The effect of pyridoxamine supplementation on microvascular function in type 2 diabetes: a double-blind randomized placebo-controlled cross-over trial

Published: 07-03-2024
Last updated: 30-01-2025

Primary objective: to study whether pyridoxamine supplementation in type 2 diabetes improves microvascular function in the eye, kidney and skin, and reduces markers of endothelial dysfunction and glycation.Secondary objective: to study whether...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON56635

Source
ToetsingOnline

Brief title
PYRAMID trial

Condition

- Diabetic complications
- Vascular injuries

Synonym
Type 2 diabetes, vascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Diabetes Fonds

Intervention

Keyword: Advanced glycation end products, Microvascular function, Pyridoxamine, Type 2 diabetes

Outcome measures

Primary outcome

The primary study parameter is the central retinal arteriolar diameter (CRAE)

as measured with retinal funduscopy.

Secondary outcome

Sensitivity analyses of the primary study parameter are:

• Microvascular function measured in the eyes with retinal funduscopy, adaptive

optics funduscopy, optical coherence tomography angiography (OCT-A) and dynamic

vascular analysis

• Microvascular function measured in the skin with laser Doppler flowmetry.

• Microvascular function measured as plasma markers of endothelial dysfunction

and glycation.

• Microvascular function measured in kidneys by urine albumin and estimated

glomerular filtration rate.

Other study parameters

• age,

• sex,

• alcohol use,

• lipid profile,

• immunological profile,

• baseline fasting glucose,

• HbA1c,

• glucose metabolism and β-cell function,

• AGE measurements in skin and blood plasma,

• concentration of MGO,

• glyoxal and 3-deoxyglucose in blood plasma,

• adipokine and inflammatory marker levels in blood plasma,

• markers of dicarbonyl stress and oxidative stress in urine,

• hepatic fat content,

• blood pressure,

• heart rate/ECG,

• anthropometric measurements,

• medical history,

• medication use, and

• potential (serious) adverse effects.

• For monitoring the compliance, the vitamers pyridoxamine, pyridoxal, pyridoxine, and their phosphorylated derivatives will be measured in plasma by UPLC-MS/MS.

Study description

Background summary

People with diabetes have an increased risk of malfunctioning of the small blood vessels, e.g. in the eye and kidney, which can lead to blindness and kidney failure. These are serious complications, but to date there are no options to improve specifically the function of the small blood vessels.
But why do diabetics have such an increased risk of dysfunction of the small blood vessels? We have shown that a high glucose concentration in the blood plays an important role in the dysfunction of, particularly, the small blood vessels. A possible explanation for this dysfunction is an increased production of methylglyoxal, which arises from the breakdown of glucose. Methylglyoxal is a small but highly reactive molecule that can damage various organs and tissues. In several studies, we found that methylglyoxal is increased in type 1 and type 2 diabetes and that methylglyoxal is associated with dysfunction of the smaller blood vessels. In our previous research in small laboratory animals, we have shown that methylglyoxal directly causes damage of the small blood vessels. Because of these potentially harmful effects of methylglyoxal, we have tried to reduce methylglyoxal. In small laboratory animals, we have found that the vitamin B6 isoform pyridoxamine inhibits the formation and accumulation of methylglyoxal, and improves vascular function. In a clinical trial in overweight people, we found that supplementation of pyridoxamine is safe and that methylglyoxal levels can be reduced, and we found indications of an improvement in vascular function.

Study objective

Primary objective: to study whether pyridoxamine supplementation in type 2 diabetes improves microvascular function in the eye, kidney and skin, and reduces markers of endothelial dysfunction and glycation.

Secondary objective: to study whether pyridoxamine supplementation in type 2 diabetes improves glucose metabolism and beta cel function, methylglyoxal, glyoxal and 3-deoxyglucose concentrations in blood plasma, advanced glycation endproduct (AGE) concentrations in blood plasma and skin, adipokines and inflammation markers in plasma, liver fat, blood pressure and heart rate/ECG, and anthropometric measurements.

Study design

The study will be conducted in a randomized, double blind, placebo-controlled manner. This intervention study includes two intervention periods of 8 weeks in a crossover design with a washout period of 4 weeks.

Intervention

Pyridoxamine, a vitamin B6 vitamer (Supersmart, Luxembourg). Placebo, capsule identical to pyridoxamine but without the active substance (i.e. pyridoxamine) (Supersmart, Luxembourg).

The daily dosage (300 mg) pyridoxamine or placebo will be supplied as three capsules of 100mg each per day, and are taken shortly before or during the meal.

Study burden and risks

Benefit: the potential benefit of participating in this study is directly related to the (possible) beneficiary effects of pyridoxamine. Pyridoxamine is able to effectively inhibit the formation of advanced glycation endproducts (AGEs). Regarding the negative effects of AGE accumulation in the body, e.g. vascular damage, this counteractive effect of pyridoxamine on its own could be considered beneficial. Considering the significant burden of diabetes-related vascular damage and the lack of effective treatment options, it is of importance to investigate new potential medications to tackle these morbidities.

The intervention, pyridoxamine, has been used in clinical trials before. With a dose of 300mg pyridoxamine daily, the adverse event rate did not differ from placebo intervention.

Although the number of tests performed on visiting days (4) is considerable, the burden associated with participation in this research is thought to be acceptable, because of the merely non-invasive character of the tests. Solely getting IV access is invasive and carries a small risk of hematoma, infection or collapse. This procedure is performed by experienced staff. The use of mydriatic eye drops holds a small risk (<0.1%) of adverse events. This risk is further minimized by obtaining information on medical history and by measuring intraocular pressure. This protocol is extensively applied in The Maastricht Study.

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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 years,
- Diagnosis of type 2 diabetes,
- Generalized microvascular dysfunction, i.e.
o eGFR 30-60 mL/min/1.73m2, and/or
o Microalbuminuria albumin/creatinine ratio 3-30 mg/mmol, and/or
o Retinopathy (not proliferative), and/or
o Neuropathy (any).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Uncontrolled diabetes (i.e., hypoglycaemia >2 times/week and/or unstable HbA1c >9%),
- Intraocular pressure >=30 mmHg,
- History of glaucoma,
- Diagnosis of proliferative diabetic retinopathy,
- Diagnosis of diabetic macula edema,
- Albumine-creatinine ratio >30 mg/mmol,
- eGFR <30 mL/min/1.73m2,
- Diagnosis of epilepsy,
- Active cardiovascular disease (e.g. stroke, coronary artery disease, congestive heart failure, cardiac shunts, history of cardiac surgery, pulmonary hypertension, cardiac arrhythmias, family history of ventricular arrhythmias or sudden cardiac death),
- Alcohol usage >4 U/day,
- Drugs abuse,

- Use of systemic glucocorticosteroids,
- Higher grade hypertension (> 179 mmHg SBP and/or > 109 mmHg DBP),
- Diagnosis of inflammatory disease,
- Use of an investigational product within the previous month,
- Unstable body weight (no drastic changes in lifestyle before or during the intervention are allowed, this means no weight gain or loss >3 kg in the last two months),
- Pregnancy or lactation,
- Change in use of oral contraceptives 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 to end of study,
- Insufficient knowledge of the Dutch language,
- Inability to provide written informed consent.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-05-2024
Enrollment:	40
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	07-03-2024
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-01-2025
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	NL85203.068.23