contributes to the dysregulation of adipokines and insulin resistance. In animal models we recently demonstrated that pyridoxamine, a

natural vitamin B6 vitamer and inhibitor of AGE/ALE generation, attenuates dysregulation of adipokines, vascular dysfunction, and the development of insulin resistance . We hypothesize that accumulation of AGEs and ALEs could influence obesity-associated vascular dysfunction, insulin resistance, and an impaired adipokine profile, and want to investigate the physiological influence of a dietary intervention with pyridoxamine.

*** Addendum: Substudy of the Pyridoxamine trial ***
Objective: The objective is to study the compliance and metabolisation of pyridoxamine in plasma and urine with UPLC-MS/MS. To measure the uptake and bioavailability in plasma following 3 x daily intake of pyridoxamine (protocol 1). To measure the plasma/urine metabolites and pharmacokinetics (protocol 2). Participants will be recruited locally via posters and our website/facebook page. We can also contact previously-screened individuals who where too healthy to participate before.
Study design: We will conduct a small study with the dietary supplement pyridoxamine dihydrochloride. Five subjects will undergo the following protocols.
1) Intake of 3 times 66.66 mg pyridoxamine separated over 3 standardized meals during the day (i.e. identical as the pyridoxamine trial; 66.66 mg/capsule). In total 20 plasma samples of 4 mL will be collected over 24 hours and a 24h urine collection will be performed.
2) Intake of 200 mg of pyridoxamine at once in the morning (this is for the calculation of the pharmacokinetics, to show the metabolisation with a single admission dosage). In total 20 samples of 4 mL will be collected over 24 hours and a 24h urine collection will be performed.
3) As control for dietary effects or possible Vitamin B6 content, 2 subjects will eat the same as abovementioned protocols (1 & 2) but without pyridoxamine supplementation.
Protocol 1 and 2 will be performed during one single day; the day will be completely standardised with regard to food intake and physical activity. All participants will receive the exact same meals and drinks, at the same time points. A financial compensation of 75 euros will be offered for each visit (two or three visits in total).
Study population: The study population will consist of five healthy subjects older than 18, with no disease or medication use. Volunteers (men and women) will be locally recruited and telephonically screened for possible exclusion criteria (medication use & current diseases).
Intervention: All 5 subjects will take the same pyridoxamine supplement and during the day blood will be collected. With a single venous cannula, a maximum collection of 100mL (80mL specifically) of blood will be collected during one day. We also collect 24h urine samples.
To reduce variation, this protocol will be performed twice by the same subjects (protocol 1 and 2). Two volunteers will run through protocol 3 as a control for dietary intake. *

Study objective

The objective is to study the possible effects of AGE/ALE reduction on vascular function as primary endpoint, insulin sensitivity, and adipokine levels in abdominally obese subjects. We will investigate the following parameters:
1) Micro- and macrovascular function by means of skeletal muscle contrast-enhanced ultrasound (CEUS) measurements, skin capillary videomicroscopy, skin laser doppler flowmetry (LDF), flow mediated dilation (FMD), and arterial stiffness (pulse wave velocity and local stiffness).
2) Whole body insulin sensitivity using a hyperinsulinemic, euglycemic clamp and glucose metabolism using an OGTT
3) AGE measurements in blood plasma and skin (skin autofluorescence (SAF)).
4) Adipokine, endothelial function marker, and inflammation marker measurements in plasma.

Study design

We will conduct a short-term (8 weeks), double blind, randomized, placebo-controlled trial with the dietary supplement pyridoxamine dihydrochloride, a metabolic variant of pyridoxal phosphate and a member of the vitamin B6 group. The study has a parallel design and includes three study groups of each 40 participants, bringing the number of participants at a total of 120. The groups consist of a placebo treatment, a 25 mg/day pyridoxamine dosage, and a 200 mg/day pyridoxamine dosage. After baseline measurements all subjects will be randomized in one of these three groups.

Intervention

All subjects will undergo an intervention consisting of three capsules per day, during 8 continuous weeks. One group will receive a placebo treatment, another a dosage of 25 mg pyridoxamine per day, and the last will receive a dosage of 200 mg pyridoxamine per day.

Study burden and risks

Participants will visit the study center for a screening visit and two main study days, one before and one after the intervention, for measurements of vascular function and a hyperinsulinemic euglycemic clamp test. Additionally, a 24h urine collection and 24h blood pressure measurement will be returned in a short visit, which we aim to combine with an OGTT (during which a food frequency questionnaire (FFQ) will be filled out).
At the study days, measurements of vascular function will be performed in a fasted state, before and during a hyperinsulinemic euglycemic clamp test for determination of insulin sensitivity. Participants will be requested to abstain from alcohol 24 hours prior to the measurements and not to perform strenuous exercise 48 hours before the study days.

The total amount of blood drawn during a study day is approximately 180 ml (9 ml during the screening visit). This amount does not carry any risk, however subjects are not allowed to donate blood 8 weeks prior to investigation.
Micro- and macrovascular measurements carry virtually no risk. The contrast agent administered during the contrast-enhanced ultrasound of the skeletal muscle has proven to be a safe imaging modality in previous investigations and post-marketing studies. An infrequent side effect of the hyperinsulinemic, euglycemic clamp test is hypoglycemia.
The two main study days will occupy ~7 hours. The screening visit only takes 1 hour. Although the number of measurements performed during a study day is considerable, the burden for the participants is limited since these measurements are all performed in the supine position and are merely non-invasive, with the exception of contrast-enhanced ultrasound.
Pyridoxamine: In multiple Phase 1 and 2 clinical studies with pyridoxamine, adverse event rates were similar to those seen in subjects receiving placebo. The only adverse events that showed an increase over placebo were observed in the highest dose of 600 mg daily, these were small increases in diarrhea and constipation and this mild increase was not noticeable in the 300mg group. No studies have yet described any directly related side affects of pyridoxamine supplementation, while in many studies higher dosages than the ones supplemented in this study (up to 200 mg daily) were used. Furthermore, the participating subjects in our study are abdominally obese individuals without emerged cardiac, pulmonary, or metabolic disease. Placebo treatment holds no risks.
Patients from the control group (placebo) will not have any direct health benefit from participation. As for the other groups, the potential benefit is directly related to the beneficiary effects of pyridoxamine. Pyridoxamine is a natural form of vitamin B6 and it is proven that this molecule is able to effectively inhibit the formation of AGEs and ALEs.

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

- Abdominal obesity: Waist circumference for men should be above 102 cm, for women above 88 cm.
- Caucasian (because of skin fluorescence and capillary microscopy measurements)
- Aged 18-75 years

Exclusion criteria

- Diabetes mellitus (i.e. using anti-diabetic medication, fasting glucose >7.0 mmol/L, HbA1c >6.5%).
- Active or history of cardiovascular disease (e.g. 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)
- Hyperlipidemia (defined as serum total cholesterol > 8 mmol/L or TG > 4 mmol/L)
- Smoking will be allowed. Smokers will be excluded only if they smoke >10 cigarettes per day.
- High alcohol usage (>4 U/day) or drug abuse
- Use of medication known to influence glucose metabolism or vascular function (e.g. glucocorticosteroids, NSAID's)
- Exclusion of higher grade hypertension (> 179 mmHg SBP and/or > 109 mmHg DBP) in order not to expose subjects to unnecessary risks. Medication is allowed.
- Known allergic reaction to ultrasound contrast-agent
- Pulmonary or inflammatory disease
- Kidney failure or electrolyte disorders
- Use of dietary supplements or an investigational product within the previous month

- Unstable body weight (no drastic changes in life style before or during the intervention are allowed, this means no weight gain or loss >3 kg in the last two months)
- Pregnancy or lactation
- No change in use of oral anticonceptiva or IUD (12 weeks prior of during the intervention)
- Unwillingness to give up being a blood donor (or having donated blood) from 8 weeks prior to the start of the study and during the study
- Insufficient knowledge of the Dutch language

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:	Recruiting
Start date (anticipated):	31-10-2016
Enrollment:	172
Type:	Actual

Ethics review

Approved WMO

Date:	13-07-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	28-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-07-2020
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
CCMO	NL51023.068.16