Restriction of dietary AGEs to prevent diabetes in overweight individuals: a randomized controlled trial

Published: 31-01-2018
Last updated: 15-05-2024

The objective of this project is to study the effects of low levels of dietary AGEs in overweight subjects on insulin sensitivity, *-cell function, micro- and macrovascular function, and gut microbiota. The obtained insights can be used to attenuate...

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

Summary

ID

NL-OMON48992

Source
ToetsingOnline

Brief title
de-AGE-ing study

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: NWO

Intervention

Keyword: Advanced Glycation End-products, Clinical trial, Insulin sensitivity, Vascular function

Outcome measures

Primary outcome

The primary objective of this study is to investigate the effect of dietary AGE restriction on whole-body insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp.

Secondary outcome

Additionally, we aim to investigate the effects of restriction of dietary AGEs on cardio-metabolic health, biomarkers of AGEs, inflammation, and the gut microbiota. We will investigate the following parameters:

- Micro- and macrovascular function by means of skeletal muscle contrast-enhanced ultrasound (CEUS) measurements, skin capillary videomicroscopy, skin laser Doppler flowmetry, arterial flow mediated dilation (FMD), and arterial stiffness (pulse wave velocity and local stiffness).
- AGE measurements in blood plasma and skin. The latter by means of skin autofluorescence (SAF).
- Glucose metabolism and *-cell function during two consecutive 30-min hyperglycaemic steps.
- Markers of endothelial function, inflammation, and adipokine markers in blood plasma
- Gut microbiota using 16s rRNA sequencing

Study description

Background summary

Current efforts to arrest the epidemic of type 2 diabetes mellitus (T2DM) have had limited success. Thus there is an urgent need for effective approaches to prevent the development of T2DM. It is widely accepted that the current epidemic is driven by an increase in global food abundance and reduced food quality, making changes in diet a key determinant of the T2DM epidemic. Dietary factors can affect cardio-metabolic health; among these factors, advanced glycation end-products (AGEs) in food are potential risk factors for insulin resistance and T2DM.

AGEs are a heterogeneous group of unavoidable stable bioactive compounds. Endogenous formation of AGEs is a continuous naturally occurring process, and is the result of normal metabolism. However, increased formation of AGEs occurs during ageing and under hyperglycaemic conditions. AGEs are implicated in the development of diabetes and vascular complications.

Over the past several decades, methods of food processing have changed and meals now contain excess fat and sugar and are most susceptible for the formation of AGEs. In addition, AGEs in food are highly desirable due to their profound effect on shelf life, sterility, flavour, colour, and thus food consumption. Hence, a substantial portion of AGEs are derived from exogenous sources, particularly food. These exogenous AGEs are potential risk factors for insulin resistance and the development of T2DM. We recently found that dietary AGEs represent a significant source of circulating AGEs, and have similar pathogenic properties compared to their endogenous counterparts including the development of insulin resistance and T2DM. Taken together, dietary AGEs are proposed to play a pivotal role in the development and progression of T2DM and its complications. Reduction of dietary intake of AGEs may therefore be an alternative strategy to reduce the risk of vascular disease and insulin resistance. We therefore hypothesize that dietary restriction of AGEs in overweight individuals improves insulin sensitivity, *-cell function, and vascular function.

Study objective

The objective of this project is to study the effects of low levels of dietary AGEs in overweight subjects on insulin sensitivity, *-cell function, micro- and macrovascular function, and gut microbiota. The obtained insights can be used to attenuate the development of diabetes, and to improve metabolic health in

populations at risk.

Study design

We will conduct a double-blind randomized controlled trial in overweight subjects in two parallel groups in which the enrolled subjects will follow a standard diet with either a low AGEcontent or a high AGE content, to determine whether low dietary AGEs can improve insulin sensitivity, *-cell function, and vascular function. We will use state-of-the-art UPLC-MS/MS to measure AGEs and our recently developed dietary AGE database. We will prescribe diets which differ greatly in AGE content, but which are carefully matched for energy and macronutrients. Before and after the intervention period of 4 weeks, all subjects will undergo a hyperinsulinemic-euglycemic clamp to determine insulin sensitivity. In addition, we will combine these outcomes with macro- and microvascular function, beta-cel function, gut microbial composition, and biomarkers of AGEs, endothelial dysfunction and of low-grade inflammation,

Intervention

All subjects will undergo an intervention consisting of a prescribed diet during 4 continuous weeks. Subjects will follow either a low AGE-diet or a habitual Dutch diet. Both diets will be similar in energy and macronutrients, and differ greatly in the amount of AGEs (approximately 75% difference)

Study burden and risks

The number of measurements in this study is quite substantial. Nonetheless, we expect that the burden for the subjects is limited since all measurements are performed in a supine, relaxed, and comfortable position and are merely non-invasive. In addition to the measurements, participants undergo a partial restricted lifestyle by following a dietary intervention for four weeks. This could exert some unexpected low levels of strain on the subjects (e.g. stress, unhappiness). However participants will receive detailed information and are informed about the procedures of this study. Therefore, we do not expect substantial discomfort or harm for the participants. Participants will experience no harm from following the standard diet, because it is a habitual Dutch diet. Therefore, participants will experience no additional exposure to dietary AGEs. Additionally, potential benefits of participating in this study are directly related to the possible beneficiary effects of AGE restriction.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

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 * 102 cm, and for women * 88 cm.
- Caucasian
- Aged 18 years and older
- BMI * 25 kg/m2

Exclusion criteria

- Diabetes (i.e. using anti-diabetic medication, fasting glucose >7.0 mmol/L, HbAc1 > 6.5%).
- Active of 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).
- Hyperlipidaemia (defined as serum total cholesterol > 8 mmol/L or TG > 4 mmol/L).
- Lipid lowering medication (e.g. statins).
- Use of medication known to influence glucose metabolism, vascular function, and/or lipid metabolism (e.g. statins, glucocorticosteroids, NSAID*s).

- Inability to stop anti-hypertensive medication for 8 weeks. Exclusion of higher grade hypertension (> 179 mmHG SBP and/or > 109 mmHg DBP) in order not to expose subjects to unnecessary risks).
- Pulmonary or inflammatory disease
- Kidney failure or electrolyte disorder
- Pregnancy or lactation
- No change in use of oral anticonceptives or IUD (12 weeks before the intervention).
- Unstable body weight (weight gain or loss > 3 kg in the last 2 months).
- Known allergic reaction to ultrasound contrast-agent
- Smoking (active or cessation <1 year prior to screening date).
- High alcohol usage (>4 U/day) or drug abuse
- Use of dietary supplements or an investigation product within the previous month
- Significant food allergies/intolerance
- Vegetarianism
- Subjects who intend to donate blood during the intervention or subjects who have donated blood less than three months before the start of the intervention.
- Participation in another biomedical trial during the past 30 days.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2018
Enrollment:	137
Type:	Actual

Ethics review

Approved WMO Date:	31-01-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-11-2018
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

ID: 20660
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL63215.068.17
OMON	NL-OMON20660