Near-infrared Fluorescence Optical Imaging in Early Rheumatoid Arthritis: A Comparison to Magnetic Resonance Imaging and Ultrasonography

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ABSTRACT. ***Objective.*** Near-infrared fluorescence optical imaging (FOI) is a novel imaging technology in the detection and evaluation of different arthritides. FOI was validated in comparison to magnetic resonance imaging (MRI), greyscale ultrasonography (GSUS), and power Doppler ultrasonography (PDUS) in patients with early rheumatoid arthritis (RA).
Methods. Hands of 31 patients with early RA were examined by FOI, MRI, and US. In each modality, synovitis of the wrist, metacarpophalangeal joints (MCP) 2–5, and proximal interphalangeal joints (PIP) 2–5 were scored on a 4-point scale (0–3). Sensitivity and specificity of FOI were analyzed in comparison to MRI and US as reference methods, differentiating between 3 phases of FOI enhancement (P1–3). Intraclass correlation coefficients (ICC) were calculated to evaluate the agreement of FOI with MRI and US.
Results. A total of 279 joints (31 wrists, 124 MCP and 124 PIP joints) were evaluated. With MRI as the reference method, overall sensitivity/specificity of FOI was 0.81/0.00, 0.49/0.84, and 0.86/0.38 for wrist, MCP, and PIP joints, respectively. Under application of PDUS as reference, sensitivity was even higher, while specificity turned out to be low, except for MCP joints (0.88/0.15, 0.81/0.76, and 1.00/0.27, respectively). P2 appears to be the most sensitive FOI phase, while P1 showed the highest specificity. The best agreement of FOI was shown for PDUS, especially with regard to MCP and PIP joints (ICC of 0.57 and 0.53, respectively), while correlation with MRI was slightly lower.
Conclusion. FOI remains an interesting diagnostic tool for patients with early RA, although this study revealed limitations concerning the detection of synovitis. Further research is needed to evaluate its full diagnostic potential in rheumatic diseases. (J Rheumatol First Release May 1 2015; doi:10.3899/jrheum.141244)

Key Indexing Terms:
FLUORESCENCE OPTICAL IMAGING   RHEUMATOID ARTHRITIS   SENSITIVITY
MAGNETIC RESONANCE IMAGING   ULTRASONOGRAPHY   SPECIFICITY

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease leading to joint destruction and deformity. Because of the low sensitivity of conventional radiography in the early phase of the disease, ultrasonography (US) and magnetic resonance imaging (MRI) are increasingly used to depict synovitis[1,2,3,4]. US comprises the application of greyscale US (GSUS) and power Doppler mode US (PDUS). GSUS shows morphologic aspects such as synovial thickening, joint effusion, or erosive bony changes, while PDUS is used for the quantification of hypervascularization as a sign for active inflammation. MRI combines the depiction of morphologic aspects and vascularity and is considered the gold standard imaging modality in RA[5,6]. For better patient comfort, the clinical application of low-field MR scanners with a magnetic field strength of < 1T was introduced, and studies have shown that sensitivity of low-field MRI is comparable to the usually performed high-field MRI[5,7,8,9,10].

In recent years, there was an increasing interest in optical imaging techniques focusing on the detection of active arthritis in animal models and humans[11,12,13,14,15,16,17,18,19]. Near-infrared fluorescence optical imaging (FOI) with

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nonspecific dyes, most commonly indocyanine green (ICG), has become a promising tool for the detection and monitoring of arthritides; it is less expensive than MRI and less time-consuming than both MRI and US[13,14,15,20,21,22,23]. However, to date few data are available to support the wide use of FOI for routine diagnosis of early RA.

Our study aims to assess sensitivity and specificity of FOI in patients with early RA, using MRI and US as references, to evaluate its diagnostic potential in the clinical routine setting.

MATERIALS AND METHODS

Study design. Prior to the study, approval of the local ethics committee was obtained. Patients with early RA according to the American College of Rheumatology/European League Against Rheumatism classification criteria[24] were recruited between May 2013 and September 2013 and underwent MRI, US, and FOI within 2 weeks. Exclusion criteria were symptom duration of more than 12 months, therapeutic application of gluco-corticoids, disease-modifying antirheumatic drugs (DMARD), or biologics; as well as skin lesions (small wounds, scratches, etc.). All patients gave written informed consent.

Near-infrared FOI. FOI was performed applying the Xiralite imaging system (Xiralite X4, Mivenion GmbH), following a standardized procedure as described[14,15]. Briefly, the patient's hands are placed on a preformed hand rest. After intravenous (IV) bolus administration of 0.1 mg/kg body weight ICG (ICG-Pulsion, PULSION Medical Systems SE), a dynamic image dataset of 360 pictures was acquired by an LED camera at a wavelength of 740 nm and a frequency of 1/s over a period of 6 min. FOI data were automatically reconstructed by the integrated software XiraView 3.6 (Figure 1). All FOI examinations were analyzed by an experienced rheumatologist (SGW). Wrist, metacarpophalangeal joints (MCP) 2–5, and proximal interphalangeal joints (PIP) 2–5 were semiquantitatively scored on a 4-point ordinate scale (0: no enhancement, 1: ≤ 25%, 2: 25–50%, 3: > 50%

enhancement of the affected joint area). Scores distinguished between 3 phases of enhancement: phase 1 (P1) includes all images until clearly increased signal intensities are visible in the fingertips; phase 2 (P2) comprises all images during increased signal intensities in the fingertips; phase 3 (P3) covers all images from the end of P2 until the end of the image stack[15]. Additionally, PrimaVista mode (PVM), an automatically generated composite image of all FOI phases, was scored analogically.

MRI examinations. All MRI examinations were performed on a 0.31T MR scanner (O-scan, Esaote Biomedica). Patients were positioned on a chair in front of the MRI device with the clinically dominant hand placed in the permanent magnet using a dedicated dual phased-array hand coil. The imaging protocol was chosen in accordance with the guidelines of the RA study group of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative[25,26,27]. The following sequences were acquired: coronal gradient-echo (GRE), short-tau inversion recovery, coronal T1-weighted spin-echo (SE), and coronal T1-weighted 3-D GRE sequences before and after IV bolus administration of 0.2 mmol/kg body weight Dotarem (Guerbet), a gadolinium-based contrast agent[10]. The examination procedure had an average duration of 30 min. The T1-weighted 3-D GRE datasets were used for the reconstruction of axial views. MR images were evaluated by a radiologist with 5 years of expertise in musculoskeletal imaging (MK). Synovitis of the wrist (distinguishing between distal radioulnar, radiocarpal, intercarpal, and carpometacarpal joints) and MCP joints 2–5 was scored semiquantitatively on a 4-point ordinate scale (0–3) according to the OMERACT–Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) criteria[25,26]. PIP joints 2–5, which are not part of the RAMRIS, were scored in similar fashion as described[7]. For further analysis and comparability to FOI, all compartments of the wrist were summarized and transformed into a sum score.

US examinations. These examinations of the patients' clinically dominant hand were performed (Mylab 70 XVG) both in GSUS and PDUS. Wrist (radiocarpal, ulnocarpal, and midcarpal compartment), MCP joints 2–5, and PIP joints 2–5 were examined using both dorsal and palmar views. Synovitis of each joint was semiquantitatively evaluated with regard to synovial hyper-trophy and effusion (GSUS) as well as to synovial hypervascularization
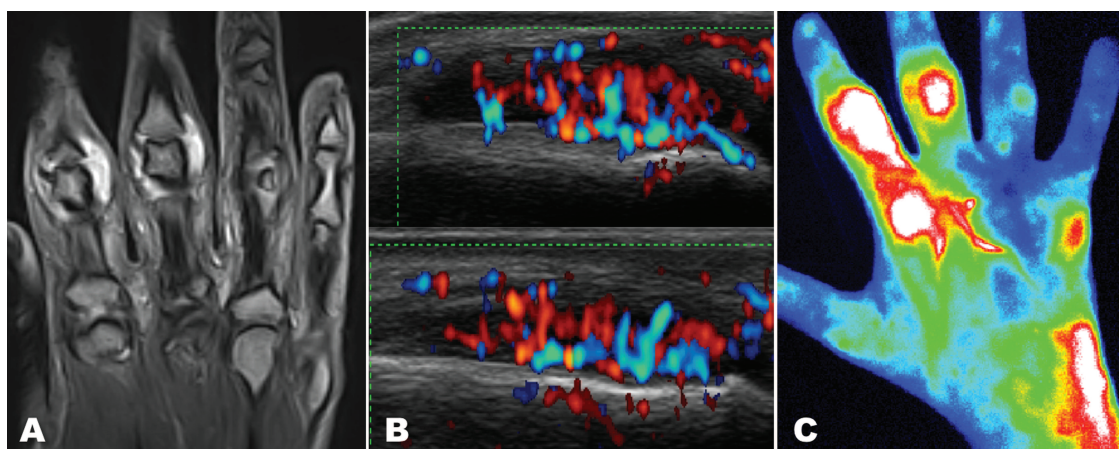
Figure 1. MRI, US, and fluorescence optical imaging in rheumatoid arthritis. A. T1-weighted 3-D gradient-echo sequence of the right hand after intravenous bolus application of a gadolinium-based contrast agent (Dotarem) in coronal orientation showing a thickened and strongly enhancing synovial membrane of the PIP joints II and III (corresponding to a synovitis score of 3 according to the OMERACT RAMRIS[26]). B. PDUS of PIP joints II (upper) and III (lower), showing strong synovial hypervascularization in both joints. C. FOI hand examination, phase 1 (prior to increased signal intensities in the fingertips): Corresponding to the MRI and PDUS examinations, the right hand shows a strong indocyanine green enhancement in PIP joints II and III, but also in the MCP II and V as well as at the ulnar aspect of the wrist (corresponding pictures not shown for MRI and US examinations). MRI: magnetic resonance imaging; US: ultrasonography; OMERACT RAMRIS: Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring; FOI: near-infrared fluorescence optical imaging; MCP: metacarpophalangeal joints; PDUS: power Doppler ultrasonography; PIP: proximal interphalangeal.

(PDUS) and scored on a 4-point (0–3) scale, as described[14,28]. Average duration of the examination was 20 min. All examinations were performed by a rheumatologist well-experienced in musculoskeletal ultrasonography (SO).

Statistical analysis. Sensitivity and specificity of the 3 FOI phases and PVM were analyzed in comparison to MRI as well as to US (GSUS and PDUS) because both are established diagnostic methods for the detection and evaluation of disease activity in RA within the clinical routine setting. Joints were regarded as positive when graded 1 or higher when applying the different imaging techniques. Agreement of FOI with MRI and US was assessed by calculation of ICC. ICC were interpreted as follows: ≤ 0.2: poor; 0.3–0.4: fair; 0.5–0.6: moderate; 0.7–0.8: strong; and > 0.8: excellent agreement[29,30]. Statistical analysis was performed by the statistical department of the Berlin Cancer Center (Tumorzentrum Berlin).

RESULTS

Descriptive statistics. Thirty-one patients (22 female; mean age 50.9 ± 13.3 yrs) with a mean disease duration of 5.6 ± 3.2 months (ranging from 1–11 mos) were enrolled. Demographic and clinical data of the study population are presented in Table 1. All patients underwent the FOI, MRI, and US examinations within 2 weeks (mean 3.3 ± 3.8 days; most patients received all examinations at the same day). Altogether, 279 joints (31 wrists, 124 MCP, and 124 PIP joints) were evaluated on MRI, US, and FOI. During this prospective study, no adverse events occurred and no missing data were imputed.

Comparison of FOI with MRI, GSUS, and PDUS. Sensitivity and specificity of each FOI phase (P1–3), PVM, and the overall FOI examination were calculated in comparison to MRI, GSUS, and PDUS. Additionally, ICC were calculated to evaluate the agreement of FOI with these reference methods.

FOI compared to MRI. Overall sensitivity/specificity of FOI compared to MRI was 0.81/0.00 (wrist), 0.49/0.84 (MCP), and 0.86/0.38 (PIP), respectively (Table 2). The intermediate phase (P2) turned out to be highly sensitive, especially with regard to the wrist (0.77) and PIP joints (0.85), while speci-

ficity was weak (0.00 and 0.41, respectively). A markedly lower sensitivity was found for MCP joints (0.43) although corresponding specificity was higher (0.84). On the other hand, sensitivity was 0.69 and 0.54 for wrist and PIP joints, respectively, for P3, with a corresponding specificity of 0.00 and 0.82, respectively. P1 sensitivity was moderate in all joints (0.32–0.54), but specificity was high (0.96–1.00). PVM showed a sensitivity/specificity of 0.65/0.60 (wrist), 0.24/0.93 (MCP), and 0.58/0.74 (PIP).

The strongest agreement was found for PIP joints with an overall ICC of 0.50, with best correlations found for P2 (0.49) and PVM (0.51). Results regarding MCP joints were 0.48 (overall) and 0.45 (P2), followed by P1 with 0.38, while P3 and PVM were markedly lower compared to PIP joints (Table 3).

FOI compared to GSUS. Overall sensitivity/specificity of FOI compared to GSUS was 0.84/0.00 (wrist), 0.52/0.77 (MCP), and 0.82/0.23 (PIP), respectively; best sensitivities were found for P2 with 0.80 (wrist) and 0.82 (PIP), while specificity was low (0.00 and 0.27, respectively). Concerning MCP joints, P2 had a lower sensitivity (0.45), combined with a markedly higher specificity of 0.77 (Table 2). For P1, sensitivity was moderate (0.33–0.52), while specificity was high for all joints (0.75–0.88). PVM sensitivity/specificity was 0.64/0.50 (wrist), 0.27/0.91 (MCP), and 0.61/0.60 (PIP).

Overall agreement of FOI with GSUS was 0.34 and 0.33 for PIP and MCP joints, respectively (Table 3).

FOI compared to PDUS. Overall sensitivity/specificity of

Table 1. Clinical and laboratory data of the study population (n = 31).

Characteristic	Mean (SD); range
Age, yrs	50.94 (± 13.26); 26–75
Disease duration, mos	5.6 (± 3.24); 1–11
CRP, mg/dl	2.28 (± 3.26); 0.13–11.6
ESR, mm/h	30.14 (± 24.16); 4–80
RF, U/ml	49.57 (± 77.32); 1.3–259.8
ACPA, U/ml	153.15 (± 301.17); 5.9–1135.1
DAS28, 0–10	4.8 (± 1.31); 1.6–7.69
Tender joint count	7.78 (± 7.56); 1–25
Swollen joint count	4.95 (± 4.51); 1–19
VAS patient, 0–100	61.91 (± 21.88); 20–95
VAS physician, 0–100	51.82 (± 21.83); 20–90
Morning stiffness, min	43.5 (± 75.99); 0–240

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor (IgM); ACPA: anticitrullinated peptide antibodies; DAS28: 28-joint Disease Activity Score; VAS: visual analog scale.

Table 2. Sensitivity and specificity of fluorescence optical imaging (FOI) compared to magnetic resonance imaging (MRI), greyscale ultrasonography (GSUS), and power Doppler ultrasonography (PDUS) as reference methods.

Phase	MRI		GSUS		PDUS	
	Se	Sp	Se	Sp	Se	Sp
Wrist						
All	0.81	0.00	0.84	0.00	0.88	0.15
P1	0.54	1.00	0.52	0.75	0.63	0.69
P2	0.77	0.00	0.80	0.00	0.81	0.15
P3	0.69	0.00	0.68	0.00	0.63	0.15
PVM	0.65	0.60	0.64	0.50	0.63	0.38
MCP 2–5						
All	0.49	0.84	0.52	0.77	0.81	0.76
P1	0.37	0.96	0.36	0.88	0.67	0.89
P2	0.43	0.84	0.45	0.77	0.70	0.78
P3	0.15	1.00	0.13	0.95	0.23	0.95
PVM	0.24	0.93	0.27	0.91	0.41	0.89
PIP 2–5						
All	0.86	0.38	0.82	0.23	1.00	0.27
P1	0.32	0.97	0.33	0.85	0.69	0.88
P2	0.85	0.41	0.82	0.27	1.00	0.29
P3	0.54	0.82	0.42	0.52	0.69	0.63
PVM	0.58	0.74	0.61	0.60	0.88	0.59

All: overall value for FOI comprising all phases; P1: early phase; P2: intermediate phase; P3: late phase of enhancement; PVM: PrimaVista mode; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; Se: sensitivity; Sp: specificity.

Table 3. Agreement of fluorescence optical imaging (FOI) with magnetic resonance imaging (MRI) and ultrasonography shown by intraclass correlation coefficients (ICC).

ICC	Phase	MRI	GSUS	PDUS
Wrist				
	All	–0.063	–0.024	0.361
	P1	0.329	0.245	0.532
	P2	–0.097	–0.075	0.318
	P3	–0.340	–0.385	–0.159
	PVM	0.081	–0.012	0.131
MCP 2–5				
	All	0.475	0.333	0.568
	P1	0.375	0.294	0.660
	P2	0.445	0.287	0.538
	P3	0.217	0.120	0.437
	PVM	0.264	0.173	0.370
PIP 2–5				
	All	0.500	0.343	0.534
	P1	0.443	0.335	0.661
	P2	0.485	0.306	0.513
	P3	0.447	0.202	0.425
	PVM	0.505	0.355	0.528

GSUS: greyscale mode in ultrasonography; PDUS: power Doppler mode in ultrasonography; All: overall value for FOI comprising all phases; P1: early phase; P2: intermediate phase; P3: late phase of enhancement; PVM: PrimaVista mode; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints.

FOI with PDUS as the reference method was 0.88/0.15 (wrist), 0.81/0.76 (MCP), and 1.00/0.27 (PIP). Best sensitivity was shown for P2 (0.70–1.00), with low corresponding specificity in PIP joints (0.29) and wrist (0.15); while for MCP joints, specificity of P2 was 0.78 (Table 2). P1 showed a lower sensitivity (0.63–0.69), whereas corresponding specificities were good to excellent (0.69–0.89). PVM sensitivity/specificity was 0.63/0.38 (wrist), 0.41/0.89 (MCP), and 0.88/0.59 (PIP).

Overall ICC were 0.36 (wrist), 0.57 (MCP), and 0.53 (PIP), with best correlations shown for P1 with 0.53 (wrist), 0.66 (MCP), and 0.66 (PIP), while P2 resulted in lower ICC of 0.32, 0.54, and 0.51, respectively (Table 3).

DISCUSSION

Near-infrared FOI is a new imaging technology for diagnostic purposes and followup in rheumatic joint diseases. FOI with IV administration of nonspecific fluorophores, such as ICG, depicts disturbances of microvascularization of the examined area. Under inflammatory conditions, vascularization is usually increased compared to healthy tissues, because of highly dysregulated neovascularization[31,32]. MRI and US are capable of depicting inflammatory thickening and hypervascularization of the synovial membrane in RA, which is suspected of leading to bone and joint destruction in the course of disease[17,32,33,34,35,36,37]. In studies with animal models, FOI has shown to be an appropriate imaging method for the detection of arthritis[18,19]; however, only a few in vivo studies have been conducted in humans to evaluate FOI as a diagnostic approach in arthritides[11,13,14,15,17,22,23]. In all these studies, as in this present study, FOI was well tolerated and no adverse events were reported.

To our knowledge, our study is the first to analyze FOI with regard to different joint groups (PIP, MCP, and wrist joints) in comparison to both MRI and US in a cohort of early untreated patients with RA. Because both MRI and US are established imaging methods in early RA, in our study, sensitivity and specificity of FOI under definition of 3 different enhancement phases (P1–P3) were evaluated with MRI as well as GSUS and PDUS as reference examinations.

Highest sensitivity has been shown for P2, especially with regard to the wrist (0.77–0.81) and PIP joints (0.82–1.00), but with unsatisfactory corresponding specificity (0.00–0.41). Sensitivity of P1 and P3 were markedly lower; although their specificity was much higher compared to P2 (Table 2). These results correspond to the findings of 2 other studies that could show that P2 is the most sensitive phase and that P1 and P3 are attributed with higher specificities but lower sensitivities[14,15]. Nevertheless, MCP joints constitute an exception in our study: P2 sensitivity (0.43–0.70) is lower than for wrist and PIP joints, but with remarkably higher corresponding specificity (0.77–0.84). Analogous findings have been found in prior studies. Meier, et al compared FOI joint-wise; however, they summarized the carpal joints and MCP joints as a subgroup and compared it to a subgroup consisting of PIP plus DIP joints[13]. Here, sensitivities and specificities were 0.35 and 0.93 for carpal/MCP joints and 0.60 and 0.85 for PIP/DIP joints, respectively. According to analyses by Schafer, et al, FOI is more sensitive with regard to the carpal and PIP joints compared to MCP joints[23]; this is confirmed by the results of our study.

The automatically generated composite image (PVM) has shown variable results. PVM has formerly been evaluated in 2 studies showing strong agreement of PVM with MRI as well as clinical examination and moderate to good specificity values; however, sensitivity was moderate in both studies[14,15].

Highest sensitivity values and good agreement rates were found when using PDUS as a reference method. These findings are concordant with the results of 1 study[14] and reflect the fact that PDUS, like FOI (especially P1), primarily evaluates joint hypervascularization regardless of morphological aspects, which are also represented by ICC. GSUS, however, depicts morphological aspects only. As a consequence, correlation to FOI is weak. In contrast, MRI is able to show morphology, hypervascularization, and increased permeability of arterial vessel walls, leading to extravasation of the contrast agent into inflamed areas, while ICG half-life is too short (owing to extensive plasma protein binding and quick metabolization in the liver) to extravasate in sufficient amounts. Higher specificities of P3 (phase after increased signal intensities in the fingertips) indicate the depiction of a certain extravasation by FOI due to increased capillary

permeability, which has also been discussed by Werner, *et al*, who found best specificities and high agreement rates for P1 and P3[15]. This investigation is in part supported by the study of Fischer, *et al*, who reported about arthritic joints that partly show early enhancement and others showing late enhancement[11]. Again, a study by Meier, *et al*[22] highlighted the importance of early FOI uptake. Indeed, early enhancement of contrast agents is currently widely discussed as an important marker for synovial vascularity in the context of MRI studies[38,39,40,41]. On the other hand, Schafer, *et al* found best results for intermediate (P2) and late enhancement (P3), applying dynamic raw data analysis, although their definition of phases substantially differs from this present study, because phases are defined by time only (P1: 0–120 s; P2: 120–240 s, P3: 240–360 s)[23].

Our study revealed high sensitivity scores of P2 (phase during increased signal intensities in the fingertips); however, these high scores combined with poor specificity and low correlation with MRI and US. This raises the question of whether the discriminatory power of this semiquantitative analysis is high enough to differentiate between physiological enhancement (like in the fingertips) and beginning hypervascularization. The occurrence of false-positive findings, especially in P2, has been discussed: Werner, *et al* reported normal FOI results in healthy control subjects of 95% to 98%[14,15]. Thus, the authors conclude that the disagreement of FOI with MRI and US does not result from false-positive findings, but rather from "subclinical inflammation" not yet detectable by MRI and US[14,15]. In a study by Fischer, *et al*, however, FOI was positive in 8 out of 70 joints in healthy volunteers (11.4%)[11].

The dynamic analysis of FOI enhancement has shown to be advantageous with regard to a more standardized and objective image analysis[11,17,22,23]. Different approaches have been described so far: 3 studies performed a quantitative analysis of joint enhancement under consideration of the enhancement of the fingertips[11,17,23] and another study compared the rate of early enhancement and areas under the curve for both FOI and MRI, with good to excellent agreement rates also in comparison to the clinical examination[22]. These studies appear promising compared to the results of some studies that applied a semiquantitative analysis of FOI[13].

Despite careful planning, this study has some limitations. The geometric arrangement of the camera and light-emitting diodes of the Xiralite system limit the depiction of inflammation at the palmar aspect of the hands. Fluorescence signals may be overlaid by fibrous or muscular structures and fatty tissue, for example with regard to MCP and wrist joints, resulting in a lower detection rate compared to other imaging methods. This is especially true if using cross-sectional imaging methods such as MRI and US, which allow for a more detailed anatomic resolution. Further, FOI unselectively depicts hypervascularized or inflamed areas, so that local hypervascularity in skin lesions, such as small wounds or scratches, may overlay joint structures or even mimic synovitis and lead to false-positive findings because of its nature as a projection imaging technique. Therefore, as mentioned in the methods section, having these conditions was an exclusion criterion for our study. Other known confounders are tendinitis and tenosynovitis of extensor and flexor tendons. In our study, tenosynovitis was scored additionally on MR images as well as US; however, no significant differences were found under inclusion and exclusion of tenosynovitis into the statistical analysis. The method is further limited by ICG because of its high protein binding rate and quick metabolization in the liver[13,17]. For better comparability with MRI, dyes with a lower binding rate and a longer half-life would be preferable, especially for better interpretability of the late phase.

Our study has shown variable results owing to 3 phases of FOI enhancement and different analytic aspects. As discussed, comparability to other studies is limited because different analytic approaches have been applied (quantitative vs semiquantitative assessment; variable arrangement of FOI phases; correlation of articular enhancement with enhancement in the fingertips, etc.), a practice that once more illustrates the lack in consistent standards for image analysis and grading of FOI. Further studies should apply clear patient cohorts and should comprise comparative dynamic analyses of MRI and FOI, if possible with histopathological correlation. Another interesting approach would be the analysis of sensitivity and specificity of FOI in combination with clinical and laboratory variables in comparison to MRI as gold standard, which might represent the diagnostic setting in the clinical routine. In addition, longitudinal studies, as performed by Meier, *et al*[22], would allow for the evaluation of FOI with regard to clinical monitoring of patients with arthritis. However, most importantly, larger groups of healthy volunteers need to be examined to clarify the value of FOI for a reliable detection of arthritic joints.

Near-infrared FOI is a fast, nonionizing imaging modality with some potential for application in the diagnostic setting of rheumatic conditions, although this study showed an unreliable sensitivity and specificity of FOI compared to established imaging methods. Nevertheless, our results suggest that the phase-wise approach for a semiquantitative analysis of FOI is necessary and that phase 1 appears to be the most promising for the detection of arthritis although these results partly contradict prior studies. More studies are warranted to elucidate the value of FOI for reliable detection of inflammatory joint disease and for followup assessment of disease activity in patients with rheumatic disease, both in the clinical routine setting and in the context of clinical trials.

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