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The effect of a magnesium supplement on arterial calcification and arterial stiffness in individuals with type 2 diabetes

Submission date
04/05/2022

Recruitment status
No longer recruiting

Registration date
28/07/2023

Overall study status
Completed

Last Edited
31/03/2026

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
People with type 2 diabetes have an increased risk of heart disease. Vascular calcification is common in people with type 2 diabetes and is associated with a higher risk of heart disease. However, people with type 2 diabetes have calcium builds up on the medial layer of the artery. This form of vascular calcification causes stiffening of the blood vessel wall. This stiffening of the arteries is undesirable because it increases the risk of cardiovascular disease. For example, stiffening of the arteries can cause the heart muscle to stiffen, which can lead to heart failure. The stiffening of the arteries must therefore be controlled and preferably even be reduced. This may be possible by taking three magnesium capsules per day. The aim of this study is to find out whether taking magnesium daily in a supplement can reduce vascular calcification and stiffness in people with type 2 diabetes. The knowledge gained from this research may contribute to improved treatment of vascular calcification and stiffness in people with type 2 diabetes.

Who can participate?
Patients who have participated in the SMART-ARTEMIS study or the Early-HFpEF study (both Dutch cohort studies), aged 50-80 years, with type 2 diabetes and medial arterial calcification

What does the study involve?
The study involves a total of four visits over a period of 6 months. Overall, the visits will take about 1.5 hours. Oral magnesium citrate supplements or placebo supplements have to be taken daily for 6 months. At screening and at the first follow-up after 3 months, participants will undergo a blood sampling for plasma magnesium concentrations and measurement of arterial stiffness. At baseline and at the second follow-up after 6 months, participants will undergo blood sampling for magnesium as well as cardiovascular biomarkers, will hand in a 24-hour urine collection and will undergo measurements of arterial stiffness. Dietary intake of magnesium will be assessed by a short food frequency questionnaire at the start of the study and the second follow-up after 6 months.

What are the possible benefits and risks of participating?
Oral magnesium citrate supplements have a good safety profile and previous studies reported a

low rate of side events (mainly gastrointestinal such as diarrhea, nausea, and vomiting) that usually only occur when used in very large doses. Blood sampling may cause discomfort and may result in bruising that continues up to a few days after the examinations. Determination of arterial stiffness is a non-invasive procedure method and no discomfort is expected. Participants gain no individual benefit from their participation in the study. However, the study is expected to increase the understanding of arterial stiffness and arterial calcification as a mechanism for increased heart disease risk in type 2 diabetes, and may ultimately lead to a new treatment.

Where is the study run from?
Diabetes Research Centre (Netherlands)

When is the study starting and how long is it expected to run for?
November 2021 to October 2024

Who is funding the study?
Netherlands CardioVascular Research Committee (CVON) (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Magnesium supplementation as a strategy to reduce serum calcification propensity and vascular stiffness in people with type 2 diabetes: a double-blind, randomized, placebo-controlled parallel trial

Acronym
Mg-MAC

Study objectives
Oral magnesium supplementation could improve calcification propensity and reduce vascular stiffness in people with type 2 diabetes, thereby representing a novel preventive strategy that may reduce their risk of cardiovascular disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 15/05/2023, Amsterdam UMC Medical Research Ethics Committee (Amsterdam UMC MREC) (Van der Boechorststraat 7, Amsterdam, 1081BT, Netherlands; +31 (0)20-4445585; metc@amsterdamumc.nl), ref: 2022.0524 - Mg-MAC
2. Approved 15/05/2023, Medical Ethics Committee of Amsterdam UMC, location VUmc (postal address: not available due to working from home due to the COVID-19 pandemic; +31 (0)20-44 45585; metc@vumc.nl), ref: 2022.0524 - NL81281.029.22

Study design
Single-center interventional double-blind randomized placebo-controlled parallel trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Vascular stiffness in people with type 2 diabetes

Interventions
The goal is to investigate the effect of daily intake of 350 mg of magnesium citrate oral supplementation over a period of 6 months on serum calciprotein particle maturation time (T50), a measure of calcification propensity, and on vascular stiffness, in people with type 2 diabetes (T2D). The trial will be performed in a double-blind fashion (blinding for participants, investigators and outcome assessors) with two equal groups of 37 participants. To ensure the double-blind design, optically similar capsules will be packed and coded by the laboratory, which will provide the study medication (magnesium supplements and placebo). The randomization will be performed by a statistician not involved in the study by using a randomization list. Blocked randomization (blocks of 4) will be used to ensure good balance of participant characteristics in each group. Randomization will be stratified on sex, two strata of age and on two strata of the carotid-femoral pulse wave velocity (c-f PWV) to prevent misbalance of age and baseline c-f PWV values at randomization. Allocation will be determined by using a computerized random number generation process. All study products will be sequentially numbered.

Intervention Type
Supplement

Primary outcome(s)
1. Serum T50 measured using nephelometry at 3 and 6 months after baseline
2. Carotid-femoral pulse wave velocity (c-f PWV) measured using applanation tonometry at 3 and 6 months after baseline

Key secondary outcome(s))
1. Total magnesium measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 3 and 6 months after baseline
2 Sodium measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
3. Potassium measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
4. Calcium measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
5. Phosphate measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
6. Urea measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
7. Total protein measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
8. Creatinine measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
9. Triglycerides measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
10. Total cholesterol measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
11. LDL-cholesterol measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
12. HDL-cholesterol measured in heparin vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
13. Fasting plasma glucose measured in NaF vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline
14. HbA1C measured in EDTA vials using standard laboratory tests at the Dijklander Hospital Laboratorium at 6 months after baseline

Completion date
11/10/2024

Eligibility

Key inclusion criteria
1. Age 50-80 years
2. T2D
3. Presence of a predominantly MAC pattern on the CT scan
4. c-f PWV >12 m/s
5. Ability to provide informed consent prior to initiating screening visit procedures

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 years

Upper age limit
80 years

Sex
All

Total final enrolment
74

Key exclusion criteria
1. Myasthenia gravis
2. Use of medications that might interact with magnesium supplements (levothyroxine, osteoporosis medications tiludronate and alendronate, warfarin)
3. Advanced diabetes complications:
3.1. Proliferative retinopathy
3.2. Disabling polyneuropathy
3.3. Nephropathy with an estimated glomerular filtration rate (eGFR), calculated with the Jaffé method according to the Chronic Kidney Disease Epidemiology Collaboration equation <15 ml /min/1.73 m² or chronic dialysis
3.4. cardiac complications
4. Uncontrolled hyperthyroidism or active parathyroid disease
5. Chronic diarrheal disease or inflammatory bowel diseases
6. Congestive heart failure, bradycardia with a resting heart rate below 60 mmHg and systolic blood pressure less than 90 mmHg
7. Atrial fibrillation
8. Previous aortic surgery
9. Severe hepatic insufficiency
10. Malignancy or other non-cardiac conditions limiting life expectancy to <3 years
11. Using food supplements that contain magnesium, or unwilling to stop 2 weeks before randomization
12. Mental or legal incapacitation to provide informed consent
13. Plasma magnesium concentration <1.5 mg/dl or >2.6mg/dl at screening

Date of first enrolment
06/09/2023

Date of final enrolment
11/04/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
Diabetes Research Centre Hoorn
Maelsonstraat 7
Hoorn
Netherlands
1624 NP

Sponsor information

Organisation
Amsterdam UMC Location VUmc

ROR
https://ror.org/00q6h8f30

Funder(s)

Funder type
Research organisation

Funder Name
Netherlands CardioVascular Research Committee (CVON)

Results and Publications

Individual participant data (IPD) sharing plan
The data will be stored at the Diabetes Research Centre in Hoorn and at the Department of Epidemiology & Data Science of the Amsterdam UMC. First, all desired analyses will be carried out by the involved researchers. Once these analyses are finished and the articles are published, the research group is open to collaborations and the data may be shared in a confidential and anonymized matter.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		26/03/2026	31/03/2026	Yes	No