BMJ Open

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-095283
Article Type:	Protocol
Date Submitted by the Author:	18-Oct-2024
Complete List of Authors:	Greveling, Mark; UMC Utrecht, Department of Rheumatology and Clinical Immunology Ong, Voon H.; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Denton, Christopher; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Foppen, W.; UMC Utrecht, Department of Radiology and Nuclear Medicine Herman, Amin; St Antonius Hospital, Department of Rheumatology Jeffries-Owen, Nick; SRUK Kortekaas, Marion; Leids Universitair Medisch Centrum, Department of Rheumatology; Flevoziekenhuis, Rheumatology Masselink, Ilse; UMC Utrecht, Department of revalidation Mulder, Douwe J.; UMCG, Department of Internal Medicine, Division of Vascular Medicine Schriemer, Rita; NVLE, Dutch Patient Organization for Systemic Autoimmune Diseases Vonk, Madelon; Radboudumc, Department of Rheumatology de Vries-Bouwstra, Jeska; Leids Universitair Medisch Centrum, Department of Rheumatology Welsing, Paco; UMC Utrecht, Department of Rheumatology and Clinical Immunology Mastbergen, Simon; UMC Utrecht, Department of Rheumatology and Clinical Immunology Spierings, Julia; UMC Utrecht, Department of Rheumatology and Clinical Immunology
Keywords:	RHEUMATOLOGY, Ultrasound < RADIOLOGY & IMAGING, Observational Study

Administrative information

Title

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study

Authors

Mark J. Greveling*, Voon H. Ong, Christopher P. Denton, Wouter Foppen, Amin Herman, Nick Jeffries-Owen, Marion Kortekaas, Ilse Masselink, Douwe J. Mulder, Rita Schriemer, Madelon C. Vonk, Jeska K. de Vries-Bouwstra, Paco Welsing, Simon Mastbergen, Julia Spierings

*corresponding author. m.j.greveling@umcutrecht.nl, Heidelberglaan 100, 3584CX Utrecht, the Netherlands

Trial registration

Data category	Information
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT06133244
Date of Registration in Primary Registry	15-11-2023
Secondary Identifying Numbers	NL85445.041.23
Source(s) of Monetary or Material Support	UMC Utrecht, ReumaNederland
Primary Sponsor	UMC Utrecht
Secondary Sponsor(s)	N/A
Contact for Public Queries	handsome@umcutrecht.nl +3188 7555 5555
Contact for Scientific Queries	handsome@umcutrecht.nl +3188 7555 5555
Public Title	Getting a grip on hand function impairment in systemic sclerosis
Scientific Title	Hand Function Impairment in Systemic Sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME) Study
Countries of Recruitment	The Netherlands United Kingdom

Health Condition(s) or Problem(s) Studied	Systemic sclerosis
Intervention(s)	Diagnostic Tests: Imaging, blood samples, functional tests, and physical examination
Key Inclusion and Exclusion Criteria	Study Population Patients (18 years and older) with: 1. SSc with hand contractures 2. SSc patients without contractures and disease duration of < 4 years 3. VEDOSS patients Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion Criteria: Age > 18 years Exclusion Criteria: Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion
Study Type	Observational
Date of First Enrollment	19-04-2024
Sample Size	300
Recruitment Status	Recruiting
Primary Outcome(s)	Determination of risk factors for hand function impairment in systemic sclerosis (SSc) patients with early disease, very early disease, and established hand impairment (contractures) at 2 years follow-up
Key Secondary Outcomes	Identify underlying mechanisms

	Validation of the Dutch PASTUL questionnaire
Ethics Review	Approved on 19-03-2024
Completion date (estimated)	04-2028
Summary Results	N/A
IPD sharing statement	Undecided

Protocol version
V1.3 6-06-2024

Abstract

Introduction The majority of all systemic sclerosis (SSc) patients experience hand function impairment. The exact cause for this impairment is yet unknown. As impaired hand function hugely impacts daily functioning and quality of life, there is a high unmet need for effective treatments. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to increase insights into the factors contributing to hand function impairment. The objective of this study is to identify risk factors and underlying mechanisms leading to hand function impairment in SSc.

Methods and analysis This is a longitudinal observational multicentre study in patients with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) and SSc under care of the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboudumc, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Medical history, clinical status, nailfold capillaroscopy, skin assessments, serum biomarker analysis, ultrasound, elastography and MRI will be performed and results related to hand function measurements.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee NedMec (MREC NedMec) in the Netherlands and by HRA and Health and Care Research Wales (HCRW) in the UK. Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Trial registration number NCT06133244

Keywords

Systemic sclerosis, hand function, imaging, biomarkers, observational

Word count:

3035

Strengths and limitations of this study

- This is the first study that extensively assesses the hand function in systemic sclerosis patients
- This is a large prospective international multidisciplinary study with a follow-up of 2 years in 300 patients
- This is the first study that explores elastography of tendons in the hand
- The results of this study can guide future clinical trials and development of treatment for hand function impairment in systemic sclerosis
- Conclusions can be limited due to the lack of prior research for comparison and the heterogeneity of the disease

Introduction

Background and rationale

Systemic sclerosis (SSc) is a rare disease characterized by inflammation, fibrosis, and vasculopathy [1]. Clinical presentation is heterogeneous and includes skin thickening and internal organ involvement. Thus far, studies in SSc mainly focused on organ damage and mortality. However, other disease manifestations have a tremendous impact on quality of life and daily functioning.

Around 90% of SSc patients experience hand function limitation, which leads to impaired daily functioning and work participation [2,3]. An important cause of impaired hand function is contractures of the hand, which are reported in half of the patients [4]. Contractures are reported more frequently in patients with diffuse cutaneous systemic sclerosis (dcSSc) and associated with anti-topoisomerase I (ATA) positivity [5]. Only a few studies explored imaging techniques in SSc hands. Thickening of the A1 pulley and flexor tendons was associated with hand disability in a small group of patients (n=29). Soft tissue calcifications were seen in affected tendons, but this has not been studied in more detail [6,7]. In other small studies, ultrasound and MRI showed subclinical synovitis or tendinitis and bone erosions, which could also contribute to impaired hand function [7,8]. Shear wave elastography (SWE), a new imaging modality to assess the elastic properties and stiffness of soft tissue, has been studied in SSc skin and muscles but no studies have assessed hand tendons. Moreover, no studies explored tenosynovial changes and underlying biological mechanisms, especially in correlation with imaging or functional tests. This leaves clinicians 'in the dark' regarding diagnostic work-up and effective management. Current management for hand symptoms includes exercises, splints, and sometimes immunosuppressive therapies. However, it is unknown which treatment is suitable for which patient and the efficacy of immunosuppressive drugs has not been confirmed in trials. As impaired hand function in SSc hugely daily functioning and with that quality of life, there is a high unmet need for effective treatments [9]. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to study this problem in more detail to guide optimal treatment development.

This study aims to enhance the understanding of the mechanisms underlying hand function impairment in patients with systemic sclerosis (SSc), including development from the early phase in very early disease of systemic sclerosis (VEDOSS). The study is based on three key hypotheses: 1) Hand function in SSc is affected through various pathways involving joints, tendons, skin, and/or microcirculation. 2) Prior to the development of contractures, tissue changes—such as inflammation, fibrosis, or decreased elasticity—can be detected using imaging techniques. 3) Patients with hand impairment can be categorized into distinct subgroups based on clinical and imaging features, as well as protein markers, which may reflect different activated biological pathways.

Objectives

Primary objective

To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.

Secondary objectives

To determine risk factors and categorize patients with hand function impairment into subgroups based on clinical, immunological, and/or imaging characteristics, thereby guiding future research toward personalized treatment strategies

To assess the impact of hand function impairment on quality of life, daily functioning, work, and participation, and explore how these impacts relate to the identified mechanisms and patient subgroups

Methods

Patient and public involvement statement

Members of the Dutch (NVLE) and UK (SRUK) systemic sclerosis patient organizations are involved in every step of this project. They have been involved in the study design and during the development of the protocol, a qualitative study was performed to explore patients' functional complaints and (unmet) needs. The study protocol has been co-produced to ensure representation and input from those with personal experiences. All questionnaires have been checked on content and feasibility. During all meetings with the entire research team, patients will be involved to share their opinions on decisions being made and provide advice on recruitment and dissemination of results.

Study setting

This is a longitudinal observational international study in patients with VEDOSS and SSc who are under care at the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG) Leiden UMC (LUMC), Radboud UMC, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years.

Study population

Patients (n=300; 18 years and older) with:

1) SSc with hand contractures (n=50)
2) SSc patients without hand contractures (n=200) and disease duration of < 4 years
3) VEDOSS patients (n=50)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Age >18 years
2) For patient populations 1) and 2):

a. Diagnosis of SSc according to the 2013 EULAR-ACR classification criteria for SSc [10]
For patient population 3):

b. Diagnosis of VEDOSS, defined as the presence of RP, puffy fingers, SSc-specific autoantibodies, and abnormal nailfold capillaroscopy, while not fulfilling the 2013 EULAR-ACR classification criteria for SSc [11].

3) Only for patient population 1):

a. Hand contractures are defined as a range of motion < 75% of the normal range of at least one small hand joint of [12].

4) Willing and be able to understand the study information and sign the informed consent form.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

1) Age < 18 years
2) Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion

Study procedures

Three patient groups are included and then followed for 24 months. Table 1 shows the study procedures and data collection in these three groups.

Table 1: Overview of study procedures

	Baseline	6 months	12 months	24 months
Informed consent	x			
Medical history	x			
Nailfold capillaroscopy	x			x
Clinical status	x	x	x	x
Skin assessment	x	x	x	x
PROMs	x	x	x	x
Serum and plasma collection	x	x	x	x
Hand function assessment	x	x	x	x
Ultrasound	x	x	x	x
Elastography *	x	x	x	x
MRI *	x			
Vascular imaging **	x	x	x	x

*Sub-analysis comparing MRI with ultrasound features. UMC Utrecht only

** Sub-analysis assessing hand circulation extensively with ultrasound using a 70mHz probe. UMC Groningen only

Medical history

Clinical data collected in routine care will be retrieved at baseline. Age, sex, height, educational level, ethnicity, and auto-antibody status (ANA negative/positive, line blot and scleroderma blot auto-antibodies) are collected.

In addition, data will be collected on previous tobacco use, vasoactive and immunosuppressive medication use and dosage, digital ulcers, pitting scars, gangrene, clinical arthritis, myositis, interstitial lung disease, pulmonary hypertension, and scleroderma renal crisis.

Nailfold capillaroscopy

A capillaroscope with a magnification of 200x is used to assess all fingers, including the thumbs. At least two adjacent fields of a linear millimetre in the middle of each finger are captured and stored. Images will be scored according to EULAR criteria centrally on normal or abnormal/scleroderma patterns [13].

Clinical status

- weight, blood pressure, (change) in tobacco use, (change in) occupation, (changes in) immunosuppressive and/or vasoactive medication use and dosage,
- new onset interstitial lung disease (y/n), pulmonary hypertension (y/n), scleroderma renal crisis (y/n)
- Hb (mmol/L), ESR (mm/h), CRP (mg/L), CK (IU/L).

Skin assessment

The modified Rodnan skin score (mRSS) (assessed by trained investigators), presence of digital ulcers (if yes: count, location), pitting scars (if yes: count, location), gangrene (if yes: location), calcinosis cutis in the hands (if yes: location), clinical arthritis ((if yes: site and joint count), and myositis will be assessed/recorded [14].

PROMs

Patient Related Outcome Measurements will be collected in the week of the study visit and the following questionnaires will be collected:

- Cochin Hand Function Scale (CHFS), containing 18 questions, structured in 5 distinct categories, designed to evaluate hand function in kitchen activities, dressing, personal hygiene, office, and other generic activities [15].
- brief Satisfaction with Appearance Scale (SWAP), containing six questions about subjective body image dissatisfaction and the perceived social impact [16].
- IMTA Productivity Cost Questionnaire (IPCQ), a standardized instrument for measuring and valuing health-related productivity losses [17].
- Utrecht Scale for Evaluation of Rehabilitation (- Participation) (USER-P), which measures both subjective and objective participation in the community [18].
- Health-related quality of life (EQ5D5L), that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression [19].
- Self-assessment of skin thickening (PASTUL), a self-reported measure of skin thickness in the upper limb [20].
- Scleroderma Health Assessment Questionnaire (SHAQ), which measures disease status changes [21].

Serum and plasma collection

Two blood samples will be collected (both a maximum of 10 ml) to obtain both serum and plasma samples during each visit. The venepuncture is performed at routine outpatient or daycare unit visits. Aliquots of both serum and plasma samples will be stored at -80 C degrees. Serum and plasma analysis will include measurement of levels of immunological markers (including cytokines) and fibrotic markers.

Hand function assessment

At all study visits, hand function will be assessed by trained investigators. Hand mobility is assessed with the range of motion of the wrist joint, range of motion of the finger joints, delta Finger-to-Palm distance [22], and the mHAMIS [23]. Grip strength is measured with the

JAMAR® dynamometer and JAMAR pinch dynamometer® for the two-point pinch, three-point pinch, and lateral pinch.

Ultrasound

Ultrasound will be performed by an operator/physician trained in musculoskeletal ultrasound. An ultrasound machine with a high-frequency probe (linear or hockey stick with 8-24MHz) will be used. Images of all study sites will be stored and rated centrally by the coordinating researcher in conjunction with ultrasound experts afterwards. The presence of arthritis of the wrist, distal radio-ulnar joint (DRUJ), metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints will be assessed using validated semiquantitative methods in B-mode and power Doppler setting if there was grey-scale evidence of inflammation. Furthermore, the presence of osteophytes is assessed. The first to fifth flexor and extensor tendons of both hands will be assessed longitudinally. Tenosynovitis and sclerotic thickening of tendon(-sheaths) and calcifications within tendons will be evaluated. The pulley and tendons are measured at the at the MCP joint. The fingers of the dominant hand will be assessed with ultrasound for vascular involvement. Dig 2 will be assessed standardly. In addition, fingers with ulceration if present on other fingers will be assessed. Additionally, intima media thickness (IMT) will be measured in dig 2. All arteries per finger will be assessed at the proximal phalangeal part. Qualitative scoring is performed. See Appendix 1, imaging protocol, for the full ultrasound protocol.

Elastography

In addition to the ultrasound assessment, fibrosis of the first to fifth flexor and extensor tendons of both hands will be measured quantitatively using shear wave elastography (SWE) in a subgroup of patients at the UMC Utrecht (n=100). SWE is measured with the ultrasound machine GE healthcare LOGIQ E10s using the linear ML4-20 transducer.

Vascular imaging

Another addition to the ultrasound assessment is the extensive vascular evaluation performed in patients in the UMC Groningen (n=35). The vascular protocol entails ultrasound measurements of IMT performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) which uses an ultra-high frequency ultrasound transducer (max 70 MHz). Finger pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

MRI

In a subgroup of patients included at the UMC Utrecht (n=50), a contrast-enhanced 3 Tesla MRI of the dominant hand will be done at baseline, recording the presence of synovitis, joint capsule thickening of the wrist, MCP and PIPs, and thickness or inflammation of tendons and tendon sheaths of the hands. The researcher will determine whether there are no contra-indications according to the MRI screening form used in the UMC Utrecht. The entire MRI protocol is shown in Appendix 1, imaging protocol.

Outcomes

Main study parameter/endpoints

The correlation between the Cochin Hand Function Scale (CHFS) scores and circulating biomarkers, as well as changes observed through imaging, over a two-year follow-up period will be assessed.

Secondary study parameters/endpoints

- The change in hand function at 2 years, reflected by the Cochin Hand Function Scale (CHFS) and hand function measures.
- Predictive value of imaging features and circulating biomarkers at baseline for change of hand impairment at follow-up.
- Distinct subgroups of patients based on clinical, immunological, and imaging characteristics.
- Health-related quality of life (EQ5D-5L), daily functioning (S-HAQ), work (IPCQ), and participation (USER-P) in relation to CHFS.

Sample size

For multivariable regression analysis with a continuous outcome, we need at least 10 patients per variable studied according to rule of thumb. As we anticipate including 300 patients we will be able to validly study 30 variables for their association with the (progressive) hand impairment (including patient subgroup as a covariate in the analysis) with sufficient power. We will also perform more explorative subgroup analyses per patient population as well as use data reduction techniques (e.g. principal component analysis) and/or analysis techniques more suitable for analysing outcomes with many independent variables compared to the number of patients (like partial-least squares regression or Lasso regression). Furthermore, we will explore clusters of patients developing hand function impairment using imaging and protein biomarkers to inform our multivariable analyses. Missing data will be accounted for using multiple imputation. With the above calculation and strategy, we think our cohort of 300 patients will be sufficient to obtain meaningful results.

Recruitment and consent

Subjects will be informed about the study by their treating physician and receive an information letter. Thereafter, they will have the possibility to ask questions, either during a face-to-face appointment or over the phone with the investigator or research nurses. They will be allowed sufficient time, but at least 24 hours, to consider their participation. If the subject wants to participate, a meeting will be set for signing the consent form and explaining the study procedure. This will take place at a day/time suitable for the patients, ideally combined with routine care appointments.

Data management

Data handling is described in detail in the data management plan. This has been approved by the data manager of the UMC Utrecht.

Data from patients will be handled with care, taking into consideration the required confidentiality as stated by the Dutch 'AVG ('Law for the Protection of Personal Information'), the 'Wet Gemeenschappelijke Behandelings Overeenkomst' ('Law Common Treatment Agreement'), and the privacy policy of the UMC Utrecht. The electronic patient files will be used as the source for the clinical data. Data will be pseudonymized and the key will be stored in a separate secured folder at each clinical site.

Patient material will be encoded and stored at the UMC Utrecht, department of Rheumatology & Clinical Immunology. Patient material is only used to answer the questions in this study, material is not stored for biobank purposes. Only the local investigators are permitted access to the code key. Research documents, from which patient identity can be deduced will only be accessible for third parties (for example monitors, auditors, and inspection by competent authorities) after specific consent by the participant in the informed consent document. Research documents will be kept up to 15 years after ending the research.

In all local centers, images and patient material will be stored according to local protocol and collected and analysed centrally.

Monitoring and Quality Assurance

A central independent monitor will perform yearly monitoring according to the Monitoring Plan.

Statistical methods

To predict decline in hand function (defined as an increase CHFS) at 6, 12, and 24 months we will use linear/logistic regression analysis, with as independent variables/predictors baseline patient characteristics, as well as short term (over 6 months) changes in clinical scores, imaging markers and biomarkers. When needed we will use (regression) techniques suitable for a high variable to patient/outcome ratio (see section Statistics/Power calculation)

Characteristics at baseline and changes over time seen on ultrasound will be reported for the number of patients with tenosynovitis, arthritis and/or calcifications in tendons, the mean thickness and elastography of tendons, and the A1 pulley. Linear mixed models will be used to analyse changes over time (both with time defined as follow-up time or as time since early disease/VEDOSS) regarding hand function scores and to relate these changes to changes in ultrasound and serum/plasma biomarkers.

Also joint modelling of the multivariate longitudinal data (i.e. the clinical scores, imaging- and biomarkers measured over time) and time-to-event (i.e. development of limitations of hand function) will be performed. In this analysis so called 'latent trajectories' in the longitudinal markers (i.e. not directly observed subgroups of patients with a distinct course in longitudinally measured 'markers') will be related to the development of the outcome (in this case limitations in hand function). Results can be used to obtain more insight into the development of limitations in hand function, and the possible existence of subgroups regarding the development of hand function limitations. Models may also be used to 'dynamically' predict the outcome over time. The patient subgroups (VEDOSS/SSc with/without hand impairment) will be taken appropriately into account in all analyses and/or subgroup analyses will be performed.

To further explore subgroups in patients with/without hand function limitations. Baseline clinical, imaging-, and biomarkers as well as changes over time in markers will be used in a

cluster analysis. As most likely different types of variables (i.e. linear, binary, and categorical) will be included we will use an algorithm suitable for this like k-medoid cluster analysis using partitioning around medoids. The validity of different solutions regarding the number of clusters will be evaluated using statistical criteria (e.g. silhouette width, calculated based on Gower distances) as well as clinical relevance by expert opinion (also considering the results of the above analyses) to derive a final solution. Possible confounders will be assessed and corrected for.

Ethics and dissemination

The Medical Research Ethics Committee NedMec (MREC NedMec) reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements, the MREC NedMec issued an approval for the Netherlands. HRA and Health and Care Research Wales (HCRW) has approved the study in the UK. The study will be conducted according to the principles of the Declaration of Helsinki (2013). Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Funding

This project is funded by the Dutch Arthritis foundation (ReumaNederland, project number: 22-1-403).

Competing interests

None

Author statement

Primary research team (University Medical Centre Utrecht, The Netherlands), responsible for study design, data collection, data management, data analysis, data interpretation, report writing, and decision to submit.

Dr. J. Spierings, PI

Dr. S.C. Mastbergen, co-PI

Drs. M.J. Greveling, coordinating researcher

Participating research team sponsor (University Medical Centre Utrecht, The Netherlands), advising on study design, collaborating on data collection, data management, data analysis, and data interpretation.

Dr. P. Welsing, methodologist

Dr. A. Marijnissen, study coordinator

Dr. W. Foppen, radiologist

R. Boot, research nurse

S. Mast, specialist nurse

I. Masselink, occupational therapist

A. Conception, lab analist

Dr. M.P. Jansen, MRI-expert

External participating research team, advising on study design, collaborating on data collection, data management, data analysis, and data interpretation.

Dr. D.J. Mulder, internist, Groningen University Medical Centre, The Netherlands

Dr. J.K. De Vries-Bouwstra, rheumatologist, Leiden University Medical Centre, The Netherlands

Dr. M.C. Vonk, rheumatologist, Radboud University Medical Centre, The Netherlands

Dr. A. Herman, rheumatologist, St. Antonius hospital Nieuwegein, The Netherlands

Dr. M. C. Kortekaas, rheumatologist and MSUS expert, Leiden University Medical Centre, The Netherlands

Prof. C.P. Denton, rheumatologist, Royal Free Hospital – University College London, United Kingdom

Dr. V.H. Ong, rheumatologist, Royal Free Hospital – University College London, United Kingdom

Prof. D. Abraham, Royal Free Hospital – University College London, United Kingdom

Drs. S. Rodolfi, clinical research fellow, Royal Free Hospital – University College London, United Kingdom

External advisors, advising on study design, data collection and data analysis

Drs. M.R. Schriemer, Dutch systemic sclerosis patient organisation (NVLE)

D. Dittmar, Dutch systemic sclerosis patient organisation (NVLE)

E. Blamont, UK systemic sclerosis patient organisation (SRUK)

N. Jeffries-Owen, UK systemic sclerosis patient organisation (SRUK)

K. Fligelstone, Royal Free Hospital patient partner

This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

References

1 Adigun R, Goyal A, Hariz A. Systemic Sclerosis. *StatPearls*. Published Online First: 8 May 2022.

2 Kwakkenbos L, Sanchez TA, Turner KA, *et al.* The association of sociodemographic and disease variables with hand function: A Scleroderma Patient-centered Intervention Network cohort study. *Clin Exp Rheumatol*. 2018;36:S88–94.

3 Bérezné A, Seror R, Morell-Dubois S, *et al.* Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. *Arthritis Care Res (Hoboken)*. 2011;63:277–85. doi: 10.1002/ACR.20342

4 Avouac J, Walker U, Tyndall A, *et al.* Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. *J Rheumatol*. 2010;37:1488–501. doi: 10.3899/JRHEUM.091165

5 Buni M, Joseph J, Pedroza C, *et al.* Predictors of Hand Contracture in Early Systemic Sclerosis and the Effect on Function: A Prospective Study of the GENISOS Cohort. *J Rheumatol*. 2019;46:1597–604. doi: 10.3899/JRHEUM.180093

6 Tagliafico A, Panico N, Serafini G, *et al.* The thickness of the A1 pulleys reflects the disability of hand mobility in scleroderma. A pilot study using high-frequency ultrasound. *Eur J Radiol*. 2011;77:254–7. doi: 10.1016/J.EJRAD.2010.05.013

7 Hughes M, Bruni C, Cuomo G, *et al.* The role of ultrasound in systemic sclerosis: On the cutting edge to foster clinical and research advancement. *J Scleroderma Relat Disord*. 2021;6:123–32. doi: 10.1177/2397198320970394

8 Schanz S, Henes J, Ulmer A, *et al.* Magnetic resonance imaging findings in patients with systemic scleroderma and musculoskeletal symptoms. *Eur Radiol*. 2013;23:212–21. doi: 10.1007/S00330-012-2584-1

9 Van Leeuwen NM, Ciaffi J, Liem SIE, *et al.* Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants. *Rheumatology (Oxford)*. 2021;60:3646–55. doi: 10.1093/RHEUMATOLOGY/KEAA827

10 Van Den Hoogen F, Khanna D, Fransen J, *et al.* 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72:1747–55. doi: 10.1136/ANNRHEUMDIS-2013-204424

11 Bellando-Randone S, Del Galdo F, Lepri G, *et al.* Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). *Lancet Rheumatol*. 2021;3:e834–43. doi: 10.1016/S2665-9913(21)00244-7

12 Bálint Z, Farkas H, Farkas N, *et al.* A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis. *Clin Exp Rheumatol*. 2014;32.

13 Smith V, Herrick AL, Ingegnoli F, *et al.* Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev*. 2020;19:102458. doi: 10.1016/J.AUTREV.2020.102458

14 Khanna D, Furst DE, Clements PJ, *et al.* Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord*. 2017;2:11. doi: 10.5301/JSRD.5000231

15 Duruöz MT, Poiraudeau S, Fermanian J, *et al.* Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. *J Rheumatol*. 1996;23:1167–72.

16 Jewett LR, Hudson M, Haythornthwaite JA, *et al.* Development and validation of the brief-satisfaction with appearance scale for systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2010;62:1779–86. doi: 10.1002/ACR.20307

17 Bouwmans C, Krol M, Severens H, *et al.* The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value in Health*. 2015;18:753–8. doi: 10.1016/J.JVAL.2015.05.009

18 Post MWM, Van Der Zee CH, Hennink J, *et al.* Validity of the Utrecht Scale for Evaluation of Rehabilitation-Participation. *Disabil Rehabil*. 2012;34:478–85. doi: 10.3109/09638288.2011.608148

19 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 2011;20:1727–36. doi: 10.1007/S11136-011-9903-X/TABLES/5

20 Spierings J, Ong V, Denton CP. PASTUL questionnaire: a tool for self-assessment of scleroderma skin during the COVID-19 pandemic. *Ann Rheum Dis*. 2021;80:819–20. doi: 10.1136/ANNRHEUMDIS-2020-219775

21 Steen VD, Medsger TA. The value of the health assessment questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum*. 1997;40:1984–91. doi: 10.1002/ART.1780401110

22 Torok KS, Baker NA, Lucas M, *et al.* Reliability and validity of the delta finger-to-palm (FTP), a new measure of finger range of motion in systemic sclerosis. *Clin Exp Rheumatol*. 2010;28:S28.

23 Sandqvist G, Nilsson JÅ, Wuttge DM, *et al.* Development of a modified hand mobility in scleroderma (HAMIS) test and its potential as an outcome measure in systemic sclerosis. *J Rheumatol*. 2014;41:2186–92. doi: 10.3899/JRHEUM.140286

Appendix 1
Imaging protocol

Ultrasound

Materials

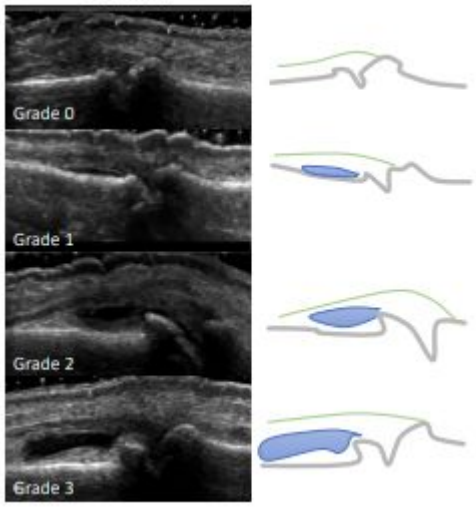
A high-end ultrasound machine (i.e. GE Logiq E10s, GE Healthcare, United States) will be used, equipped with one multifrequency linear probe and a high frequency (hockey stick) probe.
Settings will be optimized for each machine and settings stay stable during the entire study period. The sonographer is allowed to modify depth and focus.

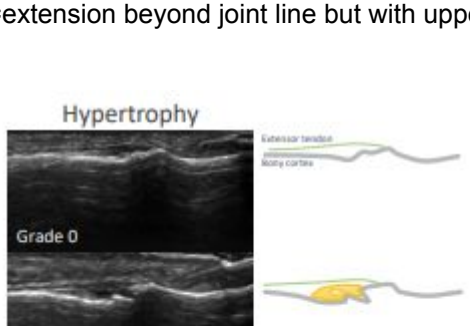
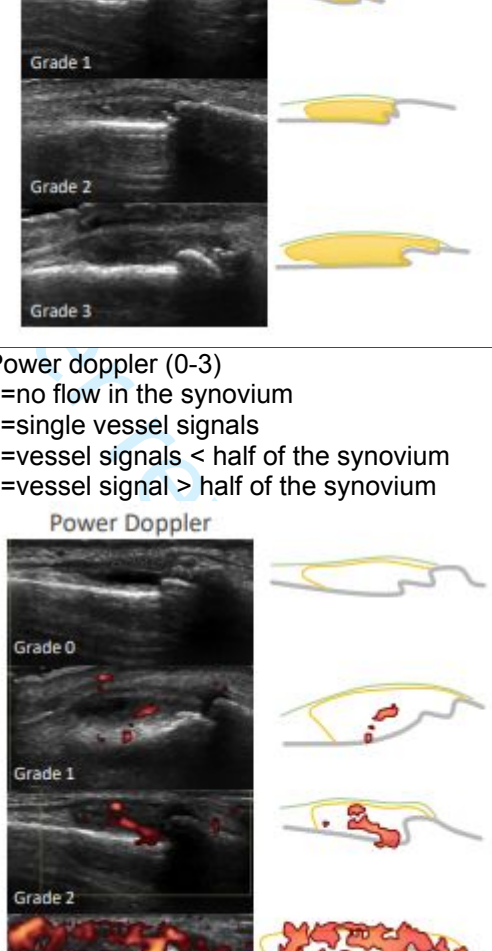
Variables

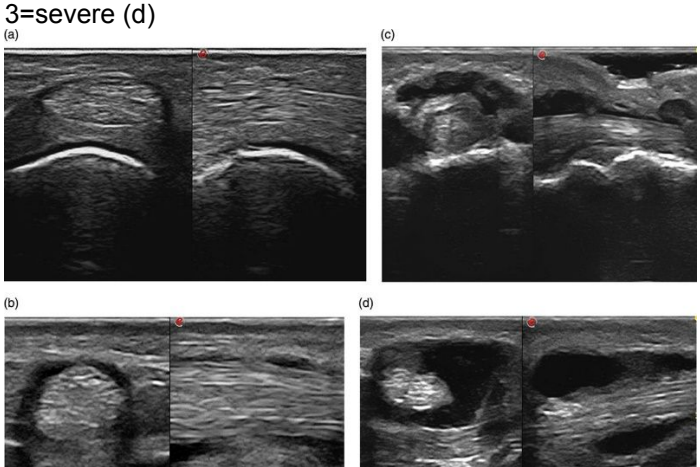
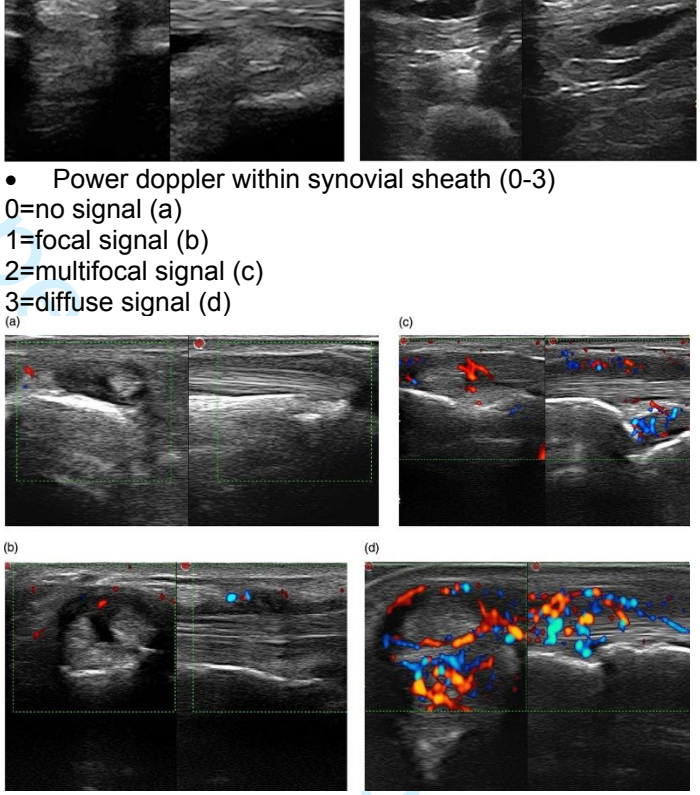
Outcomes	Area
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Synovial hypertrophy (1) Abnormal hypoechoic intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Osteophytes Bone spurs at the end of bones	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Tenosynovitis (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	Dorsal • Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar • Finger flexor digitorum (SUP/PROF) 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	Dorsal • Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar • Finger flexor digitorum (SUP/PROF) 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level
Thickening of finger flexor and extensor tendons (3)	• Central slip of extensor tendons 2-5 at MCP level • Extensor pollicis longus and brevis at MCP level • Finger flexors 2-5 (sup+prof) at MCP level

	• Flexor pollicis longus and brevis at MCP level
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	Volar • Digits 1-5
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	Volar • A1 pulley 1-5 at the MCP level
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	Volar • radial artery of the index finger at MCP – DIP traject • proper palmar digital arteries of digit 2-5 • Princeps pollicis artery
Intima-media thickness Thickness of tunica intima and tunica media.	Volar • radial artery of the index finger digit at the MCP – DIP traject •
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	• Finger flexor tendons 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level • Finger extensor tendons 2-5 at MCP level • Extensor pollicis longus and brevis at MCP level

Scoring

Outcomes	**Scoring**
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	B-mode (GS 0-3) 0 = none 1 = minimal 2 = moderate 3 = severe 
Synovial hypertrophy (1)	B-mode (GS 0-3)

Abnormal hypoechoic intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.	0=none 1=up to the level of the horizontal line connecting bone surfaces of the joint 2=extending beyond joint line but with upper surface concave or flat 3=extension beyond joint line but with upper surface convex 
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Power doppler (0-3) 0=no flow in the synovium 1=single vessel signals 2=vessel signals < half of the synovium 3=vessel signal > half of the synovium 
Osteophytes Bone spurs at the end of bones	• Presence y/n
Tenosynovitis (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	• Tenosynovitis (0-3) 0=no (a) 1=minimal (b) 2=moderate (c)

	3=severe (d)  • Power doppler within synovial sheath (0-3) 0=no signal (a) 1=focal signal (b) 2=multifocal signal (c) 3=diffuse signal (d) 
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	• Presence y/n
Thickening of finger flexor and extensor tendons (3)	Tendon width (max)
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	• Presence y/n • Location: tendon, tendon sheat, periarticular, soft tissue • Number per finger
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It	• Max width (transverse) of every finger

appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	• Occlusion 0 = normal 1 = abnormal 2 = (near) occlusion • Number of occluded arteries for each digit (0-2)
Intima-media thickness Thickness of tunica intima and tunica media.	• Intima-media thickness (mean max)
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	• Velocity (meters per second) • Stiffness (kiloPascals)

Procedure

Ultrasound examination will be performed at baseline, 6 months, 12 months, and 24 months in all patients.

Patients will be positioned with their hands resting on a table with extended fingers facing the examiner. If full extension is not possible due to hand contractures or when in doubt during the scoring of synovial thickening and effusion in the joints, the joint can be assessed in (slightly) flexed position.
For the joints and extensor tendons, patients will rest the palms of the hands on the table. For flexor tendons, calcinosis, vascular assessment and flexor tendons, patients will rest the dorsum of the hand on the table for evaluation of the volar aspect longitudinally and transversely.
Any abnormalities of the flexor tendons will be confirmed in a cross-sectional view. Whereas, any joint abnormalities will be confirmed using a dorsal longitudinal scan.

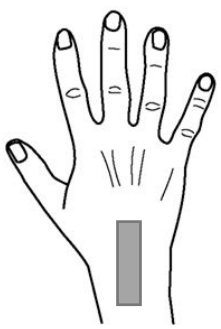
The sonographers at the study sites will be trained on this ultrasound protocol. Examinations are reported in an eCRF, one image/video for each measure will be stored. When deemed necessary, more images/videos can be stored. Measurements are done afterwards on the stored images by the coordinating researcher.

Ultrasound imaging starts with the right hand and the linear probe according to the steps below. After all measurements of the right hand are completed, the left hand is imaged according to the same steps. Vascular imaging is only conducted in the dominant hand. In the UMCU only, elastography is performed

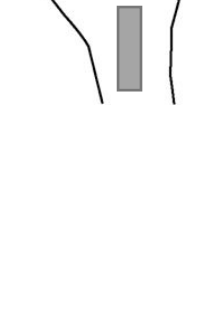
Additionally, at the UMCG a more extensive protocol will be performed as substudy. The vascular protocol entails ultrasound measurements performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) and an ultra-high frequency ultrasound transducer (70 MHz). Nailfold capillaroscopy (NCM) will be performed with a handheld DinoLite CapillaryScope 200 Pro (DinoLite Europe BV). Finger and toe pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

Wrist bones

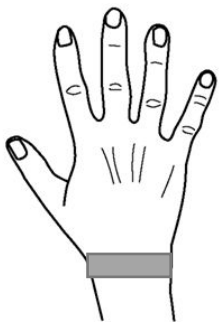
- **Radiocarpal**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **Intercarpal**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

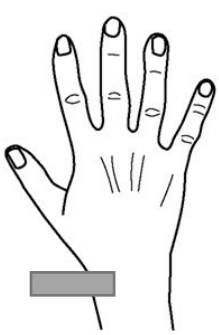


- **Distal radio-ulnar joint (DRUJ)**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

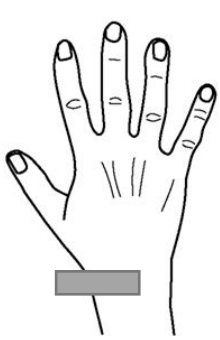


Compartments of extensor tendons

- **Wrist extensor compartment 1**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

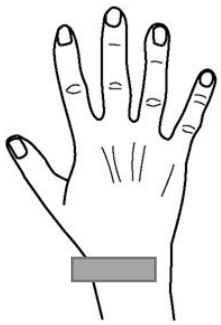


- **Wrist extensor compartment 2**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

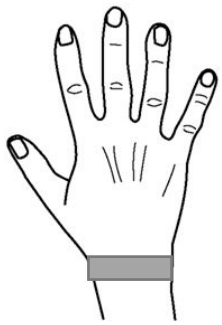


- **Wrist extensor compartment 3**

- Tenosynovitis
  - 0 = no
  - 1 = minimal
  - 2 = moderate
  - 3 = severe
- Power doppler within synovial sheath
  - 0 = no signal
  - 1 = focal signal
  - 2 = multifocal signal
  - 3 = diffuse signal
- Tenosynovial effusion
  - Presence y/n



- **Wrist extensor compartment 4**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n



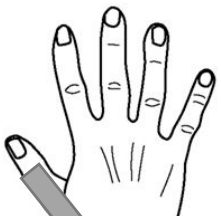
- **Wrist extensor compartment 5**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

- **Wrist extensor compartment 6**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

Switch to the hockey stick probe!

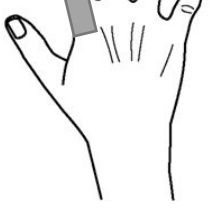
At MCP 1 level

- **MCP 1**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Extensor pollicus longus and brevis at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



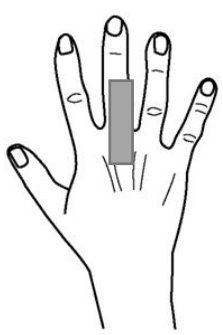
At MCP 2 level

- **MCP 2**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendon 2 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



At MCP 3 level

- **MCP 3**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendon 3 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)

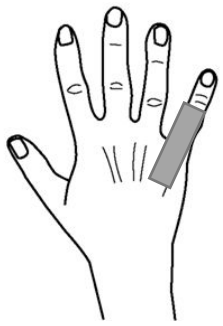


At MCP 4 level

- **MCP 4**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendons 4 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)

At MCP 5 level

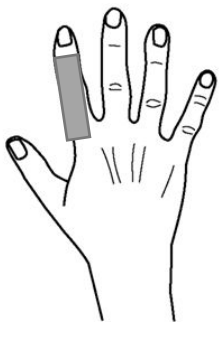
- **MCP 5**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendons 5 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



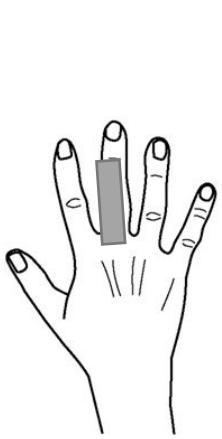
At (P)IP level

- **IP**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

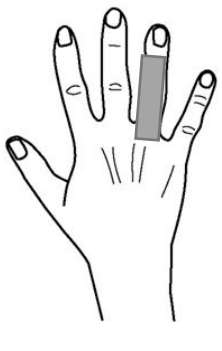
- **PIP 2**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **PIP 3**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **PIP 4**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **PIP 5**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

Ask subject to turn their hand with the palmar side up!

Palmar side of digit 1

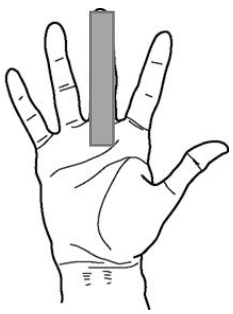
- **Flexor pollicus longus and brevis at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 1**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

Palmar side of digit 2

- **Finger flexors (sup + prof) 2 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 2 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 2**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

Palmar side of digit 3

- **Finger flexors (sup + prof) 3 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 3 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 3**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

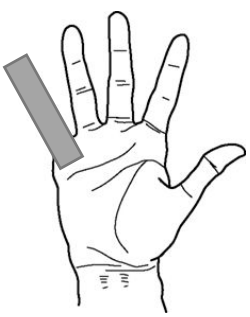


Palmar side of digit 4

- **Finger flexors (sup + prof) 4 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 4 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 4**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

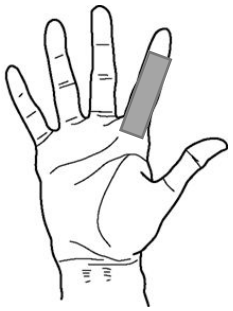
Palmar side of digit 5

- **Finger flexors (sup + prof) 5 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 5 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 5**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger



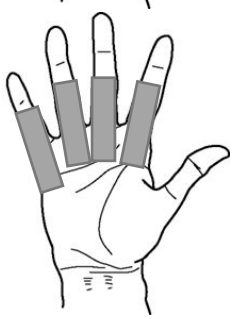
Only look at the arteries in the dominant hand!

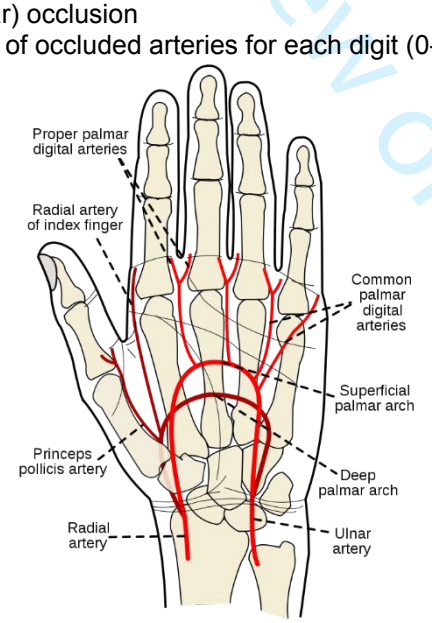
- **Radial artery index finger at MCP-DIP section**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion
  - Intima media thickness
    - Max thickness on section



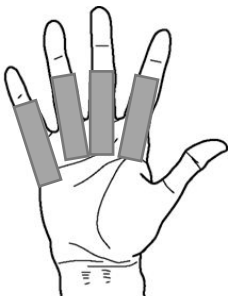
- **Princeps pollicus artery at MCP-IP section**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion

- **Proper palmar digital arteries of digit 2-5 at MCP level**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion
    - Number of occluded arteries for each digit (0-2)





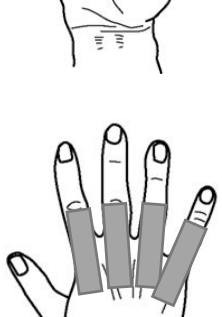
Elastography only in UMCU and only in dominant hand, use linear probe!



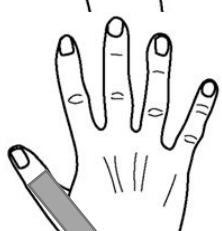
- **Finger flexor tendons 2-5 at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

- **Flexor pollicus longus and brevis at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

Ask subject to turn their hand with dorsal side up



- **Finger extensor tendons 1-5 at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)



- **Extensor pollicus longus and brevis at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

MRI assessment

Materials

A 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) with dedicated surface coils.

Variables

Outcomes	Area	Scoring
Synovitis or tenosynovitis (9) Hyperintense signal on both STIR and fat-saturated post-gadolinium images in a thickened articular and tendon sheath synovium	• Radiocarpal • Intercarpal • MCPs 2-5 • PIPs 2-5	• Synovitis None/Focal/Diffuse / of Mild/moderate /severe • Tenosynovitis None/Focal/Diffuse
Erosions (10) Sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, with a cortical break visible in two adjacent planes.	• Radiocarpal • Intercarpal • MCPs 2-5 • PIPs 2-5	• Presence • Number • Location (specify joint)
Bone edema	• AREA	• None/mild/moderate/severe

Procedure

The MRI examination will be performed on the dominant hand. Non-enhanced transverse and coronal T1-weighted, fast spin-echo T2-weighted and short-tau inversion recovery (STIR) and/or fat-saturated proton-density sequences will be performed with contrast enhancement.
A radiologists will assess the MRI images and reported the scores in an eCRF. The MRI will be performed at baseline in the first 50 patients participating at the UMC Utrecht. MRI examinations will be performed on the day of the baseline ultrasound and read without knowledge of hand function scores.

References

1. Mathiessen A, Hammer HB, Terslev L, Kortekaas MC, D'Agostino MA, Haugen IK, et al. Ultrasonography of Inflammatory and Structural Lesions in Hand Osteoarthritis: An Outcome Measures in Rheumatology Agreement and Reliability Study. Arthritis Care Res (Hoboken). 2022 Dec 1;74(12):2005–12.
2. Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint P V., Filippucci E, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis. 2013 Aug;72(8):1328–34.
3. Hughes M, Manning J, Moore T, Herrick AL, Chitale S. Ultrasound findings in finger flexor tendons in systemic sclerosis: A cross-sectional pilot study. 5(1):77–82.
4. Tagliafico A, Panico N, Serafini G, Ghio M, Martinoli C. The thickness of the A1 pulleys reflects the disability of hand mobility in scleroderma. A pilot study using high-frequency ultrasound. Eur J Radiol. 2011 Feb 1;77(2):254–7.
5. Guerini H, Pessis E, Theumann N, Le Quintrec JS, Campagna R, Chevrot A, et al. Sonographic Appearance of Trigger Fingers. Journal of Ultrasound in Medicine. 2008 Oct 1;27(10):1407–13.
6. Sato J, Ishii Y, Noguchi H. Comparison of the Thickness of Pulley and Flexor Tendon Between in Neutral and in Flexed Positions of Trigger Finger. Open Orthop J. 2016 Mar 30;10(1):36.
7. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open. 2018;4(1).
8. Drakonaki E. Ultrasound elastography for imaging tendons and muscles. J Ultrason [Internet]. 2012 Jun 30 [cited 2023 Oct 2];12(49):214. Available from: /pmc/articles/PMC4579737/
9. Schanz S, Henes J, Ulmer A, Kötter I, Fierlbeck G, Claussen CD, et al. Magnetic resonance imaging findings in patients with systemic scleroderma and musculoskeletal symptoms. Eur Radiol. 2013 Jan 29;23(1):212–21.
10. Østergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. Vol. 30, Journal of Rheumatology. 2003 [cited 2023 Aug 4]. p. 1385–6 OMERACT rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. Available from: https://pubmed.ncbi.nlm.nih.gov/12784422/

BMJ Open

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-095283.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Feb-2025
Complete List of Authors:	Greveling, Mark; UMC Utrecht, Department of Rheumatology & Clinical Immunology Ong, Voon H.; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Denton, Christopher; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases Foppen, W.; UMC Utrecht, Department of Radiology and Nuclear Medicine Herman, Amin; St Antonius Hospital, Department of Rheumatology Jeffries-Owen, Nick; SRUK Kortekaas, Marion; Leids Universitair Medisch Centrum, Department of Rheumatology; Flevoziekenhuis, Rheumatology Masselink, Ilse; UMC Utrecht, Department of revalidation Mulder, Douwe J.; UMCG, Department of Internal Medicine, Division of Vascular Medicine Schriemer, Rita; NVLE, Dutch Patient Organization for Systemic Autoimmune Diseases Vonk, Madelon; Radboudumc, Department of Rheumatology de Vries-Bouwstra, Jeska; Leids Universitair Medisch Centrum, Department of Rheumatology Welsing, Paco; UMC Utrecht, Department of Rheumatology & Clinical Immunology Mastbergen, Simon; UMC Utrecht, Department of Rheumatology & Clinical Immunology Spierings, Julia; UMC Utrecht, Department of Rheumatology & Clinical Immunology; University College London, Div of Medicine, Dep of Inflammation, Centre for Rheumatology and Connective Tissue Diseases
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Radiology and imaging, Research methods, Immunology (including allergy)
Keywords:	RHEUMATOLOGY, Ultrasound < RADIOLOGY & IMAGING, Observational Study

Administrative information

Title

Hand function impairment in Systemic sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME), a longitudinal observational multicentre study protocol

Authors

Mark J. Greveling*, Voon H. Ong, Christopher P. Denton, Wouter Foppen, Amin Herman, Nick Jeffries-Owen, Marion Kortekaas, Ilse Masselink, Douwe J. Mulder, Rita Schriemer, Madelon C. Vonk, Jeska K. de Vries-Bouwstra, Paco Welsing, Simon Mastbergen, Julia Spierings

*corresponding author. m.j.greveling@umcutrecht.nl, Heidelberglaan 100, 3584CX Utrecht, the Netherlands

Trial registration

Data category	Information
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT06133244
Date of Registration in Primary Registry	15-11-2023
Secondary Identifying Numbers	NL85445.041.23
Source(s) of Monetary or Material Support	UMC Utrecht, ReumaNederland
Primary Sponsor	UMC Utrecht
Secondary Sponsor(s)	N/A
Contact for Public Queries	handsome@umcutrecht.nl +3188 7555 5555
Contact for Scientific Queries	handsome@umcutrecht.nl +3188 7555 5555
Public Title	Getting a grip on hand function impairment in systemic sclerosis
Scientific Title	Hand Function Impairment in Systemic Sclerosis: Outcomes, Mechanisms, and Experience (HANDSOME) Study
Countries of Recruitment	The Netherlands United Kingdom

Health Condition(s) or Problem(s) Studied	Systemic sclerosis
Intervention(s)	Diagnostic Tests: Imaging, blood samples, functional tests, and physical examination
Key Inclusion and Exclusion Criteria	Study Population Patients (18 years and older) with: 1. SSc with hand contractures 2. SSc patients without contractures and disease duration of < 4 years 3. VEDOSS patients Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion Criteria: Age > 18 years Exclusion Criteria: Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion
Study Type	Observational
Date of First Enrollment	19-04-2024
Sample Size	300
Recruitment Status	Recruiting
Primary Outcome(s)	To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.
Key Secondary Outcomes	To determine risk factors and categorize patients with hand function impairment into subgroups based on clinical, immunological, and/or imaging

	characteristics, thereby guiding future research toward personalized treatment strategies To assess the impact of hand function impairment on quality of life, daily functioning, work, and participation, and explore how these impacts relate to the identified mechanisms and patient subgroups
Ethics Review	Approved on 19-03-2024
Completion date (estimated)	04-2028
Summary Results	N/A
IPD sharing statement	Undecided

Protocol version
V1.3 6-06-2024

Abstract

Introduction The majority of all systemic sclerosis (SSc) patients experience hand function impairment. The exact cause for this impairment is yet unknown. As impaired hand function hugely impacts daily functioning and quality of life, there is a high unmet need for effective treatments. With the availability of new imaging modalities, biomarkers, and lab techniques, opportunities arise to increase insights into the factors contributing to hand function impairment. The objective of this study is to identify risk factors and underlying mechanisms leading to hand function impairment in SSc.

Methods and analysis This is a longitudinal observational multicentre study in patients with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) and SSc under care of the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG), Leiden UMC (LUMC), Radboudumc, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Medical history, clinical status, nailfold capillaroscopy, skin assessments, serum biomarker analysis, ultrasound, elastography and MRI will be performed and results related to hand function measurements.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee NedMec (MREC NedMec) in the Netherlands and by HRA and Health and Care Research Wales (HCRW) in the UK. Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Trial registration number NCT06133244

Keywords

Systemic sclerosis, hand function, imaging, biomarkers, observational

Word count:

3117

Strengths and limitations of this study

- This is the first study that extensively assesses the hand function in systemic sclerosis patients
- This is a large prospective international multidisciplinary study with a follow-up of 2 years in 300 patients
- This is the first study that explores elastography of tendons in the hand
- The study is conducted in collaboration with patient associations
- Conclusions can be limited due to the lack of prior research for comparison and the heterogeneity of the disease

Introduction

Background and rationale

Systemic sclerosis (SSc) is a rare disease characterized by inflammation, fibrosis, and vasculopathy [1]. Clinical presentation is heterogeneous and includes Raynaud phenomenon, cutaneous manifestations, musculoskeletal manifestations, gastrointestinal manifestations, pulmonary manifestations, cardiac manifestations, and renal manifestations. Thus far, studies in SSc mainly focused on organ damage and mortality. However, other disease manifestations have a tremendous impact on quality of life and daily functioning.

Around 90% of SSc patients experience hand function limitation, which leads to impaired daily functioning and work participation [2,3]. An important cause of impaired hand function is contractures of the hand, which are reported in half of the patients [4]. Contractures are reported more frequently in patients with diffuse cutaneous systemic sclerosis (dcSSc) and associated with anti-topoisomerase I (ATA) positivity [5]. Only a few studies explored imaging techniques in SSc hands. Thickening of the A1 pulley and flexor tendons was associated with hand disability in a small group of patients (n=29). Soft tissue calcifications were seen in affected tendons, but this has not been studied in more detail [6,7]. In other small studies, ultrasound and MRI showed subclinical synovitis or tendinitis and bone erosions, which could also contribute to impaired hand function [7,8]. Shear wave elastography (SWE), a new imaging modality to assess the elastic properties and stiffness of soft tissue, has been studied in SSc skin and muscles but no studies have assessed hand tendons. Moreover, no studies explored tenosynovial changes and underlying biological mechanisms, especially in correlation with imaging or functional tests. This leaves clinicians 'in the dark' regarding diagnostic work-up and effective management. Current management for hand symptoms includes exercises, splints, and sometimes immunosuppressive therapies. However, it is unknown which treatment is suitable for which patient and the efficacy of immunosuppressive drugs has not been confirmed in trials. As impaired hand function in SSc hugely daily functioning and with that quality of life, there is a high unmet need for effective treatments [9]. With the availability of improved imaging modalities such as ultrasound, MRI and elastography, biomarkers in serum and plasma, and lab techniques such as proteomics, opportunities arise to study this problem in more detail to guide optimal treatment development.

This study aims to enhance the understanding of the mechanisms underlying hand function impairment in patients with systemic sclerosis (SSc), including development from the early phase in very early disease of systemic sclerosis (VEDOSS). The study is based on three key hypotheses: 1) Hand function in SSc is affected through various pathways involving joints, tendons, skin, and/or microcirculation. 2) Prior to the development of contractures, tissue changes—such as inflammation, fibrosis, or decreased elasticity—can be detected using imaging techniques. 3) Patients with hand impairment can be categorized into distinct subgroups based on clinical and imaging features, as well as protein markers, which may reflect different activated biological pathways.

Objectives

Primary objective

To identify underlying mechanisms responsible for hand function impairment in systemic sclerosis (SSc) patients.

Secondary objectives

To determine risk factors and categorize patients with hand function impairment into subgroups based on clinical, immunological, and/or imaging characteristics, thereby guiding future research toward personalized treatment strategies

To assess the impact of hand function impairment on quality of life, daily functioning, work, and participation, and explore how these impacts relate to the identified mechanisms and patient subgroups

Methods

Patient and public involvement statement

Members of the Dutch (NVLE) and UK (SRUK) systemic sclerosis patient organizations are involved in every step of this project. They have been involved in the study design and during the development of the protocol, a qualitative study was performed to explore patients' functional complaints and (unmet) needs. The study protocol has been co-produced to ensure representation and input from those with personal experiences. All questionnaires have been checked on content and feasibility. During all meetings with the entire research team, patients will be involved to share their opinions on decisions being made and provide advice on recruitment and dissemination of results.

Study setting

This is a longitudinal observational international study in patients with VEDOSS and SSc who are under care at the Department of Rheumatology & Clinical Immunology of the University Medical Centre Utrecht (UMCU), St Antonius Hospital Nieuwegein, UMC Groningen (UMCG) Leiden UMC (LUMC), Radboud UMC, or Royal Free Hospital (RFH) London. Patients will be followed for 2 years. Inclusion started in April 2024 and is open until April 2026, the expected end date is April 2028.

Study population

Patients (n=300; 18 years and older) with:

1) SSc with hand contractures regardless of disease duration (n=50)
2) SSc patients without hand contractures (n=200) and disease duration of < 4 years
3) VEDOSS patients (n=50)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Age >18 years
2) For patient populations 1) and 2):

a. Diagnosis of SSc according to the 2013 EULAR-ACR classification criteria for SSc [10]
For patient population 3):

b. Diagnosis of VEDOSS, defined as the presence of RP, puffy fingers, SSc-specific autoantibodies, and abnormal nailfold capillaroscopy, while not fulfilling the 2013 EULAR-ACR classification criteria for SSc [11].

3) Only for patient population 1):

a. Hand contractures are defined as a range of motion < 75% of the normal range of at least one small hand joint of [12].

4) Willing and be able to understand the study information and sign the informed consent form.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

1) Age < 18 years

2) Patients with diabetic cheiroarthropathy and Dupuytren's disease, based on expert opinion. (other diseases or overlap syndromes are not excluded)

Study procedures

Three patient groups are included and then followed for 24 months. Table 1 shows the study procedures and data collection in these three groups.

Table 1: Overview of study procedures

	Baseline	6 months	12 months	24 months
Informed consent	x			
Medical history	x			
Nailfold capillaroscopy	x			x
Clinical status	x	x	x	x
Skin assessment	x	x	x	x
PROMs	x	x	x	x
Serum and plasma collection	x	x	x	x
Hand function assessment	x	x	x	x
Ultrasound	x	x	x	x
Elastography *	x	x	x	x
MRI *	x			
Vascular imaging **	x	x	x	x

*Sub-analysis comparing MRI with ultrasound features. UMC Utrecht only

** Sub-analysis assessing hand circulation extensively with ultrasound using a 70mHz probe. UMC Groningen only

Medical history

Clinical data collected in routine care will be retrieved at baseline. Age, sex, height, educational level, ethnicity, and auto-antibody status (ANA negative/positive, line blot and scleroderma blot auto-antibodies) are collected.

In addition, data will be collected on previous tobacco use, vasoactive and immunosuppressive medication use and dosage, digital ulcers, pitting scars, gangrene, clinical arthritis, myositis, interstitial lung disease, pulmonary hypertension, and scleroderma renal crisis.

Nailfold capillaroscopy

A capillaroscope with a magnification of 200x is used to assess all fingers, including the thumbs. At least two adjacent fields of a linear millimetre in the middle of each finger are captured and stored. Images will be scored according to EULAR criteria centrally on normal or abnormal/scleroderma patterns [13].

Clinical status

- weight, blood pressure, (change) in tobacco use, (change in) occupation, (changes in) immunosuppressive and/or vasoactive medication use and dosage,
- new onset interstitial lung disease (y/n), pulmonary hypertension (y/n), scleroderma renal crisis (y/n)
- Hb (mmol/L), ESR (mm/h), CRP (mg/L), CK (IU/L).

Skin assessment

The modified Rodnan skin score (mRSS) (assessed by trained investigators), presence of digital ulcers (if yes: count, location), pitting scars (if yes: count, location), gangrene (if yes: location), calcinosis cutis in the hands (if yes: location), clinical arthritis ((if yes: site and joint count), and myositis will be assessed/recorded [14].

PROMs

Patient Related Outcome Measurements will be collected in the week of the study visit and the following questionnaires will be collected:

- Cochin Hand Function Scale (CHFS), containing 18 questions, structured in 5 distinct categories, designed to evaluate hand function in kitchen activities, dressing, personal hygiene, office, and other generic activities [15].
- brief Satisfaction with Appearance Scale (SWAP), containing six questions about subjective body image dissatisfaction and the perceived social impact [16].
- IMTA Productivity Cost Questionnaire (IPCQ), a standardized instrument for measuring and valuing health-related productivity losses [17].
- Utrecht Scale for Evaluation of Rehabilitation (- Participation) (USER-P), which measures both subjective and objective participation in the community [18].
- Health-related quality of life (EQ5D5L), that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression [19].
- Self-assessment of skin thickening (PASTUL), a self-reported measure of skin thickness in the upper limb [20].
- Scleroderma Health Assessment Questionnaire (SHAQ), which measures disease status changes [21].

Serum and plasma collection

Two blood samples will be collected (both a maximum of 10 ml) to obtain both serum and plasma samples during each visit. The venepuncture is performed at routine outpatient or daycare unit visits according to standard protocol protocol in a non-fastened state and not taking diurnal changes into account due to practical feasibility [22]. Aliquots of both serum and plasma samples will be stored at -80 C degrees. Serum and plasma analysis will include measurement of levels of immunological markers (including cytokines) and fibrotic markers.

Hand function assessment

At all study visits, hand function will be assessed by trained investigators. Hand mobility is assessed with the range of motion of the wrist joint, range of motion of the finger joints, delta

Finger-to-Palm distance [23], and the mHAMIS [24]. Grip strength is measured with the JAMAR® dynamometer and JAMAR pinch dynamometer® for the two-point pinch, three-point pinch, and lateral pinch.

Ultrasound

Ultrasound will be performed by an operator/physician trained in musculoskeletal ultrasound. An ultrasound machine with a high-frequency probe (linear or hockey stick with 8-24MHz) will be used. Images of all study sites will be stored and rated centrally by the coordinating researcher in conjunction with ultrasound experts afterwards. The presence of arthritis of the wrist, distal radio-ulnar joint (DRUJ), metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints will be assessed using validated semiquantitative methods in B-mode and power Doppler setting if there was grey-scale evidence of inflammation. Furthermore, the presence of osteophytes is assessed. The first to fifth flexor and extensor tendons of both hands will be assessed longitudinally. Tenosynovitis and sclerotic thickening of tendon(-sheaths) and calcifications within tendons will be evaluated. The pulley and tendons are measured at the at the MCP joint. The fingers of the dominant hand will be assessed with ultrasound for vascular involvement. Dig 2 will be assessed standardly. In addition, fingers with ulceration if present on other fingers will be assessed. Additionally, intima media thickness (IMT) will be measured in dig 2. All arteries per finger will be assessed at the proximal phalangeal part. Qualitative scoring is performed. See Appendix 1, imaging protocol, for the full ultrasound protocol.

Elastography

In addition to the ultrasound assessment, fibrosis of the first to fifth flexor and extensor tendons of both hands will be measured quantitatively using shear wave elastography (SWE) in a subgroup of patients at the UMC Utrecht (n=100) [25]. SWE is measured with the ultrasound machine GE healthcare LOGIQ E10s using the linear ML4-20 transducer.

Vascular imaging

Another addition to the ultrasound assessment is the extensive vascular evaluation performed in patients in the UMC Groningen (n=35). The vascular protocol entails ultrasound measurements of IMT performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) which uses an ultra-high frequency ultrasound transducer (max 70 MHz). Finger pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously [26]. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands) [27].

MRI

In a subgroup of patients included at the UMC Utrecht (n=50), a contrast-enhanced 3 Tesla MRI of the dominant hand will be done at baseline, recording the presence of synovitis, joint capsule thickening of the wrist, MCP and PIPs, and thickness or inflammation of tendons and tendon sheaths of the hands. The researcher will determine whether there are no contra-

indications according to the MRI screening form used in the UMC Utrecht. The entire MRI protocol is shown in Appendix 1, imaging protocol.

Outcomes

Main study parameter/endpoints

The correlation between the Cochin Hand Function Scale (CHFS) scores and circulating biomarkers, as well as changes observed through imaging, over a two-year follow-up period will be assessed.

Secondary study parameters/endpoints

- The change in hand function at 2 years, reflected by the Cochin Hand Function Scale (CHFS) and hand function measures.
- Predictive value of imaging features and circulating biomarkers at baseline for change of hand impairment at follow-up.
- Distinct subgroups of patients based on clinical, immunological, and imaging characteristics.
- Health-related quality of life (EQ5D-5L), daily functioning (S-HAQ), work (IPCQ), and participation (USER-P) in relation to CHFS.

Sample size

For multivariable regression analysis with a continuous outcome, we need at least 10 patients per variable studied according to rule of thumb. As we anticipate including 300 patients we will be able to validly study 30 variables for their association with the (progressive) hand impairment (including patient subgroup as a covariate in the analysis) with sufficient power. We will also perform more explorative subgroup analyses per patient population and calculate variance inflation factors (VIFs) as well as use data reduction techniques (e.g. principal component analysis) and/or analysis techniques more suitable for analysing outcomes with many independent variables compared to the number of patients (like partial-least squares regression or Lasso regression). Furthermore, we will explore clusters of patients developing hand function impairment using imaging and protein biomarkers to inform our multivariable analyses. Missing data will be accounted for using multiple imputation. With the above calculation and strategy, we think our cohort of 300 patients will be sufficient to obtain meaningful results.

Recruitment and consent

Subjects will be informed about the study by their treating physician and receive an information letter. Thereafter, they will have the possibility to ask questions, either during a face-to-face appointment or over the phone with the investigator or research nurses. They will be allowed sufficient time, but at least 24 hours, to consider their participation. If the subject wants to participate, a meeting will be set for signing the consent form and explaining the study procedure. This will take place at a day/time suitable for the patients, ideally combined with routine care appointments.

Data management

Data handling is described in detail in the data management plan. This has been approved by the data manager of the UMC Utrecht.

Data from patients will be handled with care, taking into consideration the required confidentiality as stated by the Dutch 'AVG ('Law for the Protection of Personal Information'), the 'Wet Gemeenschappelijke Behandelings Overeenkomst' ('Law Common Treatment Agreement'), and the privacy policy of the UMC Utrecht. The electronic patient files will be used as the source for the clinical data. Data will be pseudonymized and the key will be stored in a separate secured folder at each clinical site.

Patient material will be encoded and stored at the UMC Utrecht, department of Rheumatology & Clinical Immunology. Patient material is only used to answer the questions in this study, material is not stored for biobank purposes. Only the local investigators are permitted access to the code key. Research documents, from which patient identity can be deduced will only be accessible for third parties (for example monitors, auditors, and inspection by competent authorities) after specific consent by the participant in the informed consent document. Research documents will be kept up to 15 years after ending the research.

In all local centers, images and patient material will be stored according to local protocol and collected and analysed centrally.

Monitoring and Quality Assurance

A central independent monitor will perform yearly monitoring according to the Monitoring Plan.

Statistical methods

To predict decline in hand function (defined as an increase CHFS) at 6, 12, and 24 months we will use linear/logistic regression analysis, with as independent variables/predictors baseline patient characteristics, as well as short term (over 6 months) changes in clinical scores, imaging markers and biomarkers. When needed we will use (regression) techniques suitable for a high variable to patient/outcome ratio (see section Statistics/Power calculation)

Characteristics at baseline and changes over time seen on ultrasound will be reported for the number of patients with tenosynovitis, arthritis and/or calcifications in tendons, the mean thickness and elastography of tendons, and the A1 pulley. Linear mixed models will be used to analyse changes over time (both with time defined as follow-up time or as time since early disease/VEDOSS) regarding hand function scores and to relate these changes to changes in ultrasound and serum/plasma biomarkers.

Also joint modelling of the multivariate longitudinal data (i.e. the clinical scores, imaging- and biomarkers measured over time) and time-to-event (i.e. development of limitations of hand function) will be performed. In this analysis so called 'latent trajectories' in the longitudinal markers (i.e. not directly observed subgroups of patients with a distinct course in longitudinally measured 'markers') will be related to the development of the outcome (in this case limitations in hand function). Results can be used to obtain more insight into the development of limitations in hand function, and the possible existence of subgroups regarding the development of hand function limitations. Models may also be used to 'dynamically' predict the outcome over time. The patient subgroups (VEDOSS/SSc with/without hand impairment) will be taken appropriately into account in all analyses and/or subgroup analyses will be performed.

To further explore subgroups in patients with/without hand function limitations. Baseline clinical, imaging-, and biomarkers as well as changes over time in markers will be used in a cluster analysis. As most likely different types of variables (i.e. linear, binary, and categorical) will be included we will use an algorithm suitable for this like k-medoid cluster analysis using partitioning around medoids. The validity of different solutions regarding the number of clusters will be evaluated using statistical criteria (e.g. silhouette width, calculated based on Gower distances) as well as clinical relevance by expert opinion (also considering the results of the above analyses) to derive a final solution. Possible confounders will be assessed and corrected for.

Ethics and dissemination

The Medical Research Ethics Committee NedMec (MREC NedMec) reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements, the MREC NedMec issued an approval for the Netherlands. HRA and Health and Care Research Wales (HCRW) has approved the study in the UK. The study will be conducted according to the principles of the Declaration of Helsinki (2013). Results will be published in scientific journals and presented at scientific congresses and patient meetings.

Funding

This project is funded by the Dutch Arthritis foundation (ReumaNederland, project number: 22-1-403).

Competing interests

None

Author statement

Julia Spierings is the project's guarantor and initiator, and she has been involved in every step of the process. Mark Greveling contributed to writing the protocol and was involved in the methodology for the study procedures.

Voon Ong, Christopher Denton, Amin Herman, Douwe Mulder, Madelon Vonk, Jeska de Vries-Bouwstra, and Simon Mastbergen participated in setting up the study and writing the protocol.

Wouter Foppen and Marion Kortekaas were responsible for the imaging procedures.

Nick Jeffries-Owen and Rita Schriemer served as patient representatives during the study setup.

Ilse Masselink was involved in the hand function measures.

Primary research team (University Medical Centre Utrecht, The Netherlands), responsible for study design, data collection, data management, data analysis, data interpretation, report writing, and decision to submit.

Dr. J. Spierings, PI

Dr. S.C. Mastbergen, co-PI

Drs. M.J. Greveling, coordinating researcher

Participating research team sponsor (University Medical Centre Utrecht, The Netherlands), advising on study design, collaborating on data collection, data management, data analysis, and data interpretation.

Dr. P. Welsing, methodologist

Dr. A. Marijnissen, study coordinator

Dr. W. Foppen, radiologist

R. Boot, research nurse

S. Mast, specialist nurse

I. Masselink, occupational therapist

A. Conception, lab analist

Dr. M.P. Jansen, MRI-expert

External participating research team, advising on study design, collaborating on data collection, data management, data analysis, and data interpretation.

Dr. D.J. Mulder, internist, Groningen University Medical Centre, The Netherlands

Dr. J.K. De Vries-Bouwstra, rheumatologist, Leiden University Medical Centre, The Netherlands

Dr. M.C. Vonk, rheumatologist, Radboud University Medical Centre, The Netherlands

Dr. A. Herman, rheumatologist, St. Antonius hospital Nieuwegein, The Netherlands

Dr. M. C. Kortekaas, rheumatologist and MSUS expert, Leiden University Medical Centre, The Netherlands

Prof. C.P. Denton, rheumatologist, Royal Free Hospital – University College London, United Kingdom

Dr. V.H. Ong, rheumatologist, Royal Free Hospital – University College London, United Kingdom

Prof. D. Abraham, Royal Free Hospital – University College London, United Kingdom

Drs. S. Rodolfi, clinical research fellow, Royal Free Hospital – University College London, United Kingdom

External advisors, advising on study design, data collection and data analysis

Drs. M.R. Schriemer, Dutch systemic sclerosis patient organisation (NVLE)

D. Dittmar, Dutch systemic sclerosis patient organisation (NVLE)

E. Blamont, UK systemic sclerosis patient organisation (SRUK)

N. Jeffries-Owen, UK systemic sclerosis patient organisation (SRUK)

K. Fligelstone, Royal Free Hospital patient partner

This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

References

1 Adigun R, Goyal A, Hariz A. Systemic Sclerosis. *StatPearls*. Published Online First: 8 May 2022.

2 Kwakkenbos L, Sanchez TA, Turner KA, *et al.* The association of sociodemographic and disease variables with hand function: A Scleroderma Patient-centered Intervention Network cohort study. *Clin Exp Rheumatol*. 2018;36:S88–94.

3 Bérezné A, Seror R, Morell-Dubois S, *et al.* Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. *Arthritis Care Res (Hoboken)*. 2011;63:277–85. doi: 10.1002/ACR.20342

4 Avouac J, Walker U, Tyndall A, *et al.* Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. *J Rheumatol*. 2010;37:1488–501. doi: 10.3899/JRHEUM.091165

5 Buni M, Joseph J, Pedroza C, *et al.* Predictors of Hand Contracture in Early Systemic Sclerosis and the Effect on Function: A Prospective Study of the GENISOS Cohort. *J Rheumatol*. 2019;46:1597–604. doi: 10.3899/JRHEUM.180093

6 Tagliafico A, Panico N, Serafini G, *et al.* The thickness of the A1 pulleys reflects the disability of hand mobility in scleroderma. A pilot study using high-frequency ultrasound. *Eur J Radiol*. 2011;77:254–7. doi: 10.1016/J.EJRAD.2010.05.013

7 Hughes M, Bruni C, Cuomo G, *et al.* The role of ultrasound in systemic sclerosis: On the cutting edge to foster clinical and research advancement. *J Scleroderma Relat Disord*. 2021;6:123–32. doi: 10.1177/2397198320970394

8 Schanz S, Henes J, Ulmer A, *et al.* Magnetic resonance imaging findings in patients with systemic scleroderma and musculoskeletal symptoms. *Eur Radiol*. 2013;23:212–21. doi: 10.1007/S00330-012-2584-1

9 Van Leeuwen NM, Ciaffi J, Liem SIE, *et al.* Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants. *Rheumatology (Oxford)*. 2021;60:3646–55. doi: 10.1093/RHEUMATOLOGY/KEAA827

10 Van Den Hoogen F, Khanna D, Fransen J, *et al.* 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72:1747–55. doi: 10.1136/ANNRHEUMDIS-2013-204424

11 Bellando-Randone S, Del Galdo F, Lepri G, *et al.* Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). *Lancet Rheumatol*. 2021;3:e834–43. doi: 10.1016/S2665-9913(21)00244-7

12 Bálint Z, Farkas H, Farkas N, *et al.* A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis. *Clin Exp Rheumatol*. 2014;32.

13 Smith V, Herrick AL, Ingegnoli F, *et al.* Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev*. 2020;19:102458. doi: 10.1016/J.AUTREV.2020.102458

14 Khanna D, Furst DE, Clements PJ, *et al.* Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord*. 2017;2:11. doi: 10.5301/JSRD.5000231

15 Duruöz MT, Poiraudeau S, Fermanian J, *et al.* Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. *J Rheumatol*. 1996;23:1167–72.

16 Jewett LR, Hudson M, Haythornthwaite JA, *et al.* Development and validation of the brief-satisfaction with appearance scale for systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2010;62:1779–86. doi: 10.1002/ACR.20307

17 Bouwmans C, Krol M, Severens H, *et al.* The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value in Health*. 2015;18:753–8. doi: 10.1016/J.JVAL.2015.05.009

18 Post MWM, Van Der Zee CH, Hennink J, *et al.* Validity of the Utrecht Scale for Evaluation of Rehabilitation-Participation. *Disabil Rehabil*. 2012;34:478–85. doi: 10.3109/09638288.2011.608148

19 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 2011;20:1727–36. doi: 10.1007/S11136-011-9903-X/TABLES/5

20 Spierings J, Ong V, Denton CP. PASTUL questionnaire: a tool for self-assessment of scleroderma skin during the COVID-19 pandemic. *Ann Rheum Dis*. 2021;80:819–20. doi: 10.1136/ANNRHEUMDIS-2020-219775

21 Steen VD, Medsger TA. The value of the health assessment questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum*. 1997;40:1984–91. doi: 10.1002/ART.1780401110

22 Srikanth KK, Lotfollahzadeh S. Phlebotomy. *Chest*. 2023;143:1831. doi: 10.1378/chest.12-2537

23 Torok KS, Baker NA, Lucas M, *et al.* Reliability and validity of the delta finger-to-palm (FTP), a new measure of finger range of motion in systemic sclerosis. *Clin Exp Rheumatol*. 2010;28:S28.

24 Sandqvist G, Nilsson JÅ, Wuttge DM, *et al.* Development of a modified hand mobility in scleroderma (HAMIS) test and its potential as an outcome measure in systemic sclerosis. *J Rheumatol*. 2014;41:2186–92. doi: 10.3899/JRHEUM.140286

25 Taljanovic MS, Gimber LH, Becker GW, *et al.* Shear-Wave Elastography: Basic Physics and Musculoskeletal Applications. *Radiographics*. 2017;37:855. doi: 10.1148/RG.2017160116

26 Elgendi M. On the Analysis of Fingertip Photoplethysmogram Signals. *Curr Cardiol Rev*. 2012;8:14. doi: 10.2174/157340312801215782

27 Mynard JP, Kondiboyina A, Kowalski R, *et al.* Measurement, Analysis and Interpretation of Pressure/Flow Waves in Blood Vessels. *Front Physiol*. 2020;11:564252. doi: 10.3389/FPHYS.2020.01085/BIBTEX

Appendix 1
Imaging protocol

Ultrasound

Materials

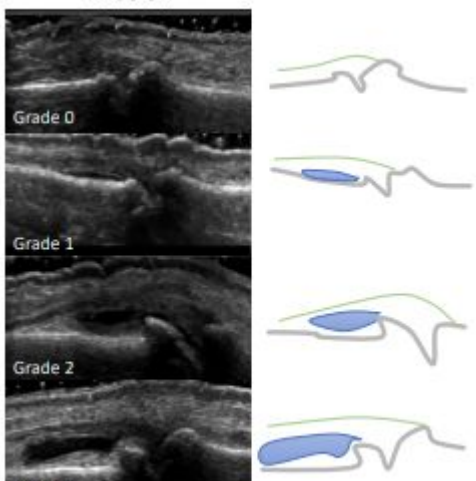
A high-end ultrasound machine (i.e. GE Logiq E10s, GE Healthcare, United States) will be used, equipped with one multifrequency linear probe and a high frequency (hockey stick) probe.
Settings will be optimized for each machine and settings stay stable during the entire study period. The sonographer is allowed to modify depth and focus.

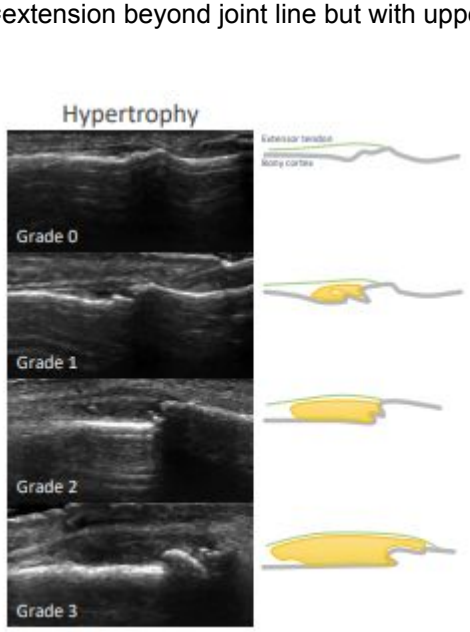
Variables

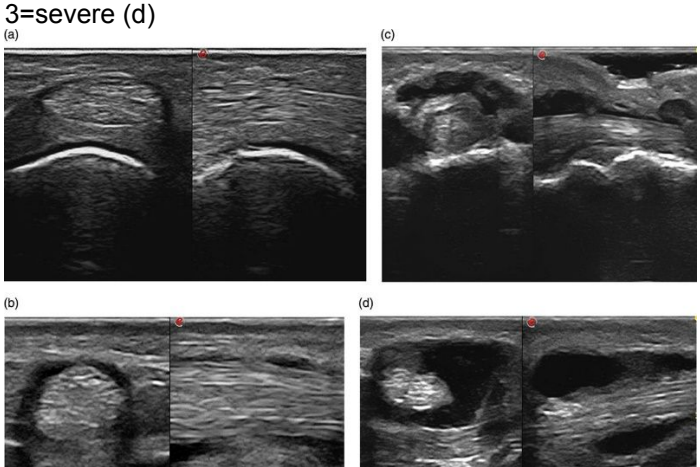
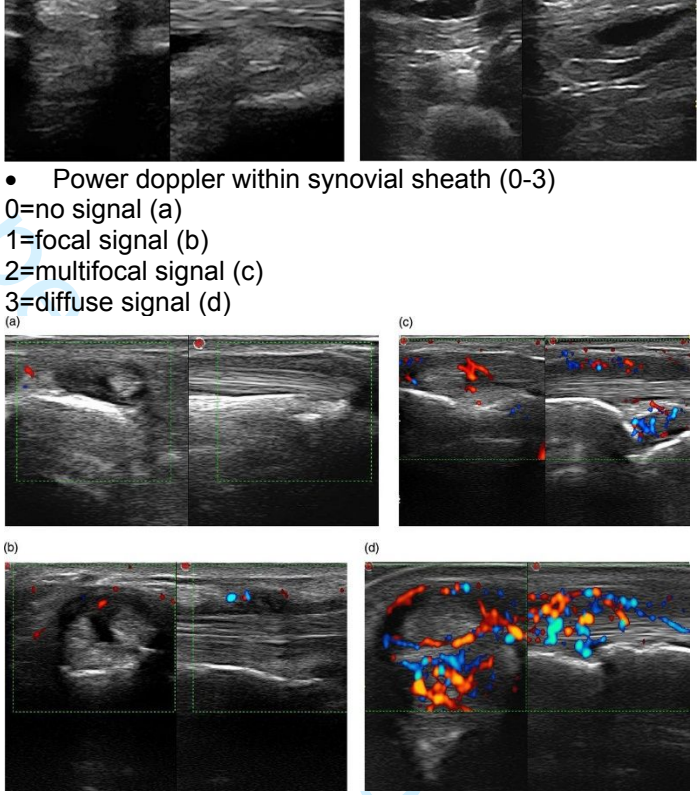
Outcomes	Area
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Synovial hypertrophy (1) Abnormal hypoechoic intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Osteophytes Bone spurs at the end of bones	Dorsal • Radiocarpal • Intercarpal • Distal radio-ulnar joint (DRUJ) • MCPs 1-5 • PIPs 2-5 • IP
Tenosynovitis (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	Dorsal • Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar • Finger flexor digitorum (SUP/PROF) 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	Dorsal • Wrist extensor compartment 1 (APL/EPB), 2 (ECRB/ECRL), 3 (EPL), 4 (EDC/EIP), 5 (EDM), 6 (ECU) Volar • Finger flexor digitorum (SUP/PROF) 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level
Thickening of finger flexor and extensor tendons (3)	• Central slip of extensor tendons 2-5 at MCP level • Extensor pollicis longus and brevis at MCP level • Finger flexors 2-5 (sup+prof) at MCP level

	• Flexor pollicis longus and brevis at MCP level
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	Volar • Digits 1-5
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	Volar • A1 pulley 1-5 at the MCP level
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	Volar • radial artery of the index finger at MCP – DIP traject • proper palmar digital arteries of digit 2-5 • Princeps pollicis artery
Intima-media thickness Thickness of tunica intima and tunica media.	Volar • radial artery of the index finger digit at the MCP – DIP traject •
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	• Finger flexor tendons 2-5 at MCP level • Flexor pollicis longus and brevis at MCP level • Finger extensor tendons 2-5 at MCP level • Extensor pollicis longus and brevis at MCP level

Scoring

Outcomes	Scoring
Joint effusion (1) Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal	B-mode (GS 0-3) 0 = none 1 = minimal 2 = moderate 3 = severe 
Synovial hypertrophy (1)	B-mode (GS 0-3)

Abnormal hypoechoic intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal.	0=none 1=up to the level of the horizontal line connecting bone surfaces of the joint 2=extending beyond joint line but with upper surface concave or flat 3=extension beyond joint line but with upper surface convex 
Doppler signals (1) Flow signal in the synovium must be in synovial hypertrophy to be considered as a sign of synovitis	Power doppler (0-3) 0=no flow in the synovium 1=single vessel signals 2=vessel signals < half of the synovium 3=vessel signal > half of the synovium
Osteophytes Bone spurs at the end of bones	• Presence y/n
Tenosynovitis (2) Abnormal anechoic and/or hypoechoic tendon sheath widening related to the presence of tenosynovial abnormal fluid and/or hypertrophy	• Tenosynovitis (0-3) 0=no (a) 1=minimal (b) 2=moderate (c)

	3=severe (d)  • Power doppler within synovial sheath (0-3) 0=no signal (a) 1=focal signal (b) 2=multifocal signal (c) 3=diffuse signal (d) 
Tenosynovial effusion (2) Presence of displaceable abnormal anechoic or hypoechoic material within the synovial sheath, either localized or surrounding the tendon	• Presence y/n
Thickening of finger flexor and extensor tendons (3)	Tendon width (max)
Calcifications Hyperechoic foci with or without shadowing at volar site the digits.	• Presence y/n • Location: tendon, tendon sheat, periarticular, soft tissue • Number per finger
Thickening of A1 pulley (4,5) This annular structure situated at the level of the MCP joint consists of a strap surrounding the flexor tendon sheath. It	• Max width (transverse) of every finger

appears as a hypoechoic band superficial to the flexor tendon sheath. Normal thickness in neutral position 0.38mm (SD 0.15) and hooked/contracted position 0.37mm (SD 0.15).(6)	
Occlusion digital arteries Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain.(7)	• Occlusion 0 = normal 1 = abnormal 2 = (near) occlusion • Number of occluded arteries for each digit (0-2)
Intima-media thickness Thickness of tunica intima and tunica media.	• Intima-media thickness (mean max)
Shear wave elastography (8) Stiffness of the tissue (UMCU only)	• Velocity (meters per second) • Stiffness (kiloPascals)

Procedure
Ultrasound examination will be performed at baseline, 6 months, 12 months, and 24 months in all patients.

Patients will be positioned with their hands resting on a table with extended fingers facing the examiner. If full extension is not possible due to hand contractures or when in doubt during the scoring of synovial thickening and effusion in the joints, the joint can be assessed in (slightly) flexed position.
For the joints and extensor tendons, patients will rest the palms of the hands on the table. For flexor tendons, calcinosis, vascular assessment and flexor tendons, patients will rest the dorsum of the hand on the table for evaluation of the volar aspect longitudinally and transversely.
Any abnormalities of the flexor tendons will be confirmed in a cross-sectional view. Whereas, any joint abnormalities will be confirmed using a dorsal longitudinal scan.

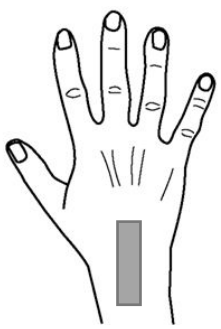
The sonographers at the study sites will be trained on this ultrasound protocol. Examinations are reported in an eCRF, one image/video for each measure will be stored. When deemed necessary, more images/videos can be stored. Measurements are done afterwards on the stored images by the coordinating researcher.

Ultrasound imaging starts with the right hand and the linear probe according to the steps below. After all measurements of the right hand are completed, the left hand is imaged according to the same steps. Vascular imaging is only conducted in the dominant hand. In the UMCU only, elastography is performed

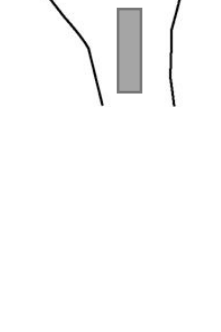
Additionally, at the UMCG a more extensive protocol will be performed as substudy. The vascular protocol entails ultrasound measurements performed with the Visual Sonics Vevo MD (FujiFilm, Tokyo, Japan) and an ultra-high frequency ultrasound transducer (70 MHz). Nailfold capillaroscopy (NCM) will be performed with a handheld DinoLite CapillaryScope 200 Pro (DinoLite Europe BV). Finger and toe pressures will be measured with photoelectric plethysmography (Biopac MP-160, Biopac Systems Inc., Goleta, CA, USA) and pressure cuffs on 5 fingers simultaneously. Doppler spectral analysis will be performed with the SMT Vicorder II (Wave Medical Heerenveen, the Netherlands).

Wrist bones

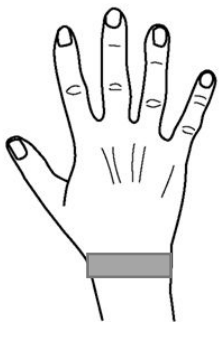
- **Radiocarpal**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **Intercarpal**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

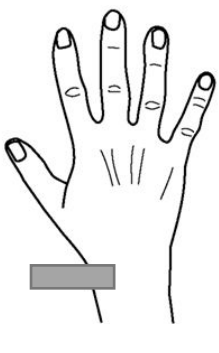


- **Distal radio-ulnar joint (DRUJ)**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

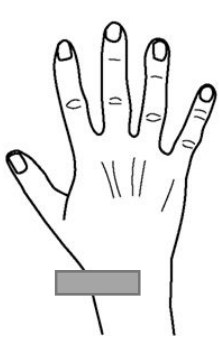


Compartments of extensor tendons

- **Wrist extensor compartment 1**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

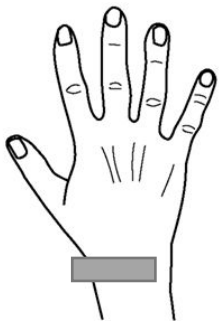


- **Wrist extensor compartment 2**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

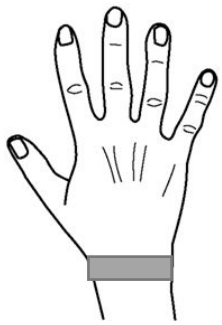


- **Wrist extensor compartment 3**

- Tenosynovitis
  - 0 = no
  - 1 = minimal
  - 2 = moderate
  - 3 = severe
- Power doppler within synovial sheath
  - 0 = no signal
  - 1 = focal signal
  - 2 = multifocal signal
  - 3 = diffuse signal
- Tenosynovial effusion
  - Presence y/n

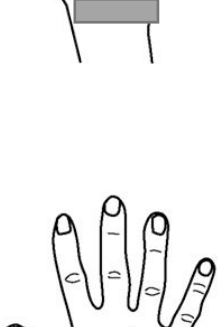


- **Wrist extensor compartment 4**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n



- **Wrist extensor compartment 5**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n

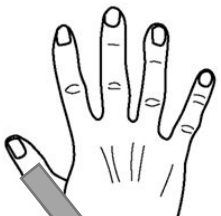
- **Wrist extensor compartment 6**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n



Switch to the hockey stick probe!

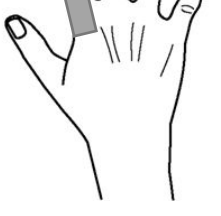
At MCP 1 level

- **MCP 1**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Extensor pollicus longus and brevis at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



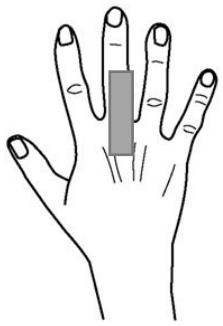
At MCP 2 level

- **MCP 2**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendon 2 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



At MCP 3 level

- **MCP 3**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendon 3 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)

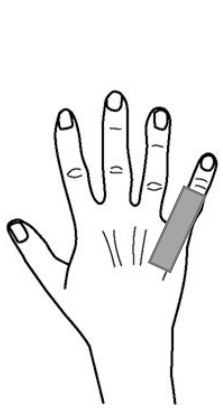


At MCP 4 level

- **MCP 4**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendons 4 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)

At MCP 5 level

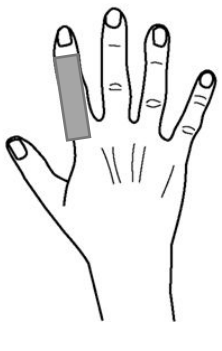
- **MCP 5**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n
- **Central slip of extensor tendons 5 at MCP level**
  - Thickening of extensor tendons
    - Tendon width (max)



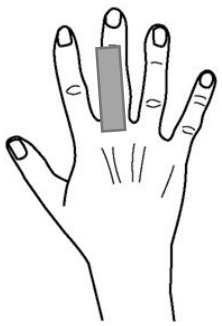
At (P)IP level

- **IP**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n

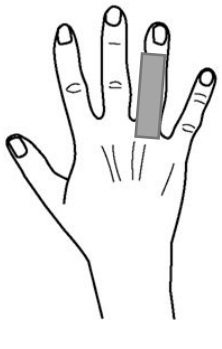
- **PIP 2**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



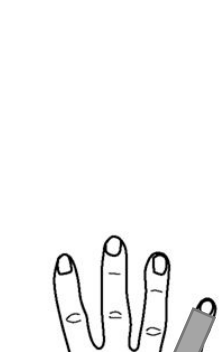
- **PIP 3**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **PIP 4**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



- **PIP 5**
  - Joint effusion
    - 0 = none
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Synovial hypertrophy
    - 0 = none
    - 1 = up to the level of the horizontal line connecting bone surfaces of the joint
    - 2 = extending beyond joint line but with upper surface concave or flat
    - 3 = extension beyond joint line but with upper surface convex
  - Doppler signal
    - 0 = no flow in the synovium
    - 1 = single vessel signals
    - 2 = vessel signals < half of the synovium
    - 3 = vessel signal > half of the synovium
  - Osteophytes
    - Presence y/n



Ask subject to turn their hand with the palmar side up!

Palmar side of digit 1

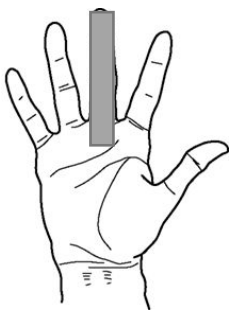
- **Flexor pollicus longus and brevis at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 1**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

Palmar side of digit 2

- **Finger flexors (sup + prof) 2 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 2 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 2**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

Palmar side of digit 3

- **Finger flexors (sup + prof) 3 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 3 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 3**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

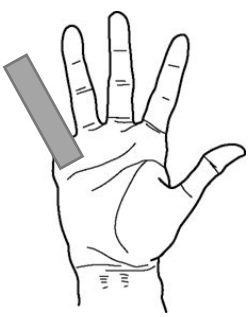


Palmar side of digit 4

- **Finger flexors (sup + prof) 4 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 4 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 4**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger

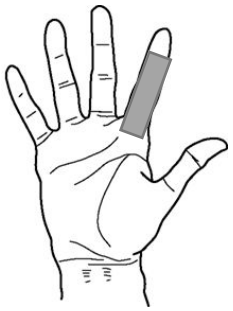
Palmar side of digit 5

- **Finger flexors (sup + prof) 5 at MCP level**
  - Tenosynovitis
    - 0 = no
    - 1 = minimal
    - 2 = moderate
    - 3 = severe
  - Power doppler within synovial sheath
    - 0 = no signal
    - 1 = focal signal
    - 2 = multifocal signal
    - 3 = diffuse signal
  - Tenosynovial effusion
    - Presence y/n
  - Thickening of flexor tendons
    - Tendon width (max)
- **A1 pulley 5 at MCP level**
  - Thickening of A1 pulley
    - Max width (transverse)
- **Digit 5**
  - Calcifications
    - Presence y/n
    - Location
    - Number per finger



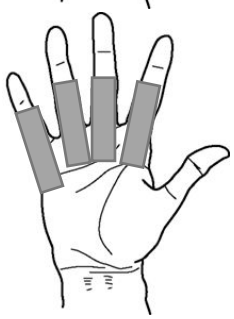
Only look at the arteries in the dominant hand!

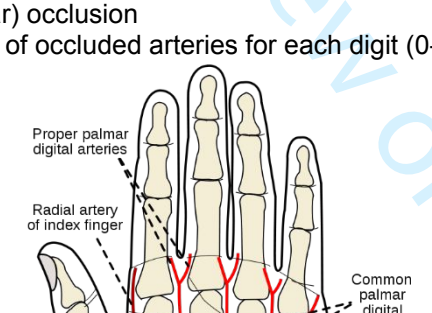
- **Radial artery index finger at MCP-DIP section**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion
  - Intima media thickness
    - Max thickness on section



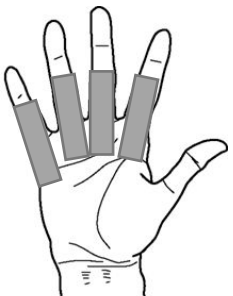
- **Princeps pollicus artery at MCP-IP section**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion

- **Proper palmar digital arteries of digit 2-5 at MCP level**
  - Occlusion
    - 0 = normal
    - 1 = abnormal
    - 2 = (near) occlusion
    - Number of occluded arteries for each digit (0-2)





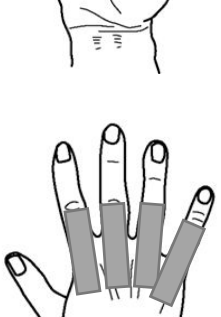
Elastography only in UMCU and only in dominant hand, use linear probe!



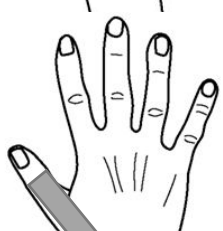
- **Finger flexor tendons 2-5 at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

- **Flexor pollicus longus and brevis at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

Ask subject to turn their hand with dorsal side up



- **Finger extensor tendons 1-5 at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)



- **Extensor pollicus longus and brevis at MCP level**
  - Shear wave elastography
    - Velocity (meters per second)
    - Stiffness (kiloPascals)

MRI assessment

Materials

A 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) with dedicated surface coils.

Variables

Outcomes	Area	Scoring
Synovitis or tenosynovitis (9) Hyperintense signal on both STIR and fat-saturated post-gadolinium images in a thickened articular and tendon sheath synovium	• Radiocarpal • Intercarpal • MCPs 2-5 • PIPs 2-5	• Synovitis None/Focal/Diffuse / of Mild/moderate /severe • Tenosynovitis None/Focal/Diffuse
Erosions (10) Sharply marginated bone lesion, with correct juxta-articular localisation and typical signal characteristics, with a cortical break visible in two adjacent planes.	• Radiocarpal • Intercarpal • MCPs 2-5 • PIPs 2-5	• Presence • Number • Location (specify joint)
Bone edema	• AREA	• None/mild/moderate/severe

Procedure

The MRI examination will be performed on the dominant hand. Non-enhanced transverse and coronal T1-weighted, fast spin-echo T2-weighted and short-tau inversion recovery (STIR) and/or fat-saturated proton-density sequences will be performed with contrast enhancement.

A radiologists will assess the MRI images and reported the scores in an eCRF. The MRI will be performed at baseline in the first 50 patients participating at the UMC Utrecht. MRI examinations will be performed on the day of the baseline ultrasound and read without knowledge of hand function scores.

References

1. Mathiessen A, Hammer HB, Terslev L, Kortekaas MC, D'Agostino MA, Haugen IK, et al. Ultrasonography of Inflammatory and Structural Lesions in Hand Osteoarthritis: An Outcome Measures in Rheumatology Agreement and Reliability Study. Arthritis Care Res (Hoboken). 2022 Dec 1;74(12):2005–12.
2. Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint P V., Filippucci E, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis. 2013 Aug;72(8):1328–34.
3. Hughes M, Manning J, Moore T, Herrick AL, Chitale S. Ultrasound findings in finger flexor tendons in systemic sclerosis: A cross-sectional pilot study. 5(1):77–82.
4. Tagliafico A, Panico N, Serafini G, Ghio M, Martinoli C. The thickness of the A1 pulleys reflects the disability of hand mobility in scleroderma. A pilot study using high-frequency ultrasound. Eur J Radiol. 2011 Feb 1;77(2):254–7.
5. Guerini H, Pessis E, Theumann N, Le Quintrec JS, Campagna R, Chevrot A, et al. Sonographic Appearance of Trigger Fingers. Journal of Ultrasound in Medicine. 2008 Oct 1;27(10):1407–13.
6. Sato J, Ishii Y, Noguchi H. Comparison of the Thickness of Pulley and Flexor Tendon Between in Neutral and in Flexed Positions of Trigger Finger. Open Orthop J. 2016 Mar 30;10(1):36.
7. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open. 2018;4(1).
8. Drakonaki E. Ultrasound elastography for imaging tendons and muscles. J Ultrason [Internet]. 2012 Jun 30 [cited 2023 Oct 2];12(49):214. Available from: /pmc/articles/PMC4579737/
9. Schanz S, Henes J, Ulmer A, Kötter I, Fierlbeck G, Claussen CD, et al. Magnetic resonance imaging findings in patients with systemic scleroderma and musculoskeletal symptoms. Eur Radiol. 2013 Jan 29;23(1):212–21.
10. Østergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. Vol. 30, Journal of Rheumatology. 2003 [cited 2023 Aug 4]. p. 1385–6 OMERACT rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. Available from: https://pubmed.ncbi.nlm.nih.gov/12784422/