Systemic Albumin Leakage as proxy for Vascular inflAmmaTion and cardiovascular disease in diabEtes patients; the SALVATE study

Published: 30-08-2024
Last updated: 27-12-2024

Main objective:To investigate the association between systemic vascular- and urinary albumin leakage in patients with diabetes.Secondary objectives:-To investigate whether systemic vascular- and/or urinary albumin leakage is associated with systemic...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON56987

Source
ToetsingOnline

Brief title
The SALVATE study

Condition

- Renal disorders (excl nephropathies)
- Vascular disorders NEC

Synonym
Cardiovascular disease, diabetes mellitus type 2

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Projectgeld

Intervention

Keyword: Albuminuria, Cardiovascular disease, Systemic albumin leakage, Vascular inflammation

Outcome measures

Primary outcome

1. The 99mTC-HSA clearance and urine albumin-creatinine ratio (uACR) as proxy for systemic vascular albumin leakage and albuminuria:

This will be calculated via the transcapillary escape rate of 99mTC-HSA (TERalb). TERalb will be measured by the fractional disappearance rate of 99mTC-HSA from the total intravascular compartment in 1 hour after intravenous injection. Albuminuria will be defined as the amount of albumin found in the urine and will be calculated via the uACR.

Secondary outcome

2. Arterial [18F]-FDG uptake as proxy for arterial inflammation.

Arterial inflammation will be quantified as the FDG uptake maximal standardized uptake value (SUVmax). SUVmax will be corrected for the prescan glucose level. A target-to-background ratio (TBR) will be calculated by dividing the SUVmax of the arteries by the SUVmean of the caval veins (bloodpool). TBRs will be calculated for four individual segments (carotid arteries, ascending aorta and aortic arch, descending and abdominal aorta, and iliac and femoral arteries) and averaged for the total aortic tree (meanTBR).

3. Measuring the endothelial glycocalyx as proxy for systemic vascular damage.
The perfused boundary region (PBR), a marker of the glycocalyx barrier function, will be measured non-invasively in sublingual microvessels with a diameter of 5-25*µm using a Sidestream Dark Field camera (GlycoCheck BV, Maastricht, The Netherlands). Increased PBR indicates reduced glycocalyx thickness.

4. The amount of heparanase, heperan sulfate (HS) and metalloproteinase (MMP) 2 and 9 as proxy for endothelial glycocalyx damage:
The amount of heparanase will be measured via the human heparanase ELISA kit. Plasma will be used and the amount will be noted as pg/ml. HS will be measured via the human HS ELISA kit and the amount of HS will be noted as pg/ml. The amount of MMP 2 and 9 will be tested via a urinary activity assay and will be noted as mg/mmol creatinine. HS, MMP 2 and 9 will be measured by a single urinary morning void.

5. Brachial arterial blood pressure, central arterial blood pressure and carotid to femoral pulse wave velocity (PWV) will be measured as proxy for arterial stiffness. The PWV will be calculated by dividing travelled distance by transit time (PWV = distance [meters]/transit time [seconds]).

6. Nailfold capillaroscopy will be performed as a method to examine a patient*s microcirculation and assess pathological changes. Nailfold capillary images

will be collected with the Dino-lite CapillaryScope 200 PRO (MEDL4N Pro), maximum magnification 200x, measurement software Dinocapture 2.0. Stills of the capillariscopic appearance of the index fingers of both hands will be studied. Additionally, during a capillaroscopic assessment, the practitioner assesses a number of different morphological and functional changes in the capillaries. These include capillary visibility, morphology, diameter, length, distribution, density, microhaemorrhages and blood flow.

Study description

Background summary

Type 2 diabetes mellitus (T2DM) is associated with a strong increase in cardiovascular risk, which is a consequence of accelerated vascular ageing. This process is hallmarked by systemic low-grade vascular- inflammation, remodeling, calcification, and increased vascular stiffness.
However, although the association between T2DM and systemic vascular inflammation has been well established, the underlying pathophysiological mechanism is not completely understood.

Albuminuria is the first clinical indication of diabetic nephropathy and is associated with an increased risk of kidney failure and CVD, as well as low-grade inflammation. The endothelial glycocalyx, a gell-like structure covering the endothelium in all vascular beds, is the first barrier against albumin leakage. Impairment of the glycocalyx in the kidney has been shown to be associated with increased albuminuria. As a systemic factor in all vascular beds, this might be a proxy for systemic vascular albumin leakage. Furthermore, increased glomerular leakage of albumin has been demonstrated to lead to enhanced tubular exposure of albumin which elicits a pro-inflammatory milieu, causes tubulo-interstitial damage, and impairs kidney function. Measuring systemic vascular albumin leakage could therefore be a potential marker of early disease and could be causally associated with systemic vascular inflammation in chronic diseases linked to widespread vascular involvement.

This study will deliver new insights into the role of albumin leakage as a pathophysiological link between T2DM and systemic vascular inflammation. Ultimately, we hope to introduce urinary- and systemic albumin leakage as novel potential targets for early diagnosis, monitoring, and possibly more

personalized treatment of CVD.

Study objective

Main objective:
To investigate the association between systemic vascular- and urinary albumin leakage in patients with diabetes.

Secondary objectives:
-To investigate whether systemic vascular- and/or urinary albumin leakage is associated with systemic vascular inflammation.
-To investigate whether systemic vascular- and/or urinary albumin leakage is associated with damage to the endothelial glycocalyx.

Study design

Single center, cross-sectional and observational study.

Study burden and risks

Attempts will be made to have patients visit our center for assessment of all study parameters in two days. Participation in the proposed study is accompanied with only minor risks. The blood samples will be drawn by means of venepuncture. Very rarely some bleeding from the skin biopsy occurs and has to be stitched or a small hematoma occurs after injection with the [18F]-FDG PET tracer or the 99mTC-HSA.
The usage of positron emitting isotopes in the [18F]-FDG- PET/CT scan to measure the systemic inflammation translates to an exposure to ionizing radiation. Because of the potential hazards of radiation exposure, guidelines for the exposure of volunteers are laid down in *Besluit stralingsbescherming, artikel 60, staatblad 2001, 397* in accordance with the guidelines of the International Commission on Radiological Protection (ICRP). The effective dose of [18F]FDG is 0.019 mSv/MBq1 for the standard adult male. With an activity of 2 MBq/kg and a standard weight of 73.7 kg this gives a dose of a single FDG-PET scan of 2.8 mSv. In addition, a low-dose CT-scan is made for attenuation correction, giving an additional dose of 1 mSv. Therefor the total radiation dose for the FDG scans becomes: EFDG+LDCT = 2.8 + 1 = 3.8 mSv.
The injection with 350 MBq of [99mTc]HSA is associated with a radiation dose of 0.0062 mSv/MBq giving a total effective dose of: EHSA = 2.7 mSv.
The total radiation dose for this study thus becomes: Esalvate = 3.8 + 2.7 = 6.5 mSv. According to ICRP62 the total dose to the volunteers is in category 2b. Potential abnormalities found with these investigations will be communicated with the patient and their treating physician. The radiation dose is calculated by our local clinical physicist dr. A. Willemsen.

Benefits: Although participants have no direct benefit, this research may lead

to the reveal of cardiovascular diseases at an early stage as well as an extensive evaluation of their disease state, potentially allowing earlier treatment and a better outcome. Also, coincidental findings will be reported, and may be beneficial to the patients to allow a quick treatment. However, we are aware of lead time bias. Early identification of (cardiovascular) diseases may not always be a benefit when treatment options are not available (anymore).

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

- Men and women, age >= 18 years.
- Written informed consent.
- eGFR above 60 ml/min/1,73m2.
- Using renin-angiotensin system (RAS) inhibitors.

• Fulfils ADA criteria for diabetes.
o Fasting plasma glucose >= 7.0 mmol/l.
o Random plasma glucose >= 11.1 mmol/l.
o HbA1C >= 6,5%.

Exclusion criteria

• Patients who are mentally incompetent and cannot sign a Patient Informed Consent or are unwilling to sign a Patient Informed Consent.
• Women who are currently pregnant, planning to become pregnant, breastfeeding women, or women with childbearing potential not using appropriate contraceptive measures. This will be discussed during the intake conversation and women who answer yes on any of the previous questions will be excluded.
• Other causes for macroalbuminuria than nephropathy.
• Systemic auto-immune disease or vasculitis.
• Inflammation of unknown origin or sepsis.
• Patients who use immunosuppressives or anti-inflammatory drugs that could interfere with the study results.
• Recent (< 3 months) acute disease such as cardiovascular event or infection for which admission to hospital was necessary.
• Recent (< 3 months) surgical procedure, excluding procures under local anaesthetics.
• Active malignancy, excluding skin malignancies: basal cell carcinoma and squamous cell carcinoma,
• Patients who have claustrophobia.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2024

Enrollment:	30
Type:	Anticipated

Medical products/devices used

Generic name:	99mTC labeled human serum albumin
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	30-08-2024
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL83989.042.24