CALCification as an early marker of vasculopathy and organ involvement in Systemic Sclerosis

Published: 09-07-2018
Last updated: 16-11-2024

1. To assess serum calcification propensity (T50) in SSc patients compared with healthy age and gender-matched controls; 2. To assess serum T50 in SSc patients with overt calcinosis cutis as compared to age and gender-matched SSc patients without; 3...

Ethical review	Approved WMO
Status	Completed
Health condition type	Connective tissue disorders (excl congenital)
Study type	Observational invasive

Summary

ID

NL-OMON48902

Source
ToetsingOnline

Brief title
CALC-SSc study

Condition

- Connective tissue disorders (excl congenital)

Synonym
Scleroderma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Calcification, Systemic Sclerosis

Outcome measures

Primary outcome

1. Degree of serum T50;

Secondary outcome

2. Degree of other serum markers of the calcification process: calcium; phosphorus; parathormone; fetuin-A; FGF23; *Klotho;

3. Degree of blood markers involved in inflammation, calcification and endothelial dysfunction: plasma AGEs (CML, pentosidine and MG-H1); HMGB1; carbonyl markers; skin AF as marker of dermal AGE accumulation (biomarkers of the AGE-RAGE axis); ET-1; C-reactive protein, erythrocyte sedimentation rate (ESR), IL-6, whole blood IFN- I signature (biomarkers of endothelial activation and inflammation); VEGF, IL-8, angiogenic T cells, TIE2 positive monocytes (biomarkers of angiogenesis);

4. Degree of vascularopathy measured by: capillary microscopy; arterial stiffness measured by PWV; digital artery involvement assessed with ultrasound;

5. Degree of cardiac involvement by cardiac ultrasound, pulmonary involvement by conventional lung function (FVC, DLCO), and subsequent HRCT upon indication, renal involvement by kidney function (24-hours creatinine clearance, proteinuria, and glomerular erythrocyturia) and gastro-intestinal involvement by conventional oesophageal motility scan;

6. Degree of markers involved in the calcification process as well as biomarkers of progression to SSc in skin biopsies: degree of fibrosis (TGF*,

collagen); *Klotho; FGF23; myxovirus resistance gene A (MxA) which is a marker

for IFN*, TLR 4 and TLR 8;

7. Degree of fibroblasts sensitivity to calcification and proinflammatory

mechanisms by: CML-modified-bovine serum albumin (BSA); HMGB1, RAGE, and TGF*.

Other study parameters (part of substudies)

1. Degree of active large arterial vessel calcifications and in skin,

intestines, kidneys and lungs;

2. Degree of stable large vessel calcifications.

Study description

Background summary

Systemic sclerosis (SSc) is a rare progressive autoimmune disease hallmarked by severe vasculopathy, leading to skin and internal organ complications and premature mortality, for which treatment options are limited. Vasospastic attacks of the digital arteries known as Raynaud*s phenomenon (RP) are usually the first presenting symptom. Insidiously, more skin and organ involvement evolves, which is irreversible due to the underlying fibrotic processes. Therefore, it is of importance to study pathways and select potential biomarkers that precede complications, which can be easily identified and modified early in the course of the disease.
Patients with SSc are prone to enhanced calcification of skin (calcinosis cutis) and the vasculature. Active calcifications may not only occur in the skin of patients with clinically overt calcinosis cutis, but also in SSc patients without overt calcinosis. Since calcification is strongly associated with local inflammation, it may very well occur in internal organs and serve as an early proxy for long-term SSc-related complications.

Study objective

1. To assess serum calcification propensity (T50) in SSc patients compared with healthy age and gender-matched controls;
2. To assess serum T50 in SSc patients with overt calcinosis cutis as compared to age and gender-matched SSc patients without;

3. To assess other serum markers of the calcification process in SSc patients compared with healthy age and gender-matched controls as compared to age and gender-matched SSc patients without;
4. To assess serum T50 and other serum markers of the calcification process compared with established markers of the underlying disease process;
5. To assess serum T50 compared with non-invasive markers of micro- and macrovasculopathy in patients with SSc;
6. To assess serum T50 compared with SSc-related skin and internal organ complications;
7. To study associations with expression of markers involved in the calcification process in skin biopsies by immunohistochemistry;
8. To assess whether AGEs/HMGB1-RAGE interactions lead to increased IFN-1 signature and profibrotic and osteogenic differentiation of fibroblasts isolated from skin biopsies;

Substudy:
9. To assess the feasibility of imaging the active calcification process using 18F-NaF PET/CT scans in patients with SSc.

Study design

Cross-sectional case control study.

Study burden and risks

Attempts will be made to have patients visit our center only once for assessment of all study parameters. Blood drawing will be combined with routine clinical practice assessments to minimize venapuncture burden. Patients will be exposed to two 3 mm punch skin biopsies (after local anesthesia) from affected, perilesional skin and two 3 mm punch skin biopsies from unaffected skin. We want to let the location of the biopsy depend on the presence of sclerotic abnormalities or calcinisos cutis by clinical assessment. The biopsy will heal as a small, approximately 1-2 mm diameter, scar. A very low risk that the small wound could continue to bleed exists and has to be stitched. However, this procedure has been extensively performed in patients with SSc with a similar healing quality as compared to subjects without SSc.
The CT scan represents a low dose, non-contrast enhanced, CT scan (LDCT). The effective dose equivalent of 18F-NaF is 0.024 mSv/MBq, which corresponds to a radiation burden of 4.2 mSv for an injection of 175 MBq in an average patient weighing 70kg, and in total of 5.7 mSv including the attenuation correction for low dose CT (1.5 mSv), which amounts the radiation dose of one intercontinental flight. The 18F-NaF tracer is injected intravenously by infusion, very rarely an hematoma occurs. Potential abnormalities found with these investigations will be communicated with the patient and their treating physician.
Benefits: these investigations may reveal other diseases such as malignancies at an early stage as well as an extensive evaluation of their disease state,

potentially allowing earlier treatment and a better outcome.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

SSc patients:;In order to be eligible to participate in this study as an SSc patient, a subject must meet all of the following criteria:;* 18 years and older;* Formal diagnosis of Systemic Sclerosis, as determined by a total of *9 from adding the maximum weight (score) in each of the following categories (2013 ACR/EULAR criteria):;o Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion) (9 points);o Skin thickening of the fingers (only count the higher score) ;* Puffy fingers (2 points);* Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints) (4 points);o Fingertip lesions (only count the higher score) ;* Digital tip ulcers (2 points);* Fingertip pitting scars (3 points);o Telangiectasia (2 points);o

Abnormal nailfold capillaries (2 points);o Pulmonary involvement (maximum score is 2);* Pulmonary arterial hypertension (2 points) ;* Interstitial lung disease (2 points);o Raynaud*s phenomenon (3 points);o SSc-related autoantibodies (maximum score is 3);* Anticentromere (3 points);* anti*topoisomerase I [anti*Scl-70] (3 points);* anti*RNA polymerase III (3 points);* Written informed consent;Controls:;In order to be eligible to participate in this study as a patient with primary Raynaud*s phenomenon, a subject must meet all of the following criteria:;* 18 years and older;* Negatieve antinuclear antibodies (ANA) ;* Normal nailfold capillairies ;* No underlying disease;* Written informed consent;Healthy controls:;In order to be eligible to participate in this study as a healthy control, a subject must meet all of the following criteria:;* 18 years and older;* No apparent underlying chronic disease;* No signs and symptoms suggesting Raynaud phenomenon or other vascular disease;* Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;* Women who are currently pregnant, planning to become pregnant, breastfeeding women, or women with child bearing potential not using appropriate contraceptive measures;* Patients who are mentally incompetent and cannot sign a Patient Informed Consent or are unwilling to sign a Patient Informed Consent;* Vascular event in the preceding 3 months;* Chemotherapy in the preceding 3 months;* Inflammation of unknown origin, sepsis, or vasculitis;The next criteria will also be used for the substudy concerning 18F-NaF PET/CT:;* Current active bone malignancy or in the previous 6 months ;* Disorders affecting bone metabolism, e.g. hyperparathyroidism, Paget*s disease ;* Patients who have claustrophobia

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	09-01-2019
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Natrium Fluoride
Generic name:	NaF

Ethics review

Approved WMO Date:	09-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-12-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	28-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2022
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
EudraCT	EUCTR2018-001719-65-NL
CCMO	NL65651.042.18