Association between ultrasound evaluation of the joint and nail and Dynamic contrast-enhanced magnetic resonance imaging, nailbed capillaroscopy and optical coherence tomography of the nail in Psoriatic Arthritis patients with DIP-arthritis: a Multimodal Imaging Diagnostic feasibility and Accuracy study in psoriatic arthritiS (MIDAS)

Jørgen Guldberg-Møller (JG), Karen Ellegaard (KE), Christine Ballegaard (CB), Mette Mogensen (MM), Mikael Boesen (MB), Lars Erik Kristensen (LEK).

Author affiliations

JG: The Parker Institute, Department of Rheumatology. Bispebjerg and Frederiksberg Hospital, The Capital Region of Copenhagen, Denmark.
KE: The Parker Institute, Department of Rheumatology. Bispebjerg and Frederiksberg Hospital, The Capital Region of Copenhagen, Denmark.
CB: The Parker Institute, Department of Rheumatology. Bispebjerg and Frederiksberg Hospital, The Capital Region of Copenhagen, Denmark.
MM: Department of Dermatology, Bispebjerg Hospital, Copenhagen University, Bispebjerg Bakke 23, 2400 København NV.

MB: Department of Radiology, Bispebjerg Hospital, Copenhagen University, Bispebjerg Bakke 23, 2400 København NV.
LEK: The Parker Institute, Department of Rheumatology. Bispebjerg and Frederiksberg Hospital, The Capital Region of Copenhagen, Denmark.

Study protocol

A: Aim and Background (”Introduction”)

B: Method including participants (inclusion and exclusion criteria)

C: Statistical considerations

D: Side effects, risks and adverse events

E: Ensuring the integrity and privacy of participant's

F: Funding

G: Remuneration

H: Recruitment

I: Study information

J: Dissemination of study results

K: Ethical considerations

L: Insurance

M: Perspectives

N: References

A: Aim and Background ("Introduction")

Psoriatic arthritis (PsA) is seen in 5-40 % of patients with psoriasis (PsO) (1). It is a systemic inflammatory disease mainly affecting joints, spine and entheses. The disease causes pain, reduced physical performance, impaired quality of life and risk of progressive joint destruction and disability (2).

PsA is one of the most challenging clinical entities in rheumatology. The clinical presentation of the disease includes diverse articular, entheseal and dermatological features as well as varied disease course and outcomes (2–4).

Clinical insight into the nature of PsA is necessary to optimize and individualize treatment strategies. In that aspect, analyses of phenotypic- and prognostic characteristics of PsA patients are essential. Compared to rheumatoid arthritis, research in PsA is still sparse, but lately, there has been an increasing interest in the phenotypic variability and genetic subsets of the disease (5).

Imaging studies have shown anatomical relationships between nail beds, nail matrixes, extensor tendon insertion points, distal phalanges, and distal interphalangeal (DIP) joints, suggesting that psoriatic nail manifestations may actually be an extension of enthesopathy in the neighbouring structures referred to as the synovio-entheseal complex (SEC)(6–8). This enthesopathy is thought to cause microdamage of the nail bed and is believed by some researcher to be associated with psoriatic skin and nail changes by means of a Koebner response (9).

Several clinical studies support this claim in finding a strong association between nail crumbling, onycholysis, and subungual hyperkeratosis and a clinical swollen or tender DIP-joint or proximal interphalangeal (PIP) joint on the same digit (10,11).

In recognition of the importance of enthesitis in PsA, different image modalities have been applied to explore the nail and SEC.

High-resolution MRI studies lend support to the SEC by showing that DIP joint disease in PsA is associated with entheseal- and bone-based inflammation suggesting that the enthesis is either the most prominent or earliest feature of changes in PsA DIP joint disease (7). This finding has later been confirmed using [18F] fluoride positron emission tomography (hrPET) showing a diffuse pattern of bone-metabolism with focal hotspots at the enthesis and diffuse DIP involvement in PsA with hot spots where the nail is attached close to the tufts (12). This uptake pattern is compared with osteoarthritis (OA) displaying bone-metabolism at sites of erosions and osteophytes. To the

extent of our knowledge, no studies have confirmed these findings using Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

US confirmed an association between extensor tendon enthesopathy and clinical nail involvement and the dissociation between DIP joint synovitis and nail involvement. DIP extensor tendon enthesis was present in both PsO and PsA but more frequent in PsA patients which is in accordance with entheseal inflammatory involvement as a central part for the pathogenesis and development of PsA (13).

Furthermore, clinical nail changes have been linked to early entheseal abnormalities on US both at DIP joint level and remote sites showing a threefold likelihood of detecting enthesopathy on US when nail psoriasis severity index (NAPSI) score was ≥ 4 (14,15). In this context, US has proven to be advantageous to clinical examination in disclosing early nail disease. When compared with healthy subjects and patients with RA US changes especially of the ventral nail plate was higher in PsA and PsO (16). These US findings were present even though approximately half of the PsA and PsO patients did not have any clinical findings.

Another clinical tool to evaluate nail involvement is nail fold capillaroscopy where patients with PsA nail involvement presented a lower mean capillary density than healthy controls independent of presence or absence of arthritis of distal interphalangeal joints. In PsA patients with distal interphalangeal joint involvement, independent of the concomitant nail damage, a decreased diameter of the arterial and the venous limb of the capillary loop has been observed (17). A significantly lower mean capillary length and mean capillary density was found in PsA as compared with healthy individuals (18).

A promising optical imaging modality for evaluating the nail and nail fold is Optical coherence tomography (OCT) which has been proven superior to dermoscopy and video capillaroscopy in evaluating nails and nail folds. OCT in nail psoriasis is able to identify and objectively quantify novel findings such as an increased vessel size, vessel density, and thickened epidermis in the proximal nail fold, previously only seen on histopathology (19), thus being able to detect subclinical nail involvement in PsA and PsO compared with healthy controls(20). Dynamic OCT (D-OCT) enables visualization of skin microvasculature.

The use of US in clinical practice is not supported by adequate evidence, reflecting the need to determine the role of US in diagnosis and differentiation in psoriatic disease compared with other image modalities in a clinical setting.

Aim and objective

1) To compare US of the DIP- joint, entheseal and nail findings with other image modalities such as DCE-MRI, D-OCT, capillaroscopy and clinical evaluation of the nail in order to optimize the use of US in clinical practice.
    a) Primary: To compare the association of DIP joint US and nail D-OCT as proxy methods for measuring enthesitis distally.
    b) Secondary: Correlate US parameters to parameters of DCE-MRI and nailbed capillaroscopy and NAPSI-score.
    c) Exploratory: To further understand the nature of enthesitis and DIP-joint involvement in general.
        (1) Differentiate DIP- joint, bone and entheseal changes on US, DCE-MRI and D-OCT in PsA with patients with PsO with nail involvement and OA.
        (2) Discriminate between physiologic and pathologic findings in US detected tendon thickness, color Doppler activity, erosions, bony spurs and synovitis of the DIP-joint in age stratified asymptomatic participants.

B: Method including participants (inclusion and exclusion criteria)

The study will be a non-interventional multimodal imaging feasibility and accuracy study. A cohort of PsA patients in routine care by their treating rheumatologist will be enrolled in the Non-Intervention-Study (NIS) framework. The enrolment period will be 24 months - from 1st June 2018 until 1st June 2020.

Participants

Patients of at least 18 years of age diagnosed with PsA by a rheumatologist and fulfilling the CASPAR classification criteria (21) will be identified during routine care at the Departments of Rheumatology and of Dermatology both in the Region of Copenhagen and the Region of Zealand

(**Figure 1**). Ten patients diagnosed with radiologic verified OA of the DIP-joints will be recruited form Departments of Rheumatology at Bispebjerg and Frederiksberg Hospital. Ten patients diagnosed with PsO with nail involvement will be recruited from the Department of Dermatology at Bispebjerg and Frederiksberg Hospital.
30 asymptomatic participants will be recruited via poster from the staff at The Parker Institute and Department of Rheumatology and Dermatology at Bispebjerg and Frederiksberg Hospital and stratified into 18-40 years, 40-60 years and 60+ years age groups. The asymptomatic patients will only undergo US evaluation since studies on asymptomatic or healthy participants already exist in MRI, DE-OCT and videokapillaroscopy (18,20,22).
The primary study investigator (JG) will determine whether the criteria for in- and exclusion are fulfilled (**Table 1**) and inform the patients further about the content and terms of the study.

Outcome measures

Primary and secondary outcome and explorative outcomes are presented in **Table 2**.

Imaging

Ultrasound assessment of the DIP

US examinations are performed in a darkened room by two experienced sonographers blinded to the patient's clinical and laboratory data (JG, KE). Patients are asked not to talk with the operators about their clinical condition. The images of all patients will be saved in a digital archiving computer system for subsequent scoring. A GE LOGIQ 9 unit (General Electric Medical Systems, known as GE Healthcare, Little Chalfont, Buckinghamshire, UK) provided with a high-frequency probe 9 - 15 MHz is used.
Preliminary evaluation of the high-frequency matrix probe 6 - 15 MHz / hockey stick 8-18 MHz / L10-22-RS 10-22 MHz is currently underway to determine the most suitable probe for the study.

The dorsal, radial, ulnar and volar aspect of the DIP joints from 2nd to 5th fingers are assessed in the target hand to evaluate the DIP joint.
A proper amount of gel is placed on the skin in order to avoid compression on soft tissues under examination and a specific pre-set was developed for optimizing of grey scale images and to ensure sensitive to slow flow in accordance with current recommendations. GS synovial hypertrophy and CD will be semiquantitative scored 0-3 adapted from EULAR-OMERACT combined

scoring system for grading synovitis in rheumatoid arthritis (23,24). The highest score from either aspect will be counted. Erosions and new bone formation will be scored absent/present 0/1.
The dorsal aspect of DIP joints from 2nd to 5th fingers are assessed bilaterally to evaluate the enthesis. The insertion of the extensor tendon will be measured in the longitudinal plane from the bone perpendicular to the tendon and compared with the thickness of the tendon 5 mm proximal from the insertion. The insertion of the flexor tendon will be measured in the longitudinal plane from the bone surface perpendicular to the superficial side of the tendon. The Flexor and extensor tendon enthesopathy will be evaluated according to OMERACT standards (23,24).

Ultrasound assessment of the nail

US examinations are performed in a darkened room with a constant controlled temperature of 24ºC, after a 20-minute rest period. The nails are scanned on the longitudinal plane. The ultrasound gel has sufficient quantity so that the transducer exerted no compression, to avoid alteration of nail thickness or blood flow.
Each fingernail from 2nd to 5th fingers are scanned in the grayscale mode with a high-frequency probe 9 - 15 MHz frequency transducer. Doppler quantification technique will enable blood flow visualization of the nail fold by calculating the number of colored pixels in relation to the total amount of pixels in the ROI expressed as the color fraction (colored pixels/total pixels). The region of interest (ROI) is drawn from the basis of the distal phalanges, along the bony surface to the level of the nail fold and to the nail-basis. Nail bed thickness will be obtained by measuring the distance in mm. perpendicular to the skin encompassing the nail matrix, nail fold and extensor tendon from the DIP – joint from the bone surface to the nail plate at the nail fold.

Dynamic contrast-enhanced magnetic resonance imaging

The distal phalanges and DIP from 2nd to 5th fingers will be examined in a 3T Siemens Verio® MR scanner with the patient's supine and the hand along the side of the body (3T Verio) using a semi-flex 16 channel body coil and the following protocol:

Gradient echo scout (slice thickness (ST) 6mm, Field of View (FOV) 400x400mm, TE 3.69milliseconds (ms), TR 7.8ms, scan time 17seconds (sec)), Coronal T1 weighted (T1W) turbo spin echo (TSE) (ST 1.5mm, FOV 250x250mm, matrix resolution 0.3x0.3x1.5mm, TE 25 ms, TR

832ms, scan time 4min28sec), coronal STIR (STIR: ST 2.5mm, FOV 180x180mm, matrix resolution 0.9x0.8x2.5mm, TI 220ms, TE 32 ms, TR 4500ms, scan time 2min48sec) axial STIR covering the DIP-joints (ST 4 mm ST, FOV 160x160mm, matrix resolution 0.6x0.6x5mm, TI 220ms, TE 32 ms, TR 4500ms, scan time 2min30sec), Gradient echo 3D T1w VIBE (ST 0.9mm, FOV 250x250mm, matrix resolution 0.9x0.9x0.9mm, Flip angle (FA) 10degrees, TE 6ms, TR 13.5ms, scan time 2min35sec) and axial diffusion weighted images (T2-weighted single-shot spin-echo echo-planar imaging sequence with b-values 0, 50, and 800, FOV and matrix 160x160, ST 4mm) covering 2-5 DIP and DIP-joints. Simultaneously with the intravenous injection of 0.1 ml/kg body weight Gadolinium contrast (Dotarem) using a power injector (2ml per second), a sequential axial DCE-MRI gradient echo T1w (VIBE) sequence is performed in eighteen 4mm slices every 9 seconds covering the PIP and DIP joints, with 30 repetitions using the following parameters: TE 1.86, TR 5.51 FA 15degrees, matrix resolution 256x256, Total scan time 4min40 seconds). Following the DCE-MRI sequence, the 3D T1-weighted VIBE sequence of the hand is repeated. Total imaging time varies between 30-35minutes.

MRI evaluation:

The coronal and axial STIR and 3D coronal T1 gradient echo VIBE pre- and post-contrast images were used for PsAMRIS scoring including synovitis, tenosynovitis, bony proliferation, bone marrow oedema and erosions (22).

The sequential axial T1 gradient-echo DCE-MRI images are analyzed using DYNAMIKA® (www.imageanalysis.org.uk). After application of movement correction between temporal slices the data is analyzed in three independent ways: 1) a fully automatic whole hand analysis and 2) the slice with most enhancement as judged by eye is selected and a ROI is drawn around the each of the DIP 2-5 joints, each of the fingers and each of the hand muscles respectively, excluding large blood vessels from analysis, and 3) A 3dimensional (3D) ROI is drawn around the distal phalanges and DIP from 2nd to 5th fingers, excluding large blood vessels from analysis. The computed output data in the whole hand analysis and the various ROIs comprise the mean of: initial rate of enhancement (IRE), maximum enhancement (ME), number of enhancing voxels with plateau and washout enhancement pattern (N-plateau and N-washout) and their combinations N-plateau+N-washout, ME*N-plateau+N-washout and IRE*N-plateau+N-washout.

Optical coherence tomography

If psoriatic nail change is present nails and nailbeds from 2nd to 5th fingers are scanned by a trained medical doctor (MM) using a VivoSight DxOCT system with a handheld probe (Michelson Diagnostics Ltd.: CE 0459, FDA K080788). A multibeam frequency-domain OCT system with a central laser wavelength of 1-310 nm.

The nail plates are assessed longitudinally from the lunula to the distal nail and from the lateral to the medial side. The OCT probe is applied directly to the nail without intermediate gel. The scanning of each nail takes less than 1 min and cause minimal discomfort to the subjects studied. OCT provides images of the nail plate, the nail bed and the matrix up to a depth of 2 mm and a width of 6 mm. The multislice mode is used, recording 250 slices per 6 x 6 mm to provide densely sampled 3D 'bread slice' image volumes.

Images of the microcirculation in the skin are acquired using the dynamic OCT-signals (D-OCT) also termed speckle variance from the Vivosight Dx system. The method relies on the higher variation of speckles from motion such as motion from moving blood cells. The D-OCT data is collected concurrently with structural OCT data and displayed as a red overlay on the conventional OCT images. The D-OCT enables visualization of blood vessels in the skin. D-OCT images are analysed and vessel flow calculated using an integrated software tool (Michelson diagnostics Ltd. Kent, UK) and represented by an arbitrary number since D-OCT does not measure flow in m/s.

Nailfold capillaroscopy

Nailfold capillaroscopy of the nailbeds from 2nd to 5th fingers are performed with Optilia Digital Capillaroscopy System in a room with a constant temperature setting of 24°C by a trained medical examiner (JG).

The following capillaroscopic parameters are evaluated: Number of capillaries per 1 mm, capillary morphology and capillary length. The mean capillary density is calculated as a number of capillary loops in the distal row per 1 mm. Abnormal morphology is graded absent or present and include irregularly enlarged capillaries, giant capillaries, capillary ramifications and capillary disorganization. Capillaries are termed long if they exceed 300 μm and short if measured lower than 200 μm.

Clinical assessment of the nail

Modified nail psoriasis severity index (mNAPSI) was utilized to score the severity of each nail disease in PsA patients. Each nail was scored by the presence of nail pitting, crumbling, onycholysis, splinter haemorrhage, red spot lunula, hyperkeratosis and oil drop sign. Higher scores represent worse nail disease, ranging 0–13 per nail. The nail characteristics of each digit are also documented.

C: STATISTICAL METHODS

Sample Size Justification and Statistical Analysis

Fifty patients are sufficient to detect correlations (r-values) of more than 0.4 with a two-tailed p-value of 0.05 and a Beta of 0.2 (ie. 80% power). The study period is limited to 12 months which presumably allows us to enroll fifty patients with PsA and ten patients with OA and ten with PsO. R-value of 0.4 is chosen as it is considered to be a meaningful correlation in imaging studies conducted in rheumatology (23). The study is exploratory in its nature and future decision-making studies are needed to further validate the findings in this study.

Continuous variables, as well as potential rank scale or nominal variables (TBD), will be derived. The sample size is powered to the primary outcome.

D: SIDE EFFECTS, RISKS AND ADVERSE EVENTS DURING THE STUDY

Only non-invasive examinations will be performed during the study, except for administrating a venous catheter that withholds a minimal risk of infections, bruising and discomfort.

MRI is a safe procedure if radiological criterions for contraindications are upheld such as awareness of metal implants. All patients will be offered to have a conventional MRI of the DIP-joints including non-contrast enhanced sequences like T1, STIR, 3D VIBE and DWI images, but intravenous Gadolinium contrast and thus DCE-MRI will only be performed if the patient have a normal kidney function measured by an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m2, in accordance with The European Medicines Agency's guidelines on the administration of IV Gadolinium-containing contrast agents (24). In patients with normal kidney

function, most of the gadolinium contrast medium injected (over 90%) is passed out in the urine within 24 hours. The procedure holds no exposure to radiation.
No discomfort or risk is associated with the US examination or the clinical examination, except for short-term tenderness related to standard examination of sore muscular skeletal structures. If intolerable discomfort arises during any examination, the procedure will discontinue immediately. Nailfold capillaroscopy and OCT of the nails are non-invasive procedures and uses light to produce images and not ionizing radiation. The scanning of each nail takes less than 1 min for minimal discomfort to the subjects studied.

E: ENSURING INTEGRITY AND PRIVACY OF THE PARTICIPANTS

All patient-related information obtained during the study will be handled in accordance with the Danish law for the protection of personal data ("lov om behandling af personoplysninger") and the Danish health law ("sundhedsloven"). The study will be submitted to the Danish Data Protection Agency for approval. Only data regarding the diagnosis of psoriatic arthritis, skin psoriasis or osteoarthritis, disease duration, X-ray of the hands and blood tests will be obtained from the patient's journal for recruitment purposes.

F: FUNDING

The idea and design of the current study arose from researchers at the Parker Institute and Bispebjerg Hospital. None of the researchers has any conflicting or economic interests in the project. The Oak Foundation (the Parker Institute) supports the three-year PhD-study by enabling the research program (payment of clinical staff and imaging) and salary (1.566.000 dkr). A co-affiliation with Slagelse Hospital provides the PhD university fees (150.000 dkr).

G: REMUNERATION

Participants and research partners will not receive any economic compensation.

H: RECRUITMENT OF PARTICIPANTS

Patients will be recruited from outpatient clinics during routine care. The treating rheumatologist or dermatologist will orally inform possible participants about the study and hand out written

information and consent form incl. the contact information of the principal investigator (JG). Healthy participants who respond to the posters will be verbally informed about the project on the phone by the principal investigator (JG) and if interested receive written information about the study per mail. After carefully reading the written information at home patients and healthy participants will have at least 24 hours to consider the information given. Interested participants will be invited to a screening visit. The screening visit is performed in a quiet room at the Parker Institute in the presence of a delegate if preferred and begins with a Q&A session with the investigator after which the participant will have to 2 days reflection time before signed informed consent is obtained. At the screening visit, all criteria for inclusion and exclusion are reviewed.

I: STUDY INFORMATION

Study participants will be able to contact the principal investigator or the project secretary by telephone or email whenever needed during the study period.

J: DISSEMINATION OF STUDY RESULTS

Both positive, negative or inconclusive results of the study will be disseminated through publication in international peer-reviewed journals and during presentation at national and international conferences. Patients/members of The Danish Rheumatism Association and The Danish Psoriasis Association will be informed of the study and the results by public outreach in the form of layman articles and short study reports at the websites and in newsletters.

K: ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the Declaration of Helsinki for biomedical research involving human subjects (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA General Assembly, Seoul, October 2008).

The study will include human subjects characterized by being able to give informed consent, being ≥ 18 years of age, not being a part of any vulnerable groups, and being volunteers impacted by chronic disease.

From our point of view, this study withholds only minimal or no risk of harm. The DCE-MRI is associated with no radiation exposure and minimal discomfort for the participating patients comprising venous access.

Signed informed consent will be obtained from all participants. Patients will be informed that by signing a written consent they accept that information from patient hospital files regarding disease duration and diagnosis of rheumatic diseases will be collected for use in the current study.

The potential benefits of the study will be substantial since knowledge of disease mechanisms and diagnostics in PsA is warranted in the perspective of enhancing prognostic evaluation and treatment strategies in the future.

No individual benefits are obtained from participation in the study except for a thorough multidisciplinary examination and evaluation of the psoriatic disease, which may be difficult to achieve during routine care. Patients might enhance their understanding of psoriatic disease, pain mechanisms and prognosis in general during study participation.

Incidental findings

An incidental finding (IF) is defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This means that IF´s may be of variables not directly under study and may not be anticipated in the research protocol"(25).

It is good research conduct to return results only if:

(a) "the findings are scientifically valid and confirmed"

(b) "the findings have significant implications for the subjects' health concerns" and

(c) "a course of action to ameliorate or treat these concerns is readily available"(26)

L: INSURANCE

The Danish Patient Insurance Association will cover any injury that may occur to the participants during the study program.

M: PERSPECTIVE

Understanding the relationship between entheseal and DIP-joint US and nailbed vascular changes

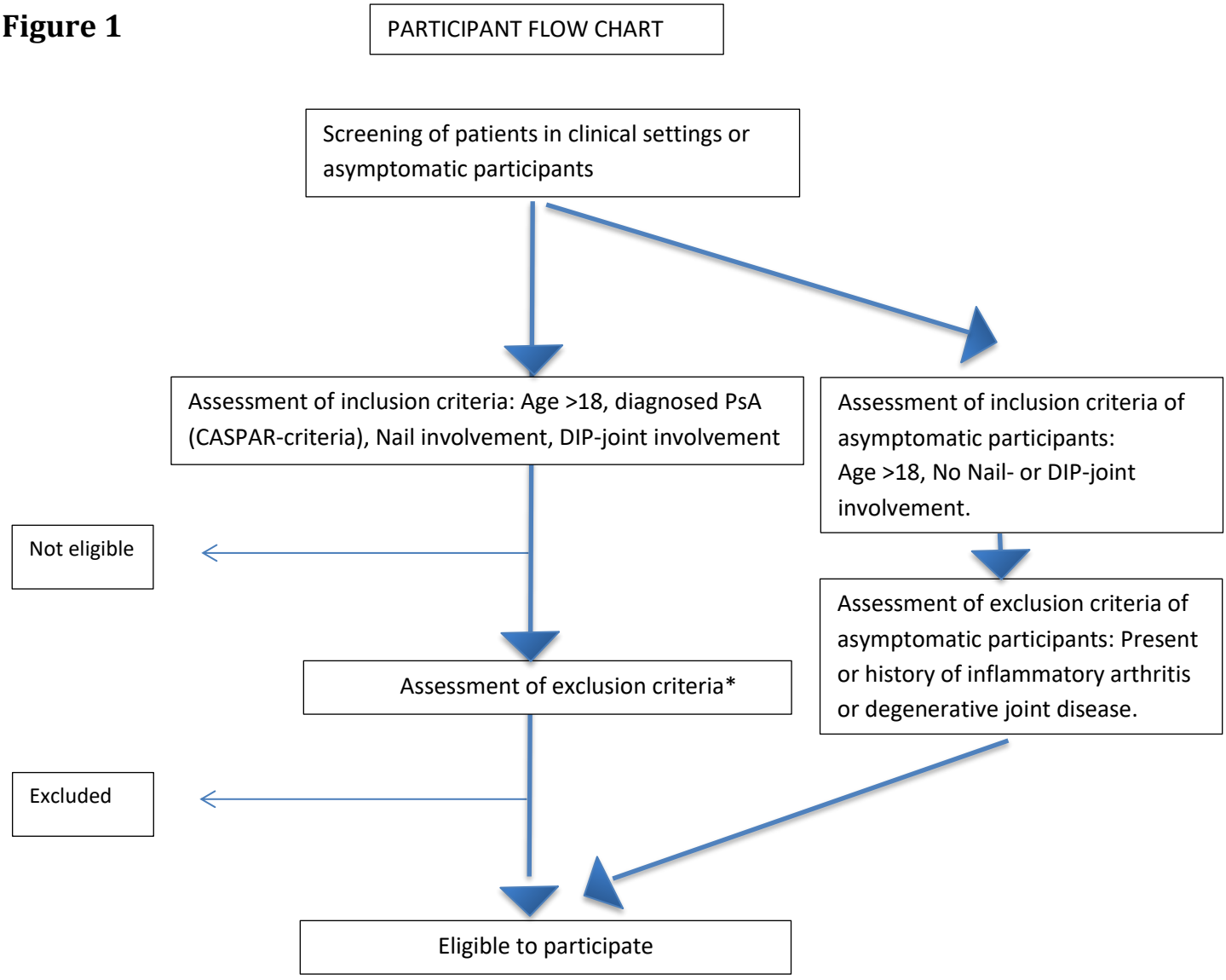
studied by OCT and capillaroscopy could result in better monitoring and detection of inflammatory activity, both in patients with DIP joint arthritis (PsA) and detection of “occult” enthesitis in patients with nail PsO.

Thus, this study could lead to changed clinical practice both in the rheumatologic and dermatologic setting. Capillaroscopy and OCT could be widely used by dermatologists, improving catchment and monitoring of patients with both nail Pso and PsA. Likewise, the rheumatologist might incorporate some of these measures in treatment practice for DIP-joint monitoring purposes.

Moreover, outcome measures and monitoring practice both clinically and in trials could be influenced by results obtained in this study.

Incorporating DCE-MRI) will further elucidate interactions and associations between nailbed, nail matrix, and DIP-joint structures. These findings are primarily for research purposes and will add to the body of knowledge more than changing clinical practice directly. A better understanding of the nature of enthesitis is needed and could contribute to a better understanding of the overall etiology, diagnosis, phenotyping, and potentially treatment-tailoring of PsA patients.

Figure 1



* Exclusion criteria: Absence of consent, pregnancy, inability to interpret the terms of the study or understand Danish, reduced kidney function expressed as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or history of chronic kidney failure, other inflammatory rheumatic diseases, treatment with oral, intra-articular or intra-muscular glucocorticoids within the past 3 weeks, treatment with mild analgesics (non-steroidal anti-inflammatory drugs, acetylsalicylic acid, acetaminophen) 24 hours prior to assessment .

Table 1

Criteria for inclusion:

- ≥ 18 years old and under 85 years
- Able to understand, read and speak Danish
- Diagnosed with PsA according to the CASPAR criteria within five years
- Diagnosed with skin psoriasis or osteoarthritis by a physician
- DIP-joint arthralgia and/or arthritis (when 1 of the following features are present: swelling, tenderness, and decreased range of motion)
- Modified nail psoriasis severity index (mNAPSI) of ≥ 5

Criteria for inclusion asymptomatic participants:

- ≥ 18 years old and under 85 years
- Able to understand, read and speak Danish
- No swollen or tender DIP-joint on clinical examination
- No nail changes

Criteria for exclusion:

- Absence of consent
- Pregnancy
- Reduced kidney function expressed as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or history of chronic kidney failure.
- Other inflammatory rheumatic diseases
- Treatment with oral, intra-articular or intra-muscular glucocorticoids within the past 3 weeks
- Treatment with mild analgesics (non-steroidal anti-inflammatory drugs, acetylsalicylic acid, acetaminophen) 24 hours prior to assessment

Criteria for exclusion asymptomatic participants:

- Absence of consent
- Present or history of inflammatory arthritis or degenerative joint disease such as osteoarthritis of the hands.

Treatment with mild analgesics (non-steroidal anti-inflammatory drugs, acetylsalicylic acid, acetaminophen) 24 hours prior to assessment

Table 2

Primary outcome*	**US:** Dorsal scan of the DIP-joint 2-5 will be semi-quantitatively scored 0-3 for Grey-scale synovitis (GSS) and 0-3 for colour Doppler (CD). The insertion of the extensor- and flexor tendon at the basis of phalanges distalis will be measured in mm. and evaluated for structural changes as well as CD signals and both will be scored as absent/present (0/1). Erosions and bone proliferation will be scores as absent/present (0/1). Blood flow of the nail fold will be visualized with Doppler quantification technique and measured as the colour fraction (%). The thickness of the nailbed will be measured in mm. A sum score of joint, entheses and nailbed changes will be calculated for each finger. **OCT:** Number of nailbed capillaries for each nail will be semiquantitatively scored 0-3 (0=> 9/mm, 1=7-8/mm, 2=4-6/mm, 3=1-3/mm). Blood flow will be visualized with D-OCT and quantified. A sum score of the number of capillary changes and blood flow will be calculated separately for each nail.
Secondary outcomes*	**US:** see above. **DCE-MRI:** An evaluation of synovitis, enthesitis and structural changes will be according to the PsAMRIS-score. **Nailfold capillaroscopy:** Number of nailbed capillaries will be semiquantitatively scored 0-3 (0=> 9/mm, 1=7-8/mm, 2=4-6/mm, 3=1-3/mm). Morphology changes will be scored as present/absent (0/1). Capillary length will scored 0 = normal (<300 µm), 1 = slightly elongated, 2 = moderately elongated, 3 = markedly elongated. A sum score of capillary changes will be calculated for each nail.
Further exploratory secondary outcomes	Multilevel logistic regression will be used to determine whether the prevalence of abnormalities differs between

	OA, PsO and PsA.

*: Correlations between US parameters and parameters of DCE-MRI, OCT, nailbed capillaroscopy and or clinical data are calculated according to Spearman. P<0.05 is considered significant. Fisher's exact test will be used to compare the proportion of abnormalities between the image modalities. Intraclass correlation coefficients (ICC) will be calculated accordingly.

N: References

1. O'Neill T, Silman AJ. Psoriatic arthritis. Historical background and epidemiology. Baillieres Clin Rheumatol [Internet]. 1994 May [cited 2017 Jun 26];8(2):245–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8076386

2. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis [Internet]. 2005 Mar 1 [cited 2017 Jun 26];64 Suppl 2(suppl_2):ii14-7. Available from: http://ard.bmj.com/cgi/doi/10.1136/ard.2004.032482

3. Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P T [Internet]. 2010 Dec [cited 2017 Jun 26];35(12):680–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21197266

4. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. Ann Rheum Dis [Internet]. 2011 Mar 1 [cited 2017 Jun 26];70 Suppl 1(Suppl 1):i77-84. Available from: http://ard.bmj.com/cgi/doi/10.1136/ard.2010.140582

5. Boehncke WH, Kirby B, Fitzgerald O, van de Kerkhof PCM. New developments in our understanding of psoriatic arthritis and their impact on the diagnosis and clinical management of the disease. J Eur Acad Dermatol Venereol [Internet]. 2014 Mar [cited 2017 Jun 26];28(3):264–70. Available from: http://doi.wiley.com/10.1111/jdv.12222

6. McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol [Internet]. 2009 Sep [cited 2017 Jun 26];23 Suppl 1:9–13. Available from: http://doi.wiley.com/10.1111/j.1468-3083.2009.03363.x

7. Tan AL, Grainger AJ, Tanner SF, Emery P, McGonagle D. A high-resolution magnetic resonance imaging study of distal interphalangeal joint arthropathy in psoriatic arthritis and osteoarthritis: are they the same? Arthritis Rheum [Internet]. 2006 Apr [cited 2017 Jun 21];54(4):1328–33. Available from: http://doi.wiley.com/10.1002/art.21736

8. McGonagle D, Tan AL, Benjamin M. The nail as a musculoskeletal appendage--implications for an improved understanding of the link between psoriasis and arthritis. Dermatology [Internet]. 2009 Dec 6 [cited 2017 Jun 26];218(2):97–102. Available from: http://www.karger.com/?doi=10.1159/000182250

9. McGonagle D, Tan AL, Benjamin M. The biomechanical link between skin and joint disease in psoriasis and psoriatic arthritis: what every dermatologist needs to know. Ann Rheum Dis [Internet]. 2008 Jan 1 [cited 2017 Jun 26];67(1):1–4. Available from: http://ard.bmj.com/cgi/doi/10.1136/ard.2007.080952

10. Sandre MK, Rohekar S, Guenther L. Psoriatic Nail Changes Are Associated With Clinical Outcomes in Psoriatic Arthritis. J Cutan Med Surg [Internet]. 2015 Jul 1 [cited 2017 Jun 21];19(4):367–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25775610

11. Lai TL, Pang HT, Cheuk YY, Yip ML. Psoriatic nail involvement and its relationship with distal interphalangeal joint disease. Clin Rheumatol [Internet]. 2016 Aug 1 [cited 2017 Jun 22];35(8):2031–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27251673

12. Tan AL, Tanner SF, Waller ML, Hensor EMA, Burns A, Jeavons AP, et al. High-resolution [18F]fluoride positron emission tomography of the distal interphalangeal joint in psoriatic arthritis--a bone-enthesis-nail complex. Rheumatology (Oxford) [Internet]. 2013 May 1 [cited 2017 Jun 27];52(5):898–

904. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kes384

13. Acosta-Felquer ML, Ruta S, Rosa J, Marin J, Ferreyra-Garrot L, Galimberti ML, et al. Ultrasound entheseal abnormalities at the distal interphalangeal joints and clinical nail involvement in patients with psoriasis and psoriatic arthritis, supporting the nail-enthesitis theory. Semin Arthritis Rheum [Internet]. 2017 May 11 [cited 2017 Aug 7]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0049017217302378

14. Castellanos-Gonz?lez M, Joven BE, S?nchez J, Andr?s-Esteban EM, Vanaclocha-Sebasti?n F, Romero PO, et al. Nail involvement can predict enthesopathy in patients with psoriasis. JDDG J der Dtsch Dermatologischen Gesellschaft [Internet]. 2016 Nov [cited 2017 Jun 23];14(11):1102–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27860304

15. Ash ZR, Tinazzi I, Gallego CC, Kwok C, Wilson C, Goodfield M, et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis [Internet]. 2012 Apr [cited 2017 Aug 7];71(4):553–6. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2011-200478

16. Sandobal C, Carbó E, Iribas J, Roverano S, Paira S. Ultrasound nail imaging on patients with psoriasis and psoriatic arthritis compared with rheumatoid arthritis and control subjects. J Clin Rheumatol [Internet]. 2014 Jan [cited 2017 Jun 21];20(1):21–4. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00124743-201401000-00004

17. Bhushan M, Moore T, Herrick AL, Griffiths CE. Nailfold video capillaroscopy in psoriasis. Br J Dermatol [Internet]. 2000 Jun [cited 2017 Jun 28];142(6):1171–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10848742

18. Lambova SN, M?ller-Ladner U. Capillaroscopic pattern in inflammatory arthritis. Microvasc Res [Internet]. 2012 May [cited 2017 Jun 27];83(3):318–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22426123

19. Aldahan AS, Chen LL, Fertig RM, Holmes J, Shah V V., Mlacker S, et al. Vascular Features of Nail Psoriasis Using Dynamic Optical Coherence Tomography. Ski Appendage Disord [Internet]. 2016 Jan [cited 2017 Aug 7];2(3–4):102–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28232916

20. Aydin SZ, Castillo-Gallego C, Ash ZR, Abignano G, Marzo-Ortega H, Wittmann M, et al. Potential Use of Optical Coherence Tomography and High-Frequency Ultrasound for the Assessment of Nail Disease in Psoriasis and Psoriatic Arthritis. Dermatology [Internet]. 2013 [cited 2017 Aug 7];227(1):45–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23988587

21. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum [Internet]. 2006 Aug [cited 2017 Jun 28];54(8):2665–73. Available from: http://doi.wiley.com/10.1002/art.21972

22. D. G, P. B, F. G, P.J. M, P. B, C.G. P, et al. Validation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. J Rheumatol [Internet]. 2015;42(12):2473–9. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L607126808%0A http://dx.doi.org/10.3899/jrheum.141010

23. Glinatsi D, Baker JF, Hetland ML, Hørslev-Petersen K, Ejbjerg BJ, Stengaard-Pedersen K, et al. Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials. Ann Rheum Dis [Internet]. 2017 Oct [cited 2017 Dec 18];76(10):1707–15. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2017-211315

24. Khawaja AZ, Cassidy DB, Al Shakarchi J, McGrogan DG, Inston NG, Jones RG. Revisiting the risks of MRI with Gadolinium based contrast agents???review of literature and guidelines. Vol. 6, Insights into Imaging. 2015. p. 553–8.

25. Wolf SM, Lawrenz FP, Nelson C a, Kahn JP, Cho MK, Clayton EW, et al. Managing incidental findings in human subjects research: analysis and recommendations. J Law Med Ethics [Internet]. 2008;36(2):219–48, 211. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1748-720X.2008.00266.x/abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2575242&tool=pmcentrez&rendertype=abstract

26. National Bioethics Advisory Commission (NBAC). Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Rockville; 1999. 1: at 72.