Fluorescence Optical Imaging

in Hand Osteoarthritis

Doctoral thesis by

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List of abbreviations

3D	Three-dimensional
ACR	American College of Rheumatology
AUC	Area under the curve
AUSCAN	Australian and Canadian Hand Index
BMI	Body Mass Index
CI	Confidence interval
CMC	Carpometacarpal joint
DAS-28	Disease Activity Score in 28 joints
DIP	Distal interphalangeal joints
DMARDs	Disease-modifying anti-rheumatic drugs
EULAR	European League Against Rheumatism
FOI	Fluorescence Optical Imaging
FOIAS	Fluorescence Optical Imaging Activity Score
GEE	Generalized estimating equations
HOAMRIS	Hand OA MRI score
ICC	Intraclass correlation coefficient
ICG	Indocyanine green
IL	Interleukin
LED	Light-emitting diode
MCP	Metacarpophalangeal joints
MRI	Magnetic resonance imaging
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis research society international

OMERACT	Outcome measures in rheumatology
OR	Odds ratio
OST	Optical spectral transmission
Pabak	Prevalence and bias adjusted kappa
Pabak-OS	Prevalence and bias adjusted kappa for ordinal scales
PCA	Percent close agreement
PEA	Percent exact agreement
PIP	Proximal interphalangeal joint[1]
RA	Rheumatoid arthritis
RCT	Randomized controlled trials
SD	Standard deviation
STT	Scaphotrapeziotrapezoid
TOMS	Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System

1. Throughout the thesis, PIP always includes 1st interphalangeal joint

List of papers

Paper I

Ø. Maugesten, S. Ohrndorf, D. Glinatsi, M. Ammitzbøll-Danielsen, Y. Kisten, M. Østergaard, L. Terslev, T. Uhlig, T.K. Kvien, I.K. Haugen

Evaluation of three scoring methods for Fluorescence Optical Imaging in erosive hand osteoarthritis and rheumatoid arthritis

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Paper II

Ø. Maugesten, A. Mathiessen, H. B. Hammer, S. Hestetun, T. K. Kvien, Till Uhlig, S. Ohrndorf, I.K. Haugen

Validity and diagnostic performance of Fluorescence Optical Imaging measuring synovitis in hand osteoarthritis: baseline results from the Nor-Hand cohort

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Paper III

Ø. Maugesten, S. Ohrndorf, B. Slatkowsky-Christensen, T. K. Kvien, T. Uhlig, I.K. Haugen

Associations between Fluorescence Optical Imaging and Magnetic Resonance Imaging and symptoms in hand osteoarthritis

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1 Introduction and background

1.1 Clinical aspects of hand osteoarthritis (OA)

1.1.1 Definitions and classification criteria

Osteoarthritis (OA) is one of the leading causes of disability and pain, affecting approximately 300 million people worldwide (1). Due to increased life expectancy, obesity, and a more sedate lifestyle the prevalence of OA is rising. Despite its considerable impact on quality of life and health care systems, no cure or efficient therapies exist so far (2). The name OA consists of *ostéon* (Greek, "related to bone"), *árthron* (Greek, "a joint"), and *-itis* (Latin, "inflammation"). Previously understood as a condition affecting cartilage secondary to "wear and tear", OA is now acknowledged to be a whole-joint disease, including the subchondral bone, synovium, joint capsule, ligaments, tendons, nerves and muscle in addition to the cartilage (3). Although any joint can be affected by OA, the knees, hips, hands, and spine are the most studied joints.

Hand OA is a heterogenous condition and is often divided into different entities based on distribution, radiographic findings or symptoms and clinical findings. Two entities of hand OA based on joint distribution are interphalangeal OA affecting the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints (nodal or non-nodal), and thumb base OA affecting the 1st carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints (3, 4). These two might coexist; however, thumb base OA is present in isolation more frequently than interphalangeal OA (5). The Kellgren Lawrence scoring system is commonly applied in hand OA research (6, 7). In a systematic search, definite radiographic hand OA on the joint level was defined as Kellgren Lawrence grade 2 or more in a clear majority of studies (95-100 %), while the definition of overall radiographic hand OA varied considerably (8).

Clinical hand OA is based on clinical features only, and the American College of Rheumatology (ACR) classification criteria for hand OA are often applied. These include 1) pain, aching, or stiffness of the hands on most days of prior month, 2) bony enlargements of at least two out of 10 selected joints (the bilateral second and third DIP and PIP joints and the thumb base), 3) less than three swollen metacarpophalangeal (MCP) joints, 4) at least two DIP joints with bony enlargements and 5) at least 2 out of 10 selected joints (the bilateral second and third DIP and PIP joints and the thumb base) with deformity (9). Diagnosis requires items 1 to 3 and either 4 or 5. These criteria do not include radiographic findings and are hampered by poor sensitivity for early OA, and new classification criteria are being developed (10). Finally, symptomatic hand OA combines radiographic and clinical findings, i.e., presence of at least one hand joint with Kellgren Lawrence grade 2, or more, and hand pain, aching or stiffness (11).

Another common way of defining hand OA subsets is to differentiate between erosive vs. non-erosive disease, based on the presence of central erosions and collapse of the subchondral plate in finger joints. It remains a contentious subject whether erosive hand OA is a distinct entity or a severe form of hand OA and it has been suggested to be a more inflammatory phenotype than non-erosive hand OA (3, 4). More power Doppler activity has been demonstrated in erosive hand OA (12), and synovitis and radiographic changes progress faster (13).

Historically, OA was defined as primary or idiopathic when the etiology was unclear. The term secondary OA was applied when an underlying event or condition was hypothesized to be the driver of the disease. This included trauma, inflammatory arthritis, avascular necrosis and infection, endocrine disorders like acromegaly and hyperparathyroidism, systemic metabolic disease like hemochromatosis, ochronosis and Wilson disease and hypermobility syndrome (14). Nonetheless, with advancing knowledge of the complexity of

the OA etiopathogenesis, it has been acknowledged that no OA is truly idiopathic, and the terms primary and secondary OA are rarely applied in current OA research (15).

1.1.2 Epidemiology

Hand OA is a widespread condition, and reported prevalence and incidence differ based on the definition of disease, age, sex and geographical factors in the population studied (3). The reported prevalence of radiographic hand OA is higher than symptomatic hand OA (16). In the Framingham study, age-standardized prevalence of radiographic hand OA was found to be 44 % in women and 38 % in men (11). Two other studies presented half and twice this prevalence; in a cohort from North-Carolina (US), the overall prevalence of radiographic hand OA in women between 40 and 53 years was estimated to be 21 %, while a Japanese study with an older population (mean 66 years old) reported a prevalence of 90 % in men and 92 % in women (17, 18).

A systematic review by Pereira *et al.* found radiographic hand OA to be more prevalent (49 %) than radiographic hip OA (15 %) and radiographic knee OA (men 32 %, women 39 %) (16). Furthermore, symptomatic hand OA (15 %) was more prevalent than symptomatic knee OA in men (8 %) and comparable to symptomatic knee OA in women (16 %). Looking at overall prevalence (symptomatic, radiographic, self-reported) of OA, hand OA was more prevalent (43.3 %) than knee OA (23.9 %) and hip OA (10.9 %). A significant sex difference was only detected in knee OA, however less studies were included for hand and hip OA.

There is no consensus on how to define the incidence and progression of hand OA. The Framingham study reported a nine-year crude incidence of radiographic hand OA to be 35 % in women and 34 % in men (11). In comparison the nine-year incidence of symptomatic hand OA was considerably lower with 10 % and 4 % in women and men, respectively. An

average of one to two joints with established hand OA progressed throughout the nine-year study period, emphasizing that hand OA is a slowly progressing disease.

Finally, in a population-based cohort in North-Carolina (US), the estimated lifetime risk for developing symptomatic hand OA in at least one hand by the age of 85 was almost one in two (47 %) for women and one in four (25 %) for men (19). The high prevalence and incidence of hand OA might explain why many health care providers and patients alike perceive the condition as an inevitable part of aging (20).

1.1.3 Comorbidity and mortality

The OA Research Society International (OARSI) published the "white paper" in 2016, stating that OA is a serious disease and highlighting the burden of OA on quality of life and health care systems, and associations between OA and mortality and morbidity (2). OA in the hip and knee has been associated with increased mortality (21, 22); however, in the Framingham study, radiographic and symptomatic hand OA was not associated with increased mortality (23). Interestingly, symptomatic hand OA was associated with an increased incidence of cardiovascular disease, although no association between hand OA and brain infarction and congestive heart failure was detected. In a Canadian retrospective cohort study and a case-control study in general practice in England and Wales, OA patients demonstrated a strong prevalence of comorbidities (24, 25). Depression, anxiety and sleep disturbances are also commonly reported in OA patients (26, 27).

1.1.4 Pathogenesis

OA affects all parts of the joint, with cartilage destruction, subchondral remodeling, osteophyte formation, bone marrow lesions, synovial hypertrophy and effusion, and muscle and ligament abnormalities. These features and their underlying processes may converge, and

gradually lead to destruction of the osteoarthritic joint. OA research in general has focused on the pathophysiology of the knee, and it is uncertain whether hand OA joints share the same processes and pathways.

Cartilage

The articular cartilage in the joint serves two purposes; absorbing daily shock and repetitive wear, and decreasing joint friction through a wide range of motions. Chondrocytes are quiescent post-mitotic building blocks of cartilage tissue and provide homeostasis in the tissue, balancing catabolic and anabolic activity (28). Healthy cartilage tissue is both aneural and avascular, and chondrocytes have a metabolism adapted to anaerobic conditions, where most of its oxygen is supplied through the synovium (29). Aging chondrocytes are exposed to biomechanical and biochemical stressors, like free extracellular matrix particles in the synovial fluid and pro-inflammatory cytokines that can make them undergo a phenotypic shift, also referred to as chondroscenescence (29). The result is a disturbance of the delicate balance between the chondrocytes' catabolic and anabolic properties, ultimately leading to chondrocyte hypertrophy, abnormal matrix production and an increased number of degrading enzymes (28, 30).

Synovium

The joint cavity is delineated by the synovium-lined joint capsule and articular cartilage on the distal bone and contains synovial fluid. The normal synovium consists of two thin layers. The intima contains two types of synoviocytes, a macrophage-like and a fibroblast-like cell, and the subintima features blood and lymphatic vessels and extracellular matrix (31, 32). Synovial fluid consist mainly of lubricin and hyaluronic acid (33), helping to reduce friction and maintain and prevent the accumulation of proteins at the articular surface (31, 34). What

initiates synovitis in the OA joint is uncertain. Synoviocytes and chondrocytes share the ability to produce pro-inflammatory cytokines (30, 35), and cross-talk between these two cell-types have been proposed to play a pivotal role in the OA pathogenesis (36). Acute or chronic joint injury has been hypothesized to expose cartilage fragments to the synovial fluid where they bind to toll-like receptors (TLR) in synoviocytes. This might in turn trigger the production of cytokines and chemokines leading to inflammatory cell infiltration and angiogenesis (37, 38). A plethora of cytokines can be found in the OA synovium; interleukin (IL)-1 beta and tumor necrosis factor-alpha are the most extensively studied cytokines; however, other pro-inflammatory mediators like IL-15, IL-17, and IL-18 and the anti-inflammatory cytokines IL-4, IL-10 and IL-13 have also been suggested to play a role (38, 39). IL-1 has been considered a key cytokine in the osteoarthritis pathogenesis and drives catabolic responses in the chondrocyte (38) through inhibiting collagen synthesis and upregulation of proteolytic enzymes (40, 41). Nevertheless, anti-IL1-alfa and beta did not demonstrate improvement of pain or imaging outcomes in erosive hand OA patients in a recent phase 2 trial (42).

Bone

Several bone-related changes can be observed in the osteoarthritic joint. Subchondral sclerosis is a prominent feature, representing the deposition of mineralized collagen. Furthermore, fibrocartilaginous bony outgrowths, also known as osteophytes, are frequently manifested on the margins of the joint as a result of increased tissue stress (43). Bone marrow lesions appear in proximity to mechanical loading and represent microstructural bone damage with necrosis and fibrosis (44). Another frequently observed OA feature is subchondral cysts, suggested to be hollow enlargements induced by synovial fluid or microfractures in the subchondral bone

(45). Finally, in erosive hand OA, central erosions, and collapse of the subchondral plate can be present (3).

1.1.5 Risk factors

The etiology of OA is multifactorial, and the knowledge of risk factors and their interaction with pathophysiological pathways is evolving. Here follows a presentation of the most studied risk factors.

Age

Increasing age is one of the main risk factors for OA. Incidence and prevalence of hand OA increase with age (11), which can be due to cumulative exposure to risk factors described in this section, as well as age-related processes like chondroscenescence and chondrocytes diminishing ability to perform tissue-repair (29, 46).

Biomechanical factors and trauma

Previous knee injury is a significant risk factor for the development of knee OA (47), while this association is less evident in hand OA. An American community-based study did not find self-reported hand injury to be a risk factor for developing hand OA (48). Although not weight-bearing, the hand is load-bearing, and the majority of the intraarticular force in the finger joints is induced by contraction of finger muscles (49). In the PIP joints, hypermobility has been shown to protect against OA (50), while in the CMC-1 joint, hypermobility and subluxation has been associated with the development of thumb base OA (51). Manual work and extensive use of pinch grip is associated with OA in the CMC-1 and interphalangeal joints, respectively, while forceful gripping has been associated with OA in the MCP joints

(52-54). In line with these findings, OA in the dominant hand would be expected to be more prevalent; however, results on handedness and OA are inconclusive (55-57).

Sex

A meta-analysis by Srikanth et al. found higher prevalence of knee and hand OA in women, while no significant difference was demonstrated for hip OA (58). The same study found no significant gender difference in hand OA severity. Furthermore, symptomatic and erosive hand OA has been demonstrated to have a female predominance (11). This discrepancy between men and women has suggested that hormonal factors play a role; however, a systematic review did not find evidence of an association between hormones and the development of hand OA (59).

Genetics

Hand OA has a polygenetic influence ranging from 39 to 65 % depending on the joint group affected, and DIP and CMC-1 seem to be the joints most prone to heritability (60, 61). The use of genome-wide association studies has helped to identify new loci with potential importance in the OA pathogenesis (62). Several OA susceptible genes involved in cartilage catabolism and chondrocyte hypertrophy have been detected (63, 64). There is also increasing evidence that epigenetic alterations of inflammatory genes play a role in the development of the disease (65, 66).

Metabolic syndrome and obesity

Osteoarthritis has been suggested to share biochemical and inflammatory factors with the metabolic-syndrome, defined as obesity, glucose intolerance, dyslipidemia and raised blood pressure, and a metabolic phenotype of OA has been described (67-70). However, looking at

hand OA in particular, Strand *et al.* found no association between metabolic syndrome and hand OA in cross-sectional and longitudinal analyses in the Framingham study (71). Furthermore, it has been proposed that obesity and hand OA are associated (5, 72, 73). As hand joints are less affected by weight gain than the hip and knee joints, the association between obesity and hand OA has been hypothesized to be caused by systemic factors (37). Obesity has been linked to chronic low-grade inflammation, and serum adipokine levels and elevated C-reactive protein levels have been proposed to influence OA (74-76). Despite these hypotheses, Magnusson *et al.* did not show any associations between body mass index (BMI) and the development of hand OA over 20 years in a case-control study (77). However, high BMI early in life demonstrated a weak association with future hand OA. Furthermore, no association was shown between obesity and hand OA in cross-sectional or longitudinal analyses in the OA Initiative supporting these findings (78).

Ethnicity

Ethnicity has been proposed to be a potential risk factor for OA, with a higher prevalence of knee OA in the black population (79, 80). In the Johnston county OA project in North-Carolina (US), lower lifetime risk of symptomatic hand OA in African Americans (29 %) compared to Caucasians (41 %) was detected (19). A recent study on data from the OA Initiative confirmed this finding with statistically significant lower odds for symptomatic, radiographic, and erosive hand OA in black subjects, also when known OA risk factors were corrected for (81).

Phenotypes and machine learning

Machine learning is the ability of a computer system to process large amounts of data with varying degrees of human input to assess patterns and outcome variables (82, 83). With

quantum computers, complex disease mechanisms can be explored with the help of large data sets from different scientific fields (84). OA is a heterogeneous condition with several described phenotypes. A phenotype is the observable features of an individual's genome (85). Overlapping and distinct phenotypes and "drivers" of OA have been proposed, such as aging-, cartilage-, metabolic-, traumatic injury-, inflammatory- and subchondral bone-driven OA (86, 87). Detecting specific OA phenotypes, like slow vs. fast progression and erosive vs. non-erosive, and applying this knowledge to include well profiled groups in future OA trials might increase the likelihood of finding efficient new therapies (88). Image analysis has been the main focus of machine learning approaches in OA (89). A recent data-driven knee OA study with 597 subjects was able to detect a progression phenotype and its associated variables (bone marrow lesions, osteophytes, medial meniscal extrusion, and urine C-terminal crosslinkend telopeptide type II collagen) (90). Tiulpin *et al.* applied deep learning with convolutional neural networks for assessment of 5960 knee radiographs from the OA Initiative according to Kellgren and Lawrence, resulting in good diagnostic performance with area under the receiver operating curve (ROC) of 0.92 with expert radiologists as reference (91).

1.1.6 Symptoms

Symptomatic hand OA vary from mild to severe and can have a substantial impact on health-related quality of life (92). The disease burden in persons with OA who have been referred to secondary care has been acknowledged to be similar to that of RA (93). Pain is a primary concern for OA patients (94). Limited joint function and stiffness is also commonly reported. OA pain can present as constant or intermittent, is often present during motion and activities, and fluctuates throughout the day (95-97). Patients most commonly characterize the pain as sore, inhibiting, and annoying, and neuropathic-like characteristics like sticking, stabbing,

burning, radiating, and creeping are also frequently reported (98). Pain mechanisms in hand OA are complicated, with biological, genetic, socio-cultural, and psychological factors contributing to the ultimate pain experience (95). Central sensitization can develop in chronic pain conditions, and is common in hand OA patients (99, 100). Furthermore, restricted hand function is commonly reported in hand OA (101-104). Manipulating and picking up smaller objects, writing, and twisting the hand are some complaints covered by common hand OA instruments (105).

Stiffness is also a frequently reported symptom in hand OA, often appearing after periods with inactivity or sleep (106). Morning stiffness lasting up to 30 minutes is common, as opposed to inflammatory arthritis where the stiffness tends to be more protracted (107). Finally, aesthetic dissatisfaction with the appearance of the hands is also reported (108).

1.1.7 Clinical assessment and diagnosis

The ACR classification criteria for hand OA are applied in research only, and there are no official diagnostic criteria for hand OA. Zhang *et al.* presented ten propositions for the diagnosis of hand OA in a European League Against Rheumatism (EULAR) task force in 2009 (109). These recommendations summarize risk factors, typical symptoms of hand OA, clinical hallmarks, and functional impairment in hand OA, recognized subsets of hand OA and relevant differential diagnoses. The task force recommends conventional radiographs if doubt about the diagnosis; however, magnetic resonance imaging (MRI) might be of higher value. Ultrasound can also be applied if uncertainty about the diagnosis (110, 111).

Clinical hallmarks of hand OA include Heberden's and Bouchard's nodes in the DIP and PIP joints, respectively. These nodes are associated with radiographic osteophytes (112, 113), and can be located on the marginal or dorsal aspect of the joint, separately or as one continuous node (114). Bony enlargements can also be present in the MCP and CMC-1 joints.

Joint swelling, warmth and redness might be present, usually due to inflammation. Joint deformities in interphalangeal OA and subluxation of the MCP-1 joint and squaring of the CMC-1 in thumb base OA might also be noted. Pain on palpation and movement, as well as limited range of motion, might be present in affected joints.

1.1.8 Management

A EULAR task force has reviewed recommendations for the management of hand OA (115). The overarching goal of hand OA treatment is to control symptoms and individualize treatment. The recommendations encompass general recommendations for all hand OA patients, from education and exercises, to more specific pharmacological therapies and surgery. Multidisciplinary management with a combination of pharmacological and non-pharmacological treatment provided by doctors, physiotherapists, occupational therapists, and nurses has been shown to give overall better patient satisfaction. However, clinical outcomes did not improve significantly in OA patients undergoing multidisciplinary follow-up (116). This section presents updated recommendations of management of hand OA in three areas; non-pharmacological, pharmacological, and surgical treatment. Non-approved treatments and potential treatment targets will be discussed briefly.

Non-pharmacological treatment

Non-pharmacological treatment is the foundation of hand OA management and should be offered to all patients. Education about the underlying cause and development of hand OA and instruction in ergonomic principles is essential (117). Furthermore, the use of assistive devices and splints has been proved to be efficacious (118, 119), and several studies have shown that orthoses in thumb base OA can lower joint pain and increase function (120-123). However, the wide selection of materials and recommended use, makes the comparison of

different studies on assistive devices difficult. Hand exercise as analgesic therapy is frequently recommended to hand OA patients and have been demonstrated to be a cost-effective measure and beneficial in reducing hand pain and finger joint stiffness (124). A metanalysis on exercise in hand OA showed a small positive effect on pain and function, without sustained effect at follow-up (125).

Established pharmacological treatment

EULAR recommendations presents topical treatments as the first pharmacological therapy of choice, due to a well-documented safety profile and effectiveness on pain (115, 126). Nonetheless, a metanalysis found that topical non-steroidal anti-inflammatory drugs (NSAIDs) were more efficient than placebo only in the two first weeks of treatment (127). Capsaicin, an analgesic chemical compound isolated from chili peppers, has been suggested as topical treatment for painful knee, hand and hip OA and is moderately effective in treating pain (128, 129). Oral NSAIDs can improve pain and function in hand OA patients (130); however, considering the safety profile, with gastrointestinal, renal, and cardiovascular side effects, these drugs should only be administered at lowest effective dose when needed. Paracetamol has been investigated predominantly in hip and knee OA, with limited clinical improvement (131). Only small studies on hand OA and paracetamol has been performed without clear improvement in pain and stiffness (132). Nevertheless, paracetamol is frequently prescribed to hand OA patients. The use of intraarticular glucocorticoids in hand OA is generally not recommended by EULAR; however, it might be considered in painful and inflamed interphalangeal joints as improvements in pain and function have been demonstrated (133). In the CMC-1 joint, on the other hand, intraarticular glucocorticoid injections have not shown improvement in pain and function (134-136). The studies on intraarticular injections in hand OA have several limitations. A small number of participants

were included, the injections were not ultrasound-guided, and ultrasound-defined inflammation was not an inclusion criterion. More extensive studies, including inflamed joints only, are needed to draw a conclusion. Recently, the use of oral Prednisolone 10 mg on erosive hand OA over 6 weeks demonstrated improvement in pain and function and a decrease in synovial thickening on ultrasound (137). Thus, prednisolone might be prescribed as a short-term therapy. This finding is supported by a study on 83 hand OA patients receiving CRx-102, a combination of dipyramidole and prednisolone (3 mg), where significantly reduced pain was demonstrated (138).

Experimental pharmacological treatment

Glucosamine sulfate and chondroitin sulfate provides the elastic and shock-absorbing qualities of cartilage. Although frequently advertised as an efficient OA treatment, there are no high-quality placebo-controlled randomized controlled trials (RCTs) performed on glucosamine sulfate in hand OA. Chondroitin sulfate, on the other hand, demonstrated a significant decrease in patients' global assessment of hand pain and stiffness as well as increased function in a placebo-controlled RCT (139). However, grip strength and use of other analgesics remained similar in the two treatment arms. This finding was supported by a systematic review of studies on chondroitin sulfate in hip, knee and hand OA that suggested a clinically relevant effect on pain; however, the studies included were deemed to have poor quality and no clear recommendation was proposed. Furthermore, only a few of the studies in this review was on hand OA (140).

Conventional synthetic and biologic disease modifying antirheumatic drugs (DMARDs) targeting different inflammatory pathways has revolutionized the prognosis and burden of disease in inflammatory joint disease during the last two decades. As synovitis plays a central role in the hand OA pathogenesis, the repurposing of these anti-inflammatory

drugs has been investigated in several RCTs in hand OA patients with predominantly negative findings (3); the anti-TNF-α inhibitors etanercept (141) and adalimumab (142-144), anti-IL-1 (145), and hydroxychloroquine (146, 147) have not demonstrated effectiveness on pain. Furthermore, a study on methotrexate in erosive hand OA did not prove efficacious, but an impact on radiographic progression according to Gent University scoring system (GUSS) was suggested (148). The lack of efficacy of these potent DMARDs in hand OA suggest that inflammation is not an appropriate treatment target in hand OA. However, it has also been argued that the limited effect of these studies is due to heterogeneous patient populations where the majority had low-degree inflammation, too low dosage of the drug examined, concomitant use of NSAIDs and a substantial placebo response making the difference between the treatment groups less pronounced.

Surgical treatment

Trapeziectomy in thumb base OA and arthrodesis and arthroplasty in interphalangeal OA should only be considered in patients not responding to pharmacological and non-pharmacological treatment (115). These recommendations lack RCTs with placebo- or sham-controlled groups, and are based on expert opinion. Also, within joint groups there is sparse evidence of the superiority of one technique over another. A systematic review of the different surgical interventions of the thumb base did not demonstrate a difference in outcome between techniques (149).

1.1.9 Developing outcome measures in hand OA

Assessing a new outcome measure for synovitis in hand OA is at core of this thesis. Outcome Measures in Rheumatology (OMERACT) is an international task force focusing on improved outcome measures in rheumatological research. The OMERACT filter is an algorithm

developed for the selection of new outcomes or the modification of existing outcomes (150). This filter focuses on validity, reliability, sensitivity to change, and feasibility, and has been applied in the development of imaging and core instruments regarding pain, physical function, patient's global assessment, health-related quality of life, joint activity, and hand strength (151-153).

1.2 Fluorescence optical imaging (FOI)

1.2.1 Background

Since Antiquity, philosophers and scientists have questioned what light is. The roman thinker Lucretius proposed in year 50 anno domini that "the light and heat of the sun; these are composed of minute atoms which, when they are shoved off, loose no time in shooting right across the interspace of air in the direction imparted by the shove" (154). In the renaissance, Isaac Newton and Johannes Kepler also advocated for light to be particles, while Robert Hooke and Christian Huygens proposed that light was a wave phenomenon. The Scottish physicist and mathematician James Clerk Maxwell brought the two theories together when he, in 1865, presented that light is an electromagnetic disturbance; a wave of electric and magnetic fields following electromagnetic laws (155).

Electromagnetic waves' properties, i.e., wavelength and frequency, vary from carcinogenic ionizing radiation with high frequencies and relatively short wavelengths to benign micro and radio waves with low frequencies and long wavelengths. Visible light is in the middle of this spectrum (Figure 1). Infrared light starts where the visible red light ends, at wavelengths around 750 nanometers (nm), and extends to wavelengths of 1 millimeter (mm). Conventional subdivisions of infrared lightning is near-infrared, mid-wavelength and long-wavelength (156). Near-infrared light has been applied in a wide range of fields, from medical

near-infrared spectroscopy (157) in pulse oximetry, to night vision goggles and fiber optics in telecommunication.

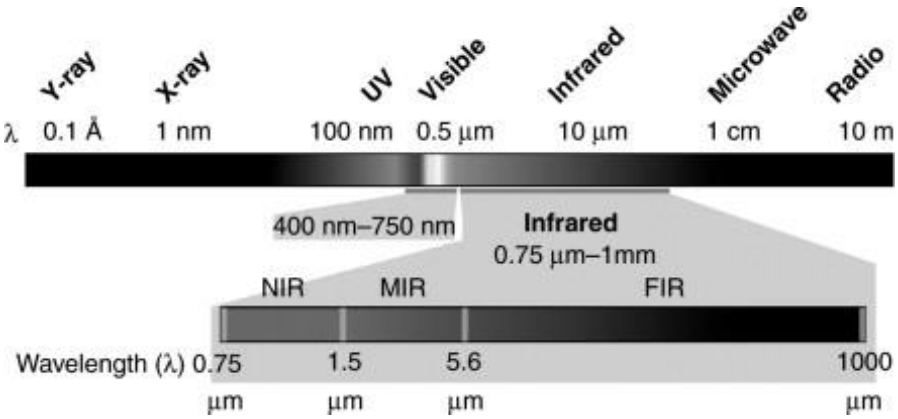

Figure 1: Electromagnetic spectrum, reprint from original paper (158) with permission from Elsevier.

Optics is defined as "The study of light and the phenomena associated with its generation, transmission, and detection" (159). Optical imaging is an umbrella term for imaging techniques that apply light from the ultraviolet to the near-infrared spectrum to detect cellular and molecular function. Optical imaging techniques can be used to create high-resolution images of the retina, brain mapping, and endoscopy, to name a few. Furthermore, fluorescence is defined as "the quality of absorbing light of a short wavelength and producing light of a longer wavelength" (159). In near-infrared FOI, unspecific, targeted or intelligent probes with a fluorophore contrast agent are injected and secondly, near-infrared light is projected onto the target site. The fluorophore absorbs the near-infrared light, and emits lower-energy light with longer wavelengths. A camera detects these signals and creates a fluorescent optical image.

1.2.2 Xiralite®

FOI of the hands can be performed with a commercially available device, the Xiralite® scanner, produced by Xiralite® GmbH (Germany) (Figure 2). The machine has approximately the size of an ultrasound machine. It consists of a hand rest, a highly sensitive camera with a charged coupled device, and light-emitting diodes (LED) (figure 3) (160). Before the examination, the patient is injected with a fluorescent dye (Indocyanine green (ICG)-pulsion, 0.1 mg/kg/body weight) and put the hands on a hand rest. The procedure is performed in a dark room, and the wrist is covered by a curtain to avoid ambient light entering the hand rest compartment and interacting with the near infrared light projected from LED lamps down on the hands. When ICG reaches the microcirculation in the hands, the fluorophore absorbs the near-infrared light from the LED lamps and emits light with lower energy and longer wavelengths, which is detected by the charged coupled device. One image per second is recorded, resulting in a total of three hundred and sixty images in one examination.

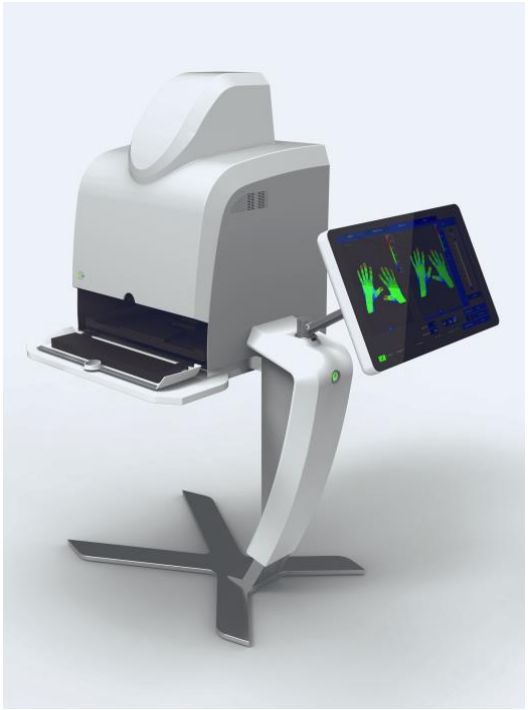

Figure 2: Xiralite® device, with kind permission from Xiralite GmbH

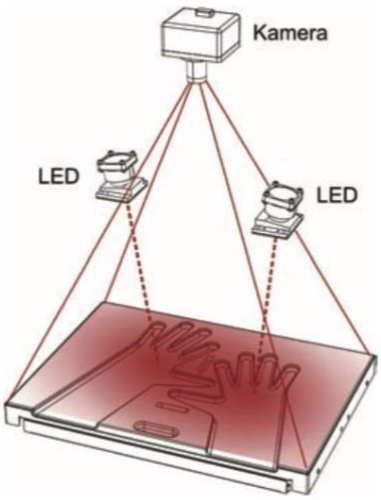

Figure 3: Xiralite® set-up, from original paper (160) with permission from Annals of the Rheumatic disease.

1.2.3 Scoring methods

The majority of studies utilizing the Xiralite® device has applied the semiquantitative FOI activity score (FOIAS) developed by Werner *et al.* (160). According to this method, three images are defined as the beginning of Phase 1, 2, and 3 based on the distribution of the contrast agent in the fingertips. Phase 1 starts with the contrast agent descending from the fingertips. Phase 2 and 3 are initiated with the absence of white and red pixels in the fingertips, respectively. The different phases start on different time points in different patients, e,g., Phase 1 can begin at image 20/360 or image 67/360, depending on the blood perfusion in the hands. The phases are defined for the left and right side separately. The XiraView software automatically generates a composite image, the Prima Vista Mode (PVM), where the 240 first images are summarized, and the contrast ("gain") of the image is

automatically adjusted (Figure 4). The meaning of the different phases remains uncertain and has not been confirmed by histology. Still, it has been suggested that Phase 1, with early enhancement, represents active disease, Phase 2 subclinical inflammation, and Phase 3 capillary leakage secondary to chronic inflammation (160, 161). Finally, dynamic methods and quantitative scoring methods have also been applied and will be discussed briefly below.

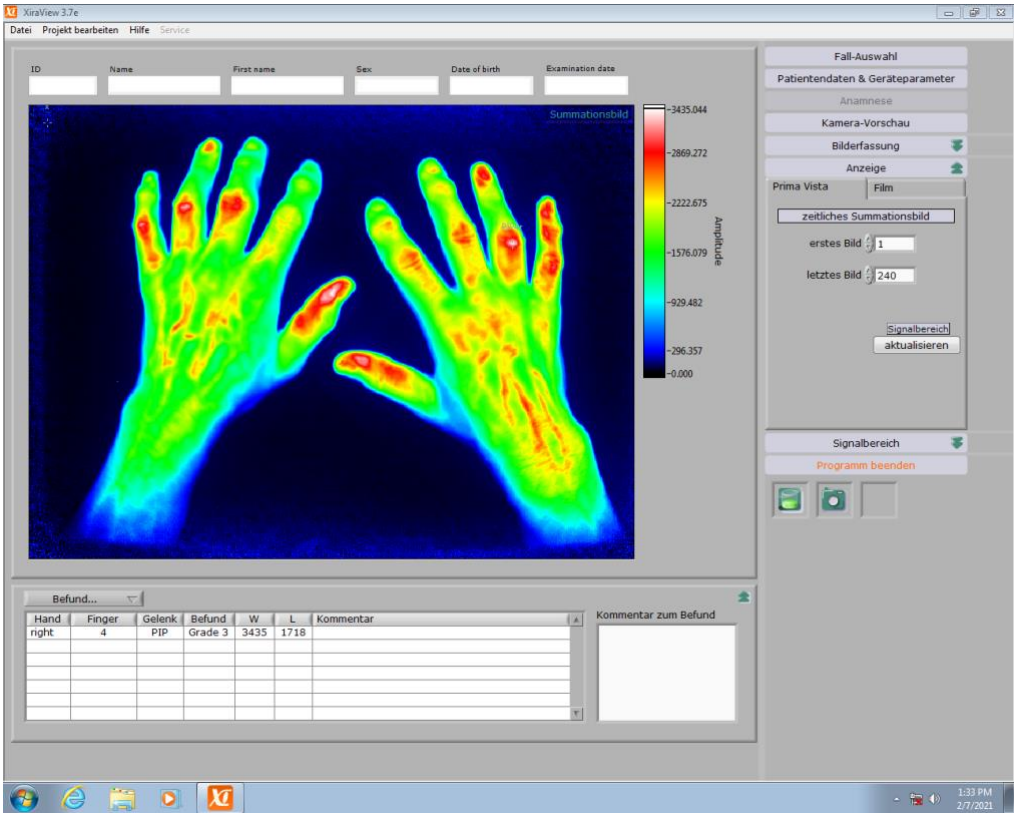

Figure 4: Screenshot of the XiraView® software with a Prima Vista Mode image of a hand OA patient with bilateral enhancement in the proximal interphalangeal joints.

1.2.4 Measurement properties

Due to its limited tissue penetration, FOI can only be applied on small joints in the hands and feet. The Xiralite® device gives two-dimensional images of the hands in an anterior-posterior view and has only been paired with morphological data from radiographs or computer tomography in animal models (162). Scars, tattoos, potential skin plaques, wounds, and rings might affect the final image, and a photo of the hands before the exam can potentially help to rule out ambiguous enhancement. Nail polish can diminish the view of the well-vascularized nail beds and make the definition of the three phases difficult. It has been debated whether FOI is applicable to all skin types, however pigmentation does not significantly affect the penetration of light in skin (163-165). Hand characteristics that might affect the final result and that cannot be ruled-out on photos are cold hands, excessive hand use before the examination, and dry skin. Images must be obtained in a dark room, and ambient light might influence the final image. Hand movement throughout the 360 seconds must also be avoided.

1.2.5 FOI in rheumatology

FOI has been applied in rheumatological research in the last decade and has focused on RA and undifferentiated arthritis. Fischer *et al.* published the first clinical study on FOI in five RA patients and presented a good correlation between FOI enhancement and MRI-defined synovitis (rho = 0.84) (166). Several studies on animal models with induced arthritis (162) and studies of optical imaging in finger joints of RA patients without the use of a contrast agent preceded this study (167, 168). Werner *et al.* assessed 25 patients with undifferentiated arthritis, and with MRI as reference good specificity was demonstrated in PVM (81 %), Phase 1 (94 %) and Phase 3 (89 %). At the same time, Phase 2 had the highest sensitivity (72 %) and poorest specificity (56 %) (160). Similar findings were presented in two papers on patients with RA (169, 170). These studies had a limited number of patients, did not demonstrate

concomitant strong sensitivity and specificity for any of the phases, and area under the curve (AUC) values were not reported. In general, the best specificity was found in Phase 1 and the best sensitivity in Phase 2. Hirano *et al.* compared FOI enhancement with MRI as reference in RA and found good values for both Phase 1 (sensitivity 85 %, specificity 94 %) and Phase 2 (sensitivity 69 %, specificity 94 %); however, only wrist and MCP joints in 6 patients were included. Finally, FOI has demonstrated good correlation with greyscale (rho = 0.58 - 0.60) and power Doppler ultrasound (rho = 0.45 - 0.59) in a study on 25 RA patients with high disease activity, however both responders and non-responders demonstrated decreased FOI enhancement after one year (171).

All studies reported above assessed the FOI scans with the FOIAS. Meier *et al.* and Thuermel *et al.* applied a different semiquantitative scoring method on patients with RA and inflammatory arthritis and detected high specificity (85%, 92%) and moderate sensitivity (40%, 57%) (172, 173). FOI can also be assessed with quantitative scoring methods. Meier *et al.* calculated a rate of early enhancement, based on joint perfusion in patients with inflammatory arthritis after initiation of anti-inflammatory treatment (174). The authors found that FOI correctly identified responders and non-responders to therapy using the simple disease activity index as reference. Schaefer *et al.* presented a quantitative fluorescence readout analysis of three phases based on time only (175). To account for different degrees of perfusion, a fluorescence ratio based on enhancement in joint and nailbed was calculated. Using this ratio, they found statistically significant more enhancement in joints with MRI- and grey scale-defined synovitis compared to using the readout analyses only. This highlights the importance of individual physiological blood flow in the FOI examination.

Beck *et al.* have investigated FOI in pediatric patients with inflammatory joint diseases and demonstrated good specificity for all phases and PVM with grey scale synovitis and power Doppler activity as reference. However, sensitivity was moderate with best values

in Phase 2 at 60 % (176). Furthermore, in systemic sclerosis, FOI has demonstrated high sensitivity and specificity in detecting inflammation and decreased perfusion (177, 178). A "green nail sign" has been suggested to be a sensitive marker for disturbed microcirculation in the nail bed in patients with psoriatic arthritis (179). Finally, only one previous study has investigated FOI in hand OA. Glimm *et al.* compared enhancement in different joint groups for hand OA and RA patients (161). They found more enhancement in the DIP joints in the hand OA patients in Phase 2 and PVM, while MCP joints had more enhancement in Phase 1 in RA patients.

1.2.6 Probes

Golovko *et al.* and D'Agostino *et al.* have published overviews of different FOI probes in RA (180, 181). Generally, these probes can be divided into non-specific, specific, and intelligent probes. While the non-specific probes give information about microcirculation, and the targeted probes demonstrate an increased amount of a molecule within a particular location, the intelligent probes yield information about biochemical pathways (180).

Firstly, non-specific probes demonstrate enhanced microcirculation, and ICG is the only Food and Drug Administration approved fluorescent dye. ICG was created by the film company Kodak in the 1950s and was approved for use in human medicine in 1956 (182). ICG is an anionic and hydrophilic fluorescent dye with maximum emission and absorption wavelengths around 826-835 nm, placing it in the near-infrared spectrum of the electromagnetic field (183). ICG has been applied in several medical fields, from the visualization of microcirculation in surgery (184), chorioretinal angiography in ophthalmology (185, 186), and liver cancer assessment (187). Allergic reactions are rare, and it has a well-established safety profile (182, 188, 189). The main caveat for ICG is its limited fluorescent efficiency. ICG is only fluorescent when it is unbound (181); however, after

injection, about 98 % is quickly bound to plasma proteins (173). ICG also has a relatively fast clearance by the liver (190). Non-specific cyanine-based probes with a lower propensity to bind to plasma proteins have been applied in mice with induced arthritis with promising results; however, these dyes have not been approved for use in human beings by American or European health authorities (191)

Secondly, targeted probes consist of a fluorescent dye connected to a substance targeting a tissue of interest. A re-purposing of target molecules applied in positron emission tomography have demonstrated promising results in FOI in animal models with induced arthritis, and the targeting of the F4/80 marker in macrophages is one example of this approach (192).

Finally, intelligent probes are non-fluorescent pre-injection due to an inhibiting substrate (a quencher). When reaching a target tissue, the quencher is removed by an enzyme and the probe turns fluorescent. A fluorescent dye activated by cathepsins, a group of proteases that play a role in the inflammatory environment of OA, was able to detect arthritis in mice with induced arthritis (193).

1.2.7 Other optical imaging modalities

Optical imaging without contrast agents are based on the difference in transferal of light through normal and pathological tissues, due to enhanced microcirculation and protein content. Optical spectral transmission (OST) has been applied in RA patients with good diagnostic performance with ultrasound as reference (194). Nevertheless, a Dutch study found moderate results with MRI as reference, while a Danish study concluded that the sensitivity of OST was not superior to clinical examination (195, 196). The diagnostic performance of OST has also been investigated in hand OA, with fair performance in the PIP joints and poor performance in the DIP joints (197).

Experimental, non-commercial models of optical imaging have also been explored in rheumatological research. Sagittal laser diffuse optical tomography applies laser light in the infrared spectrum to detect inflammatory changes in human finger joints and has been paired with photo-acoustic imaging to improve the image resolution (198-200). Optical coherence tomography has demonstrated cartilage changes corresponding to findings from histology in thumb base OA (201). Finally, photography (from Greek "drawing with light") is also optical imaging *per se* and has been proposed to be a reliable and valid tool for diagnosing hand OA (3, 202, 203).

1.3 Imaging in hand OA

1.3.1 Conventional radiography

Last year (2020) marked the 125th anniversary of the discovery of x-rays by Wilhelm Conrad Röntgen. The German mechanical engineer and physician revolutionized medical diagnostics and received the first Nobel prize in physics in 1901 for his invention (Figure 5). Röntgen experimented with a cathode that emitted electromagnetic waves with different wavelengths and discovered that some waves could penetrate substances, while solid objects created a shadow on an exposed photographic paper. Since it was uncertain what these waves represented, they were named X-rays.

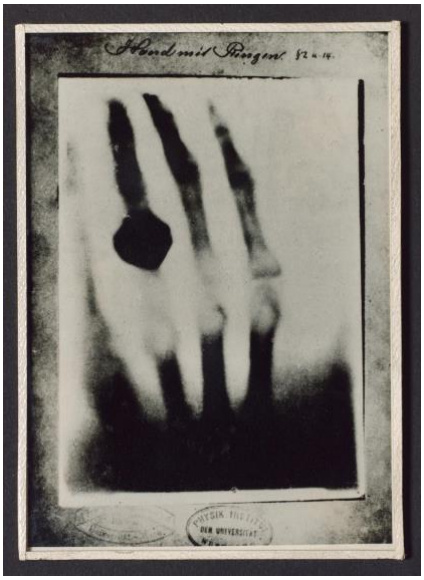

Figure 5: Copy of photograph of a radiograph of a hand, taken by Roentgen, Wurzburg, Germany, 1895. With permission from the Science Museum Group Collection.

Technical aspects

An X-ray tube is a diode consisting of a cathode and an anode, and when electrons are accelerated between the two poles, energy is converted into x-rays with heat as a byproduct. A collimator helps to collect and focus the X-rays toward the examined object (204). X-rays represent ionizing radiation with a potential health hazard. They have short wavelength (0.01-10 nanometers) and high frequency, and has the ability to dethatch electrons from atoms.

Assessment of OA with radiographs

Conventional radiography has the advantage of being inexpensive, fast, and able to depict pathological features in OA, like osteophytes, joint space narrowing, erosions, soft tissue calcifications, cysts, and subchondral sclerosis. Limitations include inability to demonstrate soft tissue abnormalities, like synovitis and cartilage, and exposure to radiation. Nevertheless, the dose of 0.001 millisieverts for a hand radiograph is minimal (205). In comparison, average

background radiation in Norway has been estimated to 5.2 millisieverts/year per person by the Norwegian Radiation Protection Authority (206).

Scoring systems

The most common scoring system in OA is the Kellgren Lawrence score (8). This is a composite score from grade 0 to 4, where grade 2 is defined as definitive OA. Points are given for the absence/presence of typical OA features such as osteophytes, joint space narrowing, sclerosis, pseudocyst formation, and altered bone ends (6, 7). The scoring system has been criticized for emphasizing osteophytes too much (60), and modified versions of the score have been proposed.

The OARSI atlas, developed in 1995 and later revised in 2007, scores osteophytes and joint space narrowing on semiquantitative 0-3 scales in the 2^{nd}-5^{th} DIP, PIP, and CMC-1 joints while the features are scored as absent/present in the 1^{st} interphalangeal joint. Malalignment, erosions, and subchondral sclerosis are scored as absent/present in DIP, PIP, and CMC-1, while subchondral cysts are scored as absent/present in PIP and CMC-1 only (207, 208). Nevertheless, this scoring method is time consuming and there is no consensus on which scores classify as definitive hand OA.

The Verbruggen Veys anatomical phase scoring system is an alternative scoring system for erosive hand OA, which is based on the assumption that the disease is progressing through predictable phases, from a stationary phase, to a joint space narrowing phase and finally to an erosive and remodeling phase (209).

The Ghent University Scoring System was recently developed to provide a more sensitive detection of progression in erosive finger joints (210). With an 11-point scale, erosive progression and remodeling are scored, defined by the amount of healthy subchondral bone, subchondral plate, and joint space width.

1.3.2 MRI

Technical aspects

MRI applies strong magnetic fields and radio waves to create images. Here follows a brief presentation of some critical concepts (211, 212).

An MRI machine consists of a main magnetic coil creating a magnetic field (B0), several gradient coils which define the different planes of magnetization, a radiofrequency transmitter coil which stirs the protons out of their position, and a system for processing the incoming MRI signals. Hydrogen atoms are present in large amounts in the human body, and the nuclei of these atoms consist of protons creating an electromagnetic field when spinning around their axis. When hydrogen nuclei are placed under B0, they align and spin around in a wobbly manner called precession. How many times the protons spin, or precess, in a minute is described by the Larmor frequency. Stronger magnetic fields create higher precession frequency. Longitudinal magnetization is created as more protons align parallel to B0. When a radiofrequency pulse is directed towards the magnetic field, this longitudinal magnetization is decreased. This will only happen when the incoming pulse has the same frequency as the precessional protons, and this phenomenon is called *resonance*, hence magnetic *resonance* imaging. The protons pick up energy from the radiofrequency pulse and precess in phase, and create a transversal magnetization. Switching off the radiofrequency pulse will lead to a decrease in the transversal magnetization and an increase in the longitudinal magnetization. Thus, switching the radiofrequency on and off leads to protons going in and out of transversal and longitudinal magnetization planes. This creates an MRI signal. Relaxation of the longitudinal and transversal magnetization is referred to as T1 and T2, respectively.

Assessment of hand OA features with MRI

MRI can visualize important pathological features in hand OA including osteophytes, cartilage thinning, erosions, bone marrow lesions, cysts, synovitis and tenosynovitis, malalignment, abnormal joint capsule and collateral ligaments (213). MRI has the benefit of a multiplanar high-quality three-dimensional (3D) representation of the joint, while drawbacks include cost, availability, and the potential need of a contrast agent. Synovial enhancement in hand OA patients is frequently detected by MRI, while varying amounts of bone marrow lesions has been reported (214, 215).

The validity of MRI in hand OA

MRI-detected osteophytes, cartilage loss, synovitis, and collateral ligaments detected by MRI have been validated against histologic specimen (216-219). MRI shows good agreement with ultrasound in detecting erosions and soft tissue changes in erosive hand OA (215), and MRI is more sensitive than radiographs in detecting osteophytes (220). Synovitis, erosions, attrition and osteophytes by MRI have been associated with pain on palpation in hand OA patients (214). In the same study, sum score of osteophytes demonstrated a negative association with grip strength, while sum score of MRI-defined synovitis demonstrated no association with measures of hand pain.

Scoring methods

The Oslo hand OA scoring system (OHOA-MRI) from 2011 assesses synovitis, erosive damage, cysts, osteophytes, cartilage space loss, malalignment, bone marrow lesions, flexor tenosynovitis and collateral ligament pathology (221). Based on this score, the semiquantiative Hand OA MRI Scoring system (HOAMRIS) was developed in 2014, including the same OA features as the Oslo hand OA scoring system, except flexor

tenosynovitis and collateral ligament pathology as these features were uncommon and demonstrated low reliability (151, 222). Good cross-sectional inter-reader reliability (Intraclass correlation coefficient (ICC) = 0.74) has been demonstrated in measuring synovitis with the HOAMRIS (151). Furthermore, the Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS) is a semiquantitative scoring system of thumb base OA developed from the HOAMRIS criteria, and measures synovitis, subchondral bone defects, osteophytes, cartilage assessment, and bone marrow lesions on semiquantitative 0-3 scores, and subluxation as absent/present (152). Good reliability in the measurement of synovitis in STT and CMC-1 joints has also been demonstrated.

1.3.3 Ultrasound

Technical aspects

Ultrasound waves have a frequency from 2 to 20 millihertz and are generated by piezoelectric crystals in the ultrasound probe. The ultrasound image is created by deflected ultrasound waves. Depending on the acoustic impedance in different tissues, shades from black to white are visualized (223). Bone deflects most of the ultrasound waves and creates a white (hyperechoic) line, while clear fluid is black (hypoechoic). Fat is yielded as black with white septae. Ultrasound has the benefit of being a non-ionizing, non-invasive technique, with the possibility of multiplanar visualization of multiple joints in an outpatient setting. The major drawback of ultrasound is its operator dependency.

Assessment of OA features with ultrasound

Several features in the hand OA joint can be visualized with grey scale ultrasound, including synovial hypertrophy and effusion, erosions, osteophytes, and cartilage thickness. Furthermore, power Doppler techniques can be applied to assess vascularization of the

synovium. Several studies have demonstrated common presence of grey scale synovitis in hand OA (224-226). Power Doppler signals are less common in hand OA patients than grey scale synovitis, however synovial hypertrophy and power doppler activity have been reported in similar amounts in certain cohorts (225, 227).

Validity of ultrasound in hand OA

Osteophytes are associated with pain on joint level (228), and patients with symptomatic hand OA have demonstrated significantly more osteophytes than asymptomatic hand OA patients (229). Wittoek *et al.* found good agreement between ultrasound and MRI in the detection of synovitis and structural features (215). Furthermore, ultrasound is more sensitive than conventional radiography in the detection of erosions and osteophytes, and also more sensitive in detecting osteophytes compared to clinical examination (215, 225, 230).

Scoring methods

Keen *et al.* developed the first ultrasound atlas and semiquantitative scoring system for hand OA features, including osteophytes, grey scale synovitis, and power Doppler activity (231). Furthermore, OMERACT and EULAR groups have developed atlases and definitions of several pathological features, including synovitis (232, 233). With the use of an ultrasonographic atlas with RA features, Hammer *et al.* demonstrated high intra- and inter-reader reliability for grey scale synovitis and power Doppler activity in the wrist, elbow, knee, talocrural, metatarsophalangeal and metacarpophalangeal joints, and this atlas has also been applied in OA studies (234). Furthermore, in erosive hand OA, Wittoek *et al.* has found good reliability for grey scale synovitis in interphalangeal joints applying the OMERACT definitions by Wakefield et al. (215, 233). Finally, Mathiessen *et al.* have developed an

ultrasound atlas for osteophytes in hand OA with excellent intra- and inter-reader reliability (230).

2. General aim and specific research questions

General aim:

Is FOI a reliable and valid outcome measure for synovitis in hand OA patients?

Objectives in paper I:

1. To assess the inter-reader reliability of three different FOI scoring methods in erosive hand OA and RA patients.

2. To quantify the distribution of FOI enhancement in different joint groups in erosive hand OA vs. RA.

3. To assess the diagnostic performance of FOI in 13 patients with erosive hand OA with MRI as reference.

Objectives in paper II:

1. To explore the distribution of FOI findings in hand OA patients and assess the amount of FOI enhancement in joints with various severity of radiographic hand OA.

2. To assess the correlation of FOI enhancement with MRI- and ultrasound-defined synovitis in hand OA patients.

3. To assess the diagnostic performance of FOI enhancement as a measure of synovitis using MRI- and ultrasound-defined synovitis as reference.

Objectives in paper III:

1. To explore the associations between FOI enhancement and pain in the same joint and the associations between the FOI sum score and the patients´ hand pain, stiffness, and physical function.

2. To assess associations between MRI and measures of pain, stiffness, and physical function.

3. Material and methods

3.1 Study design

The majority of results in this thesis are based on cross-sectional baseline data from the Nor-Hand study, an observational hand OA cohort with 300 participants. Paper II and III include baseline data from this study only. Paper I contains a cross-sectional reliability exercise with five readers, comparing three different FOI scoring methods; the FOIAS and two methods developed in Copenhagen and Stockholm. This paper includes 13 Nor-Hand patients and 13 patients from the rheumatology outpatient clinic at Rigshospitalet (Copenhagen, Denmark).

3.2 Study population

Nor-Hand cohort

The main objective of the Nor-Hand study is to validate different outcome measures (including different imaging modalities) and to explore pain in persons with hand OA. A study protocol was published, and baseline data collection was performed at Diakonhjemmet Hospital (Oslo, Norway) in 2016-2017 (235).

Participants were predominantly recruited from the rheumatology outpatient clinic at Diakonhjemmet Hospital. Sixteen of the 300 participants in the study were recruited from the OA self-management education program ("Artroseskolen") at Diakonhjemmet Hospital. Participants in this program were referred from the rheumatology outpatient clinic or directly from their primary health care physician. A minor number of the 300 study participants (n=16) contacted the project leader directly; they were employees at Diakonhjemmet Hospital who heard about the study at work or hand OA patients recruited by friends and family already included in the study. All participants were screened for eligibility before inclusion.

Inclusion criteria were age between 40 and 70 years at the time of screening and presence of hand OA features by clinical examination (Heberden's and Bouchards' nodes, bony enlargement and squaring or deformity of the thumb base) or by ultrasound (osteophytes in the interphalangeal joints or thumb base). Exclusion criteria were signs of clinical inflammatory arthritis or power Doppler activity in more than two MCP joints or the wrist, or known diagnosis of inflammatory arthritic disease or psoriasis. Furthermore, erythrocyte sedimentation rate >40 mm/hour or C-reactive protein >20 mg/L (without ongoing infection), anti-cyclic citrullinated protein or rheumatoid factor positivity, elevated ferritin (>300 micrograms/L for men and >200 micrograms/L for women and s-iron/s-total iron-binding capacity above 50%), major comorbidities, psychiatric disorders or alcohol or drug abuse were also exclusion criteria. All patients had to understand the purpose of the study and to sign an informed consent form approved by the national ethical committee.

The screening was performed on 431 patients, of whom 311 were eligible for participation and signed informed consent. Eleven participants were excluded due to missing data of essential information (e.g. hand radiographs or all questionnaires) or uncertainty about the exclusion criteria. Thus, 300 participants were included in the Nor-Hand cohort.
Out of 300 participants, 252 performed FOI, and 246 performed gadolinium-enhanced T1-weighted MRI (Table 1). We eliminated two of 252 FOI examinations due to a lack of contrast on all phases and PVM. A total of 221 participants underwent both gadolinium-enhanced T1-weighted MRI and FOI and were included in the analyses in paper II and III (Figure 6).

Table 1: Overview of missing FOI and MRI examinations

Reasons for missing FOI (n=48)	
Failing to insert an intravenous needle	18
Allergy to iodine, seafood or ICG	16
Refused fluorescent contrast	9
Missing blood test before test evening	2
Abnormal blood test before examination	1
Missing ICG at test evening	1
Artificial nails	1
Reasons for missing MRI examinations (n= 25)	
Refused exam	19
Claustrophobia	3
Pacemaker	2
Did not fit in the extremity MRI scanner	1
Reasons for missing gadolinium on MRI examinations (n= 29)	
Refused gadolinium contrast	10
Unknown	9
Allergy	8
Previous headache after gadolinium contrast	1
Abnormal blood test before examination	1
MRI; Magnetic resonance imaging, FOI; Fluorescence optical imaging, ICG; Indocyaninen green.	

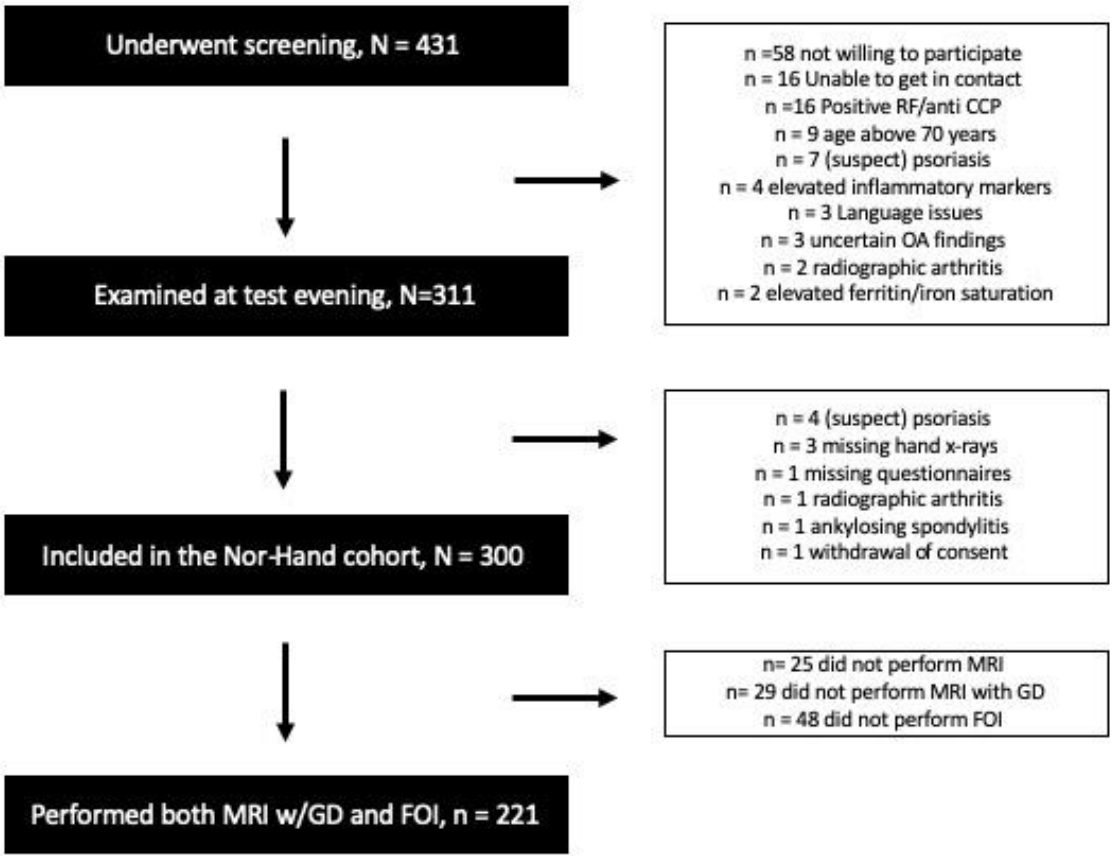

Figure 6: Flow chart of participants in the Nor-Hand cohort

Patient selection in reliability exercise

In the FOI reliability exercise in paper I, 13 RA patients from the rheumatology outpatient clinic at Rigshospitalet (Copenhagen, Denmark) were included. They were randomly selected from a group of 76 RA patients who had performed FOI, and they all had indication to start conventional synthetic DMARD or changing current treatment to conventional synthetic DMARD in combination with biologic therapy. Treatment change was initiated after the FOI examination. The 13 erosive hand OA patients in the reliability exercise were chosen randomly from the Nor-Hand cohort described above. They had at least one interphalangeal

joint in the erosive or remodeling phase according to the Verbruggen Veys anatomical phase scoring system and had performed gadolinium-enhanced T1-weighted MRI of the dominant hand.

3.3 Data collection

3.3.1 Nor-Hand cohort

We collected a broad range of data at the outpatient clinic at test evenings of three to four hours duration. The participants had blood tests withdrawn, underwent clinical joint examination, performed FOI, ultrasound of upper extremities and grip strength test. MRI and radiographs were performed before or after the test evening. This section describes the variables relevant for this thesis only, and other test results that were collected will not be described.

3.3.1.1 Self-reported data

Questionnaires regarding lifestyle, pain, and physical function were distributed before the test evenings, and the majority of patients filled out the questionnaire digitally. Paper versions were available on request. Reminders were sent out if participants did not submit the completed questionnaire. Each participant marked hand joints on a hand diagram as painful yes/no the previous 24 hours and six weeks. The Australian/Canadian OA Hand Index (AUSCAN) with three subscales on pain (5 questions), physical function (9 questions), and stiffness (one question) was completed (236). The participants were asked about general hand pain the last 24 hours on a Numeric Rating Scale (NRS) (range 0-10).

3.3.1.2 Clinical data

Patients reported comorbidities, symptom duration, and medical treatment in the questionnaire, and at the test evening, a medical student cross-checked the completeness of

these data. The use of anti-inflammatory medication was defined as oral NSAIDs or oral corticoids taken daily at the time of data collection.

The majority of clinical examinations were performed by dr. Barbara Slatkowsky-Christensen (MD, Ph.D.) who has over 20 years' clinical experience in rheumatology, specializing in hand OA. Sigrid Valen Hestetun (MD), Nina Krafft Sande (MD), and Ida K. Haugen (MD, Ph.D.) also performed clinical examinations at selected test evenings. The bilateral DIP, PIP, MCP, and CMC-1, were examined for tenderness according to the Doyle index (237). No reaction on palpation laterally and posterior-anteriorly was scored as 0, expressing pain was graded 1, frowning due to pain was graded 2, and retraction of the hand and frowning due to pain was graded 3. Weight and height were measured, and BMI was calculated. Grip strength of the dominant hand was measured with a Jamar dynamometer (238). The measurement was performed with the patient sitting in a chair with the elbow in a 90-degree angle without supporting the arm. A mean value was calculated after squeezing the dynamometer three times with 15 seconds pause.

3.3.1.3 Laboratory samples

C-reactive protein, erythrocyte sedimentation rate, ferritin, s-iron, and total iron-binding capacity were obtained at the time of screening. Blood and urine samples were collected at the test evenings. Thyroid, liver, and kidney parameters were obtained before performing MRI and FOI.

3.3.1.4 FOI

Optical images were acquired with the Xiralite® device. Participants without known allergy to iodine, seafood or indocyanine green or a previous reaction to imaging contrast, untreated hyperthyroidism (fT4 above 21 pmol/L and thyroid-stimulating hormone below 40 mL/min),

poor kidney function (glomerular filtration rate below 40 mL/min), reduced liver function (transaminases above twice the upper reference limit), or current pregnancy or breast-feeding were injected with a fluorescent dye (ICG pulsion, 0.1 mg/kg body weight) before the FOI scan. The participants inserted their hands into the Xiralite® scanner and were exposed to near-infrared light from LED lamps in six minutes. A highly sensitive camera produced 360 images (one/second) and captured the distribution and washing out of the fluorescent dye. The XiraView software generated a composite image (PVM) of the 240 first images of each examination. The images were scored according to FOIAS. Three phases were defined based on the distribution of the fluorescent dye in the fingertips, as described in the introduction. Four images per examination were evaluated in the Nor-Hand study; PVM and the first image of the three phases.

The DIP, PIP, MCP, and CMC-1 joints were graded on 0-3 scales based on colour intensity and width of enhancement. In case of uncertainties, the lowest grade was chosen. Sigrid Valen Hestetun (MD) assessed the FOI scans, after receiving training from an expert FOI reader, Sarah Ohrndorf (MD, PD). Example images with different grades of joint enhancement were demonstrated, and the two readers performed an inter-reader reliability exercise with 21 FOI examinations of hand OA patients. The readers were blinded for clinical and other imaging data, but not for age and sex. They obtained good to excellent inter-reader reliability in DIP, PIP, and MCP joints for Phase 2, 3, and PVM with ICCs for sum scores ranging from 0.87 to 0.89, while inter-reader agreement in Phase 1 was weak (ICC = 0.10) (239). Intra-reader reliability for the trained FOI reader on the same 21 patients was good to excellent for Phase 2, 3, and PVM ranging from 0.82 to 0.94, while the readers demonstrated moderate reliability in Phase 1 (ICC = 0.50).

In the reliability exercise in paper I we compared the FOIAS (also referred to as “the Berlin method” in paper I) with two semiquantitative scoring methods developed in

Stockholm and Copenhagen. In the Stockholm method, two composite images were evaluated, including the PVM generated from the 240 and 120 first images. Both images were assessed in the "temperature" palette setting in the XiraView software, as opposed to the "rainbow" palette applied in the FOIAS and Copenhagen method. After assessing these two images, the reader browsed all 360 images in the sequence to look for additional joint enhancement. Grading was based on the width and intensity of enhancement, similarly to the FOIAS. In the Copenhagen method, it is hypothesized that inflamed joints will demonstrate faster enhancement than surrounding healthy tissues. Thus, in the Copenhagen method, sharp FOI enhancement over a joint area persisting ≥ 3 images was graded from 1 to 3 based on the width of the enhancement in the third image after the initiation of enhancement (240, 241).

The composite images (PVM) scored in the FOIAS and the Stockholm method were pre-defined by the XiraView software, whereas the reader decided which image to score in Phase 1-3 images in FOIAS and in the Copenhagen method. All readers reported which image they defined as Phase 1 to 3 and which image they scored in each joint in the Copenhagen method. For assessment of feasibility, all readers recorded the time spent on scoring each of the 26 images.

3.3.1.6 MRI

MRIs were acquired with a 1.5 tesla MRI (Siemens Aera, Germany) with a 16-channel hand/wrist coil covering the fingers and thumb base of the dominant hand. Participants without contraindications (previous allergic reaction or reduced kidney function with glomerular filtration rate < 40 mL/min) received gadolinium contrast (Dotarem 279.3 mg/mL, 0.2 mL/kg body weight). A coronal TI-weighted volumetric interpolated breath-hold examination pre- and post-gadolinium injection with 0.4 mm thickness was obtained, with possibility to reconstruct into axial and sagittal planes.

We applied the HOAMRIS to assess synovitis in the DIP and PIP joints on a 0-3 scale (151, 222). MCP joints are not included in the HOAMRIS and were assessed similarly to the PIP joints. In the DIP, PIP, and MCP joints sagittal and axial planes were assessed, and consistent findings in 3 consecutive slices in both planes were required to qualify as synovitis. The TOMS atlas was applied to evaluate synovitis in the CMC-1 and STT joints in the frontal and axial planes (242). In both HOAMRIS and TOMS grade 0-3 was defined as 0 = normal; 1 = mild; 2 = moderate; 3 = severe and the 1–3 scores were defined by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. Finally, we used the Oslo hand OA MRI scoring system to assess flexor tenosynovitis on a 0-3 scale (221). Inflammation along the extensor tendon sheath was evaluated as absent/present.

All MRI examinations were scored by a Ph.D. student (Øystein Maugesten) trained in assessing synovitis in hand joints with demonstration of atlases and example images (n=20) by an experienced reader (Ida K. Haugen). An experienced radiologist (Karwan Faraj) at the radiology department at Diakonhjemmet Hospital, with special interest in musculoskeletal MRI, was consulted for guidance on assessing synovitis. The training was followed by a calibration exercise where 30 patients were scored separately in groups of 13, 7, and 10 patients. In the 13 first patients, the readers obtained a weighted kappa of 0.57. In the following seven patients, a weighted kappa of 0.72 was obtained. In the last group of 10 patients, the weighted kappa was 0.69. After the calibration exercise, joints with two or more grades discrepancy as well as joints differing between zero and one (no synovitis/synovitis) were discussed and scored by consensus. When scoring the 246 MRI scans, the Ph.D. student consulted the experienced reader in case of uncertainties. The readers were always blinded for clinical and other imaging data, but not for age and sex. Finally, the Ph.D. student re-assessed 20 images approximately three months after scoring of the MRI scans, with good intra-reader reliability in the DIP and PIP joints (weighted kappa=0.72, ICC= 0.89).

3.3.1.8 Ultrasonography

A medical student (Nikolas Ravn Aarskog) received ultrasound training by two experienced ultrasonographers (Hilde Berner Hammer (MD, Professor) and Alexander Mathiessen (MD, Ph.D.)) with demonstration of the probe and ultrasound machine, normal grey scale anatomy of the hand and presentation of an atlas with grey scale synovitis and power Doppler activity grade 1 to 3 in the bilateral DIP, PIP, MCP, and CMC-1 joints (234). We used a General Electric Logic S8 ultrasound machine with a linear 6-15 millihertz probe to assess hand joints for grey scale synovitis and power Doppler activity on 0-3 scales with the training atlas as reference. All participants had their bilateral DIP, PIP, MCP, and CMC-1 joints scanned longitudinally from the radial to the ulnar side, with transverse scanning in case of uncertainties. The ultrasonographer was blinded to other imaging data. A reliability exercise was performed by the end of the data collection with the medical student and one of the experienced ultrasonographers (Alexander Mathiessen) with consecutive enrollment of 10 patients. The two assessors obtained good inter-reader reliability with prevalence and bias adjusted kappa (Pabak) for power Doppler activity in DIP/PIP (0.85) and CMC-1 joints (0.92) and for grey scale synovitis in DIP and PIP (0.80) and CMC-1 joints (0.92) (243).

3.3.1.9 Conventional radiography

Frontal conventional radiographs of the bilateral hands with a posterior-anterior view was obtained. An experienced reader (Ida K. Haugen) blinded for clinical and other imaging data, but not for age and sex, scored the radiographs. Using the Kellgren Lawrence scale (grade 0-4) and Verbruggen Veys anatomical phase scoring system, the DIP, PIP, MCP and CMC-1 joints were scored. We defined erosive hand OA as having one or more DIP and PIP joints in

the erosive or remodeling phase of the Verbruggen Veys anatomical phase scoring system, one of several definitions for erosive hand OA (244). Further, we calculated Kellgren Lawrence sum score in Table 1 in paper II and III to give an impression of the overall severity of hand OA in the study participants. Intra-reader reliability for both scoring systems was excellent, with kappa of 0.93 (erosive vs. non-erosive) for the Verbruggen Veys score and weighted kappa on 0.92 for Kellgren Lawrence.

3.3.2 Data collection in reliability exercise

The FOIAS and the scoring methods developed in Stockholm and Copenhagen were presented and evaluated in a meeting in the Xiralite® GmbH headquarters in Berlin (Germany). Example cases of RA and hand OA patients were demonstrated and scored for all three methods. After the meeting, an atlas of the three scoring systems was developed, and one patient was scored for calibration. We included 13 erosive hand OA patients from the Nor-Hand cohort and 13 RA patients from the rheumatology outpatient clinic at Rigshospitalet (Copenhagen, Denmark) for the final reliability exercise. FOI scans in the RA patients were acquired as described above, and treatment change was performed after the FOI scan. MRI scans were not available from RA patients. Age, BMI, ethnicity, disease duration, anti-citrullinated protein antibody status, rheumatoid factor status, C-reactive protein, visual analogue scale (VAS) pain, VAS global, health assessment questionnaire and Disease Activity Score in 28 joints (DAS-28) was registered on all patients and was received from the study doctor in Copenhagen after the reliability exercise was completed.

3.4 Statistical methods

3.4.1 General considerations

For MRI, ultrasound, and conventional radiography, joints missing due to amputation, arthrodesis, or trapezioectomy were imputed with a mean value of all hand joints when calculating sum scores. The same joints remained missing when calculating frequencies and evaluating diagnostic performance. Stata versions 14.0 and 15.0 were applied for all statistical analyses throughout the thesis. Statisticians Joe Sexton and Øivind Skare at Diakonhjemmet Hospital were consulted for questions regarding analysis and coding in the statistical software.

3.4.2 Descriptive analysis and group comparisons

In all three papers, we provided demographic information about the participants in the first table. Continuous data were presented as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables were presented as the percentage of the most prevalent value. We calculated the Kellgren Lawrence sum score and presented number of patients with erosive disease to summarize the severity of OA in the participants. Sum scores of MRI, ultrasound, and FOI findings were calculated to give an overview of the inflammatory burden in the participants.

In paper I we investigated FOI enhancement in different joint groups in RA vs. erosive hand OA patients with three different FOI scoring methods. As the sum scores for FOI enhancement were not normally distributed for all scoring methods, we applied the non-parametric Mann-Whitney U test to assess differences between the two groups.

3.4.3 Reliability

In paper I, we investigated the reliability of three different scoring methods with five readers, thus ten different reader pairs. On patient level, we calculated sum scores for each participant and estimated intraclass correlation coefficients (ICC, two-way mixed-effects model, absolute agreement) of 10 reader pairs. The presented ICC value was the average of these 10 reader pairs. On joint level, we calculated linearly weighted kappa values and prevalence and bias adjusted kappa values for ordinal scales (Pabak-OS) for 10 reader pairs. We estimated mean values for reader pairs across four joint groups (DIP, PIP, MCP, wrist) for the three different methods. Furthermore, percent exact agreement (PEA) and percent close agreement with a difference of one grade across the five readers was calculated.

In paper II, we presented previously published inter-reader reliability for the scoring of FOI enhancement and grey scale synovitis and power Doppler activity. Intra-reader reliability with weighted kappa for scoring radiographic OA severity according to the Kellgren Lawrence scale and kappa for erosive vs. non-erosive was reported. Finally, we reported inter-reader reliability for MRI score of all hand joints as weighted kappa.

In paper III we reported inter- and intra-rater reliability (weighted kappa and ICC) for FOI and MRI for DIP and PIP joints only, as these were the only joints included in the analyses. Kappa and ICC values in all papers were interpreted as poor (0 - 0.2), fair (0.2 - 0.4), moderate (0.4 - 0.6), good (0.6 - 0,8) and very good (0.8 - 1.0) (245).

3.4.5 Validity

Correlation coefficients

In paper II, we estimated the validity of FOI compared to MRI- and ultrasound-defined synovitis. We calculated Spearmans' rho between sum scores for all three imaging modalities in all finger joints together (DIP, PIP, MCP) and for joint groups separately. For the comparisons of FOI and ultrasound, sum scores of both hands were calculated, while sum scores of the dominant hand were used for the comparison of FOI and MRI. We performed stratified analyses on patients with erosive hand OA vs. non-erosive hand OA.

Diagnostic performance

In paper I, we assessed the diagnostic performance of FOI measuring synovitis with MRI as reference in a small group of erosive hand OA patients (n=13). Sensitivity, specificity, negative (NPV), and positive predictive value (PPV) and PEA were calculated.

In paper II, we continued investigating the diagnostic performance of FOI measuring synovitis in 221 hand OA patients with MRI- and ultrasound-defined synovitis as reference. We calculated sensitivity, specificity, NPV, PPV, and AUC. Analyses were repeated with an increased cut-off for MRI- and ultrasound-defined synovitis to grade 2, and FOI enhancement grade 0/1 vs. grade 2/3. Stratified analyses on patients with erosive vs. non-erosive hand OA were performed.

3.4.6 Linear and logistic regression analyses

In paper III, we applied logistic regression to assess the associations between FOI enhancement and pain last 24 hours, last six weeks, and pain on palpation. We also explored the associations between MRI-defined synovitis and the three pain variables. Generalized estimating equations (GEE) were applied to consider several joints within each patient. Furthermore, we applied multiple linear regression to investigate whether FOI enhancement was associated with AUSCAN pain, AUSCAN function and AUSCAN stiffness, grip strength

of the dominant hand, and NRS pain. The analyses were repeated for MRI-defined synovitis and the same pain, stiffness and physical function variables. We applied different regression models for each pain and physical function variable, and all analyses were adjusted for age, sex, BMI, and use of anti-inflammatory drugs. P-values below 0.05 were regarded as statistically significant.

3.5 Legal and ethical aspects

The Nor-Hand study was conducted according to the ethical principles of the Declaration of Helsinki. Written consent was collected from all participants before attending the study. The Regional Committees for Medical and Health Research Ethics (REK) approved the study (number 2014/2057). Participants could withdraw from the study at any point without explanation. Paper I included data from 13 RA patients from Rigshospitalet (Copenhagen, Denmark). These patients also signed informed consent, and the regional ethics committee in Denmark approved the study.

Xiralite® GmbH has produced the FOI device applied in this study. The Department of Rheumatology at Diakonhjemmet Hospital has leased a Xiralite® device throughout the data collection. Representatives from Xiralite® GmbH (Jörn Berger, Matthias Cziumplik) were present during the FOI meeting in Berlin before the reliability exercise in paper I. They contributed with valuable technical and practical information regarding the FOI device. None of them, or other representatives from Xiralite® GmbH, contributed to the study design, collection or interpretation of the data in this project, the writing of the manuscript, or the decision to publish the data. The authors have not received funding from Xiralite® GmbH. None of the external funders influenced the protocol, methods, analysis, or drafting of the research papers.

Participation on test evenings was not remunerated, however food and coffee were provided, and transportation cost was covered in certain circumstances. Contrast-enhanced

imaging procedures were only performed in the absence of contraindications. The written informed consent included information about a low radiation dose of 0.001 millisieverts (equivalent to 3 hours of naturally occurring background radiation) for hand radiographs.

Finally, the involvement of the study participants has been a priority. A representative of the participants, Mrs. Thalita Blanck, has been involved in the development of the study protocol and has given valuable feedback throughout the test evenings. After the baseline collection was finished, we organized a seminar for all participants with a presentation of preliminary results and a question and answer session.

4. Summary of results

Paper I

Our first objective was to assess the inter-reader reliability of the FOIAS and two semiquantitative scoring methods developed in Stockholm and Copenhagen. Secondly, we wanted to investigate the distribution of FOI findings in different joint groups in patients with RA and erosive hand OA with these three methods. Finally, we assessed the diagnostic performance for FOI measuring synovitis in erosive hand OA with MRI-defined synovitis as reference.

We found good inter-reader agreement on patient level with a very good ICC for FOIAS PVM, good values for FOIAS Phase 2 and 3, and the Stockholm method, while the Copenhagen method and FOIAS Phase 1 showed moderate agreement. On joint level, Pabak-OS across all methods were moderate to good with FOIAS PVM being the strongest (0.78) followed by FOIAS Phase 1 (0.69), the Stockholm method (0.63) and FOIAS Phase 3 (0.62). The Copenhagen method (0.56) and FOIAS Phase 2 (0.50) had moderate reliability. Similar reliability for erosive hand OA and RA was found when performing separate analyses for the two diagnoses.

We found more FOI enhancement in the DIP and PIP joints in the erosive hand OA patients for three different FOI scoring methods, although statistically significant differences were detected in the DIP joints only. The RA patients demonstrated more FOI enhancement in the MCP joints, while no consistent differences between diagnoses were observed in the wrist. The erosive hand OA patients demonstrated overall more enhancement in the hands than the RA patients by FOIAS PVM ($p<0.001$), FOIAS Phase 2 ($p=0.12$), and the Stockholm method ($p=0.03$).

Finally, we calculated diagnostic performance for FOI measuring synovitis with MRI-defined synovitis as reference in the erosive hand OA patients. The erosive hand OA patients featured frequent inflammation and only 4/107 DIP and PIP joints had no MRI-defined synovitis. FOIAS PVM and Phase 1 were the most specific phases (91%), while FOIAS Phase 2 was the most sensitive (91 %). The PEA for the different methods ranged from 52 to 75 %.

We concluded that FOI enhancement can be assessed with moderate to good reliability with three different scoring methods in patients with erosive hand OA and RA. We found significantly more enhancement in the DIP joints in erosive hand OA patients, while RA patients had more enhancement in the MCP joints. The diagnostic performance of FOI with MRI as reference demonstrated good specificity for FOIAS Phase 1 and good sensitivity for FOIAS Phase 2, respectively, however only 13 patients were included and larger studies are needed to explore this finding.

Paper II

In this second paper, we examined the frequency of FOI enhancement according to FOIAS and MRI- and grey scale-defined synovitis and power Doppler activity in different joint groups. Secondly, we assessed the amount of FOI enhancement in joints with increasing degree of radiographic hand OA. Finally, we investigated the validity and diagnostic performance of FOI as a measure of synovitis in hand OA using MRI- and ultrasound-defined synovitis as a reference.

We found no FOI enhancement in the thumb base, although 81 % of the participants had MRI-defined synovitis grade 1 – 3 in CMC-1 and/or STT joints. Sixty-one % of all STT and CMC-1 joints demonstrated MRI-defined synovitis grade 1 – 3, and the CMC-1 joint was more commonly affected (69 %) than the STT joint (54 %). Ultrasound of the bilateral hands also demonstrated frequent activity in the thumb base with grey scale synovitis grade 1 – 3 in 26 % of CMC-1 joints and power Doppler activity grade 1 - 3 in 19 % of CMC-1 joints. MCP joints showed frequent low-grade MRI-defined synovitis (32 % of joints, predominantly grade 1) while FOI and ultrasound demonstrated sparse findings in this joint group. The PIP joints demonstrated more enhancement than the DIP joints in Phase 2, 3, and PVM and more frequent MRI-defined synovitis, while ultrasound-defined grey scale synovitis, power Doppler and Phase 1 enhancement were more common in the PIP joints. Joints with increasing Kellgren Lawrence grade and Verbruggen Veys score demonstrated more FOI enhancement in PVM compared to normal joints.

We found poor to fair Spearman's correlation coefficients between FOI enhancement and synovitis defined by MRI (0.01 - 0.24) and ultrasound (0.12 - 0.25). The diagnostic performance of FOI with MRI-defined synovitis as reference demonstrated good specificity in Phase 1 (99 %) and Phase 3 (90 %), and the best sensitivity in Phase 2 (58 %). However, weak AUC-values for FOI enhancement with MRI-defined synovitis as reference was

detected (0.50 – 0.61). Similar results were found with grey scale synovitis as reference (AUC 0.51 – 0.63). When increasing the cut-off for MRI-defined synovitis to grade 2 or more, the diagnostic performance increased slightly.

To conclude, FOI was not able to detect enhancement in the thumb base. Joints with an increasing degree of radiographic OA had more FOI enhancement than normal joints. Correlation between FOI enhancement and MRI- and ultrasound-defined synovitis was poor to fair. Although Phase 1 and 3 had good specificity, and Phase 2 moderate sensitivity, none of the phases or PVM demonstrated overall good diagnostic performance and AUC-values were low.

Paper III

The main objective of this third paper was to explore associations between FOI enhancement according to FOIAS and pain, stiffness and physical function. Associations between MRI and the same hand symptom variables were also assessed.

Only interphalangeal joints were included in the analysis due to no enhancement in the thumb base and little to no enhancement in the MCP joints. On joint level, FOI enhancement on PVM was associated with pain during the last 24 hours (OR (95 % CI) grade 1: 1.24 (1.06, 1.45) and grade 2-3: 2.0 (1.6, 2.4)) and similar associations with a dose-response relationship was found for FOI and pain last six weeks and tenderness on palpation. The same dose-response relationship was found between MRI-defined synovitis and pain last 24 hours (OR (95 % CI) grade 1: 1.4 (1.1, 1.8), grade 2: 3.4 (2.4, 4.7), grade 3: 5.2 (3.1, 8.6)), and the two other pain variables.

On patient level, FOI sum scores were weakly associated with NRS hand pain and AUSCAN physical function, while there were no associations between FOI sum scores and AUSCAN pain and stiffness. The sum score of MRI-defined synovitis was also weakly associated with NRS hand pain, AUSCAN hand pain and physical function, although not statistically significant.

To conclude, FOI enhancement was associated with self-reported pain in the same joint last 24 hours and six weeks, and with tenderness on palpation. MRI-defined synovitis demonstrated numerically stronger associations with the same pain variables. On patient level, FOI enhancement showed no to weak association with measures of pain, stiffness and physical function. Similarly, no significant associations were found between MRI-defined synovitis and the same hand symptom variables.

5. General discussion

5.1 Methodological aspects

This section presents strengths and limitations regarding study design and population, imaging techniques, scoring systems, clinical examination, questionnaires, and statistical methods.

5.1.1 Study design

The main body of this thesis and all data in paper II and III are based on cross-sectional baseline data from the Nor-Hand study. This study includes 300 participants who performed FOI, MRI, ultrasound, radiographs, clinical examination and pain testing. It is one of the larger hospital-based observational hand OA studies to date. We have analyzed baseline data only, and the collection of follow-up data is ongoing.

With baseline data, we can assess frequencies, reliability, associations, and diagnostic performance. Without longitudinal data, we were not able to explore causal relationships and predictors for structural change and disease progression. In an observational study, particular caution must be exercised not to introduce systematic bias, as patients are not randomized into different groups. Systematic bias, i.e., selection bias, information bias or confounding, can weaken the internal validity of the results and limit the generalizability of findings.

5.1.2 Study population

The Department of Rheumatology at Diakonhjemmet Hospital serves a large part of the metropolitan area of Oslo, contributing to a varied socio-economic composition of the patient cohort. The majority of participants in the Nor-Hand study were recruited to screening by a

rheumatologist at the outpatient clinic at Diakonhjemmet Hospital, and we hypothesize that our participants had a higher disease activity, and more symptoms than hand OA patients in primary health care. Furthermore, they might have been referred to specialist health care due to uncertainty about the diagnosis, and might not be representative for the average hand OA patient. Although the majority of patients were recruited from the outpatient clinic, the cohort was not strictly hospital-based. Some participants were invited to screening after contacting the study coordinator directly and others were recruited through the OA self-management education program. Including very motivated patients who requested participation in the study, as well as participants in self-management programs, might have introduced selection bias in the cohort.

Too narrow inclusion criteria might limit the generalizability of findings while applying too broad inclusion criteria can introduce excess variability in the data. Proven hand OA by clinical examination or ultrasound was the first inclusion criterion. As opposed to the ACR hand OA criteria, hand pain or stiffness was not required, as we also wanted to recruit patients with early and/or low-degree OA. Patients had to be 40 to 70 years old at the time of inclusion. Follow-up exams after four and eight years were planned, and to avoid loss to follow-up the age limit at inclusion was set to 70 years. The lower limit was set to 40 years, as hand OA is rare in younger age groups (11).

5.1.3 FOI

The FOI examination was performed in a standardized setting at each test evening. Any extraordinary features present were noted in the XiraView® software. Taking photos of the hands to document potential factors influencing the final result, i.e. nail polish, rings, tattoos, and scars, could be an option in future studies. In retrospect, we would have added washing of

hands in lukewarm water to secure similar temperature in all hands and also the application of a neutral moisturizer to avoid artifacts from dry skin (167).

In the reliability exercise in paper I, three different semiquantitative scoring methods were compared. These had a moderate to good inter-reader reliability; however, the FOIAS was the one reaching highest inter-reader reliability and best diagnostic performance in measuring synovitis on a small sample of erosive hand OA patients. It is also the FOI scoring method most commonly referred to in the literature. Thus, we applied FOIAS to assess all FOI scans in the Nor-Hand cohort.

In the FOIAS, three phases are defined based on the distribution and washing-out of the contrast agent. The experienced FOI reader and the reader of FOI scans decided to score the first image in each phase, as these have strict definitions. We hypothesized that this would improve reliability. However, in previous studies by Werner *et al.*, Phase 2 is not assessed as one image only (160, 169). As the beginning of Phase 2 often demonstrates rich enhancement and becomes too sensitive, a final score is given after scrolling through the whole phase to give a more correct representation of the joint.

Cost should also be considered. The FOI device has approximately the same price as an average ultrasound device and is considerably cheaper than an MRI machine. Compared to ultrasound, the FOI exam has the additional cost of ICG of approximately 300 NOK/30 EUR per examination.

5.1.4 MRI

Due to cost and no conclusive evidence on handedness and degree of hand OA, we obtained MRI of the dominant hand only (57, 246). Furthermore, we wanted to include the MCP joints as limited data has been published on the presence of synovitis in these joints in hand OA patients. Compared to the commonly affected DIP, PIP, and thumb base joints, radiographic

findings in MCP joints are relatively uncommon in hand OA, as demonstrated in the population-based Framingham study (11). Nevertheless, a recent study applying ultrasound to assess cartilage in a small cohort of RA and hand OA patients found the MCP joints to be commonly affected in hand OA and with similar prevalence as in RA (247).

Due to feasibility, all imaging procedures were not performed on the same day. FOI and ultrasound were performed on the test evening, while the MRI was performed mean (SD) 9 (14) days after. Low-grade MRI-defined synovitis might be a normal finding and might fluctuate (248). However, we found good correlation between ultrasound and MRI-defined synovitis (rho=0.58), suggesting minor variation in the degree of synovitis between the test evening and the MRI examination.

Gadolinium contrast is contraindicated in acute kidney failure and if glomerular filtration rate <30 ml/min (249, 250). We obtained gadolinium-enhanced MRI scans of all participants, given no previous allergic reactions to radiographic contrast agents or reduced kidney function (GFR < 40 mL/min). Gadolinium has long been considered a benign contrast agent. However, recent studies have suggested that repeated gadolinium-enhanced MRI examinations might lead to deposits of gadolinium in the basal cell ganglia of the brain (251). Other studies have reported gadolinium deposition in bone (252), skin (253), and liver tissue (254). The impact of the deposited gadolinium in different organ systems and the duration of the deposition post-examination remains unknown. The patients performed only one MRI examination in this study; however, we did not routinely ask participants about previous gadolinium exposure.

One average bolus of Dotarem for a 70 kg patient cost approximately 300 NOK/30 EUR. The cost and maintenance of an MRI machine vary depending on technology and local agreements; however, it is more expensive than ultrasound machines and optical imaging devices.

When assessing synovitis on MRI scans of the hand, several pitfalls must be considered. As described by McQueen *et al.,* the timing of gadolinium injection is essential for the assessment of synovitis in the post-gadolinium image (255). The intravenously injected gadolinium contrast will ultimately end up in the small synovial vessels and in the interstitium of the synovial membrane. This happens at different rates depending on the individual physiology, and thus, the thickness of the synovium might be over- and underestimated according to when the images are taken. It has been suggested that images should be acquired within 10 minutes after the administration of contrast agent to obtain the best contrast between synovium and joint fluid (256). In the Nor-Hand study, the post-contrast images were taken approximately 5 minutes and 15 seconds after the injection of gadolinium. Finally, metal, movement, and susceptibility artifacts must also be kept in mind, the latter due to adjacent tissues with different susceptibility to magnetization, for example soft tissue and trabecular bone (255).

5.1.5 Contrast agents

Gadolinium contrast is better tolerated than iodine-based radiocontrast, and severe allergic reactions are rare (257, 258). ICG, applied in FOI, has a well-established safety profile, and severe allergic reactions are estimated to 0.05 % (182, 188, 259). ICG contains a small amount of iodine. Previous allergic reactions to radiocontrast are often erroneously referred to as seafood allergy or iodine allergy. Iodine plays an important role in several physiological processes in all human beings, and anaphylactoid reactions (type 1 reactions) to iodine are not theoretically possible (260). Furthermore, seafood allergy does not increase the risk of allergic reactions to radiocontrast more than other food-allergies (261). Nevertheless, to avoid misunderstandings, no gadolinium or ICG was administered if allergies to seafood, iodine or radio contrast were reported.

5.1.6 Patients self-reported measures and clinical examination

AUSCAN pain and NRS hand pain describe slightly different aspects of hand pain. The NRS consists of one question about general hand pain. A recall period of 24 hours is commonly applied and was also chosen for this study (262). The AUSCAN pain subscale includes five questions, with four questions concerning pain in activity and one about pain at rest. Thus, AUSCAN pain might pick up activity-related pain to a larger extent than NRS pain. Several factors contribute to the general hand OA pain experience in addition to structural changes, like psychosocial factors, sensitization, and genetics (95, 263). Focusing on absence/presence of pain in separate joints might remove some of the effect of psychosocial factors and central sensitization on general hand pain. Thus, we asked participants to mark painful joints last 24 hours and last six weeks on hand diagrams and assessed tenderness on joint level by clinical examination.

5.2 Statistical aspects

5.2.1 Reliability

Several statistical methods can be applied to calculate reliability, depending on the numbers of readers, if the measure is a continuous or categorical variable and if the categorical variable is ordinal or nominal.

In the reliability exercise in paper I, agreement on both patient and joint level was evaluated. On the patient level, we created sum scores for the total amount of hand FOI enhancement using different semiquantitative FOI scoring methods and calculated ICC values with two-way mixed-effect models with absolute individual agreement. A total of five readers participated in ten possible combinations of reader pairs. We presented the mean value of the

ten reader pairs as well as the range from weakest to best agreement to show the variety in reliability between reader pairs.

On joint level PEA, weighted kappa values and Pabak-OS were presented (264, 265). PEA assess the percentage of similar scorings; however, it does not take into consideration that similar scorings might be due to chance. This consideration is incorporated when calculating Cohen's kappa. Furthermore, Cohen's kappa can be weighted linearly, for example giving a discrepancy of one grade between readers less importance than a difference of two or three grades. Non-independence of findings is required when calculating Cohen's kappa; thus one joint can only be measured once, and scores from different readers must be independent (266).

The weighted kappa coefficient represents the proportion of agreement higher than that expected by pure chance but does not consider the prevalence of scores and bias of accessors (264, 267). Firstly, a prevalence effect might be introduced when the total percentage of agreements on the positive classification (FOI enhancement) differs from that of the negative classification (no FOI enhancement) between two readers. Secondly, bias is a potential pitfall in the estimation of a kappa value. The disagreement in the total proportion of positive and negative cases between two readers might lead to a large or small bias index. A high bias index affects smaller kappa values, while a high prevalence index affects higher kappa values (Figure 7) (268).

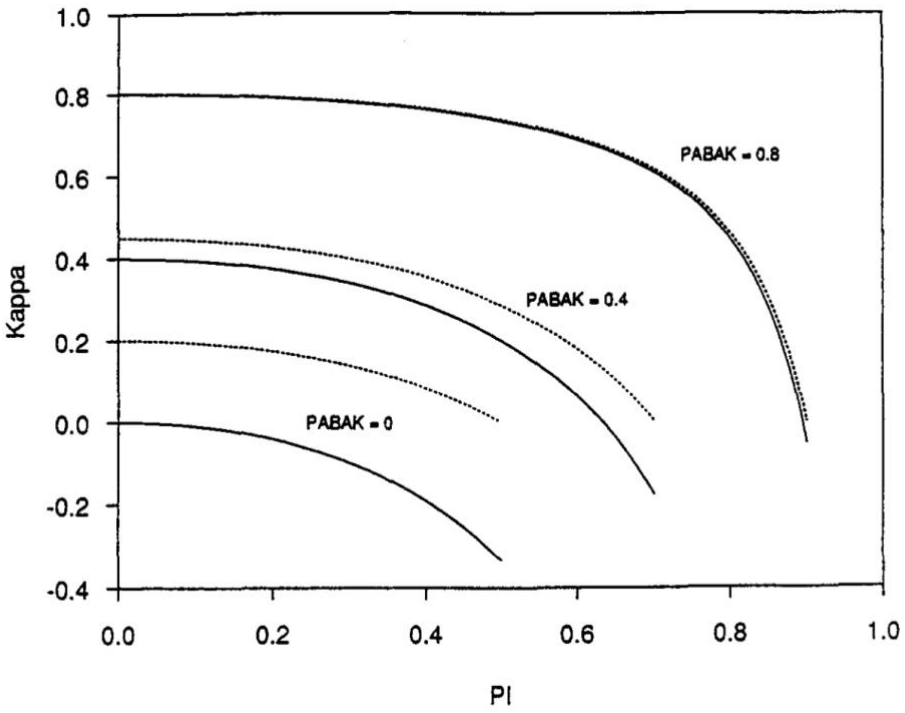

Figure 7: Relationship of kappa to prevalence index for three values of Pabak, as marked, and in each case for a bias of zero (solid line) and for the maximum possible bias (dotted line). Figure from original paper (268) with permission from Journal of Clinical Epidemiology.

Kappa values might be adjusted for prevalence and bias. The resulting coefficient is known as prevalence and bias adjusted kappa value (Pabak), and can also be linearly weighted for ordinal variables (268). The use of Pabak has been criticized for creating a hypothetical value without bias between readers and differences in prevalence, and that these effects on kappa are interesting per se and should not be adjusted for (264, 269). It has been suggested to always present Pabak values with their corresponding weighted kappa value, the separate proportions of positive and negative agreements or original data in a contingency table, so that the reader can assess the effect of prevalence and bias (268, 270, 271). We initially applied the Pabak-OS calculator by Vannest *et al.* (272), and secondly, a statistician (Øyvind Skare) at Diakonhjemmet Hospital made an algorithm for Pabak-OS in Stata 14. We

calculated Pabak-OS values for all ten reader pairs and presented mean values of these ten pairs.

5.2.2 Validity

The validity of FOI measuring synovitis in hand OA is at the core of this thesis. The four main types of validity include content, face, criterion, and construct validity. Content validity investigates whether a test includes all aspects of the disease, while face validity takes biologic coherence into account, and measures if a test represents the true nature of the disease. When assessing criterion validity, a test is compared to an already validated, true gold standard. It is not certain whether synovitis in the arthritic joint has a true imaging gold standard (273). When assessing whether FOI is a valid measure of synovitis in hand OA we assess construct validity, where the test (FOI) is compared with other tests (MRI and ultrasound) measuring the same construct (synovitis). We applied correlation, agreement, diagnostic performance and logistic and linear regression to explore the validity of FOI measuring synovitis in hand OA.

Correlation assess the relationship between two variables, while agreement is applied for concordance between two measures of a variable (274). The difference between these two terms can be visualized in a scatter plot. A good correlation can be detected if the dots fall on a straight line, while good agreement would require the dots to fall on a straight line at 45 degrees (275). Thus, a test with good agreement will result in a high correlation coefficient, whereas a strong correlation coefficient not necessarily yields a high agreement (276). Pearsons' r and Spearmans' rho are common measures of correlation. Both ranges from -1 to +1 and presents the strength and direction of the association. Pearsons' r is applied for continuous variables that are normally distributed, while Spearmans' rho is a nonparametric

rank correlation coefficient (277). Calculated sum scores were not normally distributed for all FOI phases and were based on ordinal scales, thus we applied Spearmans' rho.

To assess diagnostic performance, we applied calculations of sensitivity, specificity, PPV, NPV and AUC. We used binary outcomes (diseased/non-diseased), and for the primary analyses, we used FOI grade 0 vs. grade 1 - 3 with MRI-defined synovitis grade 0 vs. grade 1 - 3 and ultrasound-defined grey scale synovitis grade 0 vs. grade 1 - 3 as reference. We performed the analyses with different cut-offs for the three modalities to assess if the diagnostic performance increased with a stricter definition of enhancement/synovitis.

5.2.3 Regression

Confounding factors for linear and logistic analyses on FOI enhancement and pain and MRI and pain were assessed using directed acyclic graphs. We corrected the regression analyses for age and sex as these factors might influence both pain and degree of inflammation. Several studies have presented associations between obesity and low-degree inflammation (278-280) and obesity and pain (281), and thus we adjusted for BMI. Finally, anti-inflammatory drugs might affect both pain and degree of inflammation. Although few patients were regular users of anti-inflammatory drugs such as NSAIDs and prednisolone (n=31), this covariate was also added to the final model.

6. Main results

6.1 Demographics

Among the 221 participants in the Nor-Hand study who performed MRI and FOI, the majority were women (88 %), with a mean (SD) age of 60.6 (6.2) years. They were slightly overweight with a mean (SD) BMI of 26.2 (4.7) kg/m^2. Ninety-two % fulfilled the ACR hand

OA criteria and 34 % had erosive hand OA defined as having at least one interphalangeal joint in the erosive or remodeling phase of the Verbruggen Veys anatomical phase score. The mean (SD) NRS hand pain was 3.7 (2.3).

6.2 Reliability

One FOI sequence consists of 360 images. The semiquantitative scoring method FOIAS is the most commonly applied in the literature (160, 161, 169-171, 176, 177, 179, 282, 283), however quantitative methods are also reported (173-175, 284). The reliability of the FOIAS was compared with two semiquantitative FOI scoring methods developed in Copenhagen and Stockholm on 13 patients with erosive hand OA and 13 patients with RA. The best inter-reader reliability was found for FOIAS PVM on both joint level (Pabak OS = 0.78, weighted kappa = 0.51) and patient level (ICC = 0.85). The Stockholm method presented good agreement (ICC = 0.65, Pabak OS = 0.63) while the Copenhagen method (ICC = 0.46 Pabak OS=0.56) had moderate agreement. Reliability did not differ substantially when performing separate analyses on erosive hand OA and RA patients.

No previous studies have presented reliability data on the Stockholm or Copenhagen method. The FOIAS has previously demonstrated good inter-reader (weighted k = 0.73) and intra-reader reliability (weighted k = 0.71) for experienced readers in early RA, while a lower inter-reader agreement was found for the less experienced reader (weighted k = 0.55) (169). The latter value corresponds with our weighted kappa. Meier *et al.* did not apply the FOIAS and found lower inter-reader (k = 0.47) and intra-reader reliability (k = 0.50) in 45 patients with inflammatory joint disease (173).

There are several limitations to the reliability exercise in paper I. Best reliability was found in a reader pair from the same institution, who had previously worked together with a semiquantitative FOI scoring method. Furthermore, one of the readers differed substantially

from the remaining four readers, and reliability for Phase 1 was improved when analyses were repeated without this reader. This underlines the importance of calibration before a reliability exercise. Due to busy clinical schedule for many readers, only one patient was scored by consensus with the three semiquantitative scoring methods at a webinar before the reliability exercise. In retrospect, we would have performed a calibration exercise with more cases and possibly have scored the cases separately before the webinar. Finally, due to feasibility and time constraints, we did not calculate intra-reader reliability for the three scoring methods, which would have yielded a complete representation of the reliability of the three methods.

Phase 1 has previously been hypothesized to capture active inflammation in inflammatory joint diseases (161). We demonstrated low reliability for Phase 1, in line with a reliability exercise between two readers on the Nor-Hand data (239). In paper I, we hypothesized that Phase 1 had the lowest reliability due to rapid changes in the distribution of the fluorescent dye at the beginning of the examination. Furthermore, the onset of Phase 1 is defined as fluorescent enhancement descending from the fingertips, and we registered that readers interpreted this differently. Scoring different images (for example image 39/360 instead of 44/360) at the beginning of the image sequence resulted in clear discrepancies in joint enhancement, while scoring of different images within a broad range in Phase 2 and 3 (i.e., image 220/360 vs. image 280/360) still yielded good reliability. We hypothesize that this is due to slow changes in the distribution of the fluorescent dye by the end of the examination.

6.3 FOI-enhancement in erosive hand OA vs. rheumatoid arthritis

Erosive hand OA and RA have distinct patterns of hand joint involvement, with RA predominantly affecting MCP and wrist joints while hand OA has a predilection for the DIP and CMC-1 joints. PIP is commonly affected in both diseases.

In paper I, we compared patients with erosive hand OA and RA using three different FOI scoring methods. FOI enhancement patterns differed between the two diseases. We found statistically significantly more enhancement in the DIP joints in the hand OA group for all methods, comparable to findings by Glimm *et al.* (161). The RA group, on the other hand, demonstrated numerically more FOI enhancement in the MCP joints for all three methods. We did not find consistent differences between the groups in the wrist joints for any of the methods.

Glimm *et al.* demonstrated more enhancement in Phase 1 in the wrist, MCP, and PIP in the RA patients (n=67) compared to hand OA patients (n=23) (171). We studied a smaller sample of RA (n=13) and erosive hand OA patients (n=13) and did not find more enhancement in the RA group in Phase 1. Using the PVM and the Stockholm method, the erosive hand OA patients had indeed statistically significantly overall more enhancement than the RA patients. From a clinical perspective, RA typically involves florid inflammation, while OA tends to have low-grade synovitis. Given the severity of symptoms in the RA group, with indication to start or switch therapy and high disease activity score with mean (SD) DAS28 of 5.3 (0.7), it would be interesting to explore why the erosive hand OA patients still presented overall more enhancement. Firstly, 10 out of 13 RA patients were already treated with DMARDs, and ongoing treatment when the FOI was performed might have obscured the difference between the diseases. Secondly, erosive hand OA has been suggested to be a more inflammatory phenotype than non-erosive hand OA, and we found frequent MRI-defined synovitis and FOI enhancement in the erosive hand OA group. It is difficult to conclude on the level of synovitis in the RA group, as we lack MRI scans from these patients. Differences between inflammatory features in hand OA and RA might also explain the difference, and will be further discussed in the section on diagnostic performance.

6.4 Prevalence of FOI, MRI and ultrasound findings in joint groups

A total of 221 participants from the Nor-Hand cohort performed FOI, MRI, ultrasound, and conventional radiographs. They demonstrated a wide range of radiographic findings and synovitis.

The median Kellgren Lawrence sum score (range 0 - 120) was 28.8, comparable to the findings of n=106 patients in the Oslo hand OA cohort (Median (interquartile range) Kellgren Lawrence sum score 26 (15 - 41)) (220). The number of patients with erosive disease was 34 %, lower than comparable hand OA studies by Wittoek *et al.* (62 %), and the Oslo hand OA cohort by Haugen *et al.* (60 %) (220, 285).

MRI-defined synovitis was detected in the thumb base (CMC-1 and/or STT) in 81 % of the participants, and in 61 % of the total CMC-1 and STT joints of the dominant hand. The CMC-1 joint demonstrated synovitis more frequently (69 %) than the STT joint (54 %). Twenty-six percent of the CMC-1 joints had grey scale synovitis, while 19 % demonstrated power Doppler activity. Remarkably, none of the participants showed FOI enhancement in the thumb base. We are not aware of other studies reporting FOI enhancement in this joint region, most likely because it is located too deep and is surrounded by more subcutaneous tissue than the interphalangeal joints. We conclude that this is a significant limitation in the use of FOI in hand OA. This could possibly be solved by a 3D device with the pairing of dorsal, palmar, medial, and lateral images to encompass the whole joint region.

MRI-defined synovitis was more often detected in the PIP joints than in the DIP joints, while grey scale synovitis and power Doppler activity were more frequently detected in the DIP joints. Hand OA is more common in the DIP joints and it is surprising that MRI did not demonstrate more enhancement in this joint group. The DIP joints are smaller than the PIP joints. Enhancement in three consecutive MRI slices was required to qualify as synovitis, and this could have been more difficult to fulfill in the small DIP joints. PVM and Phase 2 and 3

demonstrated most enhancement in the PIP joints, while Phase 1 had most activity in the DIP joints. Although frequent low-grade inflammation was detected in the MCP joints by MRI, this was rarely the case for ultrasound and FOI. These results contrast with the findings of Glimm *et al.*, who investigated the distribution of FOI enhancement in 23 hand OA patients and detected more MCP enhancement for all FOIAS phases and PVM (161). A different definition of vascular structures might explain the different findings. Structures resembling vessels should not be scored as enhancement, and particularly at the wrist and MCP joints, this enhancement can be ambiguous and difficult to categorize.

Overall, MRI was the modality with most positive findings. The majority of positive joints had low-degree synovitis, particularly in the MCP joints. MRI has demonstrated to be more sensitive than ultrasound in detecting synovitis (286). However, it is also debated whether the low-degree gadolinium enhancement found on MRI represents pathology or a normal finding. Several studies have found low-degree synovitis in MCP and wrist joints in healthy subjects, and the clinical relevance of these findings should be interpreted with caution (248, 287, 288).

6.5 Diagnostic performance of FOI

FOI, MRI, grey scale and power Doppler ultrasound and conventional radiographs were performed on 221 participants. DIP, PIP, MCP, and thumb base joints (CMC-1 and STT with MRI, CMC-1 with ultrasound, and thumb base as a whole for FOI) were assessed on semiquantitative 0-3 scales and radiographs were scored according to Kellgren Lawrence score and Verbruggen Veys anatomical phase score. We found good correlation between sum scores of MRI and grey scale synovitis for all hand joints summarized ($r = 0.58$) and in all joint groups except the MCP joints ($rho = -0.04$). Correlation between grey scale synovitis and power Doppler activity was good for all joint groups ($rho = 0.79$). FOI demonstrated poor

to fair correlations with MRI-defined synovitis and correlated poorly with grey scale synovitis. PVM correlated with MRI-defined synovitis in the PIP joints with rho=0.32, while correlations between PVM and synovitis by MRI and grey-scale synovitis by ultrasound were poor in the DIP joints (rho=0.00 to 0.14). These results differ from correlation coefficients reported on FOI and MRI, and FOI and ultrasound, in inflammatory joint diseases. With a similar near-infrared optical imaging device, Fischer *et al.* presented strong correlation between MRI and FOI in five RA patients (rho=0.84), while Werner *et al.* applied the Xiralite® scanner and found moderate correlation between grey scale synovitis and FOI (rho = 0.40) in patients with arthritis (160, 166).

Percentage agreement between FOI (enhancement yes/no) and MRI (synovitis yes/no) ranged from 53 to 61 %, whereas the percentage agreement between FOI and ultrasound (synovitis yes/no) was 57 to 89 %. We presented the distribution of these agreements with number of positive FOI joints out of number of positive MRI joints and amount of negative FOI joints out of negative MRI joints. When comparing FOI and MRI, good agreement was mostly due to negative joints, while ultrasound and FOI had a more heterogeneous picture with agreement on negative joints in Phase 1 and Phase 3, while Phase 2 and PVM had a higher percentage of agreement on positive joints.

Diagnostic performance for FOI was calculated with sensitivity, specificity, PPV, NPV, and AUC using MRI-defined synovitis and grey scale synovitis as reference. The highest specificity with MRI as reference, with corresponding low sensitivity, was found for Phase 1 (99%), while the strongest sensitivities were found for Phase 2 (58 %) and PVM (48 %). High NPV was demonstrated for FOI with grey scale synovitis as reference, proposing that negative joints were unlikely to have grey scale synovitis. Nevertheless, low PPV values suggested that FOI enhancement is not corresponding to grey scale synovitis. FOI

demonstrated similar diagnostic performance with power Doppler and grey scale synovitis as reference.

The diagnostic performance was affected by MRI-defined synovitis being more prevalent than grey scale synovitis, particularly in the MCP joints. Thus, FOI demonstrated higher PPV and lower NPV with MRI as reference compared with ultrasound. We repeated the analyses using MRI synovitis grade 2 or higher as reference, and sensitivity, specificity, and AUC improved to the level of grey scale synovitis. Nonetheless, the findings of AUC values from 0.50 to 0.61 for FOI with MRI as reference and AUC of 0.51 to 0.63 for FOI and ultrasound suggest poor discrimination.

A trend for higher proportion of joints with FOI enhancement in PVM in joints with increasing Kellgren Lawrence and Verbruggen Veys scores was detected. A hypothesis for this finding is that bone remodeling with increased vascularity of the periphery of bone might demonstrate FOI enhancement.

We did not find AUC values for semiquantitative FOI scores with MRI or ultrasound as reference in the literature, making our weak findings difficult to compare. Other studies applying a semiquantitative FOI score in RA, undifferentiated arthritis and juvenile idiopathic arthritis have demonstrated better sensitivity in Phase 1 with MRI and ultrasound as reference (160, 169, 170, 283), supporting the hypothesis that early enhancement represents active inflammation with rich vascularization (161). Our participants had relatively few joints with power Doppler activity, with a mean sum score of 2.4 joints in DIP and PIP joints in the bilateral hands, which may explain the sparse enhancement and poor diagnostic performance in Phase 1. We expected better diagnostic performance in hand OA patients in Phase 2 and 3 as these phases have been suggested to be a measure of subclinical inflammation and increased capillary permeability, respectively (169). Nevertheless, sensitivity and specificity

in these phases were lower than previously reported values in RA and early arthritis (160, 169, 170).

A hallmark of inflammatory arthritis is increased leukocytes in synovial fluid. Although synovitis in hand OA and RA can be indistinguishable, several features might differ: leukocyte count in RA tend to be higher than in OA (289) and different subgroups of multinucleated giant cells have been detected in the two diseases (290, 291). Furthermore, a dynamic contrast-enhanced MRI study of finger joints suggested different pharmacokinetic patterns in patients with hand OA and RA (292). From a clinical perspective, hand OA often presents with chronic inflammation with minimal vascularization compared to the active inflammation of RA. The difference in synovial anatomy and mechanisms of angiogenesis in these two conditions could explain why FOI performs poorly in hand OA. We hypothesize that true FOI enhancement in hand OA due to synovitis possibly gets camouflaged by substantial background noise from the unspecific fluorescent dye. Nevertheless, separate analyses on erosive hand OA, hypothesized to be a more inflammatory entity, did not yield consistent improvement in the diagnostic performance of FOI.

MRI-defined flexor tenosynovitis was uncommon in the Nor-Hand cohort, and most common around the MCP joints. We hypothesize that these structures are located too deep, comparable to the CMC-1 joint, to affect the final result. Performing stratified analyses on the presence or absence of tenosynovitis in RA, Krohn *et al.* detected no essential changes in sensitivity and specificity, supporting this assumption (170). Peritendinous inflammation along the extensor tendons seems likely to be detectable by the dorsal-palmar view of the FOI device. However, none of the patients demonstrated this feature on MRI. Finally, extra-articular hypervascularity due to inflamed subcutaneous tissues might have contributed to FOI enhancement. Nevertheless, this feature was not assessed on the MRI scans.

Our findings of low correlation and diagnostic performance for FOI in hand OA might be explained by the scoring method. Firstly, FOIAS is primarily developed for inflammatory joint diseases and has only been applied on hand OA patients in one previous study (161). Secondly, FOIAS takes differences in blood circulation of the hands into consideration through defining different phases based on contrast distribution and the automatic adjustment of gain in PVM. However, this can also be done by quantitative scoring methods, possibly with better results (174, 175, 284). Furthermore, machine learning remains an exciting option in future FOI research. Pairing the dynamic pixel enhancement in different regions of interest with more established imaging markers could perhaps yield a scoring algorithm with improved validity for measuring synovitis in hand OA.

Finally, our findings are limited by the lack of a control group. Healthy controls and controls with arthralgia and no sign of inflammation have demonstrated minimal FOI enhancement in previous studies (160, 169, 172, 176, 177). Klein *et al.* reported some enhancement in the wrist in their control group, hypothesized to be caused by mechanical stress before the examination (282). Prominent vessel-structures and enhancement located outside the region of interest can frequently be seen in healthy controls and arthritic patients alike, and should not be scored as enhancement.

Fluorescent enhancement has corresponded to synovitis on histology in rodents with induced arthritis (162). However, our findings of poor correlation and poor to moderate diagnostic performance of FOI with MRI and ultrasound as reference and increasing FOI enhancement in joints with increasing degree of radiographic hand OA limits our understanding of what FOI measures in hand OA patients.

6.6 FOI and pain

Two-hundred and twenty-one study participants performed FOI and MRI and marked painful hand joints in the last 24 hours and six weeks on a hand diagram. Clinical examination of tender joints was performed. Only DIP and PIP joints were included in the logistic regression analysis, due to minor enhancement in MCP joints and no enhancement in the thumb base. We found a clear dose-response relationship between PVM, Phase 2, and Phase 3 and pain in the same joint during the last 24 hours and six weeks, as well as tenderness on palpation, while Phase 1 had little enhancement and demonstrated a clear dose-response relationship for pain last 24 hours only. We dichotomized the Phase 1 scores as absence/presence of enhancement and found statistically significant associations with all three pain variables.

Furthermore, we performed calculations with MRI-defined synovitis as the independent variable and the same three pain variables. We found numerically stronger associations between MRI and all three pain variables and detected the same dose-response relationship observed for FOI and pain. This is in line with previous findings from the Nor-Hand study where grey scale synovitis and power Doppler activity were associated with self-reported pain last 24 hours and six weeks and tenderness on palpation with similar strengths of association (243).

On patient level, associations between sum scores of FOI enhancement and measures of pain, stiffness, and physical function were calculated. All participants completed NRS hand pain, AUSCAN pain, AUSCAN physical function, and AUSCAN stiffness subscale and performed grip strength tests. The same analyses were repeated with MRI-defined synovitis sum score as the independent variable. In the linear regression analysis with NRS hand pain as the dependent variable, we found weak associations to PVM, Phase 2, and Phase 3, while no association to Phase 1 or MRI was demonstrated. Neither FOI nor MRI were associated with AUSCAN pain and AUSCAN physical function subscale, or grip strength, except for a

weak association between Phase 3 and AUSCAN physical function subscale. Finally, we found an inverse association between sum scores of MRI-defined synovitis and AUSCAN pain, AUSCAN physical function, and NRS hand pain. However, none of these associations were statistically significant.

MRI- and ultrasound-detected synovitis and radiographic findings have not shown strong and consistent associations with pain on patient level in previous hand OA studies (214, 243, 293). The thumb base joints were not included in the analyses, and these joints might affect functional outcomes more than the interphalangeal joints and explain the lack of association with AUSCAN physical function subscale and grip strength. On the other hand, weak statistically significant associations were detected between FOI and NRS hand pain, while no statistically significant associations were detected between FOI and AUSCAN pain subscale. NRS hand pain reflects overall pain in the hand, while AUSCAN pain subscale consists of 5 items where the majority relates to pain during activities. These questions might be challenging to answer if patients avoid certain activities due to pain and might also be affected by limited capacity to perform certain activities. The NRS hand pain question is more general and might reflect the patients' average pain during the day to a larger extent than AUSCAN pain. Finally, this discrepancy might be due to spurious associations without clinical relevance, as we performed a large number of linear regression analysis.

7. Conclusions

7.1 Answer to research questions

Objectives in paper I:

1. To assess the inter-reader reliability of three different FOI scoring methods in erosive hand OA and RA patients.

FOI scans of patients with erosive hand OA and RA can be assessed with moderate to good reliability with three different semiquantitative scoring methods, and the best reliability was obtained for the preset PVM image from FOIAS.

2. To quantify the distribution of FOI enhancement in different joint groups in erosive hand OA vs. RA.

Erosive hand OA patients showed statistically significantly more enhancement in the DIP joints than RA patients. Numerically more enhancement was found in the PIP joints in the OA patients and in the MCP joints in the RA patients. No consistent differences for the wrist joints were detected. Patients with erosive hand OA demonstrated overall more enhancement than RA patients.

3. To assess the diagnostic performance of FOI in 13 erosive hand OA patients with MRI as reference.

The highest sensitivity was found for Phase 2 (91 %), while the highest specificities was found for PVM (91 %) and Phase 1 (91 %) and the Stockholm method (85 %). FOI showed best specificity and sensitivity in the PIP joints.

Objectives in paper II:

1. To explore the distribution of FOI findings in hand OA patients and assess the amount of FOI enhancement in joints with increasing degree of hand OA

FOI was not able to detect synovitis in the thumb base, although the hand OA patients demonstrated frequent inflammation in these joints by ultrasound and MRI. Phase 1 had limited enhancement, while Phase 2, 3, and PVM showed frequent enhancement in the DIP and PIP joints. The MCP joints were rarely affected, in line with grey scale synovitis and power Doppler activity. Conversely, low-degree MRI-defined synovitis in the MCP joints was frequent. More FOI enhancement was detected in finger joints with an increasing degree of radiographic OA severity and erosions.

2. To assess the correlation between FOI enhancement in hand OA and MRI- and ultrasound-defined synovitis in hand OA patients

FOI had poor to fair correlation with ultrasound-defined synovitis and poor correlation with MRI-defined synovitis for all joint groups (DIP, PIP and MCP). The strongest correlation between FOI and MRI was found in the PIP joints, while the DIP joints showed the weakest correlation. MRI-defined synovitis and grey scale synovitis correlated well (rho = 0.58) in the 221 participants. A good correlation was also detected between power Doppler activity and grey scale synovitis (rho = 0.79).

3. To assess the diagnostic performance of FOI enhancement as a measure of synovitis using MRI- and ultrasound-defined synovitis as reference.

Concomitant good sensitivity and specificity was not detected for PVM or any of the phases, and AUC values were low. Phase 1 and 3 with MRI or ultrasound as reference demonstrated an AUC of 0.50 and 0.57, respectively. Phase 2 had the best sensitivity (58 %), while Phase 1 had best specificity (99 %). Phase 1 has been hypothesized to represent active inflammation and was less sensitive in hand OA patients compared to previous findings in inflammatory joint diseases. FOI demonstrated poorer diagnostic performance with MRI rather than ultrasound as reference, which may be explained by the high prevalence of low-grade MRI-defined synovitis, particularly in the MCP joints. When increasing the cut-off for MRI synovitis to grade 2 or higher, FOI had similar diagnostic performance to FOI with grey scale and power Doppler ultrasound as reference. Diagnostic performance and correlations did not improve in analyses on erosive hand OA patients only.

Objectives in paper III:

1. To explore the associations between FOI enhancement and pain on joint level and the associations between FOI and measures of pain, stiffness, and physical function on patient level.

FOI enhancement was associated with pain in the same joint last 24 hours, last 6 weeks and with tenderness on palpation. The associations demonstrated a clear dose-response

relationship. On patient-level, there were no to weak associations between sum scores of FOI and measures of pain, stiffness, and physical function.

2. To assess associations between MRI-defined synovitis and measures of pain, stiffness, and physical function.

On the joint level, a strong association with a dose-response relationship was demonstrated for MRI-defined synovitis and pain last 24 hours, pain last 6 weeks and tenderness on palpation. No statistically significant associations were detected between sum scores of MRI-defined synovitis and measures of pain, stiffness, and physical function.

7.2 Clinical implications

Hand OA is a whole joint disease where inflammation has been hypothesized to play an important role in the pathogenesis. Synovitis has been proposed as an outcome measure in future hand OA trials with disease modifying OA drugs targeting inflammation, and valid and cost-effective imaging techniques are warranted. FOI has been suggested to measure enhanced microcirculation around finger joints as a proxy for inflammation, and certain studies on FOI and inflammatory joint diseases have reported good agreement with MRI and ultrasound.

FOI enhancement can be assessed with moderate to good reliability in hand OA patients with three semiquantitative scoring methods. However, our results are questioning the validity of FOI measuring synovitis in hand OA, demonstrated by the weak correlations between FOI and MRI- and ultrasound-defined synovitis and poor to moderate diagnostic performance of FOI measuring synovitis with MRI and ultrasound as reference. Nevertheless, we found strong and dose-dependent associations between FOI enhancement and pain in the same joints, and also more FOI enhancement in joints with increasing structural damage and erosive disease. With these conflicting findings, it is difficult to conclude what FOI enhancement represents in hand OA.

There are several limitations to FOI and its use in future hand OA trials. Although the device is less expensive than an MRI machine and has similar cost as average ultrasound machines, the need for a fluorescent dye increases the cost per examination compared to ultrasound. As opposed to ultrasound and MRI, FOI does not yield any morphological information about the joints examined. Furthermore, the current technology is not able to detect synovitis in the thumb base, a frequently affected joint site in hand OA patients. An FOI device with a 3D representation of joints could possibly overcome this limitation. Finally, a machine learning approach, with an automated quantitative and dynamic scoring

method and targeting of the synovium with a more specific probe, could possibly increase the validity of FOI measuring synovitis in hand OA patients.

Moderate to good reliability was demonstrated for the FOIAS, and a clear association between FOI-enhancement and pain on joint level was detected. Furthermore, there was increasing FOI enhancement in joints with increasing degree of OA. Nevertheless, FOI scans obtained by the Xiralite® device after the injection of ICG and scored by the semiquantitative scoring method FOIAS demonstrated clear limitations as a measure of synovitis in hand OA patients with MRI- and ultrasound-defined synovitis as reference.

8. Errata

Paper 2:

1. In figure 2 the percentage of joints with MRI-defined synovitis grade 1-3 in the thumb base is reported as 81 %. The correct number is 61 %.
As reported under "Results, Frequency distribution of synovitis according to FOI, MRI, and ultrasound" 81 % of the participants demonstrated MRI enhancement in the CMC-1 and/or STT joint. However, 61 % of the total STT and CMC-1 joints examined demonstrated MRI-defined synovitis.

2. Supplementary figure 2: Erosive and remodeling phase is reported in two identical columns. The correct figure should have only one of the two columns representing joints in erosive and remodeling phase.

The above corrections have been reported to the journal.

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Evaluation of three scoring methods for Fluorescence Optical Imaging in erosive hand osteoarthritis and rheumatoid arthritis

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SUMMARY

Objective: Fluorescence Optical Imaging (FOI) demonstrates indocyanine green (ICG)-enhanced microcirculation in wrist and finger joints, as a sign of inflammation. We wanted to assess the reliability of three FOI scoring methods from Berlin, Stockholm, and Copenhagen, to assess the validity of FOI with MRI as reference and to compare enhancement in hand joints in erosive hand osteoarthritis (OA) vs. rheumatoid arthritis (RA).

Design: Five readers scored all finger and wrist joints of 26 patients with erosive hand OA and RA on semi-quantitative 0–3 scales using three different FOI scoring methods. To evaluate inter-reader reliability, we calculated the intraclass correlation coefficients (ICC) for sum scores and prevalence and bias adjusted kappa values for ordinal scales (Pabak-OS) on joint level. Enhancement in joint groups in erosive hand OA vs. RA was compared using Mann-Whitney test. Sensitivities and specificities of FOI was calculated with MRI as reference for hand OA patients only.

Results: We found moderate to good inter-reader reliability for all FOI scoring methods (Pabak-OS: 0.50–0.78, ICC: 0.43–0.85) and different patterns of enhancement in erosive hand OA vs. RA with significantly more FOI enhancement in DIP joints in erosive hand OA across all methods. With MRI as reference the different FOI scoring methods reached similar sensitivities (63–65%) and specificities (76–91%).

Conclusion: FOI enhancement can be measured reliably in erosive hand OA and RA using three different scoring methods. More DIP enhancement in erosive hand OA patients and good agreement with MRI support the diagnostic performance of FOI.

1. Introduction

Joint inflammation plays an essential role in the pathogenesis of rheumatoid arthritis (RA) and in the last decade studies have suggested that synovitis also is an important pathological component in hand osteoarthritis (OA) [1–3]. Monitoring inflammation with sensitive and cost-effective imaging techniques is important in both diseases. Inflammation assessed by imaging is not included in current remission criteria for RA, but there is increasing interest on the value of imaging-based treat-to-target strategies [22]. For treatment of hand OA there are currently no disease-modifying OA drugs (DMOADs) available and in future trials with drugs targeting synovitis, imaging might be an important and relevant outcome measure. Magnetic resonance imaging (MRI) and musculoskeletal ultrasound (US) can reliably monitor synovitis in both diseases, however MRI is hampered by high cost and limited availability and US by potential operator dependency and the need for sufficient US training. Fluorescence Optical Imaging (FOI) is a novel imaging technique using near infrared light and the fluorophore agent indocyanine green (ICG) to demonstrate enhanced microcirculation due to inflammation in wrist and finger joints. The FOI device can be

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operated by trained medical personnel, emits no radiation and is relatively inexpensive and fast. FOI has since 2010 been applied in clinical research on inflammatory joint diseases [4–9] and in a previous study on patients with undifferentiated arthritis FOI demonstrated good sensitivity and moderate specificity with MRI (n = 25; sensitivity 76%, specificity 54%) and power Doppler ultrasound (n = 74; sensitivity 74%, specificity 42%) as reference [10].

A reliable scoring method is crucial in the assessment of FOI images. The 'Berlin scoring method' developed at the Charité Universitätsmedizin Berlin as the fluorescence optical imaging activity score ('FOIAS') is the most commonly used scoring method in available literature [6,10–12]. A previous study by Werner et al. found moderate to good inter-reader reliability for the Berlin method (k = 0.71) [10] whereas Meier et al. have presented lower weighted kappa values (k = 0.47) [5].

New scoring methods have been developed at Karolinska University Hospital in Stockholm (Sweden) and at Rigshospitalet in Copenhagen (Denmark), but reliability for these two scoring methods has not yet been published. Our primary aim was to assess the inter-reader reliability of these three methods in erosive hand OA and RA patients, and to compare the degree of enhancement in different joint groups in these two diseases. Secondly, we wanted to investigate the diagnostic performance of the different FOI scoring methods in erosive hand OA patients using MRI-defined synovitis as a reference standard.

2. Methods

2.1. Patients

The erosive hand OA patients (n = 13) were randomly selected from the Nor-Hand study, where 300 patients with hand OA were recruited from the rheumatology outpatient clinic at Diakonhjemmet hospital [13]. Inclusion criteria was proven hand OA by clinical examination and/or ultrasound and no clinical sign of inflammatory arthritis. RA patients (n = 13) with the indication to start or switch synthetic DMARDs or switch from synthetic to a combination of synthetic and biological DMARDs were recruited from the rheumatology outpatient clinic at Rigshospitalet, Denmark. New treatment was initiated after the FOI examination.

The data collection was approved by the regional ethics committee in Norway and Denmark and all patients signed informed consent.

2.2. FOI examination

The Xiralite-system is the only FOI device available for clinical use in rheumatology. To perform the FOI scan, the patient receives an intravenous injection with a fluorescent dye (ICG pulsion, 0.1 mg/kg body weight) and have near-infrared light from light-emitting diodes projected down on the hands for 6 minutes. With a highly sensitive camera, 360 images (one/second) are produced, showing the flooding in, distribution and washing out of the dye. All images can be scrolled through after the examination, and a composite picture (Prima Vista Mode, PVM) from the 240 first images is automatically generated by the XiraView software. Patients with poor liver function (transaminases above twice the upper reference limit), untreated hyperthyroidism with fT4 above 21 pmol/L and thyroid-stimulating hormone (TSH) below 40 mL/min, reduced kidney function with glomerular filtration rate below 40 mL/min, pregnancy and breast-feeding or known allergy to iodine or indocyanine did not undergo FOI examination [13].

2.3. FOI scoring methods

A detailed description of the three scoring methods with an atlas and scoring sheets are available online (Supplementary file 1). In short, four images are assessed with the Berlin method; one composite picture (Prima Vista Mode, PVM) of the 240 first images (Fig. 1a) and three images representing phase 1, 2, and 3 based on the distribution and washing out of the fluorescent dye in relation to the fingertips. The readers registered which image in the sequence was defined as representative of the different phases.

The Stockholm method is evaluated in PVM of 240 and 120 images in a specific setting in the XiraView software ('temperature' palette setting, as opposed to the standard 'rainbow' palette setting), with additional scrolling through the image sequences to detect further joint enhancement. The 'temperature' palette setting is being applied as the developers of the scoring method have experienced that it might be easier to discern between enhanced and non-enhanced tissue with this setting (Fig. 1b).

Finally, the Copenhagen method assumes that inflamed tissues will demonstrate more rapid FOI enhancement than surrounding tissues. FOI enhancement is defined as the first sharply marginated enhancement over a joint area lasting ≥3 seconds when scrolling through the 360 images (Fig. 1c). When peak enhancement was detected in a joint, the readers registered which of the 360 images they assessed, and did not proceed scrolling through the remaining image sequence [14,15].

According to the Berlin and Stockholm methods each joint was graded on 0–3 scales based on color intensity and width of enhancement, while only the width of the enhancement was assessed with the Copenhagen method. The 2nd-5th distal interphalangeal (DIP), 2nd-5th proximal interphalangeal (PIP), 1st interphalangeal (IP1), 1st-5th metacarpophalangeal (MCP), first carpometacarpal (CMC1) joint and wrist were evaluated, with small differences across methods. Sum scores were based on 30 (Copenhagen, excluding the CMC1), 32 (Berlin) and 34 (Stockholm, excluding the CMC1 and interpreting the wrist as 3 joints; ulnar, radial and middle) joints. A mean FOI score from the five readers was calculated for each joint to be used in comparison with MRI.

2.4. Reliability exercise

We arranged a two-day meeting in Berlin (Germany) where all five readers (SO, DG, MA, YK, ØM) and other co-authors (IKH, MØ) participated. Two representatives from Xiralite GmbH offered technical assistance. The three FOI scoring methods were demonstrated and discussed. After the meeting, an FOI atlas was created with examples of grade 0–3 enhancement in all joint groups (except CMC1) for all methods. A calibration exercise was conducted via video conference where all participants scored one patient in consensus using the atlas. Subsequently, the reliability exercise of 26 patients was performed in which the readers were blinded for diagnosis, sex and age of the patients. Each reader scored all patients according to one by one scoring method with at least one week interval between each method and with rearrangement of the order of patients between each method. The readers started with different FOI scoring methods to avoid learning effects and better reliability favoring one method. Time spent on scoring each patient was noted to assess feasibility.

2.5. MRI

Patients with erosive hand OA from the Nor-Hand cohort underwent 1.5T MRI (Siemens Aera, Germany) of the dominant hand approximately 2 weeks after the FOI was obtained (mean (SD) 14 (8) days). The fingers and thumb base joints were covered by a 16-channel hand/wrist-coil and unless contraindications an intravenous contrast (Dotarem 279.3 mg/mL, 0.2 mL/kg body weight) was given. A T1-weighted volumetric interpolated breath-hold examination (VIBE) was reconstructed into three planes with 2 mm thickness [13], of which the axial and sagittal planes were used for evaluation of synovitis.

The images were assessed by two physicians: one experienced reader (IKH) and a PhD-student trained for assessing synovitis in the hand joints (ØM). Both readers were blinded to the FOI results and all clinical data. Synovitis in the DIP, PIP (incl. IP-1) and MCP joints were assessed on a 0–3 scale according to the Hand OA MRI scoring system (HOAMRIS) [16]. The MCP joints were scored as the PIP joints. The two readers

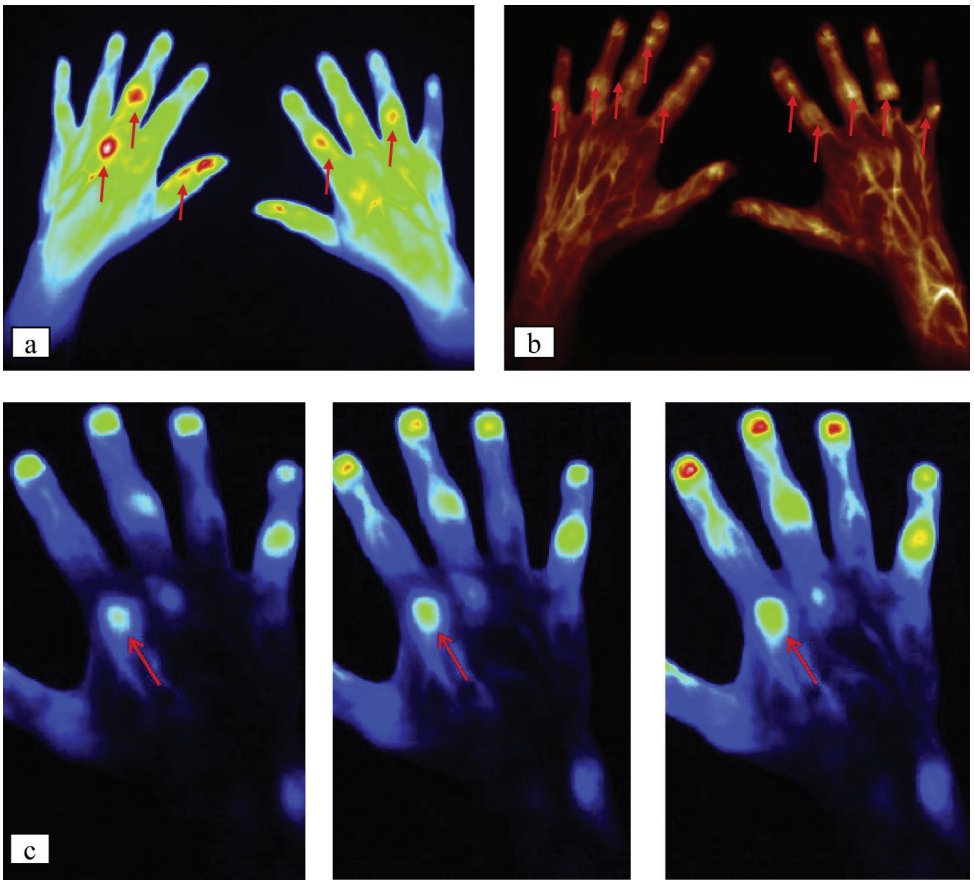

Fig. 1. a: The Berlin method, Prima Vista Mode. RA patient with enhancement in left PIP3, MCP3 and IP1, and right IP1, PIP2 and PIP4. Grading is based on signal intensity and width of enhancement. b: The Stockholm method, Prima Vista Mode 240 in temperature palette setting. OA patient with enhancement in the DIP and PIP joints. Grading is based on signal intensity and width of enhancement. c: The Copenhagen method. RA patient with enhancement in right MCP2. Grading is based on the width of enhancement in the 3rd image. Enhancement in other joints can also be seen in this image, however only one joint is assessed at a time with the Copenhagen method. See atlas in supplemental file 1 for details on grading for all methods.

reviewed all joints with disagreement regarding absence/presence of synovitis or inter-reader difference of 2 or 3 grades. The final grade was decided by consensus and an experienced radiologist (KF) was consulted if needed. In joints with one grade difference (grade 1 vs grade 2 and grade 2 vs grade 3), we used the lowest value. Tenosynovitis was assessed by one reader (ØM) according to the Oslo hand OA MRI scoring system (OHOA-MRI) [17], and consulted with KF and IKH in cases of uncertainties.

2.6. Statistics

The average sum scores of FOI enhancement for all five readers in all methods were calculated for different joint groups and for all joints together and compared in erosive hand OA vs. RA using the Mann-Whitney U-test. The CMC1 was assessed by the Berlin method only and demonstrated no enhancement. Hence, we excluded CMC1 from all analyses. The IP1 was defined as a PIP joint in all analyses. To evaluate inter-reader reliability of sum scores, we calculated the intraclass correlation coefficients (ICC, two-way mixed-effects model, absolute agreement, average of 10 reader pairs(range)). On joint level, we calculated linear weighted kappa values and prevalence and bias adjusted kappa values for ordinal scale (Pabak-OS) for pair of readers (ten pairs) and calculated mean kappa values across the four joint groups (DIP, PIP, MCP, wrist) and for all joint groups together. We assessed the percent exact agreement (PEA) and percent close agreement (PCA) with a maximum difference of one grade across the five readers. To compare FOI and MRI we calculated agreement rates for all joints together and in DIP, PIP, and MCP joints separately. The sensitivity, specificity, negative predictive and positive predictive values were calculated for FOI using MRI-defined synovitis as the reference. MRI-defined tenosynovitis was not included in the analysis due to low prevalence. For each of the three Berlin phases and the Copenhagen method we identified the images with the lowest and highest sequence number among the 5 readers. The average difference between maximum and minimum image per patient (Berlin) and per enhanced joint (Copenhagen) was then calculated for all 26 patients.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics for common variables in both studies are presented in Table 1. All patients with erosive hand OA fulfilled the American College of Rheumatology criteria for hand OA and they had substantial radiographic hand OA with mean (SD) Kellgren-Lawrence sum score of 45.3 (9) (range 0–128). All RA patients fulfilled the ACR/EULAR 2010-criteria, 69% of the patients were diagnosed within the last 2 years and had high disease activity with mean (SD) disease activity score 28 (DAS28) of 5.3 (0.7) and median (IQR) number

Table 1
Demographic and clinical characteristics.

	Erosive hand osteoarthritis (n = 13)	Rheumatoid arthritis (n = 13)
Age, mean (SD)	62 (6)	50 (12)
Sex, n (%) female	12 (92)	12 (92)
Body mass index, mean (SD) kg/m^2	25 (4)	n/a
NRS (0-10)/VAS (0–100) hand pain, median (IQR)	2 (1, 3)	60 (40, 72)
C-reactive protein, median (IQR) mg/l	3 (1, 4)	10 (7, 36)

OA (Osteoarthritis), RA (rheumatoid arthritis), NRS (Numeric Rating Scale), VAS (Visual Analogue Scale).

of 7 (5,9) swollen and 8 (6,10) tender joints. Six of the patients initiated or switched synthetic DMARD and seven patients added biological DMARD to current synthetic DMARD treatment. Three patients were DMARD naïve.

3.2. Reading of the FOI image sequence

For the Berlin method, the difference between the highest and lowest chosen image across the five readers was smallest for phase 1 with a median (IQR) of 10 (5, 22) images for the 26 patients. The difference was large for phase 2 with median (IQR) of 83 (66, 105) images and phase 3 with median (IQR) of 92 (62, 124) images. For the Copenhagen method the readers differed with median (IQR) 6 (3,10) to 10 (5,21) images for different joint groups.

The median (IQR) reading time per patient was shorter for the Copenhagen method (12 (11,14) minutes) than for the Stockholm (15 (14,17) minutes) and Berlin (17 (16,18) minutes) methods. In total the 5 readers scored 4368 joints with the Stockholm method (n = 52 missing), 3860 joints with the Copenhagen method (n = 40 missing) and for Berlin Phase 1–3 and PVM 4091 to 4123 joints (n = 37–69 missing).

3.3. Comparison of FOI-enhancement between erosive hand OA and RA patients

Comparing the two diseases we found numerically more FOI enhancement in the DIP and PIP joints in the hand OA patients, while the RA patients demonstrated more FOI enhancement in the MCP joints. Statistical significance was not reached for all methods (Table 2). No consistent differences were observed in the wrists for erosive hand OA and RA patients. The erosive hand OA patients demonstrated more enhancement in the hands than the RA patients by the Berlin PVM ($p < 0.001$), Berlin Phase 2 ($p = 0.12$) and Stockholm method ($p = 0.03$).

Table 4
Inter-reader reliability for all joints, presented as mean values of weighted kappa and Pabak OS across ten reader pairs and PEA and PCA for 5 readers.

	Mean Pabak OS	Mean W. kappa	PEA	PCA
Berlin PVM	0.78	0.51	52	92
Berlin Phase 1	0.69	0.44	50	74
Berlin Phase 2	0.50	0.44	21	61
Berlin Phase 3	0.62	0.37	29	77
Stockholm	0.63	0.40	33	66
Copenhagen	0.56	0.39	38	74

Pabak OS (Prevalence and Bias adjusted kappa values for ordinal scales), W. kappa (Weighted kappa), PCA (Percent close agreement), PEA (Percent exact agreement).

3.4. Inter-reader agreement of FOI

The ICC values were very good for the Berlin PVM while the Stockholm method and Berlin Phase 2 and 3 demonstrated good reliability (Table 3). On joint level the percent close agreement was good across all methods for all five readers (in all joint groups; Table 4). The readers had the highest percent exact agreement for Berlin PVM, and had highest agreement in the MCP joints (see supplement table 1).

Mean weighted kappa values for the ten reader pairs across all joint groups were moderate for Berlin PVM, Phase 1 and Phase 2, and fair for Stockholm, Copenhagen and Berlin phase 3. Using the Pabak-OS, we found clearly improved kappa values across all methods with moderate to good reliability (Table 4). We found moderate to very good agreement on joint level between two readers from the same center for all methods, while in Berlin phase 1 one of the five readers differed substantially from the rest, and if removing this reader from the analysis we found an ICC (min., max.) of 0.75 (0.49, 0.96). Similar reliability was found for erosive hand OA and RA except for Berlin Phase 1 where both ICC and Kappa values were stronger for RA vs. erosive hand OA (data not shown).

Table 2
Comparison of sum scores (IQR) for 5 readers across different joint groups in erosive hand OA patients vs RA patients.

Method	Diagnosis	DIP	P	PIP	P	MCP	P	Wrist	P
Berlin PVM	Erosive hand OA	4.8 (2.8, 7.6)	0.01	12.6 (11.2, 13.6)	<0.001	1.4 (0.6, 2.2)	0.41	0.4 (0.0, 1.4)	0.51
	RA	1.0 (0.2, 2.8)		6.0 (3.8, 9.0)		2.0 (1.0, 3.6)		0.2 (0.0, 0.8)	
Berlin Phase 1	Erosive hand OA	3.0 (2.4, 4.2)	<0.001	4.0 (3.0, 6.2)	0.57	0.8 (0.4, 1.0)	0.23	0.0 (0.0, 0.2)	0.28
	RA	1.4 (0.6, 2.0)		3.6 (2.4, 5.6)		2.2 (0.6, 5.0)		0.4 (0.0, 1.8)	
Berlin Phase 2	Erosive hand OA	10.2 (8.6, 11.6)	0.01	20.0 (18.8, 23.8)	0.23	6.6 (4.4, 8.8)	0.47	3.6 (2.4, 4.4)	0.01
	RA	6.4 (5.6, 6.8)		15.0 (11.6, 22.2)		10.0 (5.0, 10.8)		1.8 (0.8, 2.4)	
Berlin Phase 3	Erosive hand OA	2.6 (1.4, 2.8)	0.59	8.4 (6.4, 12.6)	0.94	2.6 (1.6, 4.0)	0.39	1.6 (0.6, 2.2)	0.03
	RA	1.2 (0.6, 3.4)		7.8 (5.4, 12.2)		3.2 (2.6, 6.8)		0.4 (0.4, 1.4)	
Stockholm	Erosive hand OA	6.4 (5.4, 9.8)	<0.001	15.2 (12.8, 17.6)	0.01	1.2 (0.8, 2.4)	0.03	1.0 (0.4, 4.2)	0.80
	RA	1.6 (0.8, 3.4)		9.4 (6.6, 12.6)		3.8 (2.2, 7.0)		1.2 (0.4, 2.4)	
Copenhagen	Erosive hand OA	4.4 (3.4, 6.4)	<0.001	10.0 (7.2, 11.0)	0.68	2.6 (1.0, 4.8)	0.11	1.2 (0.8, 1.6)	0.12
	RA	1.8 (1.0, 2.6)		7.6 (4.4, 11.4)		5.0 (2.8, 10.4)		1.8 (1.0, 3.0)	

IQR (Inter-quartile range), DIP (distal interphalangeal joint), PIP (proximal interphalangeal joint), MCP (metacarpophalangeal joint), PVM (Prima Vista Mode), RA (Rheumatoid Arhtiritis), OA (Osteoarthritis).

Table 3
Inter-reader reliability for sum scores in different joint groups. Average ICC values with range of minimum and maximum score for ten reader pairs.

	All joints ICC (min., max.)	DIP ICC (min., max.)	PIP ICC (min., max.)	MCP ICC (min., max.)	Wrist ICC (min., max.)
Berlin PVM	0.85 (0.75, 0.97)	0.73 (0.41, 0.95)	0.88 (0.79, 0.97)	0.71 (0.47, 0.96)	0.66 (0.46, 0.92)
Berlin Phase 1	0.43 (−0.17, 0.96)	0.24 (−0.08, 0.67)	0.32 (−0.11, 0.85)	0.79 (0.48, 0.99)	0.79 (0.68, 0.99)
Berlin Phase 2	0.70 (0.32, 0.98)	0.75 (0.56, 0.94)	0.72 (0.36, 0.98)	0.57 (0.08, 0.95)	0.80 (0.69, 0.93)
Berlin Phase 3	0.61 (0.25, 0.89)	0.63 (0.29, 0.83)	0.65 (0.35, 0.92)	0.55 (0.17, 0.95)	0.71 (0.55, 0.90)
Copenhagen	0.46 (0.09, 0.92)	0.64 (0.43, 0.90)	0.42 (−0.06, 0.90)	0.76 (0.52, 0.93)	0.60 (0.35, 0.86)
Stockholm	0.65 (0.44, 0.84)	0.73 (0.59, 0.88)	0.77 (0.69, 0.86)	0.76 (0.53, 0.90)	0.51 (0.10, 0.80)

ICC (intraclass correlation coefficient), DIP (distal interphalangeal joint), PIP (proximal interphalangeal joint), MCP (metacarpophalangeal joint), PVM (Prima Vista Mode).

Table 5
The agreement, sensitivity, specificity and predictive values of FOI enhancement in all joints in erosive hand OA patients using MRI as reference (182 joints).

	FOI+/MRI+[a]	FOI-/MRI-[b]	Sens.	Spes.	PPV	NPV	PEA	Pabak
Berlin PVM	83/128	49/54	65	91	94	52	73	0.45
Berlin Phase 1	45/128	49/54	35	91	90	37	52	0.03
Berlin Phase 2	117/128	20/54	91	37	78	65	75	0.51
Berlin Phase 3	65/128	40/54	51	74	82	39	58	0.15
Copenhagen	81/128	41/54	63	76	86	47	67	0.34
Stockholm	87/128	46/54	68	85	92	53	73	0.46

FOI (Fluorescence Optical Imaging), MRI (Magnetic Resonance Imaging), PPV (Positive Predictive Value), NPV (Negative Predictive Value), PEA (Percent Exact Agreement), Pabak (Prevalence and Bias Adjusted Kappa values), PVM (Prima Vista Mode).

[a] Joints with FOI enhancement in joints with MRI synovitis.

[b] Joints without FOI enhancement in joints without MRI synovitis.

3.5. Agreement between MRI and FOI in erosive hand OA patients

A total of 182 joints (13 patients, 14 joints per patient) were assessed with MRI, with no joints missing. The 13 erosive hand OA patients had substantial MRI-defined synovitis in the finger joints (DIP, PIP and MCP) with median (IQR) HOAMRIS sum score of 14 (13,15). There were only 4/107 DIP and PIP joints with no MRI-defined synovitis. Only one patient showed mild to moderate tenosynovitis in the MCP joints, thus tenosynovitis was not included in the analyses. We found the highest specificities for the Berlin PVM and Phase 1 and the Stockholm method, while Berlin Phase 2 had the highest sensitivity with a corresponding low specificity (Table 5). Among the different joint groups, the highest specificities and sensitivities were found in the PIP joints (supplement table 2).

MRI defined synovitis was present in 45/94 joints without FOI enhancement of which the majority (30 joints) was grade 1. When looking at agreement between MRI defined synovitis grade 2 and 3 vs. FOI grade 2 and 3 we found slightly improved specificity for all methods with corresponding lowering of the sensitivity (data not shown).

4. Discussion

No previous studies have evaluated the reliability and validity of different FOI scoring methods in patients with erosive hand OA and RA. In this study we found moderate to very good inter-reader reliability on patient level for all methods and moderate to good agreement on joint level for all three methods. Our findings of best agreement between two readers from the same center underlines the importance of calibration before scoring. The Berlin PVM showed consistently the strongest inter-reader reliability on both patient and joint level for all joints summarised. PVM assesses a predefined composite picture generated by the XiraView software, as opposed to the Berlin phases 1, 2, and 3 and the Copenhagen method, where the reader selects which of the 360 images to be scored according to pre-defined criteria. We found good reliability for both Berlin phases 2 and 3, even if readers differed substantially on which image they scored. On the other hand, the Copenhagen method had slightly lower agreement rates on joint and patient-level, even if the readers differed with 6–10 images only, depending on joint group. Thus, the lower reliability for the Copenhagen method and the Berlin phase 1 may be due to rapid changes in enhancement shortly after the injection of ICG. Hence, small changes in the image selection may have a large impact on the result early in the image sequence. The discrepancy between readers with regards to image selection could be explained by the readers' interpretation of the definition of phase 1, 2, and 3 in the Berlin method or "sharply marginated enhancement" as described in the Copenhagen method.

We found different FOI enhancement patterns in erosive hand OA vs. RA patients with more enhancement in the DIP joints in the OA patients across all methods, in line with a previous study by Glimm et al. [12]. We also found FOI enhancement in the DIP joints of the RA patients. While this could be due to concomitant hand OA in these patients, we do not have radiographs to verify this finding. As expected we found more enhancement in the MCP joints in the RA patients, although the difference reached statistical significance for the Stockholm method only. Phase 1 has previously been suggested to represent active inflammation [10], however we did not find significantly more enhancement in RA patients than in erosive hand OA patients in this phase. For both the Berlin PVM and the Stockholm method the erosive hand OA patients had significantly more enhancement in their hands than the RA patients, highlighting the extensive inflammatory burden in those patients. In line with these findings the erosive hand OA patients also demonstrated high levels of inflammation in finger joints on MRI. The RA patients were highly symptomatic, however we did not obtain MRI images of these patients and it is uncertain whether they had high degree of synovitis in finger and wrist-joints. DMARD treatment in 10 out of 13 of the RA patients may have lowered the inflammation in these patients, making the difference between diseases less pronounced.

This is the first study to compare FOI to MRI in erosive hand OA patients. In two previous studies on patients with undifferentiated arthritis, Werner et al. found slightly lower sensitivities (51–59%) and comparable specificities (81–87%) of FOI using the Berlin method in comparison to MRI [10,11]. More recently Hirano et al. found higher specificities and sensitivities for all 3 phases and PVM, however only 6 RA patients were examined and a limited number of joints (wrist and MCP 2–4) was included in the analysis [9]. Our findings of low sensitivity of FOI might be due to the high prevalence of MRI-defined synovitis grade 1 in our patients. The majority of joints with inflammation by one method only (i.e. FOI enhancement or MRI-defined synovitis only), demonstrated mild degree of pathology, which may be difficult to distinguish from normal findings and may not represent pathology [18,19]. Secondly, as suggested by Werner et al., the low sensitivity of FOI compared to MRI might be due to FOI demonstrating other aspects (e.g. tenosynovitis) of the inflamed joint than synovitis [10]. FOI enhancement has corresponded to histological synovitis in animal models with induced arthritis [20], however similar studies have not been performed in humans. Nevertheless, presence of FOI enhancement represents inflammation in most cases, as demonstrated by our findings of high positive predictive values across all methods. Negative predictive values were low to moderate across all methods, suggesting that a lack of enhancement cannot exclude synovitis.

The Copenhagen method was the fastest scoring method. However, in this exercise the readers had to report which image frame they scored for each enhanced joint and in patients with much activity this added several minutes to the final scoring time compared to regular scoring with the Copenhagen method [14,15]. For the Berlin method the readers reported which image they defined as phase 1, 2, and 3 which also added extra time to the total, whereas no additional information was reported for the Stockholm method. Nevertheless, our results indicate that all three methods are feasible with scoring times ranging from 12 to 17 minutes.

There are several limitations to this study. We had MRIs from the erosive hand OA patients (n = 13) only. These patients had moderate to high level of inflammation with very few joints with no synovitis, making analysis on sensitivity and specificity difficult to interpret. Thus, a larger sample and more variety of MRI findings is needed in order to explore FOIs validity in hand OA. Secondly, we only assessed one patient per scoring method in the calibration exercise and we could possibly have reached higher reliability if

a larger number of patients had been scored by consensus before the reliability exercise. Third, intra-observer agreement was not included in the reliability exercise due to feasibility reasons. Finally, our findings cannot be generalised to the general hand OA population as we only included patients with erosive hand OA who had been referred to specialist health care. The FOI technology also has its limitations [6,11,21], with 2D-images only and no available device for combining radiographic and optical images. Near infrared light also has limited tissue penetration, and from our findings the frequently inflamed CMC-1 joint was not possible to visualise with the FOI device. Finally, several precautions must be taken before performing the FOI exam, as dry skin, wounds, tattoos, nail polish, cold fingers, excessive use of the hands before the examination and ambient light in the room might influence the final result on FOI.

In conclusion, FOI enhancement can be measured reliably in erosive hand OA and RA using three different scoring methods and from our findings the Berlin PVM was the most reliable method. Numerically more DIP and PIP enhancement in erosive hand OA patients, more MCP enhancement in RA patients and good agreement with MRI support the diagnostic performance of FOI. Future larger studies are needed to confirm these findings.

Role of the funding source

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Author contributions

ØM: Study design, data collection, analyzing the data, interpretation of results, drafting the work and final approval of the paper. IKH: Study design, analyzing the data, interpretation of results, drafting the work and final approval of the paper. SO, MA, DG, YK: Study design, data collection, interpretation of results, revising the work critically and final approval of the paper. LT, TKK, TU, MØ: Study design, interpretation of results, revising the work critically and final approval of the paper.

Conflicts of interest

No relevant disclosures.

Role of xiralite GmbH

The meeting before the reliability exercise was held in the Xiralite GmbH offices in Berlin. Xiralite GmbH has not contributed to the study design, collection or interpretation of the data, the writing of the manuscript or the decision to publish the data. None of the participants have received funding from Xiralite GmbH.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2019.100017.

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Supplement table 1: Inter-reader reliability for different joint groups, presented as mean values of weighted kappa and Pabak OS across ten reader pairs and PEA and PCA for 5 readers.

	DIP				PIP				MCP				Wrist			
	Mean Pabak OS	Mean W. kappa	PEA	PCA	Mean Pabak OS	Mean W. kappa	PEA	PCA	Mean Pabak OS	Mean W. kappa	PEA	PCA	Mean Pabak OS	Mean W. kappa	PEA	PCA
Berlin PVM	0.74	0.47	49	86	0.72	0.58	40	89	0.84	0.53	60	98	0.79	0.45	50	94
Berlin Phase 1	0.69	0.26	40	68	0.56	0.30	32	61	0.83	0.60	67	88	0.81	0.61	67	83
Berlin Phase 2	0.56	0.43	17	76	0.58	0.51	21	69	0.38	0.37	15	43	0.51	0.45	17	65
Berlin Phase 3	0.77	0.36	44	98	0.57	0.40	14	71	0.56	0.30	20	65	0.62	0.40	25	87
Stockholm	0.61	0.41	39	77	0.47	0.39	20	74	0.74	0.45	53	87	0.71	0.34	62	83
Copenhagen	0.65	0.39	50	82	0.35	0.30	14	53	0.70	0.52	50	81	0.48	0.36	27	79

Pabak OS (Prevalence and Bias adjusted kappa values for ordinal scales), W. kappa (Weighted kappa), PCA (Percent close agreement), PEA (Percent exact agreement).

Supplement table 2: The agreement, sensitivity, specificity and predictive values of FOI enhancement in different joint groups in hand OA patients using MRI as reference

	DIP (52 joints)							
	FOI-/ MRI-*	FOI+/ MRI+**	Sens.	Spes.	PPV	NPV	PEA	Pabak
Berlin PVM	2/3	27/49	55	67	96	8	56	0.12
Berlin Phase 1	2/3	21/49	43	67	95	7	44	-0.12
Berlin Phase 2	0/3	44/49	90	0	94	0	85	0.70
Berlin Phase 3	3/3	17/49	35	100	100	9	38	-0.23
Copenhagen	3/3	28/49	57	100	100	13	60	0.19
Stockholm	1/3	30/49	61	33	94	5	60	0.19
	PIP (65 joints)							
	FOI-/ MRI-*	FOI+/ MRI+**	Sens.	Spes.	PPV	NPV	PEA	Pabak
Berlin PVM	1/1	54/64	84	100	100	9	85	0.69
Berlin Phase 1	0/1	23/64	36	0	96	0	35	-0.29
Berlin Phase 2	0/1	62/64	97	0	98	0	95	0.91
Berlin Phase 3	0/1	45/64	70	0	98	0	69	0.38
Copenhagen	0/1	49/64	77	0	98	0	75	0.51
Stockholm	1/1	55/64	86	100	100	10	86	0.72
	MCP (65 joints)							
	FOI-/ MRI-*	FOI+/ MRI+**	Sens.	Spes.	PPV	NPV	PEA	Pabak
Berlin PVM	46/50	2/15	13	92	33	78	74	0.48
Berlin Phase 1	47/50	1/15	7	94	25	77	74	0.48
Berlin Phase 2	20/50	11/15	73	40	27	83	48	-0.05
Berlin Phase 3	37/50	3/15	20	74	19	76	62	0.23
Copenhagen	38/50	4/15	27	76	25	78	65	0.29
Stockholm	44/50	2/15	13	88	25	77	71	0.42

* Joints without FOI enhancement in joints without MRI synovitis.

** Joints with FOI enhancement in joints with MRI synovitis

FOI (Fluorescence Optical Imaging), MRI (Magnetic Resonance Imaging), PPV (Positive Predicitive Value), NPV (Negative Predictive Value), PEA (Percent Exact Agreement), Pabak (Prevalence and Bias Adjusted Kappa values), PVM (Prima Vista Mode).

Supplement file 1:
"Evaluation of three scoring methods for fluorescence optical imaging in erosive hand osteoarthritis and rheumatoid arthritis"

Fluorescence Optical Imaging Atlas

Reliability exercise, 2018

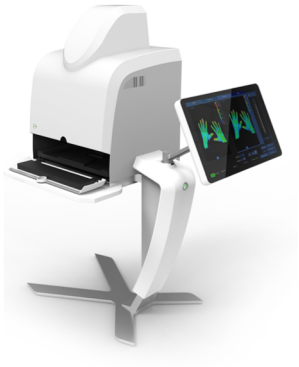


Image contribution: Berlin method, description + images: S. Ohrndorf, Copenhagen method, description + images: M. Ammitzbøll-Danielsen & D. Glinatsi, Stockholm method, description + images: Y. Kisten, DIP images in Berlin + Copenhagen: Ø. Maugesten

Outline

- Berlin method - Description, scoring sheet, examples.
- Copenhagen method - Description, scoring sheet, examples.
- Stockholm method - Description, scoring sheet, examples.

Berlin method | Copenhagen method | Stockholm method

Berlin Method - Description: **3 Phases & PVM**

For the image sequence, **3 phases** in position to the fingertips are defined regarding development of signal intensities depending on the phase of fluorescence dye flooding and individual perfusion:

- **Phase 1** includes the period between starting the investigation, application of the dye and increased signal intensities in the fingertips; the last image before the dye leaves the fingertips (in yellow or in red or in white – not in green) from distal to proximal in wrist direction is used for the scoring
- **Phase 2** begins when the dye leaves the fingertips from distal to proximal in wrist direction and stops when only red colour in the fingertips is visible; the first image with red colour in the fingertips (no white is seen anymore) is used for the scoring
- **Phase 3** begins when only yellow dots or no signal intensity can be seen in the fingertips; the first image without red dots in the fingertips is used for the scoring
- **PVM:** Prima Vista Mode. Composite picture of the 240 first FOI images.

Adapted from:
Glimm AM, Werner SG, Burmester GR, Backhaus M, Ohrndorf S. Analysis of distribution and severity of inflammation in patients with osteoarthritis compared to rheumatoid arthritis by ICG-enhanced fluorescence optical imaging and musculoskeletal ultrasound: a pilot study. Ann Rheum Dis. 2016 Mar;75(3):566-70. Supplement.
Werner S.G., Langer H.E., Schott P., Bahner M., Schwenke C., Lind-Albrecht G., Indocyanine green-enhanced fluorescence optical imaging in patients with early and very early arthritis: a comparative study with magnetic resonance imaging Arthritis Rheum. 2013 Dec 3036-3044

Berlin method | Copenhagen method | Stockholm method

Scoring of joint enhancement:

The enhancement in projection on the joint area is evaluated on the basis of the intensity of the affected joint area (reflected by its colour) as well as on the size of the enhanced joint area. On this account, the semiquantitative grading system 'fluorescence optical imaging activity score (FOIAS)' is used as follows:

Grade 0=no signal enhancement,

Grade 1=enhancement varies from yellow to red and can reach red with yellow spots, red covers ≤50% of the enhanced/affected joint area,

Grade 2=the signal intensity shows strong red colour intensity and can also include white signals, white covers ≤50% of the enhanced/affected joint area,

Grade 3=the signal intensity shows white colour intensity, white covers >50% of the enhanced/affected joint area[1]

When scoring the images, please give points for colour (colour more important than area) and affected joint area (from 0-3 each), and then let the lowest number decide the total grade per joint.

Adapted from:
Glimm AM, Werner SG, Burmester GR, Backhaus M, Ohrndorf S. Analysis of distribution and severity of inflammation in patients with osteoarthritis compared to rheumatoid arthritis by ICG-enhanced fluorescence optical imaging and musculoskeletal ultrasound: a pilot study. Ann Rheum Dis. 2016 Mar;75(3):566-70. Supplement.
Werner S.G., Langer H.E., Schott P., Bahner M., Schwenke C., Lind-Albrecht G., Indocyanine green-enhanced fluorescence optical imaging in patients with early and very early arthritis: a comparative study with magnetic resonance imaging Arthritis Rheum. 2013 Dec 3036-3044

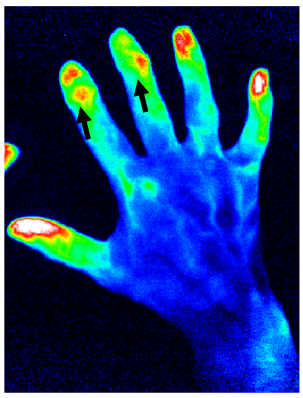
Berlin method | Copenhagen method | Stockholm method

Berlin Method; Scoring sheet

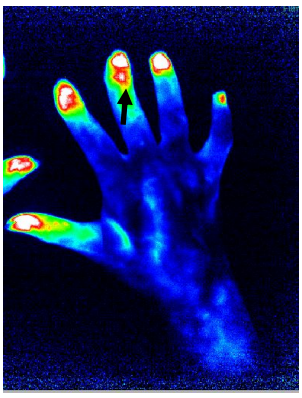
		PVM left	PVM right	Phase 1 left	Phase 1 right	Phase 2 left	Phase 2 right	Phase 3 left	Phase 3 right
wrist	1								
CMC 1	2								
MCP I	3								
MCP II	4								
MCP III	5								
MCP IV	6								
MCP V	7								
IP	8								
PIP II	9								
PIP III	10								
PIP IV	11								
PIP V	12								
DIP II	13								
DIP III	14								
DIP IV	15								
DIP V	16								
Image No. (sec.)		not needed	not needed						
Total									
Sumscore									
Duration of scoring:									

Berlin method | Copenhagen method | Stockholm method

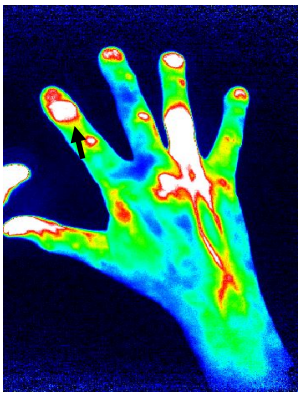
Phase 1: DIP



Grade 1



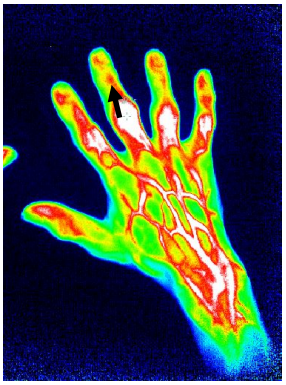
Grade 2



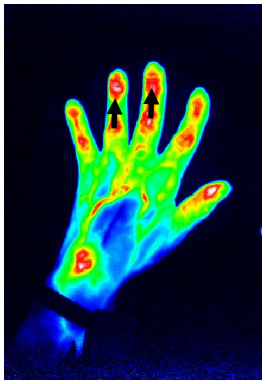
Grade 3

Berlin method | Copenhagen method | Stockholm method

Phase 2: DIP



Grade 1



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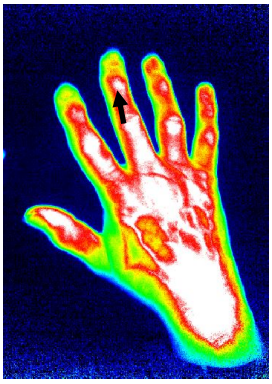


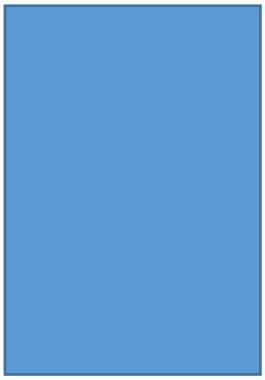
Grade 3

Berlin method | Copenhagen method | Stockholm method

Phase 3: DIP

Grade 1

Grade 2

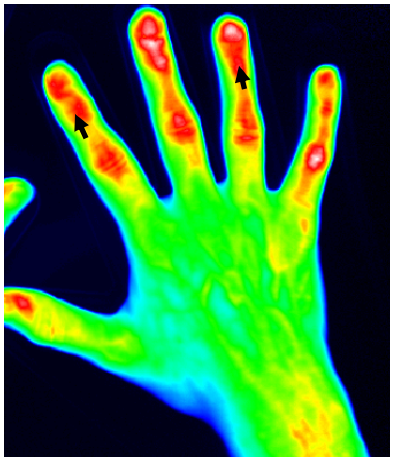


Grade 3

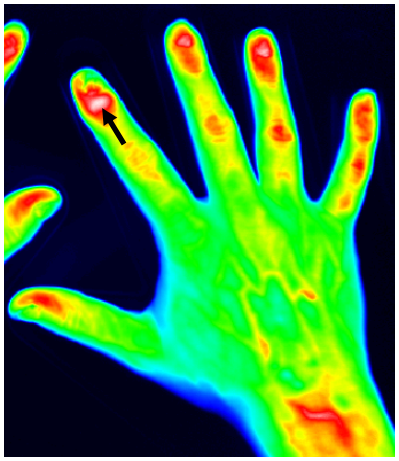
Berlin method | Copenhagen method | Stockholm method

PVM: DIP

Grade 1



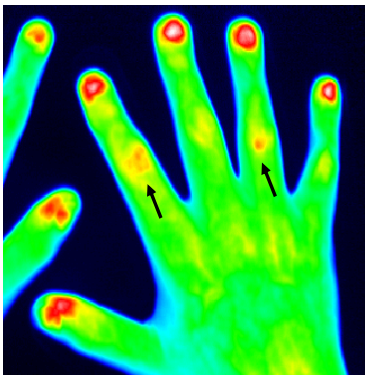
Grade 2



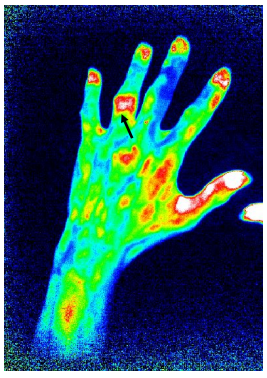
Grade 3

Berlin method | Copenhagen method | Stockholm method

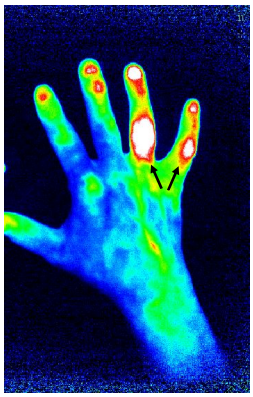
Phase 1: PIP



Grade 1



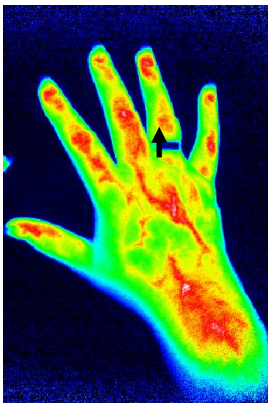
Grade 2



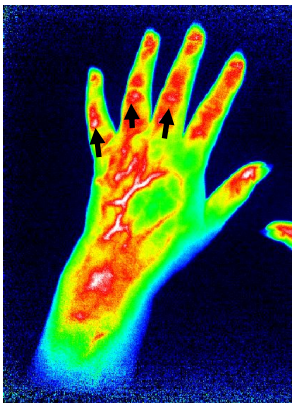
Grade 3

Berlin method | Copenhagen method | Stockholm method

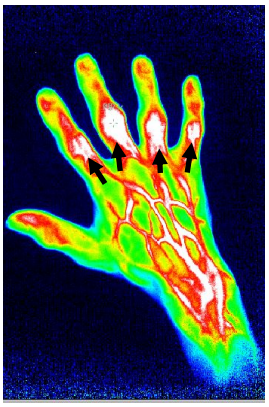
Phase 2: PIP



Grade 1



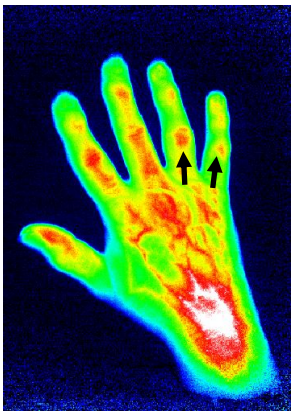
Grade 2



Grade 3

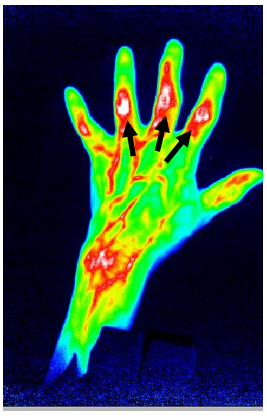
Berlin method | Copenhagen method | Stockholm method

Phase 3: PIP



Grade 1

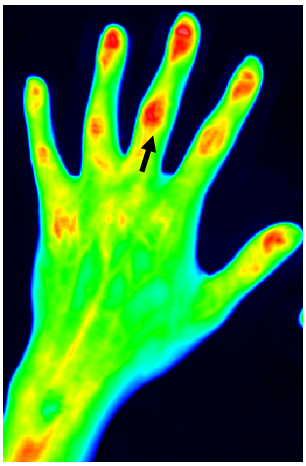
Grade 2

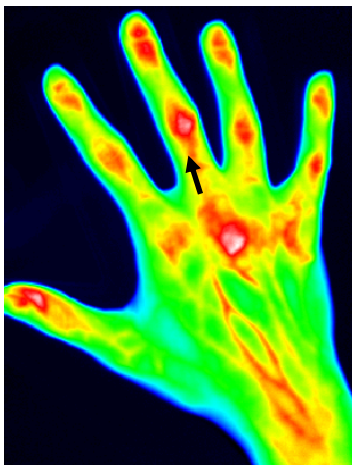


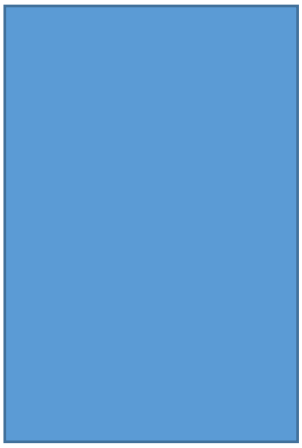
Grade 3

Berlin method | Copenhagen method | Stockholm method

PVM: PIP



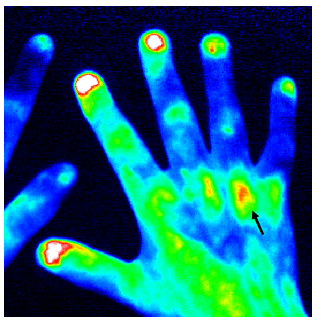


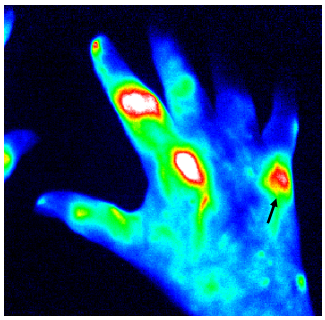


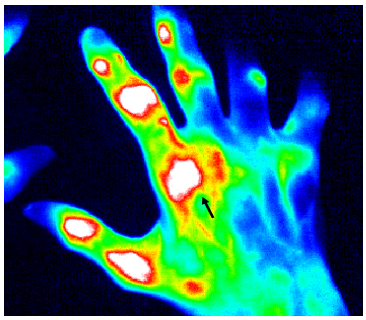
Grade 1 | Grade 2 | Grade 3

Berlin method | Copenhagen method | Stockholm method

Phase 1: MCP





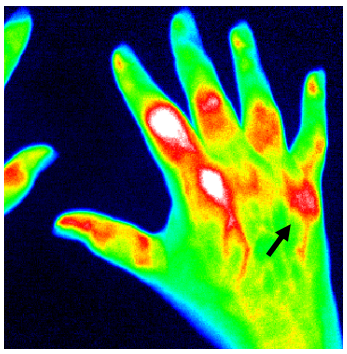


Grade 1 | Grade 2 | Grade 3

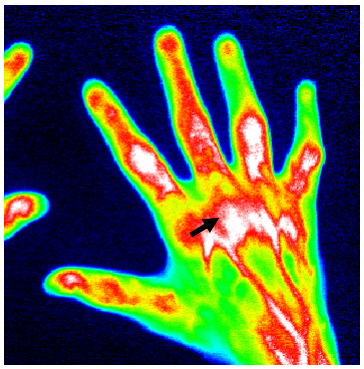
Berlin method | Copenhagen method | Stockholm method

Phase 2: MCP

Grade 1



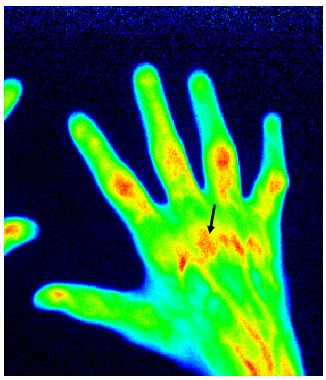
Grade 2



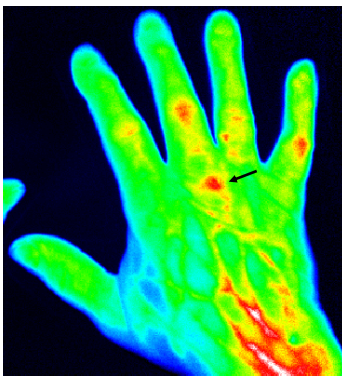
Grade 3

Berlin method | Copenhagen method | Stockholm method

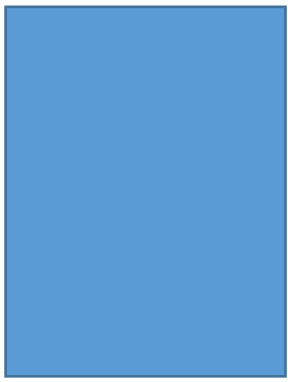
Phase 3: MCP



Grade 1



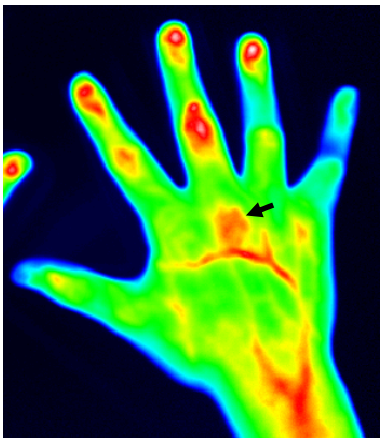
Grade 2

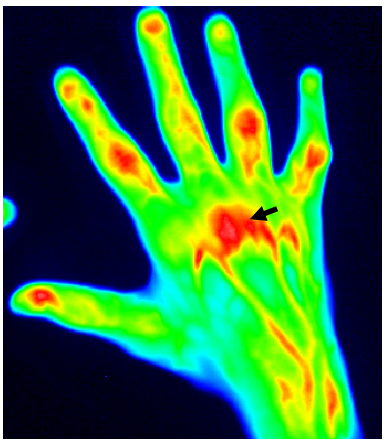


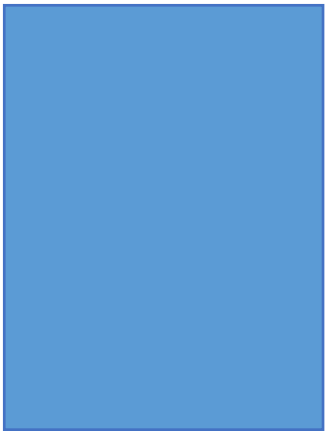
Grade 3

Berlin method | Copenhagen method | Stockholm method

PVM: MCP



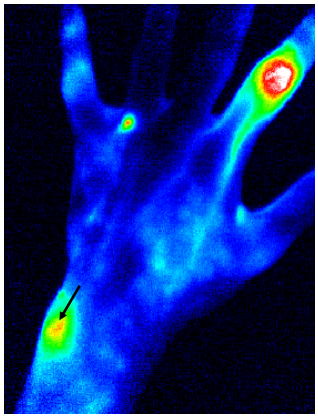


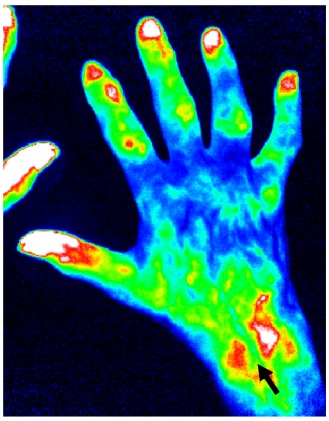


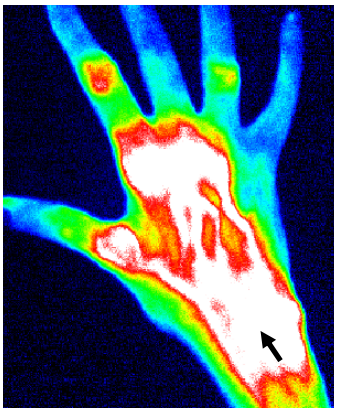
Grade 1 Grade 2 Grade 3

Berlin method | Copenhagen method | Stockholm method

Phase 1: wrist



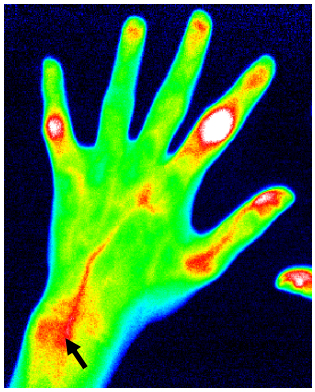




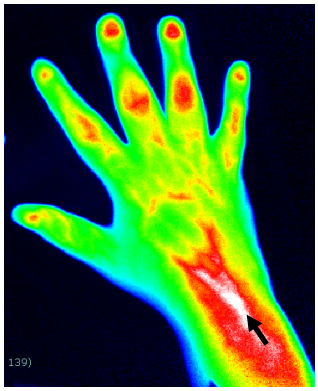
Grade 1 Grade 2 Grade 3

Berlin method | Copenhagen method | Stockholm method

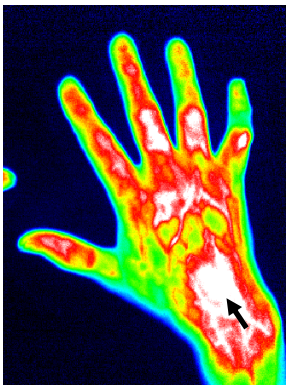
Phase 2: wrist



Grade 1



Grade 2

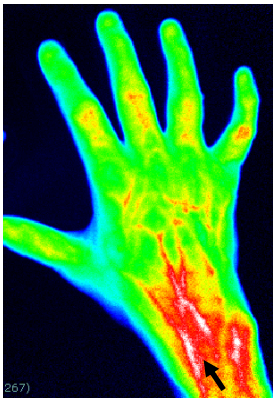


Grade 3

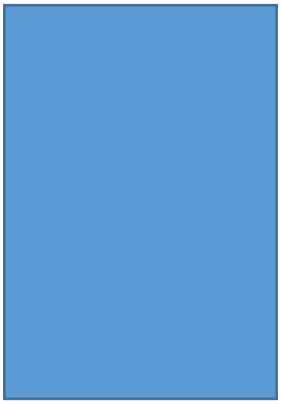
Berlin method | Copenhagen method | Stockholm method

Phase 3: wrist

Grade 1



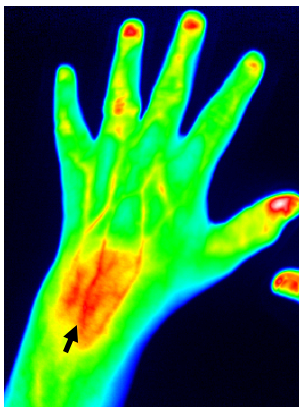
Grade 2



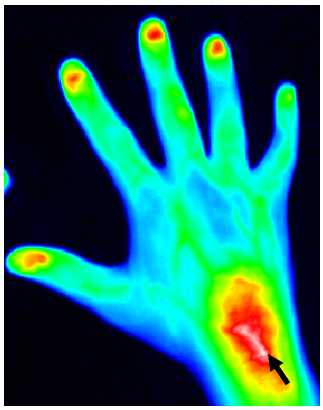
Grade 3

Berlin method | Copenhagen method | Stockholm method

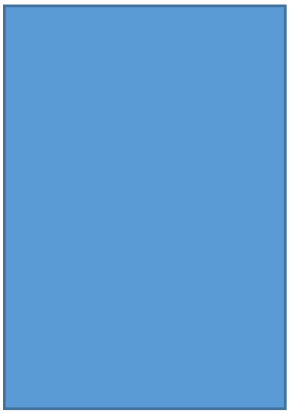
PVM: wrist



Grade 1



Grade 2



Grade 3

Berlin method | Copenhagen method | Stockholm method

Copenhagen FOI scoring system / FOIE-GRAS

- **Rationale**
- The Fluorescence Optical Imaging Enhancement-Generated Rheumatoid Arthritis Score (FOIE-GRAS) for inflammation is based on the assumption that inflamed tissues would demonstrate a more rapid enhancement than the surrounding healthy tissues.
- **Assessment**
- The wrist, 1^{st}-5^{th} MCP joints, 1^{st} IP joint and 2^{nd}-5^{th} PIP joints are assessed, but the DIP joints may also be included in the assessment. For each joint, the images are assessed sequentially from start of the injection of ICG-pulsion to peak enhancement. At the peak enhancement, the color index is adjusted (by pressing "refresh") in order to increase the discrepancy between colors.
- **Definition of inflammation**
- Inflammation is defined as a sharply marginated enhancement with clear delineation from surrounding tissues and correct anatomical location lasting ≥3 seconds.

Berlin method | Copenhagen method | Stockholm method

Scoring system

The width of the enhancement fulfilling these criteria is compared to the width of the joint in the transverse plane at the 3rd second of enhancement of that particular joint. If the first enhancing color (i.e. blue) does not remain marginated at the joint during the 3 seconds, the next enhancing color (i.e. green) is assessed using the same criteria of margination. One is allowed to assess the succeeding colors until peak enhancement, but scoring of the enhancement should always be performed in the first enhancing color that fulfills the criteria of margination. The enhancement is scored using a semi-quantitative scoring system (0–3, total range 0-66) as follows:

Grade 0: no enhancement
Grade 1: <1/3 of the joint is covered by enhancement
Grade 2: ≥1/3 but 2/3 of the joint is covered by enhancement
Grade 3: ≥2/3 of the joint is covered by enhancement

If 2 or more lesions are marginated at the 3rd second, the width of these lesions should be added.

Enhancing vessels

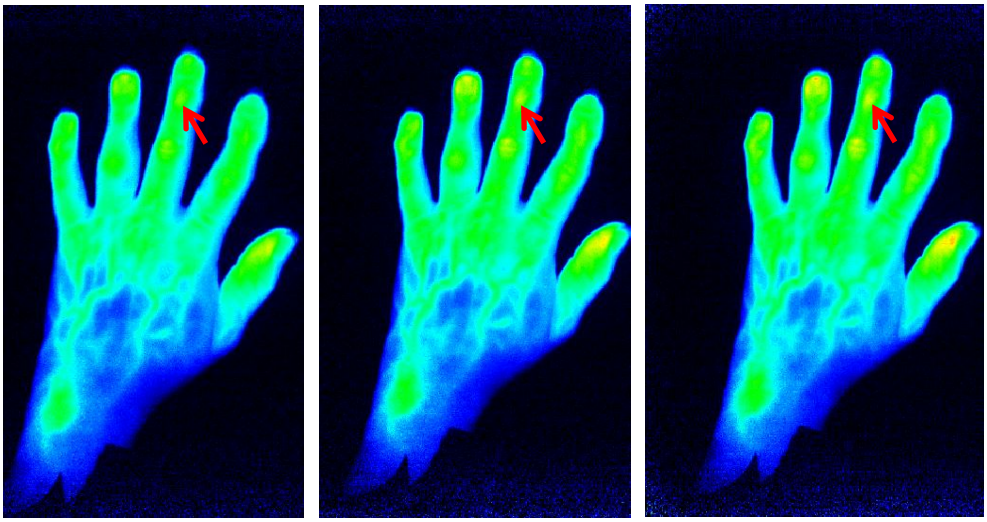
The scoring of the pathologies is performed during the phase of initial enhancement, thereby reducing the likelihood of disturbance from the enhancing veins, which become enhanced during the wash-out phase. Nevertheless, enhancing veins may occur along with the enhancement of the pathology, but the enhancing veins are often seen as longer, enhancing structures, which may involve areas both inside and outside the joint region. These structures do not fulfill the criteria of correct anatomical location and should not be scored.
Please note the time required to score each patient and which second each pathology was scored. Also note which second the image was refreshed.

Berlin method | Copenhagen method | Stockholm method

FOIE-GRAS Scoring sheet

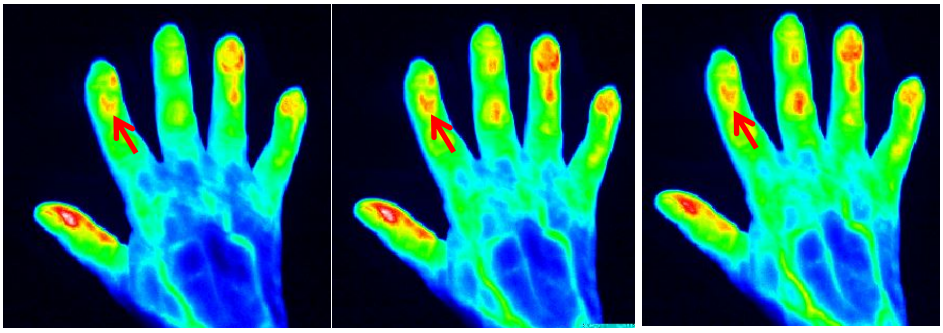
Initials									
Pt-ID									
Left hand					Right hand				
Timepoint for refreshing:					Timepoint for refreshing:				
		Scores	Timepoint for scored pathology (s)	Comments			Scores	Timepoint for scored pathology (s)	Comments
Wrist					Wrist				
MCP 1					MCP 1				
MCP 2					MCP 2				
MCP 3					MCP 3				
MCP 4					MCP 4				
MCP 5					MCP 5				
IP					IP				
PIP2					PIP2				
PIP3					PIP3				
PIP4					PIP4				
PIP5					PIP5				
DIP2					DIP2				
DIP3					DIP3				
DIP4					DIP4				
DIP5					DIP5				
Time to score the patient:									

Berlin method | Copenhagen method | Stockholm method



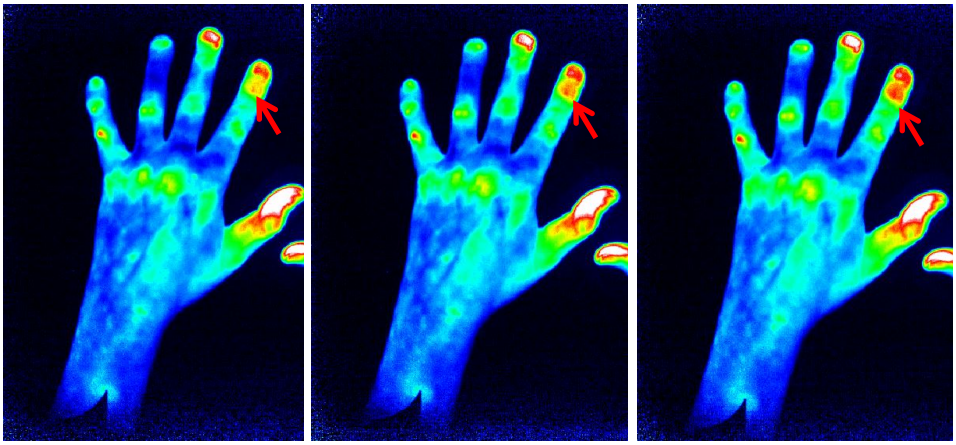
DIP score 1 (yellow)

Berlin method | Copenhagen method | Stockholm method



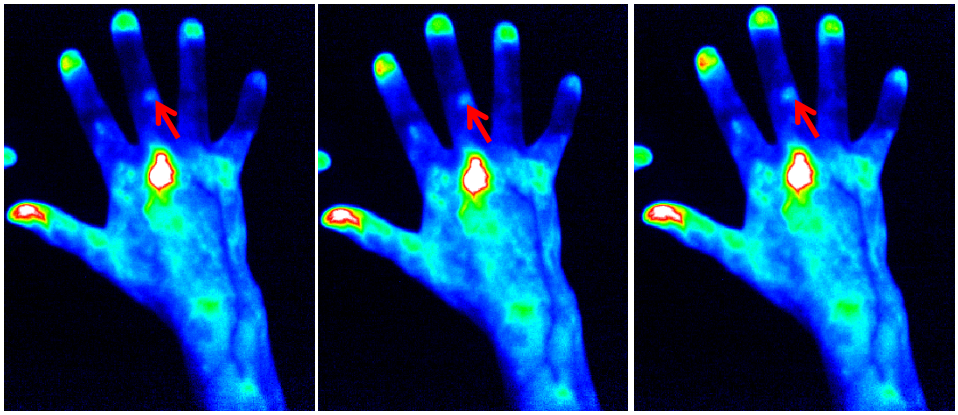
DIP score 2 (red)

Berlin method | Copenhagen method | Stockholm method



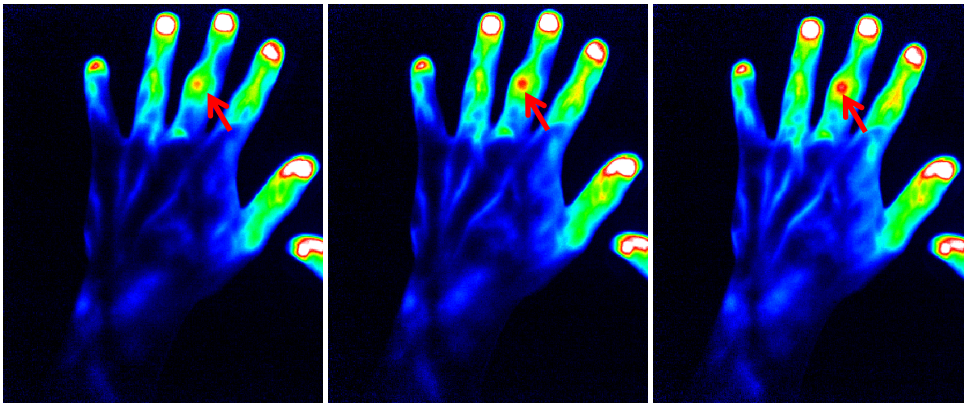
DIP score 3 (red)

Berlin method | Copenhagen method | Stockholm method



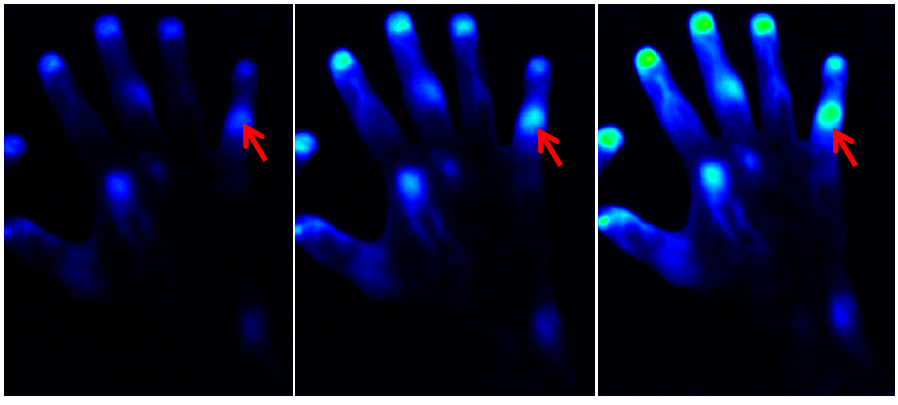
PIP score 1 (green)

Berlin method | Copenhagen method | Stockholm method



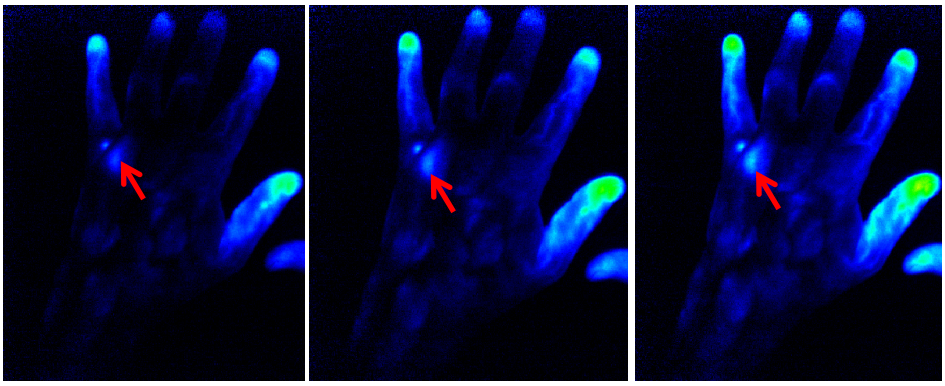
PIP score 2 (red)

Berlin method | Copenhagen method | Stockholm method



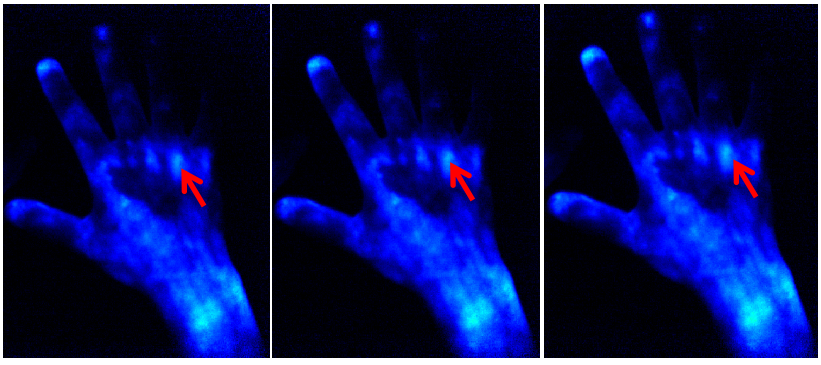
PIP score 3 (green)

Berlin method | Copenhagen method | Stockholm method



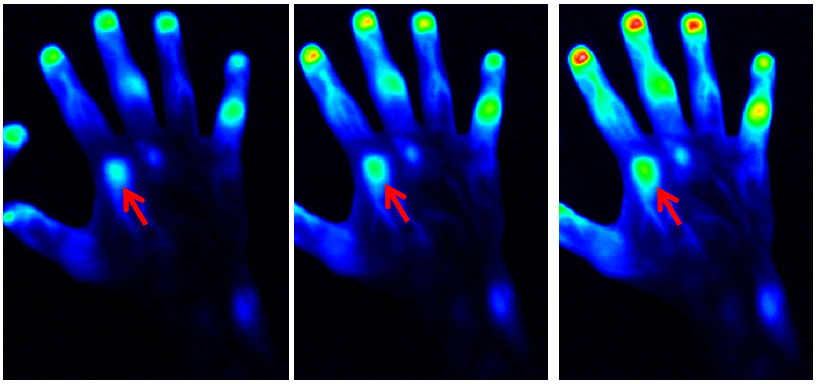
MCP score 1 (green)

Berlin method | Copenhagen method | Stockholm method



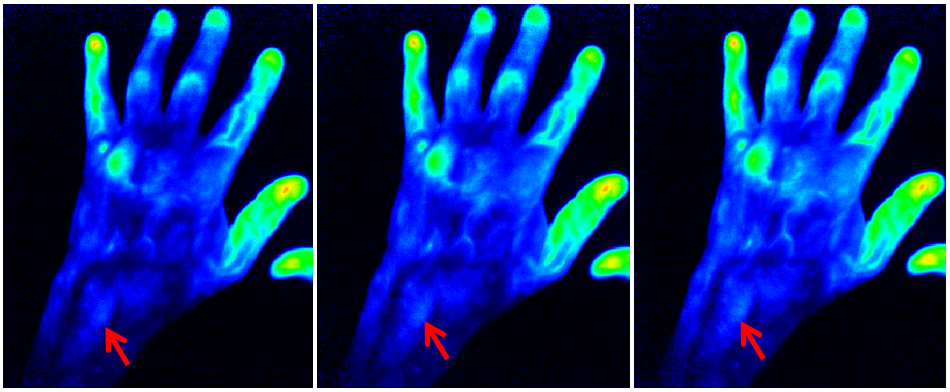
MCP score 2 (green)

Berlin method | Copenhagen method | Stockholm method



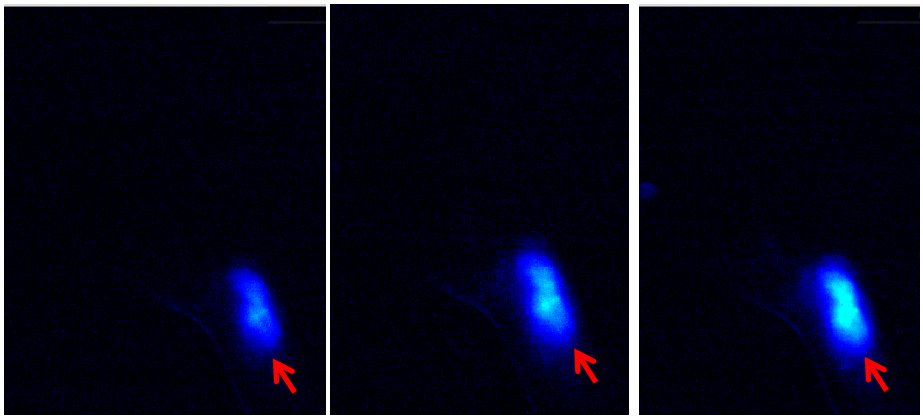
MCP score 3 (green)

Berlin method | Copenhagen method | Stockholm method



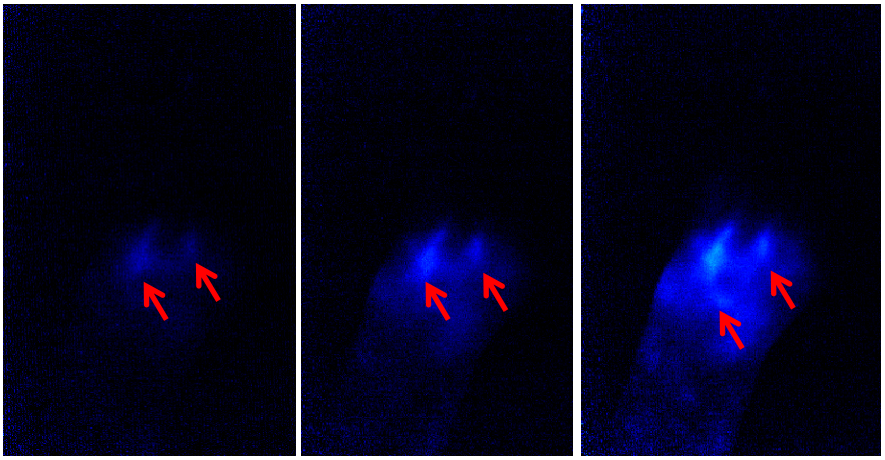
Wrist score 1 (green)

Berlin method | Copenhagen method | Stockholm method



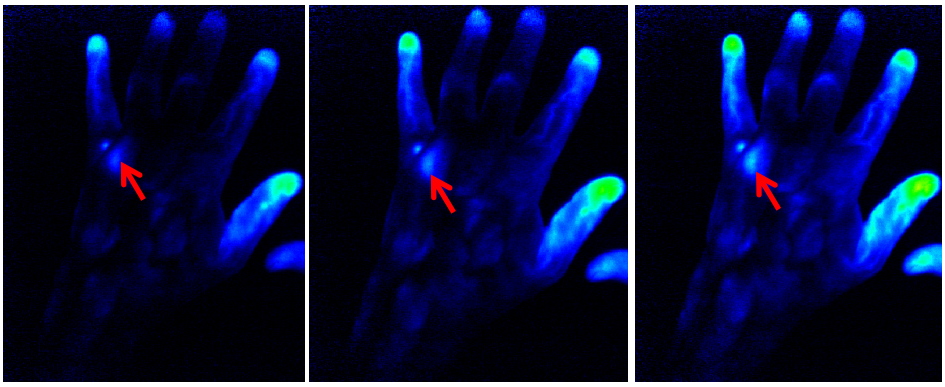
Wrist score 2 (blue)

Berlin method | Copenhagen method | Stockholm method



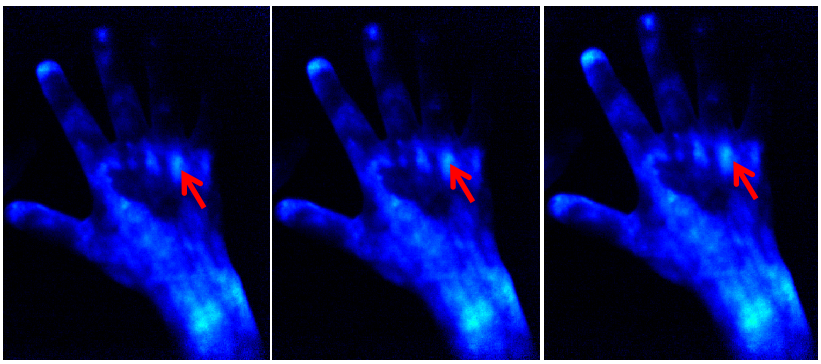
Wrist score 3 (blue)

Berlin method | Copenhagen method | Stockholm method

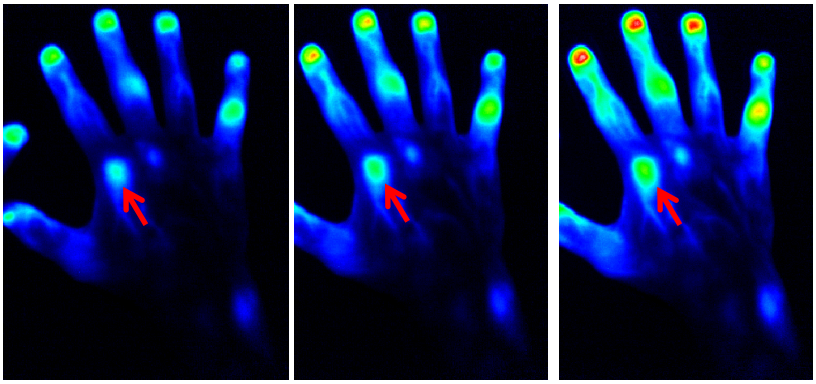


MCP score 1 (green)

Berlin method | Copenhagen method | Stockholm method



MCP score 2 (green)



MCP score 3 (green)

Stockholm method - Description

For the purpose of this study, we in Stockholm have created a semi-quantitative FOI method of evaluation , that is carried out by visual inspections of the composite image in Prima Vista Mode (PVM) 240 and PVM 120 on 'Temperature' palette settings.

The rationale for using 'temperature' settings is due to improved image contrast. The binary shaded 'temperature' colored pixels allow improved distinction of adjacent structures with intensity values outside the scaling range for the smallest and largest intensities. The increased axial and lateral resolution in this format may allow further differentiation between vessels and adjacent tissues, to include 'bony' outlines, which may appear more clearly defined in 'temperature' display.

For those joints that are FOI positive, the strength of signal intensity (weak, moderate or strong) as well as the proportions of enhanced tissue covering the joint width (<1/3rd covered; or ≥1/3rd , but <2/3rd of joint covered; or ≥2/3rd of the joint covered, according to Copenhagen proposed joint evaluation) are documented in the score sheet below.

Unsure/uncertain joints that contain ambiguous signal intensities should be 'flagged', and also evaluated in PVM 120. A quick scroll through these ambiguous joint enhancements (such as distinguishing between normal and abnormal vessel intensities) is done in real-time to clarify uncertainties. Digital/Disease Activity (DACT) automated quantitative scores are also recorded numerically for Stockholm FOI examinations, but will not be included in this part of the study.

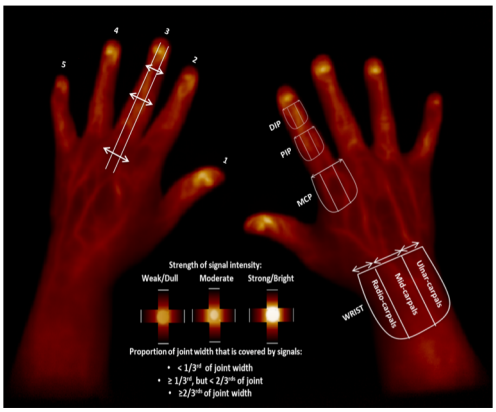
Abnormally increased focal optical signal intensities/enhancements that are seen glowing within the joint tissue boundaries in areas of high perfusion and/or capillary leakage, are regarded as FOI positive for the joint evaluated. Normal vessel enhancements without leakage, appear as narrow, tubular, well marginated structural intensities, and should be recorded if located over regions of interest.

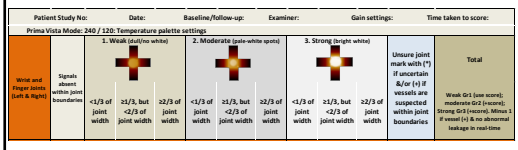
Technicalities :

- Prior to the FOI examination, photographs are taken of the hands and wrists for all patients whenever possible, to serve as a control to mark subtle skin changes (scratches, tattoos, old injuries, surgical scares etc.) that may cause ambiguous signals over joint regions of interest. Photography is complimented with FOI, ultrasound and clinical assessments in Stockholm, and may have numerous advantages regarding ambiguous signal intensities other than that of joints.
- Hand washing is also advantageous in our standard protocols for reasons described elsewhere.
- Patients advised to restrict finger and wrist movements throughout 6 minutes under darkroom conditions, and artefact reduction is well maintained for all FOI examinations.
- **IMPORTANT that the instrument settings are recorded on the score sheet for each patient, especially the peak intensity gain setting, prior to evaluation, so as to revert to exactly the same settings whenever required.**

Berlin method | Copenhagen method | Stockholm method

Stockholm method - Scoring

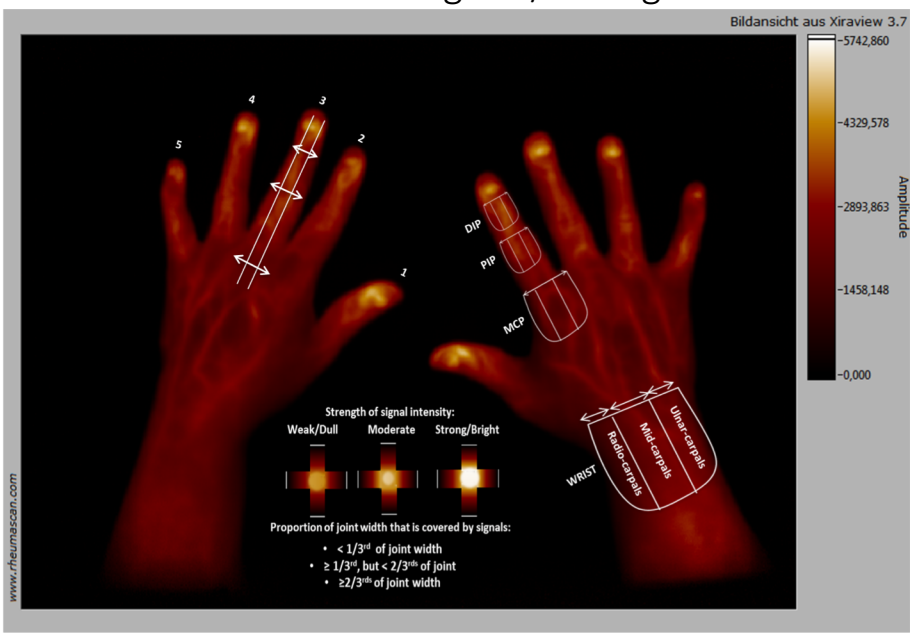




- The composite PVM image in rainbow palette settings (multiple color pixels) by default, is automatically displayed as a single image summary of 1-240 image frames. **For the Stockholm evaluation, this composite image palette settings on the lower right corner of the screen, should be changed to 'Temperature' settings, making sure that the initial gain settings are recorded on the score sheet.**
- The 17 joint regions of interest (3 wrists: radio-carpals, mid-carpals and ulnar-carpals, 5 MCP's, 1 IP, 4PIPs and 4 DIP's) for each hand, are evaluated for **the presence or absence of joint tissue inflammation**. The wrist regions are split in 3 parts as mentioned above. When evaluating the joint of interest, **an imaginary tracing around the boundaries of the joint should be made, and divided into 3 parts** as illustrated in the diagram. Each joint is graded according to the **signal strength, and proportion of the joint width that the intensity covers**. The strength of signal intensities are graded from dark to bright, as **normal ,weak, moderate or strong** as follows :(refer to the 3 intensities patterns that are illustrated in the diagram and score sheet)
  - **Normal = No focal optical signal intensities /enhancement noted;**
  - **Weak = Homogenous , dull enhancements (more towards darker shades of yellowish orange) without white spots.**
  - **Moderate = Pale, yellowish orange shades with white spots within joint boundaries (white occupies <30% of signal)**
  - **Strong= Bright, pale, mostly whitish signal intensities (>30% of signal is towards whitish shades)**
- On the score sheet, the strength of the signals intensities marked above are categorized into 3 parts according to the proportion of joint width that it covers ,**as described by the FOI Copenhagen team**, who are acknowledged for this method of evaluation to follow:
  - **No enhancement**
  - **<1/3rd of the joint is covered by enhancement**
  - **≥1/3rd but 2/3rd of the joint is covered by enhancement**
  - **≥2/3rd of the joint is covered by enhancement**
- **Any joints that have uncertain scores and/or are ambiguous, (such as vessels enhancements) should be documented, and followed-up in the next evaluation** .
- **The 2nd evaluation** is done on the **composite PVM (1-120 image time frames), maintaining the same image pre-sets** above. Importantly, in this image evaluation, **only** those **joints marked above as uncertain/ ambiguous should be scored in PVM 120 to include only new joints that appear inflamed**. If the joint marked inflamed in PVM240 image, does not appear inflamed in PVM120, it should be noted as unsure/ambiguous or uncertain signal intensities. These unsure joints are clarified by quickly scrolling through it in real-time. Those signals that are persistent (≥3 seconds) that have not been selected above, to be noted on the score sheet as such. If there are any joints that produce non-persistent (<3 seconds) signals enhancements ,or are seen as artefactual should also be noted.
- **Regions of Interest (ROI) – Joint tissue inflammation should be separated from skin or other regions within the ROI for all semi-quantitative evaluations.**

Berlin method | Copenhagen method | Stockholm method

Stockholm method – Diagram/ Pictogram



Berlin method | Copenhagen method | Stockholm method

Patient No:	Date:	Examiner:	Gain settings:	Time taken to score:

LEFT HAND Prima Vista 240 Temperature Palette settings

Wrist and Finger Joints (Left) PVM 240	Strength of Signal Intensity (0, 1, 2 or 3) 0. Normal 1. Weak (dull/no white) 2. Moderate (pale-white spots) 3. Strong (bright white)	Proportion of Joint Width Enhanced (0, 1, 2 or 3) 0. Not enhanced 1. <1/3 of joint width 2. ≥1/3, but <2/3 of joint width 3. ≥2/3 of joint width	Ambiguous joints Unsure joint &/or vessels: Mark as yes, and re-evaluate in PVM 120 & Real-Time
Wrist Ulna.			
Wrist Mid.			
Wrist Rad.			
MCP 1			
MCP 2			
MCP 3			
MCP 4			
MCP 5			
PIP 2			
PIP 3			
PIP 4			
PIP 5			
IP 1			
DIP 2			
DIP 3			
DIP 4			
DIP 5			
TOTAL			
NOTES:			

RIGHT HAND Prima Vista 240 Temperature Palette settings

Wrist and Finger Joints (Right)	Strength of Signal Intensity (0, 1, 2 or 3)	Proportion of Joint Width Enhanced (0, 1, 2 or 3)	Ambiguous joints
Wrist Ulna.			
Wrist Mid.			
Wrist Rad.			
MCP 1			
MCP 2			
MCP 3			
MCP 4			
MCP 5			
PIP 2			
PIP 3			
PIP 4			
PIP 5			
IP 1			
DIP 2			
DIP 3			
DIP 4			
DIP 5			
TOTAL			
NOTES:			

PVM 120, add new joints that appear inflamed, and re-evaluate those marked as ambiguous/unsure/suspected vessels. Previous gain settings

LEFT HAND Prima Vista 120 Temperature Palette settings/ Real-Time

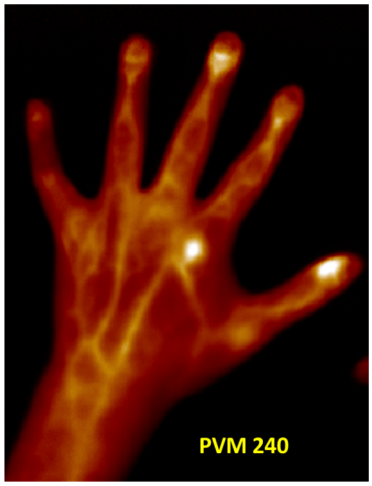
Wrist and Finger Joints (Left) PVM 120	Strength of Signal Intensity (0, 1, 2 or 3) 0. Normal 1. Weak (dull/no white) 2. Moderate (pale-white spots) 3. Strong (bright white)	Proportion of Joint Width Enhanced (0, 1, 2 or 3) 0. Not enhanced 1. <1/3 of joint width 2. ≥1/3, but <2/3 of joint width 3. ≥2/3 of joint width	Combined Scores: Total Score Weak signals (use same score); Moderate signals add 2 to score; and if Strong signals add 3 to score. Minus 1 if normal vessels seen without leakage/perfusion in real-time	Overall Grade: Combined Grades Score 0 = Grade 0; Scores (1-3) = Grade 1; Scores (4-6) = Grade 2; Scores (7-9) = Grade 3
Wrist Ulna.				
Wrist Mid.				
Wrist Rad.				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
IP 1				
DIP 2				
DIP 3				
DIP 4				
DIP 5				
TOTAL				
NOTES:				

RIGHT HAND Prima Vista 120 Temperature Palette settings/ Real-Time

Wrist and Finger Joints (Right)	Strength of Signal Intensity (0, 1, 2 or 3)	Proportion of Joint Width Enhanced (0, 1, 2 or 3)	Total Score	Combined Grades
Wrist Ulna.				
Wrist Mid.				
Wrist Rad.				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
IP 1				
DIP 2				
DIP 3				
DIP 4				
DIP 5				
TOTAL				
NOTES:				

Berlin method | Copenhagen method | Stockholm method

In the PVM 240 image evaluation, the scores were recorded on score sheet in (red), including unsure/uncertain joints (*) &/or ambiguous/ vessel signal (+) for further review in PVM 120 and in real-time.



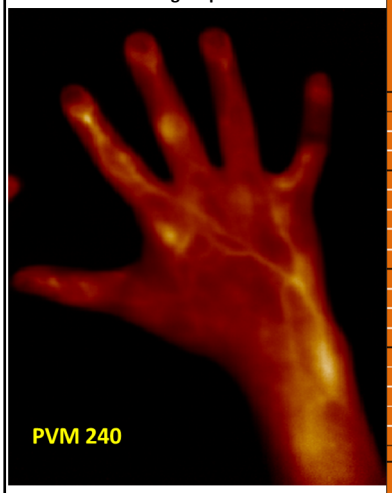
Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 2361 | Time taken to score:

Prima Vista Mode: 240 / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total: Weak Gr1 (use score); moderate Gr2 (+score); Strong Gr3 (+score). Minus 1 if vessel (+) & no abnormal leakage in real-time
LEFT HAND												
Wrist Ulna.	(0)	1	2	3	1	2	3	1	2	3		
Wrist Mid.	0	1	2	(3)	1	2	3	1	2	3	☆	
Wrist Rad.	(0)	1	2	3	1	2	3	1	2	3		
MCP 1	0	1	(2)	3	1	2	3	1	2	3		
MCP 2	0	1	2	3	1	2	3	1	2	(3)	☆ +	
MCP 3	0	1	2	(3)	1	2	3	1	2	3		
MCP 4	(0)	1	2	3	1	2	3	1	2	3	+	
MCP 5	(0)	1	2	3	1	2	3	1	2	3	+	
PIP 2	(0)	1	2	3	1	2	3	1	2	3	+	
PIP 3	(0)	1	2	3	1	2	3	1	2	3	+	
PIP 4	(0)	1	2	3	1	2	3	1	2	3	+	
PIP 5	(0)	1	2	3	1	2	3	1	2	3	+	
IP 1	0	(1)	2	3	1	2	3	1	2	3	+ ☆	
DIP 2	0	1	2	3	(1)	2	3	1	2	3	+ ☆	
DIP 3	(0)	1	2	3	1	2	3	1	2	3	+	
DIP 4	(0)	1	2	3	1	2	3	1	2	3	+	
DIP 5	(0)	1	2	3	1	2	3	1	2	3	+	
TOTAL												
NOTES: SCORE:												

Berlin method | Copenhagen method | Stockholm method

The other hand is then evaluated and recorded as previously in (red), identifying unsure/uncertain joints (*) &/or ambiguous/ vessel signals (+) for further evaluation on the PVM 120 image, and/or in real-time. MCP5 was suspicious, but normal vessel filling suspected.



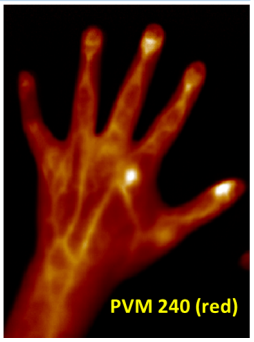
Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 2361 | Time taken to score:

Prima Vista Mode: 240 / 120: Temperature palette settings

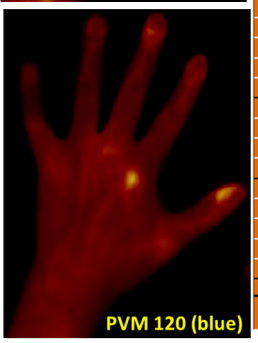
Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
RIGHT HAND												Weak Gr1 (use score); moderate Gr2 (+score); Strong Gr3 (+score). Minus 1 if vessel (+) & no abnormal leakage in real-time
Wrist Ulna.	0	1	2	3	1	2	(3)	1	2	3	+	
Wrist Mid.	0	1	2	(3)	1	2	3	1	2	3	☆ +	
Wrist Rad.	(0)	1	2	3	1	2	3	1	2	3		
MCP 1	(0)	1	2	3	1	2	3	1	2	3		
MCP 2	0	1	2	3	(1)	2	3	1	2	3		
MCP 3	(0)	1	2	3	1	2	3	1	2	3		
MCP 4	(0)	1	2	3	1	2	3	1	2	3		
MCP 5	(0)	1	2	3	1	2	3	1	2	3	+	-
PIP 2	0	(1)	2	3	1	2	3	1	2	3	+	
PIP 3	0	1	2	(3)	1	2	3	1	2	3		
PIP 4	(0)	1	2	3	1	2	3	1	2	3		
PIP 5	(0)	1	2	3	1	2	3	1	2	3		
IP 1	(0)	1	2	3	1	2	3	1	2	3		
DIP 2	0	1	2	3	(1)	2	3	1	2	3	+	
DIP 3	(0)	1	2	3	1	2	3	1	2	3		
DIP 4	(0)	1	2	3	1	2	3	1	2	3		
DIP 5	(0)	1	2	3	1	2	3	1	2	3		ˇ
TOTAL												
NOTES: SCORE:												

Berlin method | Copenhagen method | Stockholm method

Next evaluation is done on the PVM 120 image below. Only new joints that arise as FOI positive (i.e. Not inflamed previously) are to be added using another colour. The unsure joints are now graded on the same score sheet (Blue)



The adjacent example (blue), shows no additional joints being added. In fact, reduced intensity and/or no signals are seen suggesting inflammatory tissue strength &/or vessel enhancements manifesting after 120 seconds for this patient. The final was confirmed in real-time (Notes and totals documented).



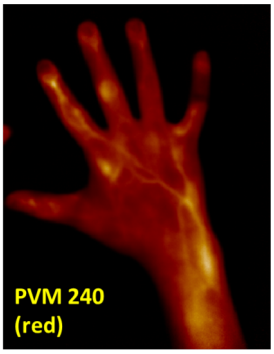
Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 2361 | Time taken to score:

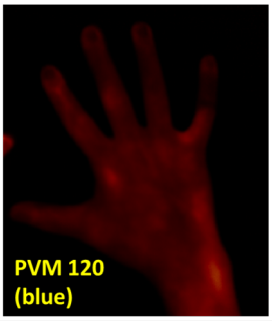
Prima Vista Mode: 240 / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
LEFT HAND												Weak Gr1 (use score); moderate Gr2 (+score); Strong Gr3 (+score). Minus 1 if vessel (+) & no abnormal leakage in real-time
Wrist Ulna.	(0)	1	2	3	1	2	3	1	2	3		0
Wrist Mid.	(0)	1	2	(3)	1	2	3	1	2	3	☆	Gr1 (3)-1
Wrist Rad.	(0)	1	2	3	1	2	3	1	2	3		0
MCP 1	0	1	(2)	3	1	2	3	1	2	3		Gr1 (2)
MCP 2	0	1	2	3	1	(2)	3	1	2	(3)	☆ +	Gr3 (3)-1
MCP 3	0	1	2	(3)	1	2	3	1	2	3		Gr1 (3)
MCP 4	(0)	1	2	3	1	2	3	1	2	3	+	0
MCP 5	(0)	1	2	3	1	2	3	1	2	3	+	0
PIP 2	(0)	1	2	3	1	2	3	1	2	3	+	0
PIP 3	(0)	1	2	3	1	2	3	1	2	3	+	0
PIP 4	(0)	1	2	3	1	2	3	1	2	3	+	0
PIP 5	(0)	1	2	3	1	2	3	1	2	3	+	0
IP 1	(0)	(1)	2	3	1	2	3	1	2	3	+ ☆	Gr1 (1) -1 = 0
DIP 2	(0)	1	2	3	(1)	2	3	1	2	3	+ ☆	Gr2 (1)-1
DIP 3	(0)	1	2	3	1	2	3	1	2	3	+	0
DIP 4	(0)	1	2	3	1	2	3	1	2	3	+	0
DIP 5	(0)	1	2	3	1	2	3	1	2	3	+	0
TOTAL	After confirming normal vessel signals in MCP4 & 5 , IP1, DIP3 &4 that had weak narrow tubular signals over the joint proportions scored above, these joints were regarded as not-inflamed . Although DIP2 contained tubular continuous signals appearing as vessel, it had weak to moderate intensities covering <1/3 of joint width, and therefore scored above. Wrist mid-carpal contained vessels, but with perfusion. MCP1, 2 & 3 were also positively scored as above.											
NOTES: SCORE:												

Berlin method | Copenhagen method | Stockholm method

The other hand below is now evaluated in the same way as we have described previously in PVM 120.





In the PVM 120 image evaluation (blue) for this hand, no additional joints were included. The stronger inflammatory signals that were seen in PVM 240, occured later in the phase, confirmed in real-time. The PVM 240 score sheet still holds as the final score for this hand. Notes and totals documented

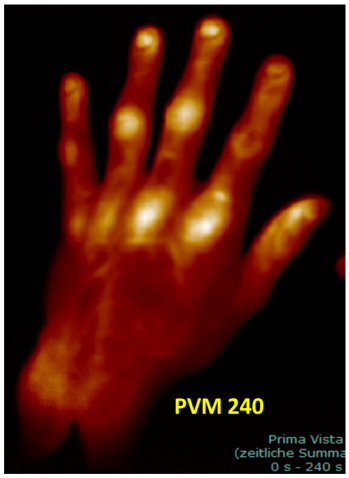
Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 2361 | Time taken to score:

Prima Vista Mode: (240) / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
RIGHT HAND												
Wrist Ulna.	0	1	2	(3)	1	2	(3)	1	2	3	+	Gr2 (3)
Wrist Mid.	(0)	1	2	(3)	1	2	3	1	2	3	☆ +	Gr1 (3)
Wrist Rad.	(0)	1	2	3	1	2	3	1	2	3		0
MCP 1	(0)	1	2	3	1	2	3	1	2	3		0
MCP 2	0	1	2	3	(1)	2	3	1	2	3		Gr2 (1)
MCP 3	(0)	1	2	3	1	2	3	1	2	3		0
MCP 4	(0)	1	2	3	1	2	3	1	2	3		0
MCP 5	(0)	1	2	3	1	2	3	1	2	3	+	0
PIP 2	0	(1)	2	3	1	2	3	1	2	3	+	Gr1 (1)
PIP 3	0	1	2	(3)	1	2	3	1	2	3		Gr1 (3)
PIP 4	(0)	1	2	3	1	2	3	1	2	3		0
PIP 5	(0)	1	2	3	1	2	3	1	2	3		0
IP 1	(0)	1	2	3	1	2	3	1	2	3		0
DIP 2	0	(1)	2	3	(1)	2	3	1	2	3	+	Gr2 (1)
DIP 3	(0)	1	2	3	1	2	3	1	2	3		0
DIP 4	(0)	1	2	3	1	2	3	1	2	3		0
DIP 5	(0)	1	2	3	1	2	3	1	2	3		0
TOTAL												
NOTES: SCORE:	After confirming vessel signals with perfusion in uncertain joints mid-wrist, ulnar, PIP2 & DIP3 in real-time, shows FOI positive and remains as scored above. MCP5 however is scored a 0 due to this enhancement reflecting normal vasculature											

Berlin method | Copenhagen method | Stockholm method

New patient: In the PVM 240 image evaluation, the scores recorded on score sheet in (red), including unsure/uncertain joints (*) &/or ambiguous/ vessel signal (+) for further review in PVM 120 and in real-time.



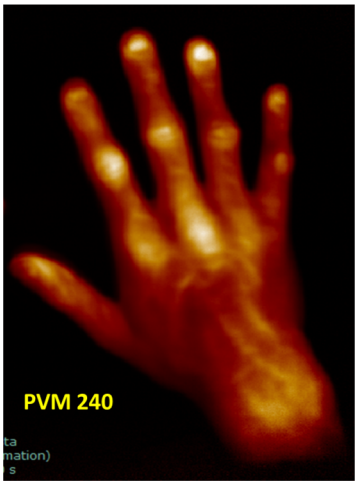
Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 3390 | Time taken to score:

Prima Vista Mode: (240) / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
LEFT HAND												
Wrist Ulna.	0	1	2	(3)	1	2	3	1	2	3	☆	
Wrist Mid.	(0)	1	2	3	1	2	3	1	2	3		
Wrist Rad.	(0)	1	2	3	1	2	3	1	2	3		
MCP 1	(0)	1	2	3	1	2	3	1	2	3		
MCP 2	0	1	2	3	1	2	3	1	2	(3)		
MCP 3	0	1	2	3	1	2	(3)	1	2	3	☆	
MCP 4	0	1	2	(3)	1	2	3	1	2	3	☆	
MCP 5	0	1	(2)	3	1	2	3	1	2	3	☆	
PIP 2	0	1	(2)	3	1	2	3	1	2	3	+ ☆	
PIP 3	0	1	2	3	1	2	(3)	1	2	3	☆	
PIP 4	0	1	2	3	1	2	(3)	1	2	3		
PIP 5	0	1	(2)	3	1	2	3	1	2	3	☆	
IP 1	0	1	(2)	3	1	2	3	1	2	3	+ ☆	
DIP 2	0	1	(2)	3	1	2	3	1	2	3	+ ☆	
DIP 3	0	(1)	2	3	1	2	3	1	2	3	+	
DIP 4	(0)	1	2	3	1	2	3	1	2	3	+	
DIP 5	0	1	2	(3)	1	2	3	1	2	3		
TOTAL												
NOTES: SCORE:												

Berlin method | Copenhagen method | **Stockholm method**

The other hand is evaluated and recorded as previously using the diagram, intensity scales and area of signal coverage as guidance. Identify unsure/uncertain joints (*) &/or ambiguous/ vessel signals (+) as prescribed previously. These are to be assessed in PVM 120 and in real-time



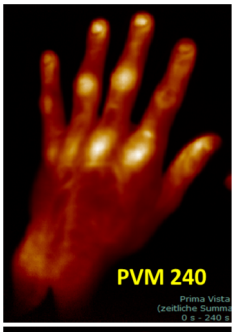
Patient Study No: Date: Baseline/follow-up: Examiner: Gain settings: 3390 Time taken to score:

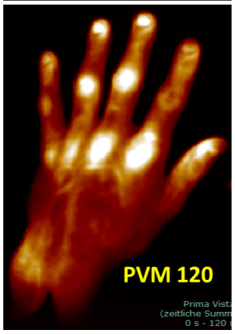
Prima Vista Mode: 240 / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
LEFT HAND												
Wrist Ulna.	0	1	2	3	1	2	3	1	2	3	☆	
Wrist Mid.	0	1	2	3	1	2	3	1	2	3		
Wrist Rad.	0	1	2	3	1	2	3	1	2	3		
MCP 1	0	1	2	3	1	2	3	1	2	3		
MCP 2	0	1	2	3	1	2	3	1	2	3		
MCP 3	0	1	2	3	1	2	3	1	2	3	☆	
MCP 4	0	1	2	3	1	2	3	1	2	3	✚☆	
MCP 5	0	1	2	3	1	2	3	1	2	3		
PIP 2	0	1	2	3	1	2	3	1	2	3	✚☆	
PIP 3	0	1	2	3	1	2	3	1	2	3	☆	
PIP 4	0	1	2	3	1	2	3	1	2	3		
PIP 5	0	1	2	3	1	2	3	1	2	3	✚	
IP 1	0	1	2	3	1	2	3	1	2	3	✚☆	
DIP 2	0	1	2	3	1	2	3	1	2	3	✚☆	
DIP 3	0	1	2	3	1	2	3	1	2	3	✚	
DIP 4	0	1	2	3	1	2	3	1	2	3	✚	
DIP 5	0	1	2	3	1	2	3	1	2	3		
TOTAL												
NOTES: SCORE:												

Berlin method | Copenhagen method | **Stockholm method**

Although the scores remain unchanged according to protocol, it was evident that for this patient, the PVM 120 showed stronger and more convincing signal intensities for each inflamed finger joint in this hand, including wrist ulnar, as confirmed in real-time for uncertain joint grades. DIP4 was seen as normal vasculature and scored 0. No new joints were added





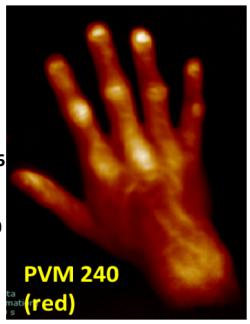
Patient Study No: Date: Baseline/follow-up: Examiner: Gain settings: 3390 Time taken to score:

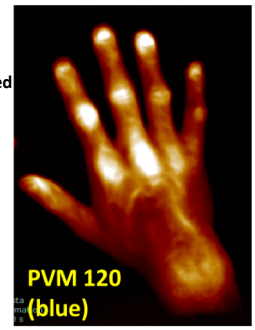
Prima Vista Mode: 240 / 120: Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white) <1/3 of joint width	1. Weak ≥1/3, but <2/3 of joint width	1. Weak ≥2/3 of joint width	2. Moderate (pale-white spots) <1/3 of joint width	2. Moderate ≥1/3, but <2/3 of joint width	2. Moderate ≥2/3 of joint width	3. Strong (bright white) <1/3 of joint width	3. Strong ≥1/3, but <2/3 of joint width	3. Strong ≥2/3 of joint width	Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
LEFT HAND												
Wrist Ulna.	0	1	2	3	1	2	3	1	2	3	☆	Gr1 (3)
Wrist Mid.	0	1	2	3	1	2	3	1	2	3		0
Wrist Rad.	0	1	2	3	1	2	3	1	2	3		0
MCP 1	0	1	2	3	1	2	3	1	2	3		0
MCP 2	0	1	2	3	1	2	3	1	2	3		Gr3 (3)
MCP 3	0	1	2	3	1	2	3	1	2	3	☆	Gr3 (3)
MCP 4	0	1	2	3	1	2	3	1	2	3	☆	Gr1 (3)
MCP 5	0	1	2	3	1	2	3	1	2	3	☆	Gr1 (2)
PIP 2	0	1	2	3	1	2	3	1	2	3	✚☆	Gr1 (2)
PIP 3	0	1	2	3	1	2	3	1	2	3	☆	Gr2 (3)
PIP 4	0	1	2	3	1	2	3	1	2	3		Gr2 (3)
PIP 5	0	1	2	3	1	2	3	1	2	3	☆	Gr1 (2)
IP 1	0	1	2	3	1	2	3	1	2	3	✚☆	Gr1 (2)
DIP 2	0	1	2	3	1	2	3	1	2	3	✚☆	Gr2 (2)
DIP 3	0	1	2	3	1	2	3	1	2	3	✚	Gr1 (1)
DIP 4	0	1	2	3	1	2	3	1	2	3	✚	0
DIP 5	0	1	2	3	1	2	3	1	2	3		Gr1 (3)
TOTAL												
NOTES: SCORE:	Although the scores remain unchanged, except MCP3, the PVM 120 showed stronger signal intensities for each inflamed finger joint including wrist ulnar, as confirmed in real-time for ambiguos scores. MCP3 however was changed due to real-time indicating strong signals rather than moderate. DIP4 was seen as normal vasculature and scored 0. No new joints were added											

Berlin method → Copenhagen method → **Stockholm method**

New joints MCP5 and DIP4 have been added as seen in PVM 120 and confirmed with real-time evaluation seen as perfused joints with OA changes as well on ultrasound. PVM 120 showed stronger signal intensities for each inflamed finger including wrist ulnar and mid-carpals.





Patient Study No: | Date: | Baseline/follow-up: | Examiner: | Gain settings: 3390 | Time taken to score:

Prima Vista Model: 240 / 120; Temperature palette settings

Wrist and Finger Joints (Left & Right)	Signals absent within joint boundaries	1. Weak (dull/no white)			2. Moderate (pale-white spots)			3. Strong (bright white)			Unsure joint mark with (*) if uncertain &/or (+) if vessels are suspected within joint boundaries	Total
		<1/3 of joint width	≥1/3, but <2/3 of joint width	≥2/3 of joint width	<1/3 of joint width	≥1/3, but <2/3 of joint width	≥2/3 of joint width	<1/3 of joint width	≥1/3, but <2/3 of joint width	≥2/3 of joint width		Weak Gr1 (use score); moderate Gr2 (+score); Strong Gr3 (+score). Minus 1 if vessel (+) & no abnormal leakage in real-time
LEFT HAND												
Wrist Ulna.	0	1	2	3	1	2	3	1	2	3	☆	Gr2 (3)
Wrist Mid.	0	1	2	3	1	2	3	1	2	3		Gr2 (3)
Wrist Rad.	0	1	2	3	1	2	3	1	2	3		0
MCP 1	0	1	2	3	1	2	3	1	2	3		0
MCP 2	0	1	2	3	1	2	3	1	2	3		Gr2 (3)
MCP 3	0	1	2	3	1	2	3	1	2	3	☆	Gr3 (3)
MCP 4	0	1	2	3	1	2	3	1	2	3	✚ ☆	Gr1 (3)
MCP 5	0	1	2	3	1	2	3	1	2	3		Added Gr1 (1)
PIP 2	0	1	2	3	1	2	3	1	2	3	✚ ☆	Gr3 (3)
PIP 3	0	1	2	3	1	2	3	1	2	3	☆	Gr2 (3)
PIP 4	0	1	2	3	1	2	3	1	2	3		Gr2 (3)
PIP 5	0	1	2	3	1	2	3	1	2	3	✚	Gr1 (2)
IP 1	0	1	2	3	1	2	3	1	2	3	✚ ☆	Gr1 (2)
DIP 2	0	1	2	3	1	2	3	1	2	3	✚ ☆	Gr1 (2)
DIP 3	0	1	2	3	1	2	3	1	2	3	✚	Gr1 (1)
DIP 4	0	1	2	3	1	2	3	1	2	3	✚	Added Gr2 (3)
DIP 5	0	1	2	3	1	2	3	1	2	3		0
TOTAL	New joints MCP5 and DIP4 have been added as seen in PVM 120 and confirmed with real-time evaluation seen as perfused joints with											
NOTES: SCORE:	OA changes on ultrasound. PVM 120 showed stronger signal intensities for each inflamed finger including wrist ulnar and mid-carpals											

II

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RESEARCH ARTICLE Open Access

Validity and diagnostic performance of fluorescence optical imaging measuring synovitis in hand osteoarthritis: baseline results from the Nor-Hand cohort

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Abstract

Objective: Fluorescence optical imaging (FOI) demonstrates enhanced microcirculation in finger joints as a sign of inflammation. We wanted to assess the validity and diagnostic performance of FOI measuring synovitis in persons with hand OA, comparing it with magnetic resonance imaging (MRI)- and ultrasound-detected synovitis.

Methods: Two hundred and twenty-one participants with hand OA underwent FOI and ultrasound (gray-scale synovitis and power Doppler activity) of the bilateral hands and contrast-enhanced MRI examination of the dominant hand. Fifteen joints in each hand were scored on semi-quantitative scales (grade 0–3) for all modalities. Four FOI images were evaluated: one composite image (Prima Vista Mode (PVM)) and three images representing phases of fluorescent dye distribution. Spearman's correlation coefficients were calculated between sum scores of FOI, MRI, and ultrasound. Sensitivity, specificity, and area under the curve (AUC) were calculated for FOI using MRI or ultrasound as reference.

Results: FOI did not demonstrate enhancement in the thumb base, and the joint was excluded from further analyses. FOI sum scores showed poor to fair correlations with MRI (rho 0.01–0.24) and GS synovitis sum scores (rho 0.12–0.25). None of the FOI images demonstrated both good sensitivity and specificity, and the AUC ranged from 0.50–0.61 and 0.51–0.63 with MRI and GS synovitis as reference, respectively. FOI demonstrated similar diagnostic performance with PD activity and GS synovitis as reference.

Conclusion: FOI enhancement correlated poorly with synovitis assessed by more established imaging modalities, questioning the value of FOI for the evaluation of synovitis in hand OA.

Keywords: Hand osteoarthritis, Xiralite, Inflammation, Synovitis, Ultrasound, MRI, Optical imaging, FOI

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Background

Hand OA is a whole joint disease, affecting the cartilage, subchondral bone, synovium, and tendons [1]; however, the importance of inflammation in the hand OA pathogenesis remains debated. Ultrasound and magnetic resonance imaging (MRI) examinations have demonstrated a significant inflammatory burden in these patients, and synovitis is associated with pain [2] and radiographic progression on joint level [3, 4]. Inflammation has been of interest as a potential treatment target in recent OA trials. Whereas previous studies were not able to show clear clinically relevant effects [5], Kroon et al. recently showed significant effects of prednisolone on pain in persons with inflammatory hand OA, further supporting the role of inflammation in the pathogenesis of pain [6].

Valid and cost-efficient evaluation of inflammation will be important in future hand OA trials using synovitis as an inclusion criteria and/or outcome measure. Ultrasound and MRI are established modalities for assessing synovitis; however, they are limited by operator dependency and availability, contraindications, and higher cost, respectively. Fluorescence optical imaging (FOI) is a novel imaging modality using near-infrared light to demonstrate indocyanine green (ICG)-enhanced microcirculation in the region around finger joints as a sign of inflammation [7]. The method is without radiation, a scan of both hands takes only 6 min, and the device can be operated by trained health professionals.

Previous studies of patients with early and undifferentiated arthritis have shown moderate sensitivity (51–54%) and good specificity (81–87%) of composite FOI images [7, 8] using MRI-detected synovitis as reference, while another study found similar sensitivity and specificity in the proximal interphalangeal (PIP) joints in persons with rheumatoid arthritis (RA) [9]. The validity and diagnostic performance of FOI measuring synovitis have not been examined in persons with hand OA. Hence, we wanted to examine the frequency of FOI enhancement in persons with hand OA and assess whether FOI is correlated with MRI- and ultrasound-detected synovitis. Further, we wanted to investigate the diagnostic performance of FOI measuring synovitis in hand OA.

Participants and methods

Study participants

We included participants from the Nor-Hand study, an observational hand OA cohort from the rheumatology outpatient clinic at Diakonhjemmet Hospital, Oslo, Norway [10]. The participants were between 40 and 70 years old with proven hand OA by clinical and/or ultrasound examination and had no suspected diagnosis of systemic inflammatory joint diseases, psoriasis, or major somatic and/or psychiatric comorbidities. Further exclusion criteria are described elsewhere [10]. All participants signed informed consent, and the study was approved by the regional ethics committee.

Fluorescence optical imaging (FOI)

The Xiralite®-system is the only FOI device available for clinical use in rheumatology. To perform the FOI scan, the patient receives an intravenous injection with a fluorescent dye (ICG pulsion, 0.1 mg/kg body weight) and have near-infrared light from light-emitting diodes (LED) projected down on the hands for 6 min. With a highly sensitive camera, 360 images (one/second) are produced, showing the flooding in, distribution, and washing out of the dye. All images can be scrolled through after the examination, and a composite picture (Prima Vista Mode (PVM)) from the 240 first images is automatically generated by the XiraView software. In short, four images are assessed with the FOI activity score (FOIAS): PVM and three images representing phases 1, 2, and 3 based on the distribution and washing out of the fluorescent dye in relation to the fingertips (Fig. 1). The distal interphalangeal (DIP) and proximal interphalangeal (PIP) including the 1st interphalangeal and metacarpophalangeal (MCP) joints and the thumb base were graded on 0–3 scales based on the color intensity and width of enhancement according to the FOIAS [8, 9, 11]. All FOI images were scored by one reader (SH) blinded for MRI and ultrasound results and all clinical data except age and sex. The reader was trained in assessing FOI images with good inter-reader reliability with an experienced reader (SO) and excellent intra-reader reliability for all phases except phase 1 (intraclass correlation coefficient for sum scores; PVM = 0.89, phase 1 = 0.10, phase 2 = 0.87, phase 3 = 0.89) in 21 patients [12]. Persons with known allergy to iodine or indocyanine, untreated hyperthyroidism with fT4 above 21 pmol/L and thyroid-stimulating hormone (TSH) below 0.5 mIE/L, poor liver function (transaminases above twice the upper reference limit), reduced kidney function (glomerular filtration rate below 40 mL/min), or pregnancy or breast-feeding did not perform the FOI scan.

Magnetic resonance imaging (MRI)

Participants without contraindications underwent 1.5 T MRI (Siemens Aera, Germany) of the dominant hand. MRI was obtained mean (standard deviation (SD)) 9 (13.9) days after the FOI scan. The fingers and thumb base joints were covered by a 16-channel hand/wrist-coil and an intravenous contrast (Dotarem 279.3 mg/mL, 0.2 mL/kg body weight) was given. A T1-weighted volumetric interpolated breath-hold examination (VIBE) was reconstructed into three planes with 2.0 mm thickness, and the axial and sagittal planes were used for evaluation of synovitis [10]. The images were scored by a PhD

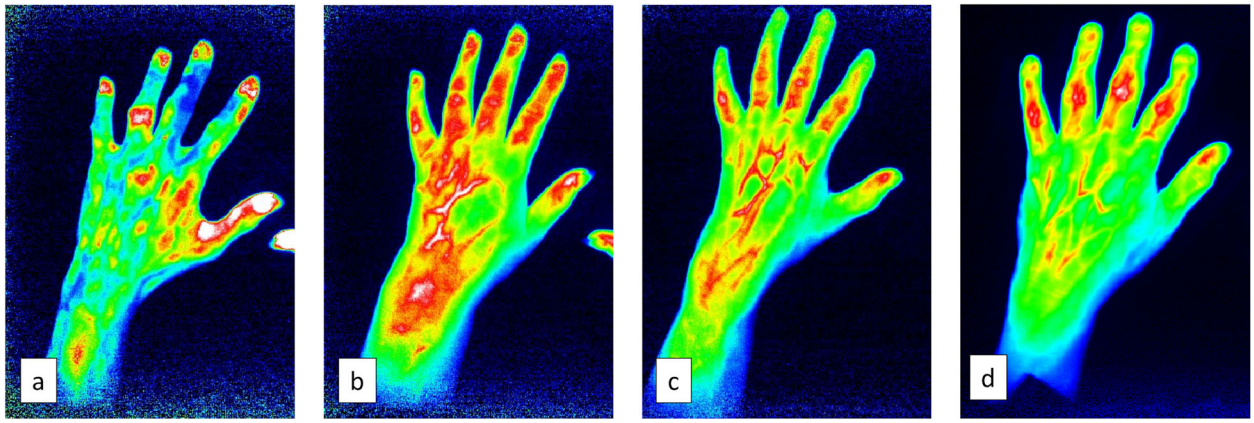

Fig. 1 Examples of the different FOI activity score (FOIAS) images: phase 1 (**a**), phase 2 (**b**), phase 3 (**c**), and Prima Vista Mode (**d**)

student (ØM) trained in assessing synovitis in hand joints. Repeated training sessions with an experienced reader (IKH) were arranged prior to the calibration exercise with demonstration of atlases and evaluation of example images ($n = 20$). For calibration, 30 patients were scored separately in intervals of 13, 7, and 10 patients. Both readers scored the images until good inter-reader reliability (weighted kappa > 0.60) was obtained. For the last 10 patients, the scorers obtained a weighted kappa of 0.69. Joints with a difference of two or more grades and scores of 0 and 1 between the readers were reassessed and scored by consensus. For the remaining patients, the experienced reader (IKH) was consulted in case of uncertainties. The MRI reader was blinded for FOI and ultrasound results and all clinical data except age and sex. Synovitis in the DIP and PIP (incl. IP1) joints was assessed on a 0–3 scale according to the Hand OA MRI scoring system (HOAMRIS) [13], and the MCP joints were scored with same criteria as the PIP joints. All finger joints were assessed in the sagittal and axial planes and had to demonstrate consistent findings in 3 consecutive slices in both planes to qualify as MRI enhancement. The 1st carpometacarpal joint (CMC-1) and scaphotrapeziotrapezoidal (STT) joints were evaluated in the frontal and axial plane and evaluated using the TOMS atlas [14]. Flexor tenosynovitis was assessed according to the Oslo hand OA MRI scoring system (OHOA-MRI) and peritendinous inflammation along the extensor tendon was evaluated as absent/present [15].

Ultrasound

A GE Logic S8 ultrasound machine with a linear 6–15 MHz probe preset for optimal gray-scale synovitis and power Doppler was used. The ultrasound examination was performed by a medical student trained by two experienced ultrasonographers (HBH, AM). A training session was arranged prior to study start with demonstration of the probe, normal B-mode musculoskeletal anatomy of the hand, and presentation of an atlas of synovitis grade 1–3 in the bilateral DIP and PIP including the first interphalangeal, MCP, and CMC-1 joints [16]. The hand joints were longitudinally scanned from the radial to the ulnar dorsal side, with additional transverse scanning in case of uncertainties. All joints were scored for gray-scale (GS) synovitis and power Doppler (PD) activity on semiquantitative 0–3 scales using the atlas from the training session as reference. The reader was blinded to MRI, FOI, and radiographic findings. The medical student and one of the experienced readers evaluated the 14 first patients together, and the medical student performed the remaining examinations independently. By the end of the data collection, a reliability exercise with the medical student and one ultrasonographer (AM) was performed, with consecutive enrollment of $n = 10$ patients with good inter-reader reliability (prevalence- and bias-adjusted kappa (PABAK) for GS in DIP/PIP (0.80) and CMC-1 joints (0.92) and power Doppler activity in DIP/PIP (0.85) and CMC-1 joints (0.92) [17].

Conventional radiographs

Frontal images of bilateral hands were obtained with posterior-anterior view. One experienced reader (IKH) evaluated the DIP and PIP including the first interphalangeal, MCP, and CMC-1 according to the Kellgren Lawrence (KL) scale (grade 0–4) [18, 19] and Verbruggen Veys (VV) anatomical phase scoring system [20]. Erosive hand OA was defined as having at least one DIP or PIP joint(s) in the erosive or remodeling phase according to the VV anatomical phase scoring system. The reader demonstrated excellent intrareader reliability for both scoring systems with weighted kappa on 0.92 (KL)

and kappa on 0.93 (erosive vs. non-erosive for the VV score).

Statistics

Frequencies for different grades of FOI enhancement and synovitis detected by MRI and ultrasound were calculated and presented in histograms. Frequencies and trend of FOI enhancement in PVM across erosive vs. non-erosive and KL grades were assessed in cross tables and presented in histograms. We calculated Spearman's correlations for sum scores of the dominant hand for MRI-detected synovitis and FOI and the bilateral hands for ultrasound-detected synovitis and FOI. For diagnostic performance, we calculated sensitivity, specificity, negative (NPV) and positive predictive values (PPV), and area under the curve (AUC) using either MRI or GS synovitis as reference. Percent agreement (PA) was calculated on FOI enhancement yes/no vs. GS/MRI synovitis yes/no. For all imaging modalities, joints missing due to amputation, trapeziectomy, or arthrodesis were imputed with an average value from the remaining joints in the same hand for sum scores, while they remained missing in calculations on frequencies and diagnostic performance. All results are presented for all joints together and for joint groups. Stratified analyses for persons with erosive hand OA vs. non-erosive hand OA were performed. Stata 14.0 was used for all the statistical analyses.

Results

Study population

Three hundred participants in the Nor-Hand cohort underwent ultrasound and radiographs of both hands. Among those, 246 participants performed MRI of the dominant hand with gadolinium contrast, and 253 participants performed FOI. One adverse event was reported due to subcutaneous administration of ICG, and the FOI images from this participant were excluded from further analyses. Finally, FOI images from two participants were excluded due to a lack of contrast enhancement. In total, 221 participants performed both FOI and MRI and were included for further analyses. The majority of participants were women, and a wide range in symptom severity, degree of inflammation, and structural damage was observed (Table 1).

Table 1 Baseline characteristics ($n = 221$)

Age, mean (SD) years	60.6 (6.2)
Women, *n* (%)	194 (88)
Body mass index, mean (SD) kg/m^2	26.2 (4.7)
ACR criteria for hand OA, *n* (%)	203 (92)
Average NRS hand pain (range 0–10)*	3.7 (2.3)
HOAMRIS synovitis sum score DIP/PIP, mean (SD) [range 0–27]**	6.4 (4.8)
Patients with flexor tenosynovitis by MRI, *n* (%)	53 (24)
GS synovitis sum score DIP/PIP, mean (SD) [range 0–54]	4.4 (5.3)
PD activity sum score DIP/PIP, mean (SD) [range 0–54]	2.4 (4.3)
FOI PVM sum score, DIP/PIP, mean (SD) [range 0–54]	14.2 (7.3)
FOI phase 1 sum score, DIP/PIP, mean (SD) [range 0–54]	0.7 (2.5)
FOI phase 2 sum score, DIP/PIP, mean (SD) [range 0–54]	21.4 (9.7)
FOI phase 3 sum score, DIP/PIP, mean (SD) [range 0–54]	4.9 (5.7)
KL sum score, (DIP/PIP/MCP/CMC-1) mean (SD) [range 0–120]	28.8 (18.0)
Erosive hand OA, *n* (%)	74 (34)

*NRS pain on 220 patients, 1 missing
**Dominant hand
ACR American College of Rheumatology, *HOAMRIS* Hand OA MRI score, *KL* Kellgren-Lawrence, *DIP* distal interphalangeal, *PIP* proximal interphalangeal, *NRS* numeric rating scale, *OA* osteoarthritis

Frequency distribution of synovitis according to FOI, MRI, and ultrasound

For GS synovitis and PD activity, 27 joints were missing due to amputation, trapeziectomy, arthrodesis, or unknown reasons. Five joints were missing due to trapeziectomy, arthrodesis, or amputation on MRI of the dominant hand. One phase 1 image, seven phase 2 images, and eight phase 3 images were excluded from analyses due to difficulties defining phases, i.e., no clear descending of the white from fingertips (phase 1) and white (phase 2) or red (phase 3) pixels persisting in fingertips.

None of the participants demonstrated FOI enhancement of the thumb base, while 81% of the participants had MRI-defined synovitis in this area (CMC-1 and/or STT). The CMC-1 joint was more frequently affected (69%) than the STT joint (54%). Ultrasound of the CMC-1 joint demonstrated less synovitis than MRI (gray-scale synovitis 26%, power Doppler activity 19%) (Fig. 2). Due to the lack of FOI enhancement in the thumb base, it was not included in further analyses. Only three MCP1 joints showed any FOI enhancement, and MRI was the only modality showing frequent findings in the MCP joints (32% of joints, predominantly grade 1). While MRI and FOI (PVM and phases 2 and 3) detected more synovitis and enhancement in the PIP joints than in the DIP joints, GS synovitis and PD activity and FOI phase 1 demonstrated more activity in the DIP joints.

None of the participants demonstrated MRI-enhanced peritendinous inflammation along the extensor tendon. Fifty-three participants had flexor tenosynovitis in one or more fingers, and the majority ($n = 46$) demonstrated grade 1 tenosynovitis adjacent to the MCP joint. Flexor tenosynovitis was not included in further analysis due to its localization on the palmar aspect of the hand and thus not detectable via FOI. When assessing frequency of FOI enhancement in PVM according to VV and KL

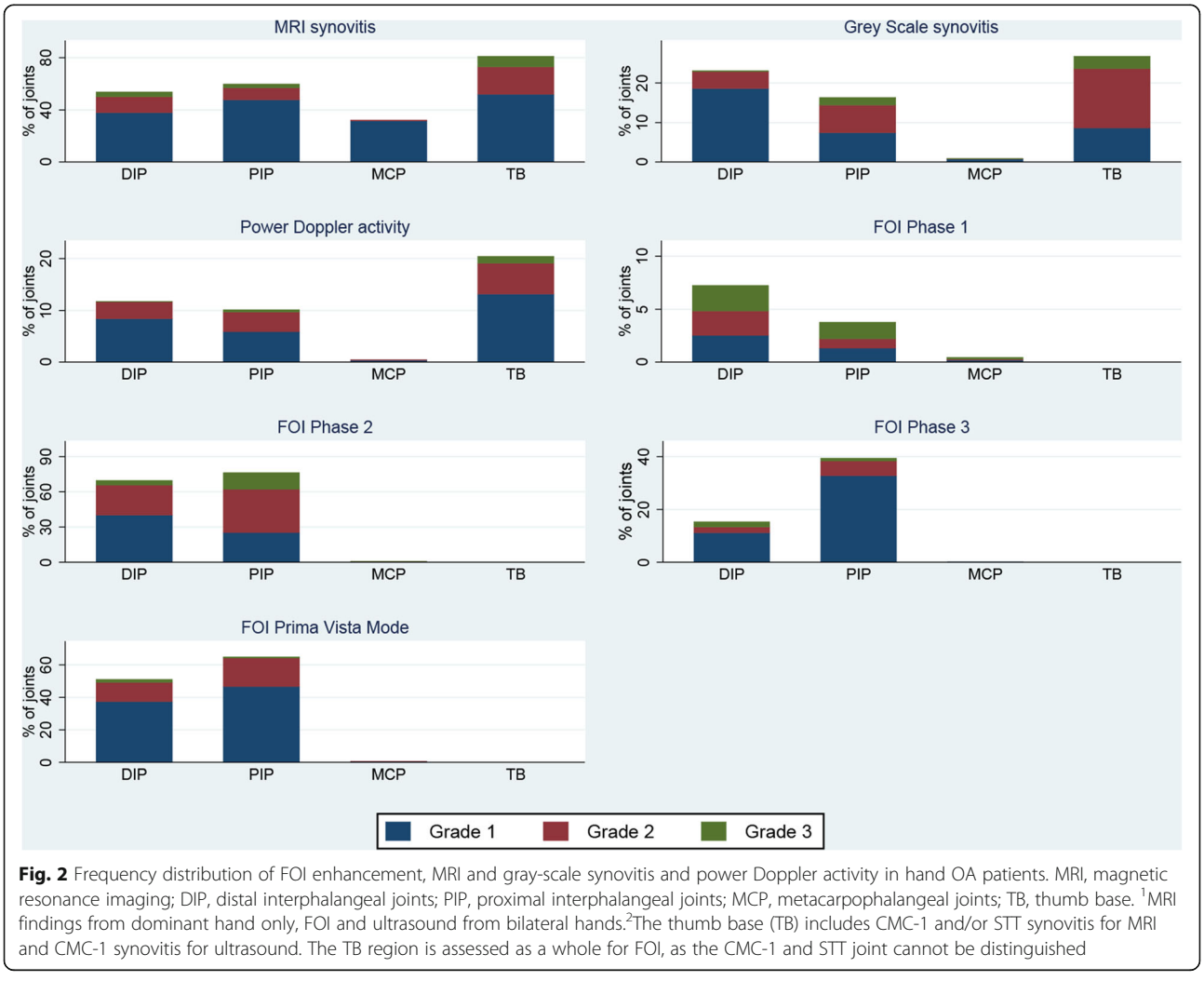

Fig. 2 Frequency distribution of FOI enhancement, MRI and gray-scale synovitis and power Doppler activity in hand OA patients. MRI, magnetic resonance imaging; DIP, distal interphalangeal joints; PIP, proximal interphalangeal joints; MCP, metacarpophalangeal joints; TB, thumb base. [1]MRI findings from dominant hand only, FOI and ultrasound from bilateral hands.[2]The thumb base (TB) includes CMC-1 and/or STT synovitis for MRI and CMC-1 synovitis for ultrasound. The TB region is assessed as a whole for FOI, as the CMC-1 and STT joint cannot be distinguished

scores, we found a significant trend for higher proportion of joints with FOI enhancement in joints with severe KL and VV grades (Online supplementary figure 1).

Correlations between FOI, ultrasound, and MRI

Good correlations were found between MRI and GS synovitis for all joint groups except in the MCP joints (Table 2). Similarly, GS synovitis and PD activity demonstrated good to very good correlations for all joint groups. Overall, the correlations between FOI and MRI were poor to fair, while FOI was poorly correlated with GS synovitis. The strongest correlation with MRI was found for PVM in the PIP joints with Spearman's rho of 0.32, while the DIP joints had consistently the weakest correlations ranging from 0.00 to 0.14 (Table 2, Fig. 3).

Diagnostic performance of FOI measuring synovitis

Using MRI and GS synovitis as reference, FOI phase 1 demonstrated the highest specificity, with corresponding very low sensitivity (Table 3). FOI PVM and phase 2 had

Table 2 Spearman's correlations for synovitis sum scores between MRI, ultrasound, and FOI

Variable 1	Variable 2	All joints	DIP	PIP	MCP
MRI*	PVM*	0.23	0.09	0.32	0.17
MRI*	Phase 1*	0.01	0.00	0.01	− 0.04
MRI*	Phase 2*	0.24	0.14	0.31	− 0.01
MRI*	Phase 3*	0.19	0.09	0.24	0.07
GS	PVM	0.15	0.07	0.26	0.20
GS	Phase 1	0.12	0.15	0.04	0.13
GS	Phase 2	0.25	0.15	0.30	0.13
GS	Phase 3	0.22	0.06	0.27	0.17
MRI*	GS*	0.58	0.45	0.60	− 0.04
MRI*	PD*	0.45	0.35	0.47	− 0.02
GS	PD	0.79	0.70	0.85	0.79

*Dominant hand

MRI magnetic resonance imaging, *GS* gray-scale ultrasound, *PD* power Doppler, *FOI* fluorescence optical imaging, *PVM* FOI Prima Vista Mode, *Phase 1* FOI phase 1, *Phase 2* FOI phase 2, *Phase 3* FOI phase 3, *DIP* distal interphalangeal joint, *PIP* proximal interphalangeal joint, *MCP* metacarpophalangeal joint

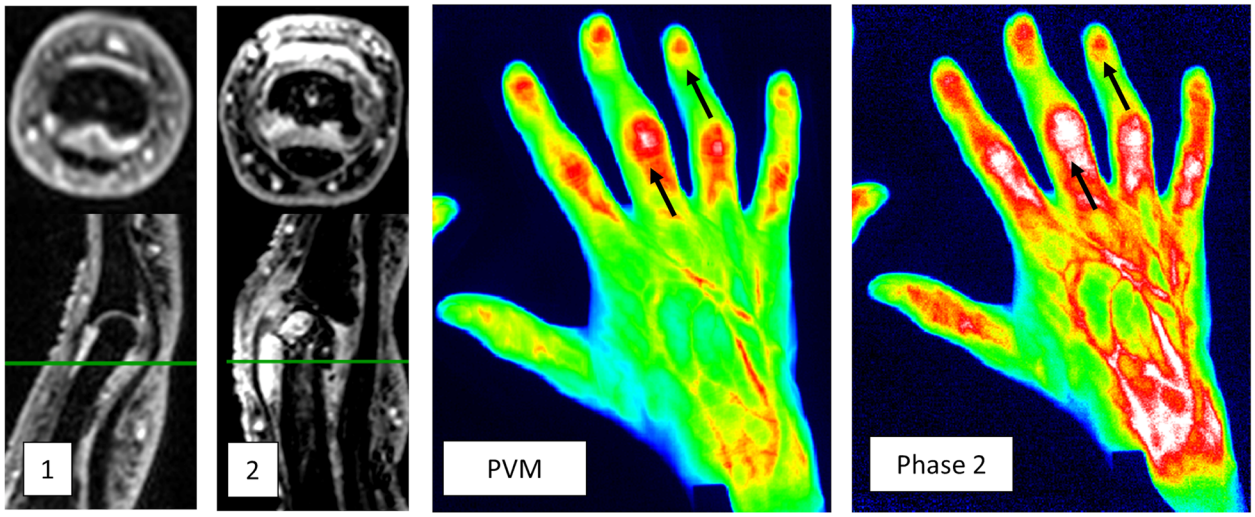

Fig. 3 MRI synovitis grade 2 on axial and sagittal plane in DIP 4 (1) and grade 3 in PIP 3 (2) compared with FOI PVM and FOI phase 2 with good agreement in PIP joint and poor agreement in DIP joint. MRI, magnetic resonance imaging; FOI, fluorescence optical imaging; PVM, Prima Vista Mode; DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint

consistently the highest sensitivities with both MRI and GS synovitis as reference, with values ranging from 48% to 69%. FOI reached high NPV with GS synovitis as reference, suggesting that joints with no FOI enhancement were unlikely to have GS synovitis. However, presence of FOI enhancement did not consistently correspond with presence of GS synovitis, demonstrated by low PPV values. GS synovitis was less prevalent than MRI synovitis, which affected the results considerably. Using MRI instead of ultrasound as reference, FOI demonstrated higher PPV and lower NPV. However, improvement of sensitivity, specificity, and AUC was found for FOI when presence of MRI synovitis was increased to grade 2 or more (Online supplementary table 1, online supplementary figure 2). The agreement between FOI (enhancement yes/no) and MRI (synovitis yes/no) ranged from 53 to 61% while the same values for ultrasound (synovitis yes/no) ranged from 57 to 89%. Using PD activity as reference, the diagnostic performance of FOI was similar to the results when GS synovitis was used as reference (data not shown).

Table 3 Diagnostic performance of FOI measuring synovitis using MRI and GS synovitis as reference

FOI	FOI+/MRI+	FOI−/MRI-	Sens.	Spec.	PPV	NPV	AUC	PA
PVM	698/1456	1180/1635	0.48	0.72	0.61	0.61	0.61	61
Phase 1	22/1442	1621/1635	0.02	0.99	0.61	0.53	0.50	53
Phase 2	814/1408	984/1585	0.58	0.62	0.58	0.62	0.60	60
Phase 3	332/1407	1408/1572	0.24	0.90	0.67	0.57	0.57	58
FOI	FOI+/GS+	FOI−/GS−	Sens.	Spec.	PPV	NPV	AUC	PA
PVM	407/688	3510/5473	0.59	0.64	0.17	0.93	0.62	64
Phase 1	16/680	5412/5454	0.02	0.99	0.28	0.89	0.51	88
Phase 2	461/667	2977/5299	0.69	0.56	0.17	0.94	0.63	58
Phase 3	152/664	4545/5273	0.23	0.86	0.17	0.90	0.56	79

FOI fluorescence optical imaging, *PVM* FOI Prima Vista Mode, *Phase 1* FOI phase 1, *Phase 2* FOI phase 2, *Phase 3* FOI phase 3, *MRI* magnetic resonance imaging, *GS* gray-scale ultrasound, *Sens.* sensitivity, *Spec.* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *PA* percent agreement, *AUC* area under the curve

Results from subgroup analysis

Correlation analyses were repeated for participants with erosive hand OA without consistent improvements in the correlations between FOI, MRI, and GS synovitis. Further, the diagnostic performance of FOI measuring synovitis with MRI and ultrasound as reference was similar in erosive hand OA and non-erosive hand OA patients (data not shown).

Discussion

This is the first study to investigate the validity and diagnostic performance of FOI in persons with hand OA. To our knowledge, the Nor-Hand study is also the largest clinical study to date comparing FOI with MRI and ultrasound.

Our hand OA patients demonstrated a significant inflammatory burden with a high percentage of joints with MRI- and ultrasound-detected synovitis, with the DIP, PIP, and thumb base joints most frequently affected. FOI demonstrated most enhancement in DIP and PIP joints, whereas no enhancement was detected in the thumb base despite inflammation in these joints being highly prevalent on both MRI and ultrasound. FOI enhancement in the thumb base has not been detected in previous studies on FOI, and we hypothesize that the CMC-1 and STT joints are located too deep to be

visualized by the limited tissue penetration of the FOI device. This represents an important limitation for the use of FOI in hand OA. The development of a 3D FOI device with pairing of lateral, medial, palmar, and dorsal images would possibly give a more complete representation of the inflamed joint and could therefore improve the correlation to MRI and ultrasound in persons with hand OA.

FOI showed poor to fair correlation with MRI and ultrasound in our cohort. In contrast, Fischer et al. found strong correlation between MRI and FOI in five RA patients with a similar near-infrared optical imaging device [21], and Werner et al. demonstrated moderate correlation between gray-scale synovitis and FOI (rho = 0.40) in patients with arthritis using the Xiralite® scanner [7]. Regarding diagnostic performance, we found moderate to very good specificities and poor to moderate sensitivities for FOI using MRI-detected synovitis as reference, with the best specificity in FOI phase 2 (99%) with corresponding low sensitivity (2%), suggesting substantial noise and false positive findings. Previous studies on RA and undifferentiated arthritis have demonstrated better specificity and sensitivity for FOI, particularly for phase 1 [7–9, 11, 22]. Phase 1 has been suggested to demonstrate active inflammation [23] and might explain the higher sensitivity of this phase in persons with RA rather than hand OA. This is supported by the finding of fewer joints with PD activity in our cohort, with mean sum score of 2.4 in DIP and PIP joints in the bilateral hands. In comparison, a group of 431 RA patients demonstrated a mean sum score of PD activity of 4.8 in the wrist, MCP 1–5 and PIP 2–3 of the dominant hand [24].

The percent agreement was better between FOI (enhancement yes/no) and ultrasound (synovitis yes/no) than FOI and MRI, most likely due to the high prevalence of low-grade MRI synovitis in our cohort. It is debated whether MRI grade 1 synovitis actually represents pathology or rather is a normal finding [25], and we found improved values when assessing the diagnostic performance and percent agreement of FOI with MRI-defined synovitis grade 2 and higher as reference.

Despite our findings of poor correlations and diagnostic performance, FOI enhancement has previously corresponded to histological synovitis in animal models with induced arthritis [26]. Interestingly, we found more FOI enhancement in joints with increasing KL and VV grade, especially in the erosive joints. Bone remodeling with increased vascularity of the bone in OA joints may have affected the enhancement, although it is unknown whether these signals can be detected by FOI. Further, it is unlikely that tenosynovitis has affected the results as the low degree of flexor tenosynovitis detected on MCP level in our cohort is located too deep to be detected by FOI, comparable to the aforementioned thumb base. Additionally, no participants had peritendinous inflammation along the extensor tendon. FOI enhancement in our participants might represent an extraarticular hypervascularity due to inflamed subcutaneous tissue; however, we did not specifically look for this feature when assessing the MRI images.

Poor agreement between FOI and MRI might also be a question of scoring method. The FOI reader in our study demonstrated good reliability with an experienced reader for phase 2 and 3 and PVM; however, phase 1 showed remarkably low inter-reader reliability (ICC = 0.10). Readers define phases 1, 2, and 3 from preset criteria and might assess different images. In a recently published paper, we found low reliability for phase 1 in both hand OA and RA patients and we hypothesized that the low agreement in phase 1 was due to rapid changes in the beginning of the FOI image sequence, while phase 2 and phase 3 had good reliability despite readers assessing images within a broad range [27]. Ultimately, the FOIAS might not be the best scoring method for analyzing the 360 images in persons with hand OA. FOI and its varying degrees of enhancement seems particularly suited for developing an automated algorithm for scoring affected joints through, e.g., machine learning, and might improve the diagnostic performance and validity of FOI in persons with hand OA. This study has several limitations. First, our participants were recruited from a rheumatology outpatient clinic, making it difficult to generalize the results to persons with hand OA in primary health care. Secondly, FOI was performed approximately 2 weeks prior to MRI. As low-grade MRI-defined synovitis might fluctuate and represent a normal finding, images should have been acquired on the same day in order to make FOI and MRI fully comparable. However, the ultrasound exam was conducted on the same day as the FOI exam and demonstrated good correlation (r = 0.58) with the MRI findings.

Conclusion

To conclude, we found poor to fair correlation between FOI enhancement and MRI- and ultrasound-detected synovitis in persons with hand OA. None of the FOI phases or PVM demonstrated both good sensitivity and specificity. Although a frequent manifestation of hand OA, FOI was not able to detect synovitis in the thumb base. Our cohort demonstrated low-grade inflammation with less vascularization, which might explain the poor results compared with previous FOI studies on systemic inflammatory joint diseases. With the current scoring method and technology available, we conclude that MRI and

ultrasound perform better than FOI for the assessment of inflammation in hand OA.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13075-020-02185-0.

Additional file 1 : Figure S1. Distribution of FOI PVM enhancement in joints with increasing degree of osteoarthritis.

Additional file 2 : Table S1. The diagnostic performance of FOI measuring synovitis using MRI grade 2 & 3 as reference.

Additional file 3 : Figure S2. ROC curves showing the AUC of FOI PVM using a) MRI grade 1-3 and b) MRI grade 2-3 as reference.

Abbreviations

ACR: American College of Rheumatology; AUSCAN: Australian and Canadian Hand Index; CI: Confidence interval; CMC-1: 1st carpometacarpal joint; CR: Conventional radiography; DIP: Distal interphalangeal joints; FOI: Fluorescence optical imaging; HOAMRIS: Hand OA MRI score; ICC: Intraclass correlation coefficient; IP: Interphalangeal; IQR: Interquartile range; JSN: Joint space narrowing; KL: Kellgren Lawrence; MCP: Metacarpophalangeal joints; MRI: Magnetic resonance imaging; OA: Osteoarthritis; PA: Posterior-anterior; PIP: Proximal interphalangeal joint; RA: Rheumatoid arthritis; SD: Standard deviation; STT: Scaphotrapeziotrapezoid

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Authors' contributions

ØM, IKH, TKK, TU, and HBH designed the study. ØM, IKH, SH, AM, and HBH participated in the acquisition of the data. ØM, IKH, HBH, TU, TKH, and AM interpreted the data. ØM and IKH drafted the work substantively and all authors read it, revised it critically, and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants signed informed consent and the study was approved by the regional ethics committee.

Consent for publication

Not applicable.

Competing interests

There are no relevant competing interests for any of the authors. The FOI device Xiralite® has been applied in this study. Xiralite GmbH has not contributed to the study design, collection or interpretation of the data, the writing of the manuscript, or the decision to publish the data. None of the authors have received funding from Xiralite GmbH.

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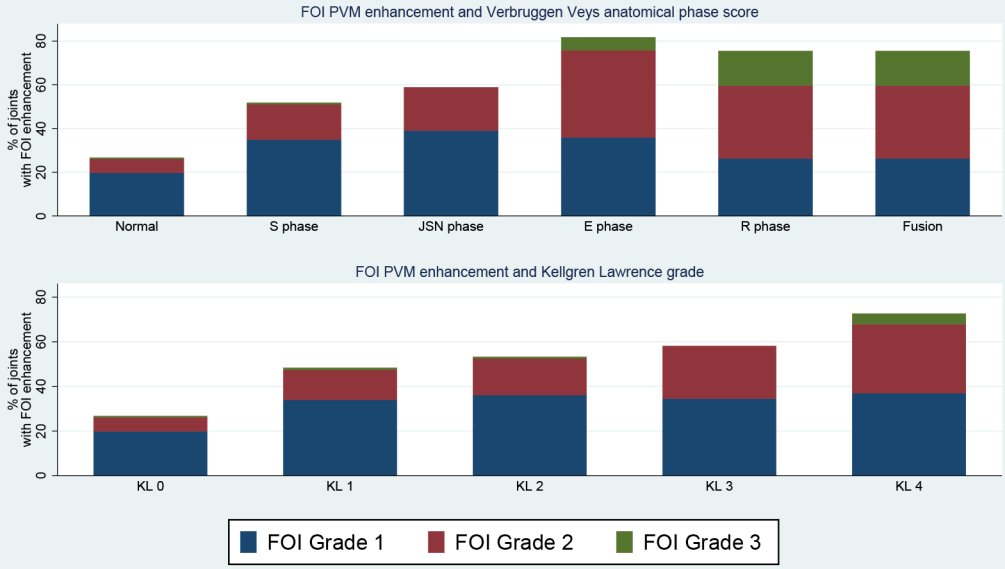
Publisher's Note

Online supplement Table S1: The diagnostic performance of FOI measuring synovitis using MRI grade 2 & 3 as reference.

FOI	FOI+/MRI+	FOI-/MRI-	Sens.	Spec.	PPV	NPV	AUC	PA
PVM	192/268	1862/2823	0.72	0.66	0.17	0.96	0.72	66
Phase 1	10/265	2786/2812	0.04	0.99	0.28	0.92	0.51	91
Phase 2	213/260	1531/2733	0.82	0.56	0.15	0.97	0.74	58
Phase 3	111/260	2334/2719	0.43	0.86	0.22	0.94	0.64	82

FOI=Fluorescence optical imaging, PVM=FOI Prima Vista Mode, Phase 1= FOI Phase 1, Phase 2= FOI Phase 2, Phase 3= FOI Phase 3, MRI= Magnetic Resonance Imaging, GS= Grey Scale Ultrasound, Sens.= sensitivity, Spec.= Specificity, PPV= Positive Predictive Value, NPV= Negative Predictive Value, PA= Percent Agreement, AUC= Area under the curve.

Online supplementary figure S1
Distribution of FOI PVM enhancement in joints
with increasing degree of osteoarthritis



FOI; fluorescence optical imaging, PVM; Prima vista mode,

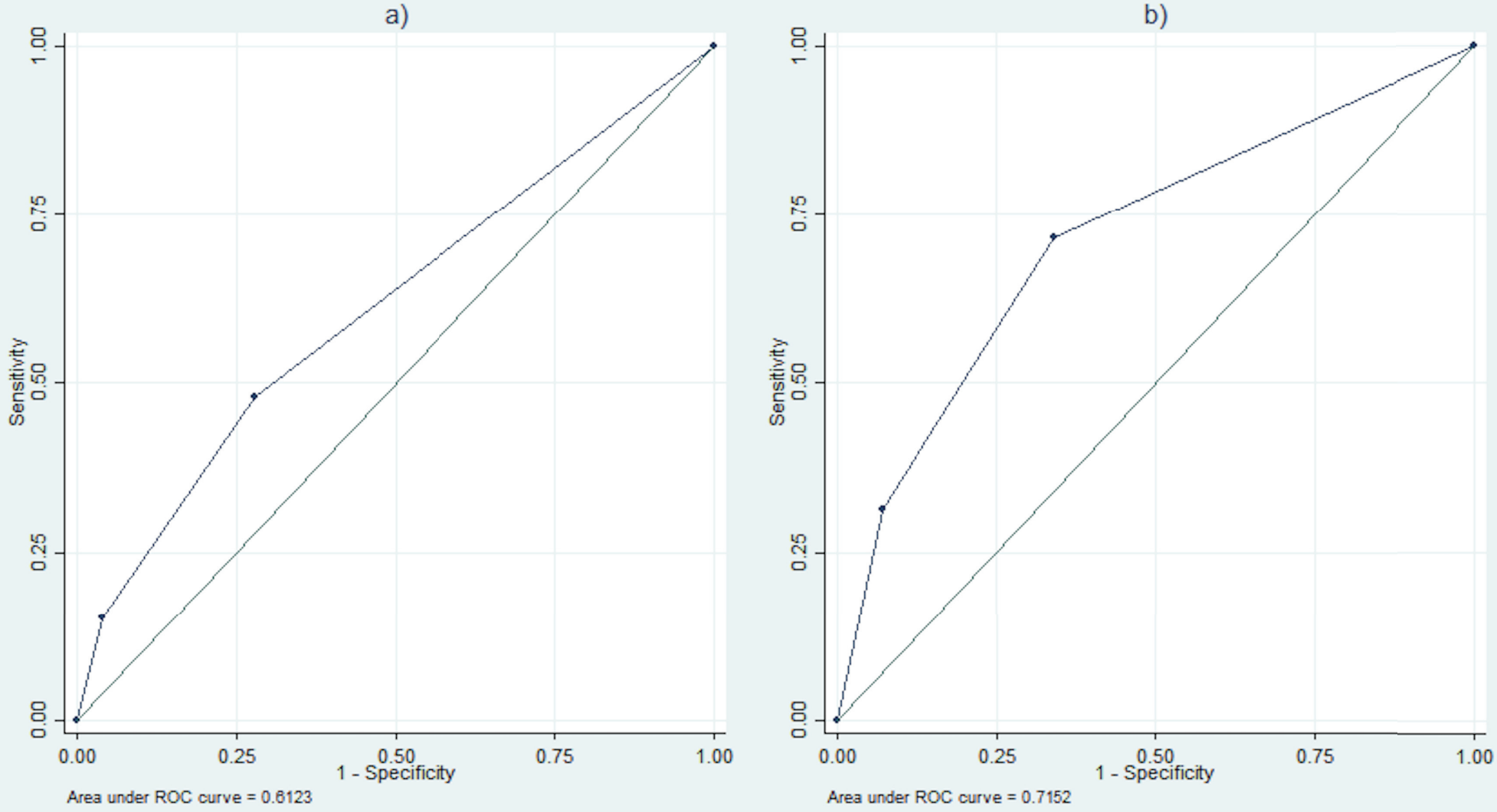
S; Stationary, JSN; Joint space narrowing, E; Erosive, R; Remodelling

Kellgren Lawrence

Online supplement figure 2:

ROC curves showing the AUC of FOI PVM using

a) MRI grade 1-3 b) MRI grade 2-3 as reference



MRI; magentic resonance imaging, FOI; fluorescence optical imaging

AUC; Area under the curve ROC; Receiver operating characteristics

III

Associations between Fluorescence Optical Imaging and Magnetic Resonance Imaging and symptoms in hand osteoarthritis

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Abstract

Objectives: To investigate whether Fluorescence Optical Imaging (FOI) enhancement and Magnetic Resonance Imaging (MRI)-defined synovitis are associated with pain and physical function in hand osteoarthritis (OA) patients.

Methods: Bilateral FOI scans and MRI of the dominant hand were available for 221 patients. Finger joints were examined for tenderness on palpation. Pain in individual finger joints during the last 24 hours and last 6 weeks and hand pain intensity by the Australian/Canadian hand index and Numeric Rating Scale were self-reported. On joint level, we applied logistic regression with generalized estimating equations to examine whether FOI enhancement and MRI-defined synovitis were associated with pain in the same joint. On subject level, we applied linear regression to assess whether FOI and MRI sum scores were associated with pain intensity and physical function.

Results: Metacarpophalangeal and thumb base joints were excluded from analyses due to little/no FOI enhancement. Finger joints with FOI enhancement on the composite image had higher odds (95% confidence interval) of pain during the last 6 weeks (grade 1: 1.4 (1.2-1.6), grade 2-3: 2.1 (1.7-2.6)). Similar results were found for joint pain during the last 24 hours and joint tenderness in fingers. Numerically stronger associations were found between MRI-defined synovitis and finger joint pain/tenderness. FOI and MRI sum scores demonstrated no/weak associations with hand pain and physical function.

Conclusion: FOI enhancement and MRI-defined synovitis were associated with pain in the same finger joint. None of the imaging modalities demonstrated consistent associations with pain, stiffness and physical function on subject level.

Keywords: hand; osteoarthritis; mri; diagnostic imaging; inflammation

Key messages:

- FOI has been suggested to measure inflammation in finger joints.
- FOI enhancement was associated with pain in the same interphalangeal joint.
- FOI enhancement was not associated with hand pain on patient level.

Introduction

Inflammation is a prominent feature in persons with hand osteoarthritis (OA), and ultrasound- and Magnetic Resonance Imaging (MRI)-detected synovitis are associated with pain in the same joint (1, 2). Synovitis has been suggested to be a treatment target, and both ultrasound- and MRI-detected synovitis have been applied as outcome measures in recent hand OA trials (4, 5). However, both modalities have their limitations, with operator dependency and high cost, respectively. Fluorescence Optical Imaging (FOI) is a fast non-ionizing imaging technique that can be operated by trained medical personnel. FOI has been suggested to demonstrate enhanced microcirculation around finger and wrist joints as a sign of inflammation and has shown moderate to good agreement with MRI in primary inflammatory joint diseases(6, 7). We recently showed that FOI exams can be assessed with good reliability in erosive hand OA (8), and persons with hand OA demonstrated FOI enhancement in distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints (9). However, we recently presented poor diagnostic performance for FOI enhancement in hand OA using MRI and ultrasound as a reference (10).

Our primary aim in this paper was to explore the associations between FOI enhancement and markers of pain on joint level and the associations between FOI sum scores and

measures of pain, stiffness and physical function on subject level. Secondly, we examined the associations between MRI-defined synovitis and symptoms in the same patient cohort.

Methods

Study participants

We included participants from the Nor-Hand study at Diakonhjemmet Hospital, Oslo, Norway. Their age ranged from 40 to 70 years and all had hand OA by clinical examination and/or ultrasound (11). All participants provided written informed consent and the study was approved by the Regional Committees for Medical and Health Research Ethics (number 2014/2057).

Fluorescence optical imaging (FOI)

The optical images were obtained with a Xiralite® scanner. Unless contraindications, the participants were injected with a fluorescent dye (indocyanine green 0.1 mg/kg body weight) prior to the FOI examination. Thereafter, the hands were inserted in the Xiralite® scanner, and near-infrared light from light-emitting diodes were projected onto the hands for six minutes. A highly sensitive camera produced 360 images (one per second) , showing the distribution of the fluorescent dye. According to the FOI activity score (FOIAS) (6, 9, 12) four images were assessed; Prima vista mode (PVM, a composite image from the 240 first images) and three images representing phase 1, 2, and 3 based on the distribution and washing out of the fluorescent dye in relation to the fingertips (Supplementary Figure 1). The DIP, PIP including the 1st interphalangeal (IP1), metacarpophalangeal (MCP) and thumb base (including the first carpometacarpal (CMC1) and scaphotrapeziotrapezoidal (STT) joints) were graded on 0-3 scales based on color intensity and width of enhancement. A medical

doctor trained in assessing FOI images with good inter-reader reliability with an experienced reader (SO) evaluated all FOI scans(10).

MRI

Unless contraindications, MRI with gadolinium contrast (Dotarem 279.3 mg/mL, 0.2 mL/kg body weight) of the dominant hand was obtained with a 1.5T MRI (Siemens Aera, Germany) covering the fingers and thumb base by a 16-channel hand/wrist coil. The axial and sagittal planes of a TI-weighted volumetric interpolated breath-hold examination (VIBE) reconstructed into three planes with 2.0 mm thickness were used for assessment of synovitis. One trained reader (ØM) scored the images after obtaining good to very good inter-reader reliability with an experienced reader (IKH) (weighted kappa: 0.69, intraclass correlation coefficient: 0.89) (10). Synovitis in the DIP and PIP (including IP1) joints was assessed on a 0-3 scale according to the Hand OA MRI scoring system (HOAMRIS)(13). The MCP joints were scored with the same criteria as the PIP joints. The CMC1 and STT joints were evaluated in the frontal and axial planes using the TOMS atlas (14).

Clinical examination

An experienced rheumatologist (BSC) examined the DIP, PIP (including IP1), MCP and thumb base joints for bony enlargement, joint tenderness and soft tissue swelling with the EULAR handbook as reference(16). The Doyle index (scale 0-3) was used to assess joint tenderness on palpation(17), and dichotomized scores were used in analyses (0=no tenderness, grade 1-3=presence of joint tenderness).

Grip strength, self-reported pain variables and pain medication

Grip strength of the dominant hand was measured twice with 15 seconds interval with a Jamar dynamometer and the mean value was calculated.

The participants marked painful hand joints during the last 24 hours and the last 6 weeks on two separate hand diagrams. They also completed the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) including 5 questions about hand pain (0-20 scale), one question on hand stiffness (0-4 scale) and nine questions on hand function (0-36 scale), all within the last 48 hours. Hand pain intensity during the last 24 hours was evaluated on a numeric rating scale (NRS) from 0=no pain to 10=worst imaginable pain, and regular use of oral non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids was self-reported.

Statistics

On joint level, we applied logistic regression analyses to investigate if FOI enhancement and MRI-defined synovitis were associated with pain. Data from the bilateral DIP/PIP joints were used in analyses of FOI and pain, whereas data from the DIP/PIP joints in the dominant hand only were used in analyses of MRI and pain. Generalized estimating equations (GEE) was applied to account for dependency between joints within each participant. Separate models were used for each of the FOI phases, PVM and MRI and the three variables on pain in individual joints.

On subject level, we calculated sum scores for FOI enhancement and MRI synovitis in the DIP/PIP joints of the dominant hand and performed linear regression analysis to explore associations with AUSCAN pain, stiffness and physical function subscales, NRS hand pain, and grip strength. All analyses were adjusted for age, sex, body mass index and daily use of oral NSAIDs or corticosteroids. Results were presented as unstandardized B coefficients with 95% confidence intervals (CI) per increase in one SD of the sum scores. Stata version 14.0 was used, and p-values<0.05 was regarded as statistically significant.

Results

Study population

Among the 300 participants in the Nor-Hand study, n=253 performed FOI. Three additional FOI exams were excluded due to lack of any fluorescence enhancement. No adverse events were reported. Among the 250 participants with available FOI examinations, n=221 performed MRI and were included in further analyses (Table 1). The mean(standard deviation, SD) interval between MRI scans and the FOI scan/clinical examination was 9.0 (13.9) days. The MCP and thumb base joint showed little and no enhancement and were excluded from further analyses.

Associations with pain in individual joints (joint level analyses)

FOI enhancement in the DIP/PIP joints was associated with pain last 24 hours, last 6 weeks and tenderness on palpation with the strongest associations observed for moderate/severe enhancement (Table 2). MRI-defined synovitis showed numerically stronger associations with pain during the last 24 hours, last 6 weeks and tenderness compared with the results on FOI.

Associations with hand pain and physical function (subject level analyses)

FOI PVM, Phase 2 and Phase 3 sum scores were weakly associated with NRS hand pain (B coefficients ranging from 0.33 to 0.43 per one SD of the sum scores), whereas no association with NRS hand pain was detected for FOI Phase 1 and MRI. No associations were found for AUSCAN pain, AUSCAN physical function and grip strength, except for an association between FOI Phase 3 and AUSCAN physical function. FOI Phase 2 and 3 were weakly

associated with AUSCAN stiffness. Although not statistically significant, inverse associations were found between sum scores of MRI-defined synovitis and AUSCAN pain, AUSCAN physical function and NRS pain (Supplementary Table 1).

Discussion

This is the first study to investigate the associations between FOI enhancement and pain in persons with hand OA. On joint level we found statistically significant associations between increasing levels of FOI enhancement and self-reported pain and tenderness by clinical examination. The associations between synovitis and pain are numerically stronger for MRI-defined synovitis (as shown in the current paper) and ultrasound-detected synovitis (shown in the same patient population)(1). However, this numerical difference in strength of associations must be interpreted with caution as their confidence intervals are overlapping. On subject level, we found no or only weak associations between sum scores of FOI enhancement and patient-reported variables and grip strength. Similarly, previous studies have shown weak associations between MRI- and ultrasound-detected synovitis and pain on subject level in persons with hand OA(1, 2). Our analyses did not include the thumb base joints, which might affect pain and function to a larger degree than DIP/PIP involvement in hand OA, and could thus explain the lack of associations with AUSCAN subscales and grip strength. We found weak but statistically significant associations between FOI sum scores (PVM, Phase 2 and 3) and NRS hand pain, while no associations were demonstrated with AUSCAN pain subscale. The majority of questions in AUSCAN pain subscale are related to pain during hand activities, while the NRS pain variable consists of one question about hand pain in the course of the last 24 hours, which does not discriminate between pain during activities or at rest. Hence, the NRS pain question might have picked up pain at rest to a

larger degree than the AUSCAN pain subscale, and could thus explain why different associations were found for the two pain measures. It is acknowledged that several factors contribute to the overall pain experience in hand OA, i.e. structural changes, genetics, pain sensitization and psychosocial factors. On joint level these factors may be less important, as illustrated by our findings of strong associations with presence of pain in the same joint, and weaker, if any, associations with the overall severity of hand pain.

Our finding of clear associations between FOI enhancement and pain in the same joint, combined with previous findings of poor correlations between FOI and MRI- and ultrasound-defined synovitis, is intriguing and raises the question of what FOI enhancement represent in persons with hand OA. Extra-articular inflammation caused by local tissue stress from protruding osteophytes or increased vascularity of the bone in OA joints due to bone remodeling are two hypotheses, and can only be confirmed by histology. Nonetheless, the previously demonstrated low diagnostic performance of FOI in hand OA suggests that FOI enhancement is associated with more noise than established imaging modalities and support the validity of MRI and ultrasound in hand OA(10).

The thumb base joints are commonly affected by OA and the lack of FOI enhancement in this joint group is an important limitation of this modality. The lack of enhancement might be explained by the joints being surrounded by more soft tissue than the DIP/PIP joints, making it more difficult to visualize the joint inflammation. Furthermore, the participants were recruited from a hospital-based cohort and the results might not be applicable to a hand OA population in primary care. MRI images were acquired on average 9 days after the FOI images and the synovitis might have fluctuated between exams. Nevertheless, since FOI was obtained on the same day as the clinical examination, a stronger, and not weaker (as shown in our analyses), association for FOI would be expected.

Finally, we scored the FOI images with the FOIAS, a semi-quantitative scoring method applied in several studies(7, 9, 12). However, quantitative and dynamic scoring methods have been applied on patients with inflammatory joint disease and could possibly have yielded stronger associations between FOI and pain in our cohort (19, 20).

In a patient perspective, pain is an important aspect. We found that FOI enhancement was strongly associated with pain on joint level. However, previous findings of poor correlation with MRI makes it difficult to conclude what aspect of the pathological process FOI represents. On subject level, FOI demonstrated weak, if any, associations with severity of hand pain and functioning in hand OA, comparable to previous findings on MRI and ultrasound.

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Author contributions: ØM, IKH, SO: a) Substantial contributions to study conception and design; and b) Substantial contributions to acquisition of data; and c) Substantial contributions to analysis and interpretation of data. TKK, TU: a) Substantial contributions to study conception and design and c) Substantial contributions to analysis and interpretation of data. BSC: b) Substantial contributions to acquisition of data and c) Substantial contributions to analysis and interpretation of data. All authors revised the final draft critically for important intellectual content and approved the final version.

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Data availability: The data underlying this article will be shared on reasonable request to the corresponding author.

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Role of Xiralite GmbH: The FOI device Xiralite® from Xiralite GmbH has been applied in this study. Xiralite GmbH has not contributed to the study design, collection or interpretation of the data, the writing of the manuscript or the decision to publish the data. None of the authors have received funding from Xiralite GmbH.

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Table 1: Clinical characteristics of the hand OA study population (N = 221)

Age, mean (SD) years	60.6 (6.2)
Sex, n (%) women	194 (87.8)
BMI, mean (SD) kg/m^2	26.2 (4.7)
Fulfillment of the ACR criteria for hand OA, n (%)	203 (91.9)
Erosive hand OA, n (%)	74 (33.5)
KL sum score, mean (SD) [range 0-120]	28.9 (18.0)
FOI PVM sum score, mean (SD) [range 0-27] [1] [2]	6.6 (3.8)
FOI Phase 1 sum score, mean (SD) [range 0-27] [1] [2]	0.4 (1.8)
FOI Phase 2 sum score, mean (SD) [range 0-27] [1] [2]	11.2 (5.2)
FOI Phase 3 sum score, mean (SD) [range 0-27] [1] [2]	2.7 (3.0)
HOAMRIS sum score, mean (SD) [range 0-27] [2]	6.4 (4.8)
Tender joint count by CE, median (IQR) [range 0-9][2]	3 (1-5)
NRS hand pain intensity, mean (SD) [range 0-10] [1]	3.7 (2.3)
AUSCAN pain, mean (SD) [range 0-20]	8.1 (4.1)
AUSCAN physical, mean (SD) [range 0-36]	12.8 (7.9)
AUSCAN stiffness, mean (SD) [range 0-4] [1]	1.63 (0.9)
Grip strength of dominant hand, mean (SD) kg	22.4 (9.4)
Regular use of anti-inflammatory drug[3], n (%)	30 (13.6)

[1] Missing values for the following variables: AUSCAN stiffness (n=1), NRS hand pain (n=1), Phase 1 (n=1), Phase 2 (n=7), Phase 3 (n=8).

[2] Sum score of DIP and PIP joints of the dominant hand only.

[3] Oral NSAIDS or corticosteroids.

ACR=American College of Rheumatology, AUSCAN=Australian/Canadian Hand Index, BMI= Body mass index, CE= clinical examination, DIP=distal interphalangeal, FOI=Fluorescence Optical Imaging, HOAMRIS=Hand OA MRI scoring system, KL=Kellgren-Lawrence, NRS=Numeric rating scale, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, PIP=proximal interphalangeal

Table 2: Associations between FOI and MRI enhancement and pain in individual DIP and PIP joints

	Self-reported pain last 24 hours OR (95 % CI)	Self-reported pain last 6 weeks OR (95 % CI)	Joint tenderness by CE OR (95 % CI)
FOI Phase 1			
Grade 0 (n=3899)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Grade 1-3 [1] (n=46)	1.87 (1.07, 3.26)	2.04 (1.20, 3.48)	2.32 (1.35, 3.99)
FOI Phase 2			
Grade 0 (n=1058)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Grade 1 (n=1307)	1.24 (1.03, 1.49)	1.28 (1.06, 1.53)	1.19 (1.01, 1.40)
Grade 2 (n=1192)	1.81 (1.48, 2.21)	1.94 (1.59, 2.36)	1.43 (1.20, 1.71)
Grade 3 (n=280)	2.08 (1.54, 2.81)	2.48 (1.85, 3.33)	1.98 (1.51, 2.60)
FOI Phase 3			
Grade 0 (n=2940)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Grade 1 (n=768)	1.28 (1.07, 1.53)	1.31 (1.09, 1.56)	1.27 (1.07, 1.49)
Grade 2+3 [2] (n=111)	1.81 (1.21, 2.71)	2.02 (1.37, 2.97)	1.93 (1.32, 2.82)
FOI PVM			
Grade 0 (n=1596)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Grade 1 (n=1665)	1.24 (1.06, 1.45)	1.37 (1.17, 1.60)	1.24 (1.08, 1.43)
Grade 2 [3] (n=701)	1.98 (1.62, 2.42)	2.09 (1.71, 2.55)	1.84 (1.53, 2.22)

MRI-defined synovitis			
Grade 0 (n=888)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Grade 1 (n=841)	1.41 (1.11, 1.80)	1.43 (1.12, 1.82)	1.63 (1.32, 2.02)
Grade 2 (n=195)	3.36 (2.39, 4.74)	3.27 (2.33, 4.59)	3.85 (2.78, 5.33)
Grade 3 (n=64)	5.15 (3.08, 8.64)	6.09 (3.69, 10.06)	9.02 (4.98, 16.35)

[1] Grade 1, 2 and 3 combined in Phase 1 due to few joints with enhancement.

[2] Grade 2 and 3 combined due to few joints with grade 3 in Phase 3.

[3] No joints with grade 3 in Prima Vista Mode.

CE=clinical examination, CI=confidence interval, DIP=distal interphalangeal, FOI=Fluorescence Optical Imaging, MRI=Magnetic Resonance Imaging, PIP=proximal interphalangeal.

Supplementary table 1: Associations between sum scores of FOI enhancement and MRI-synovitis and hand symptoms

	NRS pain B (95 % CI)	AUSCAN pain B (95 % CI)	AUSCAN physical B (95 % CI)	AUSCAN stiffness B (95 % CI)	Grip strength B (95 % CI)
FOI PVM	0.43 (0.12, 0.74)	0.46 (-0.10, 1.01)	0.76 (-0.29, 1.81)	0.11 (-0.02, 0.24)	-0.23 (-1.30, 0.85)
FOI Phase 1	0.21 (-0.09, 0.51)	0.49 (-0.04, 1.02)	0.85 (-0.16, 1.87)	0.01 (-0.11, 0.14)	0.56 (-0.47, 1.60)
FOI Phase 2	0.35 (0.03, 0.68)	0.31 (-0.27, 0.89)	0.74 (-0.37, 1.85)	0.12 (-0.02, 0.26)	0.19 (-0.95, 1.33)
FOI Phase 3	0.33 (0.01, 0.64)	0.42 (-0.14, 0.97)	1.24 (0.19, 2.30)	0.18 (0.04, 0.31)	0.00 (-1.09, 1.10)
MRI-defined synovitis	-0.26 (-0.56, 0.05)	-0.33 (-0.88, 0.22)	-0.68 (-1.71, 0.36)	0.00 (-0.13, 0.13)	0.36 (-0.70, 1.42)

Presented as unstandardized B coefficients (95 % CI) for SD of sum scores, adjusted for age, sex, BMI, and use of anti-inflammatory drugs.

AUSCAN=Australian/Canadian hand index, CI = confidence interval, DIP = distal interphalangeal, FOI = Fluorescence Optical Imaging, MRI= Magnetic Resonance Imaging, NRS= numeric rating scale, PIP = proximal interphalangeal, PVM = Prima Vista Mode.

Supplementary Figure 1:

Phase 1-3 and PVM images from a hand OA patient, with examples of enhancement grade 0-3 in 3rd PIP of the right hand. a) phase 1, grade 0; b) phase 2, grade 3; c) phase 3, grade 1; d) PVM, grade 2.

PVM; Prima Vista Mode, PIP; Proximal interphalangeal joint.