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Original article

A novel fluorescence optical imaging scoring system for hand synovitis in rheumatoid arthritis—validity and agreement with ultrasound

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Abstract

Objectives. To develop and validate a new semiquantitative fluorescence optical imaging (FOI) scoring system—the FOI Enhancement-Generated RA Score (FOIE-GRAS) for synovitis assessment in the hand.

Methods. The development of FOIE-GRAS was based on consensus of four experts in musculoskeletal imaging. Forty-six RA patients, eligible for treatment intensification and with ≥1 clinically swollen joints in the hands, and 11 healthy controls were included. FOI, ultrasound and clinical assessment of both hands were obtained at baseline and for RA patients after 3 and 6 months' follow-up. Twenty RA patients had an FOI rescan after 4 h. Synovitis was scored using FOIE-GRAS and the OMERACT ultrasound synovitis scoring system. All FOI images were scored by two readers. Inter-scan, inter- and intra-reader reliability were determined. Furthermore, FOIE-GRAS agreement with ultrasound and responsiveness was assessed.

Results. FOIE-GRAS synovitis was defined as early enhancement, and scores were based on the degree of coverage of the specific joint region after 3 s (0–3). Inter-scan, intra- and inter-reader intraclass correlations coefficients (ICC) were good to excellent for all baseline scores (0.76–0.98) and moderate to good for change (0.65–76).

The FOIE-GRAS had moderate agreement with ultrasound (ICC 0.30–0.54) for total score, a good standardized response mean (>0.80), and moderate correlation with clinical joint assessment and DAS28-CRP. The median (interquartile range) reading time per FOI examination was 133 (109, 161) s. Scores were significantly lower in controls [1 (0, 4)] than RA patients [11 (6, 19)].

Conclusion. The FOIE-GRAS offers a feasible and reliable assessment of synovitis in RA, with a moderate correlation with ultrasound and DAS28-CRP, and good responsiveness.

Key words: fluorescence optical imaging, scoring system, synovitis, rheumatoid arthritis, validity, FOIE-GRAS, ultrasound, imaging, inflammation, outcome measures

CLINICAL SCIENCE

Rheumatology key messages

- FOIE-GRAS scoring system is reliable, responsive and feasible for synovitis assessment in RA.
- FOIE-GRAS can serve as an additional or alternative to already existing outcome measures in RA.
- FOI may also allow assessment of inflammation in other diseases, such as psoriasis/psoriatic arthritis and systemic sclerosis.

Introduction

Synovitis in the hands is a hallmark of RA. Early diagnosis and close monitoring play an essential role in the disease outcome [1]. Traditionally, synovitis is assessed by clinical evaluation and the overall disease activity by composite scores, most frequently the Disease Activity Score for 28 joints (DAS28) [2]. Ultrasound and MRI are established and validated imaging modalities for assessment of synovitis [3, 4]. These imaging modalities offer a

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more sensitive joint assessment, as described in the EULAR recommendations, and may be used as supplements to clinical examination for diagnosing and monitoring disease activity [5]. However, both ultrasound and MRI have disadvantages such as duration of the examination, cost and occasional contraindications.

Fluorescence optical imaging (FOI) is a novel imaging modality suggested for assessment of inflammation (i.e. synovitis) in the hands. FOI assessment is relatively inexpensive, fast (6 min), emits no ionizing radiation and can easily be carried out by trained medical staff [6–9]. The imaging technique is based on a near infrared light source (740 nm), a near infrared camera and an intravenous injection of the fluorophore agent indocyanine green (ICG). In infrared light, ICG causes enhancement of vascularized tissue. FOI can thereby demonstrate enhanced microcirculation in wrist and finger joints caused by inflammation [10]. Side effects are mild and uncommon [11].

FOI has previously been applied in RA studies. However, there is currently no consensus on how to score synovitis as detected by FOI. The most common FOI scoring method is the FOI activity score (FOIAS), based on colour intensity and degree of enhancement [10, 12–15]. Focusing only on the early enhancement phase, however, would in theory better reflect histological signs of synovitis, i.e. the disease activity, as known from MRI studies [16, 17]. Therefore, we decided to develop and test a scoring system focusing on this.

The aim of this study was to develop and validate a new semi-quantitative FOI scoring system for assessing synovitis in the hands of RA patients, the FOI Enhancement-Generated RA Score (FOIE-GRAS), by evaluating inter-scan, inter- and intra-reader agreement, smallest detectable change (SDC), responsiveness and feasibility. Further, we tested the agreement of FOI-assessed synovitis with ultrasound, clinical and patient reported outcomes of disease activity. Finally, we compared FOIE-GRAS findings in RA patients and healthy controls.

Methods

Development of a new scoring system for synovitis

The first step was a literature search, to identify original articles using FOI for assessing inflammatory joint disease. In the second step, two experts in scoring ultrasound and MRI inflammation of the hands examined five RA patients with FOI, ultrasound and MRI of hands on the same day and thoroughly assessed and discussed the findings. The purpose was to identify elementary components of the FOI image sets indicating synovitis. Based on these steps, a FOI synovitis scoring system was developed. The preliminary scoring system was discussed between the developers and two additional experts in musculoskeletal ultrasound and MRI assessment, and a new scoring system for synovitis was agreed on—the FOIE-GRAS.

Validation of FOIE-GRAS

Patients and study design

RA patients >18 years were eligible for inclusion if they had at least one clinically swollen joint in the hand region and were planned for initiation or escalation of conventional synthetic (cs) or biologic (b) DMARD treatment prior to inclusion.

All RA participants were recruited from the rheumatology outpatient clinic at Rigshospitalet, Copenhagen, Denmark, from June 2014 to August 2016.

FOI scan, ultrasound and clinical examination of both hands were performed at baseline and after 3 and 6 months.

Healthy controls without prior history of arthritis or tendon diseases and without pain in their fingers or wrists were included as controls. They underwent FOI scan, ultrasound and clinical examination of both hands at baseline. All healthy controls were screened for items that may cause potential pitfalls as eczema, wounds, dry skin or covering of hair.

Clinical assessment, patient reported outcomes and CRP

Four trained and calibrated physicians blinded to FOI and ultrasound results performed a 28-joint assessment of swollen and tender joints [bilateral wrist, first to fifth metacarpophalangeal (MCP), first interphalangeal (IP) and second to fourth proximal interphalangeal (PIP), elbows, shoulders and knees]. DAS28 using CRP, patient global on a visual analogue scale (VAS Global) and HAQ were registered at baseline, 3 and 6 months.

FOI assessment

A Xiralite X4 (nanoPET Pharma GmbH, Berlin, Germany) was used for FOI of both hands at baseline, and 3 and 6 months' follow-up.

All participants received a bolus of i.v. ICG-Pulsion (1 mg/kg body weight) 10 s after starting the examination, allowing for 1 image/s over 6 min. Twenty RA participants had an FOI rescan after 4 h to test the inter-scan reproducibility (test–retest reliability). Room temperature was kept unchanged during the two scans and the investigators made sure that no hands were sweaty or cold during the FOI scan. The wrist, MCP 1–5, IP 1 and PIP 2–5 joints were selected for assessment. At the peak enhancement, the colour index was adjusted (by selecting the computer option 'refresh') in order to increase the discrepancy between colours. Hereafter, each joint was assessed sequentially from start of the injection of ICG-Pulsion to peak enhancement.

The image-sets were anonymized and randomized, and subsequently scored for synovitis by two independent, trained and calibrated readers, blinded to participant data but not chronology. Twenty-three random image sets were re-anonymized and re-read for assessment of intra-reader agreement. Further, the 20 inter-scan image sets were re-anonymized to test the test–re-test reproducibility.

All FOI examinations were scored according to the developed FOIE-GRAS and, to test the feasibility, the time taken to assess 10 randomly selected FOI readings of both hands at all three visits was measured.

Ultrasound assessment

Two experts in musculoskeletal ultrasound assessed the hands and fingers at baseline, and 3 and 6 months after treatment initiation. Prior to the study, a reader exercise was conducted to ensure high intra- and inter-reader agreement, showing a weighted kappa value of 0.88 and 0.95 for intra- and inter-reader agreement, respectively.

A General Electric Logiq E9 (Milwaukee, WI, USA) ultrasound unit with a high frequency linear ML 6–15 probe was used. Colour Doppler (CD) was used as it is the most sensitive Doppler modality on this machine [18]. The Doppler settings were made according to published recommendations [19]. The same Doppler settings were used for all examinations. Synovitis was assessed scored by grey scale (GS) and CD during the ultrasound examination using the semi-quantitative scoring systems proposed by the OMERACT US group [3]. Each patient was scored on joint level and with a total joint sum for GS and CD.

Ethical and legal considerations

This study was approved by the Danish National Ethical Committee on Health Research and the Danish Medical Agency (H-6-2013-002) and Medical devices (2013103279). The study was monitored by the Danish Good Clinical Practice (GCP) unit. The study was registered at the EU Clinical Trials Register (EudraCT no.: 2013-004006-26). All participants signed written informed consent prior to any study procedures.

Statistics

Descriptive statistics and the Wilcoxon signed-rank test were used to assess changes over time. Inter-scan, intra- and inter-reader agreement on sum scores were assessed using single measure intraclass correlation coefficients (ICCs). ICC values of <0.5, ≥ 0.5–0.74, ≥ 0.75–0.89 and ≥ 0.9 are indicative of poor, moderate, good and excellent reliability, respectively [20]. Percentage of exact agreement (PEA) and percentage of close agreement (PCA—defined as the percentage of the patients where the scores did not differ by >1) were calculated. Further, Bland–Altman plots (mean–difference and limits of agreement) were used to compare two measurements of the same variable. The correlation between changes in FOI assessment and clinical joint assessment, DAS28-CRP, VAS Global, CRP and HAQ was determined using Spearman's rank correlation coefficient, which was interpreted on the basis of ≥ 0.1–0.29, ≥ 0.30–0.49 and ≥ 0.5 being indicative of small, moderate and strong correlation, respectively [21]. The SDC for intra- and inter-reader scores was also calculated. Responsiveness was assessed using standardized response mean (SRM), expressed as the mean change divided by the S.D. of the change. SRM was interpreted as <0.20, ≥ 0.20–0.49, ≥ 0.5–0.79 and ≥ 0.80 being indicative of trivial, small, moderate and good responsiveness, respectively [22].

Results

Development of the FOIE-GRAS

After reviewing the literature and comparing the presentation of synovitis seen by ultrasound and MRI with five FOI examinations, early enhancement at the joint sites was a suggested indicator of synovitis. This was based on the assumption that inflamed tissue would demonstrate a more rapid enhancement than the surrounding healthy tissues.

Synovitis was defined as a sharply marginated enhancement with clear delineation from surrounding tissues lasting ≥ 3 s, and at the correct anatomical location. The width of the enhancement fulfilling the defined synovitis criteria was compared with the width of the joint in the transverse plane at the third second of enhancement. If the first enhancing colour (i.e. blue) did not remain marginated at the joint during the 3 s, the next enhancing colour (i.e. green) was assessed using the same criteria of margination. Assessing the succeeding colours until peak enhancement was allowed, but scoring of the enhancement should always be performed in the first enhancing colour that fulfils the criteria of sharp margination. The enhancement was 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: $\geq 1/3$ but $<2/3$ of the joint is covered by enhancement; and grade 3: $\geq 2/3$ of the joint is covered by enhancement. The FOIE-GRAS, including rules for assessment and potential pitfalls, is presented in Table 1 and Figure 1. Ultrasound was selected for validation of FOIE-GRAS as ultrasound is very often applied in routine care for assessing synovitis.

Validation of FOIE-GRAS

Forty-six patients (38 females, eight males) with RA and 11 healthy controls (seven females, four males) were included. Two patients withdrew their informed consent after the baseline visit (due to time issues) and one patient had only baseline and 6 months' visits. Twenty-three patients initiated bDMARDs and 23 initiated or escalated csDMARDs. Demographics and baseline characteristics are presented in Table 2. The median (IQR) age for RA patients was 50.5 (42, 59) years and for healthy controls 36 (27, 54) years. The median DAS28-CRP for RA patients was 5.0 (4.4, 5.4) and imaging sum scores (range from 0–36) as follows: GS ultrasound: 14.5 (8, 22); CD ultrasound: 8 (3, 14); FOI reader 1: 11 (6, 19); and FOI reader 2: 11 (6, 19).

Table 1 The Fluorescence optical imaging Enhancement-Generated RA Score (FOIE-GRAS)

Definition of synovitis	Synovitis was defined as a sharply marginated enhancement witd clear delineation from surrounding tissues lasting ≥3 s, at a correct anatomical joint location
Synovitis scoring	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
Joints for assessment	The wrist, 1st–5th MCP joints, 1st IP joint and 2nd–5th PIP joints are assessed, DIP joints may also be included in the assessment[a]
Rules for 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 colour index is adjusted (by pressing 'refresh') in order to increase the discrepancy between colours • The width of the enhancement fulfilling the defined synovitis criteria is compared with the width of the joint in the transverse plane at the 3rd second of enhancement • If the first enhancing colour (i.e. blue) does not remain marginated at the joint during the 3 s, the next enhancing colour (i.e. green) is assessed using the same criteria of margination • Assessing the succeeding colours until peak enhancement is allowed, but scoring of the enhancement should always be performed in the first enhancing colour that fulfils the criteria of margination • Structures not fulfilling the criteria of correct anatomical location should not be scored
Pitfalls for scoring	• Enhancing veins may occur along with the enhancement of the pathology, but the enhancing veins are often seen as longer, enhancing structures, not limited to the joint area • Dry skin, eczema or small wounds located in the joint region can mimic synovitis; however, the pattern of enhancement is often more dotted in comparison with synovitis enhancement which is confluent

[a]DIP joints assessment was not part of this study. DIP: distal interphalangeal; MCP: metacarpophalangeal; PIP: proximal interphalangeal (including 1st interphalangeal joint).

Inter-scan and intra- and inter-reader agreement of the FOIE-GRAS

Both readers scored the 20 rescan image sets and found excellent inter-scan agreement, with ICCs above 0.92 for all joint regions, and the highest inter-scan agreement (ICC above 0.97) for the PIP joint region (Table 3). Further, the intra-reader ICCs were good to excellent for all baseline and change FOI scores for both readers. The inter-reader ICCs were good to excellent for all baseline FOI scores (0.76–0.91) and moderate to good for change, with a lower baseline and change agreement for the wrist (0.65–0.76) than for the other joint regions (Table 3). The SDCs were generally low; 56% and 60% of the patients had a change >inter-reader SDC from baseline to 3 and 6 months, respectively (Table 3).

Agreement between FOIE-GRAS and ultrasound

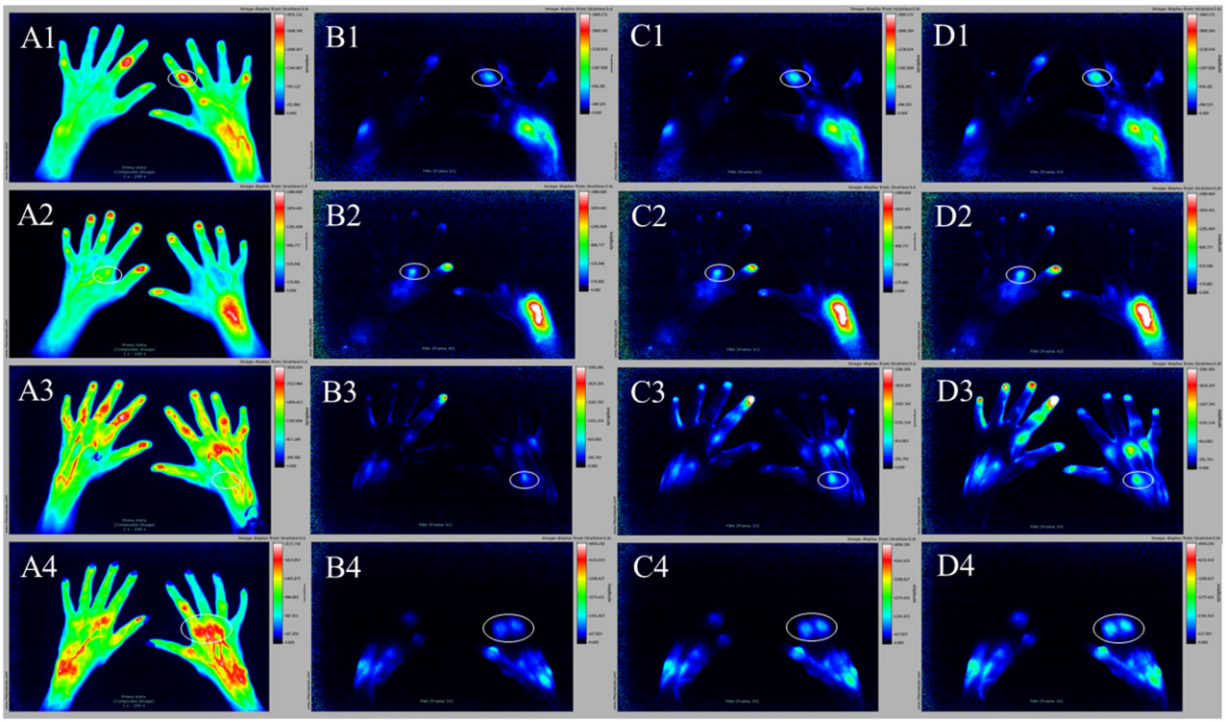
The agreement for the total sum score at baseline between FOIE-GRAS and GS ultrasound for FOI reader 1/reader 2 were as follows: PEA: 0%/7%; PCA: 11%/16.3%; and ICC: 0.30/0.31. Corresponding values for the agreement between FOIE-GRAS and CD ultrasound were as follows: PEA: 13%/7%; PCA : 22%/25,3%; and ICC: 0.41/0.31 (Supplementary Table S1, available at *Rheumatology* online). The Bland–Altman plots for FOIE-GRAS and GS/CD ultrasound sum scores illustrate that most scores were in same range (±10 in difference) with FOIE-GRAS scores slightly lower than GS and higher than CD (Supplementary Fig. S1, available at *Rheumatology* online). The PEA and PCA between FOIE-GRAS and GS/CD ultrasound for baseline scores at joint level showed the highest level of agreement for the wrist scores (Supplementary Table S1, available at *Rheumatology* online).

The agreement between FOIE-GRAS and GS ultrasound for change in total sum scores at 6 months were for reader 1 as follows: PEA: 8.7%; PCA: 17.4%; and ICC : 0.48. For reader 2 it was as follows PEA: 4.5%; PCA: 9.1%; and ICC: 0.31, (Table 4). For FOI *vs* CD ultrasound corresponding values for reader 1/reader 2 were as follows: PEA: 17.4%/4.5%; PCA: 28.1%/15.9%; and ICC: 0.54/0.38. The agreement with ultrasound at joint level was overall comparable for both readers (Table 4).

Sensitivity to change for the FOIE-GRAS and ultrasound and clinical parameters

The FOIE-GRAS total sum score for both readers decreased statistically significantly ($P < 0.01$) at 3 months, with a median score of −5 (−9, −1) for reader 1 and −5 (−13, −4) for reader 2. At 6 months, reader 1 had a median (IQR) score of −6.5 (−13, −3) and reader 2 of −9 (−13, −4). A moderate (0.6–0.8) to good (0.85–0.9) SRM was found at 3 and

Fig. 1 Fluorescence optical imaging (FOI) of the hands of four different patients with RA



A1-4, The Prima-Vista-Mode image is used as reference image. B1–4 is representing the 1st second in the scoring defined as a sharply margined enhancement with clear integrity from surrounding tissues and correct anatomical location lasting ?3 second. C1–4, representing the 2nd second and D1–4 is representing the 3th second, in this 3th second the thickness of the pathology is measured in the transverse plane of the hand. Synovitis was scored as follows: 0: no enhancement, 1: <1/3, 2: ≥1/3 but <2/3, 3: ≥2/3 of joint thickness. The white circles are representing the joint region of interest. D1, the right 2nd PIP joint was scored as 3. D2, the left 2nd MCP joint was scored as 2. D3, the right wrist joint was scored as 1. D4, the right 2nd and 3th MCP joints were both scored as 3. Abbreviations: MCP: metacarpophalangeal; PIP: proximal interphalangeal.

6 months, respectively for both readers (Table 5). For GS and CD ultrasound, a statistically significantly decrease from baseline ($P < 0.01$) was seen at both time points, with a moderate (0.7) SRM for CD at 3 months but good (0.82) at 6 months. For GS ultrasound, a good (3 months: 0.8; 6 months: 0.98) SRM was seen at both time points. Moderate correlations were seen for change at 6 months for FOI *vs* clinical joint evaluation ($P \leq 0.01$), DAS28-CRP and HAQ. For VAS-Global, a small correlation with FOI was found, but it was only significant for reader 1. No correlation was found for CRP (Supplementary Table S2, available at *Rheumatology* online)

Difference in FOIE-GRAS and ultrasound scores in RA patients *vs* healthy controls

The median (IQR) baseline FOIE-GRAS sum score for RA patients was 11 (6, 19) and for healthy controls 1 (0, 4). GS and CD ultrasound sum score was 14.5 (8, 22) and 8 (3, 14), respectively, for RA patients, and 1 (0, 1) and 0 (0, 0) for healthy controls. Baseline FOIE-GRAS, GS and CD joint scores for wrist, MCPs, IP and PIPs and total FOIE-GRAS and ultrasound sum scores for RA patients and healthy controls are shown in Supplementary Fig. S2, available at *Rheumatology* online.

Agreement between FOIE-GRAS and ultrasound scores in healthy controls

The FOIE-GRAS total sum score [1 (0, 4)] was higher than the total sum scores for GS ultrasound [1 (0, 1)] and CD ultrasound [0 (0, 0)] for healthy controls. The highest FOIE-GRAS score at joint level was 2 and was only observed in two healthy controls. For reader 1/ reader 2 89.2%/76.2% of the positive FOIE-GRAS scores was found in healthy female controls under 38 years. These healthy females had no positive ultrasound scores. The FOIE-GRAS and ultrasound scores for each healthy control are presented in Supplementary Table S3, available at *Rheumatology* online. Very dry skin, eczema or small wounds located over the joint region were identified as sources for joint region enhancement in four healthy controls.

TABLE 2 Demographics, clinical, ultrasound and laboratory characteristics of RA patients and healthy controls

	RA patients ($n = 46$)	Healthy controls ($n = 11$)
Age, median (IQR), years	50.5 (42, 59)	36 (33, 52)
Male, *n* (%)	8 (17.0)	4 (36.0)
Disease duration < 1 year, *n* (%)	30 (65.0)	—
IgM-RM positive, *n* (%)	31 (67.0)	—
Anti-CCP positive, *n* (%)	33 (72.0)	—
CRP, median (IQR), mg/l	13 (7, 29)	—
Swollen joint count (0–28), median (IQR)	6 (3, 8)	0 (0, 0)
Tender joint count (0–28), median (IQR)	6 (3, 9)	0 (0, 0)
Grey-scale US sum score (0–36), median (IQR)[a]	14.5 (8, 22)	1 (0, 1)
Colour Doppler US sum score (0–36), median (IQR)[a]	8 (3, 14)	0 (0, 0)
Grey-scale sum score (0-72)		
US extensor tenosynovitis, *n* (%)[b]	20 (43.5)	0
FOIE-GRAS sum score reader 1 (0–36)[a], median (IQR)	11 (6, 19)	1 (0, 4)
FOIE-GRAS sum score reader 2 (0–36)[a], median (IQR)	11 (6, 19)	1 (0, 4)
DAS28-CRP, median (IQR)	5.0 (4.4, 5.4)	—
HAQ (0–3), median (IQR)	1.125 (0.75, 1.375)	—
VAS Global (0–100), median (IQR), mm	68.5 (38, 83)	—
Initiation or escalation of csDMARDs, *n* (%)[c]	23 (50.0)	—
Initiation of bDMARDs, *n* (%)[c]	23 (50.0)	—

[a]US/FOIE-GRAS sum score for wrist, metacarpophalangeal, interphalangeal and proximal interphalangeal joints in both hands. [b]Number of participants with a grey-scale and colour Doppler US positive extensor tenosynovitis at the wrist level. [c]MTX: $n = 16$; combined SSZ and HCQ: $n = 5$; leflunomide: $n = 2$; TNF-α inhibitors: $n = 12$; abatacept: $n = 8$; and tozilizumab: $n = 3$. Anti-CCP: anti-cyclic citrullinated peptide; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS28: Disease Activity Score for 28 joints; FOIE-GRAS: fluorescence optical imaging Enhancement-Generated RA Score; IgM-RM: IgM rheumatoid factor; IQR: interquartile range; US: ultrasound; VAS Global: patient global visual analogue scale.

Feasibility of the FOIE-GRAS

The total time for preparation, intravenous admission and FOI examination was around 10–15 min per patient. The median (IQR) time required to score one FOI examination in this study was 133 (109, 161) s.

Discussion

This study presents the development and validation of a novel FOI assessment system (FOIE-GRAS) for scoring synovitis in hands. There was an excellent inter-scan agreement, a good to excellent intra- and inter-reader agreement and a high feasibility emphasized by the examination time of 133 s. The FOIE-GRAS had a moderate correlation with CD ultrasound, clinical assessment and DAS28-CRP for change and showed a good responsiveness during treatment. Further, we demonstrated a discriminatory ability of the scoring system with a clear difference in the FOIE-GRAS scores between RA patients and healthy controls.

The background for the development of a new FOI scoring system was interest in evaluating the early enhancement phase, to obtain the best theoretical agreement with histological signs of synovitis, and thereby a responsive scoring system that can be used for monitoring RA patients.

The FOIE-GRAS developed was designed to capture flow change in the synovium due to vasodilation or increased angiogenic activity, as seen in inflamed joints [23], and may serve as an alternative to Doppler ultrasound for assessment of synovitis. The FOIE-GRAS is also feasible, illustrated in this study by a total time for preparation, intravenous admission and FOI examination of 10–15 min and a median time of scoring the images of approximately 2 min. In contrast to ultrasound, the FOI examination can easily be delegated to a nurse or radiographer, which can substantially decrease the time consumption for the consultant.

This study is the first to report inter-scan reproducibility for FOI assessment. Our results clearly show that FOIE-GRAS is reproducible between scans; only small dissimilarities between the two scans (4 h) were observed, mainly explained by the variability seen for a semi-quantitative assessment, but also the fact that inflammatory flow can present small variations during the day, as seen in Doppler ultrasound [24]. The intra-reader

Table 3 Inter-scan, intra- and inter-reader ICC for FOIE-GRAS status scores and for change in scores and SDC at all joint levels and for total score

	ICC, SD					SDC, median (IQR)	
	Baseline	3 months' follow-up	6 months' follow-up	Change: baseline to 3 months	Change: baseline to 6 months	Change: baseline to 3 months	Change: baseline to 6 months
Inter-scan ICC for reader 1							
MCP joints	0.93 (0.83, 0.97)	—	—	—	—	—	—
PIP joints	0.98 (0.95, 0.99)	—	—	—	—	—	—
Wrist	0.92 (0.80, 0.97)	—	—	—	—	—	—
Total	0.94 (0.85, 0.98)	—	—	—	—	—	—
Inter-scan ICC for reader 2							
MCP joints	0.97 (0.93, 0.99)	—	—	—	—	—	—
PIP joints	0.97 (0.94, 0.99)	—	—	—	—	—	—
Wrist	0.93 (0.83, 0.97)	—	—	—	—	—	—
Total	0.98 (0.95, 0.99)	—	—	—	—	—	—
Intra-reader ICC and SDC for reader 1							
MCP joints	0.86 (0.70, 0.94)	0.72 (0.41, 0.88)	0.93 (0.84, 0.97)	0.76 (0.50, 0.89)	0.85 (0.67, 0.93)	4.8	3.6
PIP joints	0.95 (0.88, 0.98)	0.96 (0.90, 0.98)	0.86 (0.70, 0.94)	0.90 (0.77, 0.95)	0.90 (0.77, 0.96)	2.9	3.3
Wrist	0.82 (0.63, 0.92)	0.92 (0.82, 0.97)	0.62 (0.28, 0.82)	0.88 (0.55, 0.90)	0.91 (0.65, 0.93)	1.4	1.4
Total	0.90 (0.79, 0.96)	0.86 (0.66, 0.94)	0.83 (0.64, 0.93)	0.87 (0.72, 0.94)	0.92 (0.83, 0.97)	6.2	4.9
Intra-reader ICC and SDC for reader 2							
MCP joints	0.96 (0.91, 0.98)	0.90 (0.80, 0.95)	0.87 (0.74, 0.94)	0.87 (0.74, 0.94)	0.86 (0.72, 0.93)	3.3	3.4
PIP joints	0.95 (0.90, 0.98)	0.82 (0.66, 0.92)	0.80 (0.62, 0.90)	0.88 (0.75, 0.95)	0.85 (0.71, 0.93)	3.8	3.9
Wrist	0.92 (0.83, 0.96)	0.85 (0.70, 0.93)	0.77 (0.56, 0.89)	0.77 (0.56, 0.88)	0.85 (0.68, 0.93)	1.6	1.6
Total	0.95 (0.01, 0.98)	0.87 (0.73, 0.94)	0.87 (0.71, 0.94)	0.90 (0.79, 0.95)	0.85 (0.70, 0.93)	6.2	6.5
Inter-reader ICC and SDC							
MCP joints	0.86 (0.77, 0.92)	0.80 (0.65, 0.89)	0.76 (0.61, 0.86)	0.81 (0.67, 0.90)	0.66 (0.45, 0.80)	3.1	3.7
PIP joints	0.91 (0.84, 0.95)	0.82 (0.70, 0.90)	0.39 (0.12, 0.61)	0.79 (0.64, 0.88)	0.71 (0.53, 0.83)	2.6	3.6
Wrist	0.76 (0.60, 0.83)	0.72 (0.54, 0.84)	0.58 (0.35, 0.75)	0.67 (0.47, 0.81)	0.65 (0.45, 0.80)	1.1	1.3
Total	0.88 (0.79, 0.93)	0.84 (0.71, 0.91)	0.60 (0.37, 0.76)	0.80 (0.66, 0.89)	0.70 (0.51, 0.82)	4.8	6.2

Inter-scan, intra- and inter-reader agreement on sum scores were assessed using single measure ICCs. An ICC $\geq$0.50 was considered moderate, an ICC $\geq$0.75 was considered good and an ICC $\geq$0.90 was considered excellent. The SDC was calculated for the changes in scores and expresses the lowest amount of change that can be considered as true change and not measurement error. FOIE-GRAS: fluorescence optical imaging Enhancement-Generated RA Score; ICC: intra-class correlation coefficient; IQR: interquartile range; MCP: metacarpophalangeal; PIP: proximal interphalangeal (including first interphalangeal joint); SDC: smallest detectable change; total: total sum joint score for both hands.

TABLE 4 Agreement for change in scores between baseline and 6 month follow-up at joint, joint region and patient level

Change score		Right hand				Left hand				Both hands					
FOIE-GRAS		US GS		US CD		US GS		US DP		US GS			US CD		
		PEA	PCA	PEA	PCA	PEA	PCA	PEA	PCA	PEA	PCA	ICC, median (IQR)	PEA	PCA	ICC, SD
Agreement with ultrasound for reader 1															
MCP	1	37	76.1	65.2	80.4	47.8	76.1	69.6	87	53.3	81.6		67.4	83.7	
	2	30.4	80.4	45.7	84.8	39.1	63	47.8	76.1	39.1	78.3		46.8	80.5	
	3	26.1	80.4	37	82.6	50	78.3	65.2	82.6	45.7	81.5		51.1	82.6	
	4	50	78.3	63	80.4	54.3	87	80.4	89.1	65.2	83.7		71.7	84.8	
	5	41.3	69.6	56.5	80.4	47.8	82.6	52.2	87	46.8	78.3		54.4	83.7	
Sum	1–5	8.7	43.5	15.2	34.8	10.9	37	30.4	47.8	19.6	45.7	0.36 (0.07, 0.59)	17.4	22.8	0.30 (0.00, 0.55)
PIP	1	60.9	91.3	91.3	97.8	63	82.6	78.3	97.8	69.6	94.6		84.8	97.8	
	2	37	80.4	47.8	69.6	60.9	87	65.2	93.5	51.1	87		56.5	81.6	
	3	39.1	76.1	50	82.6	37	71.7	56.5	80.4	47.8	78.3		53.3	81.5	
	4	58.7	87	65.2	93.5	60.9	84.4	69.6	89.1	64.1	88.1		67.4	91.3	
	5	71.7	93.5	76.1	89.1	43.5	80.4	56.5	80.4	64.1	87		66.3	84.8	
Sum	1–5	23.9	39.1	39.1	60.9	17.4	37	39.1	58.7	31.5	48.9	0.38 (0.10, 0.60)	33.7	39.1	0.42 (0.18, 0.63)
Wrist		41.3	78.3	50	87	39.1	78.3	78.3	97.8	43.5	78.3	0.22 (–0.07, 0.48)	47.9	82.7	0.32 (0.04, 0,56)
Total		8.7	21.7	17.4	32.6	13	19.6	17.4	28.3	8.7	17.4	0.48 (0.22, 0.68)	17.4	28.3	0.54 (0.29, 0.72)
Agreement with ultrasound for reader 2															
MCP	1	32.6	69.8	65.1	76.7	48.8	72.1	62.8	83.7	29.5	63.6		52.3	72.7	
	2	23.3	72.1	44.2	79.1	44.2	67.4	44.2	79.1	20.5	47.7		31.8	54.5	
	3	34.9	69.8	53.5	72.1	44.2	72.1	58.1	83.7	27.3	54.5		34.1	61.4	
	4	41.9	76.7	58.1	81.4	53.5	93.0	79.1	90.7	29.5	61.4		43.2	68.2	
	5	34.9	76.7	58.1	86.0	41.9	79.1	46.5	76.7	13.6	52.3		27.3	63.6	
Sum	1–5	7.0	23.3	18.6	37.2	11.6	37.2	20.9	44.2	6.8	18.2	0.13 (−0.18, 0.41)	13.6	20.5	0.16 (−0.14, 0.43)
PIP	1	60.5	93.0	88.4	95.3	69.8	86.0	88.4	100.0	59.1	79.5		81.8	90.9	
	2	32.6	76.7	48.8	69.8	48.8	79.1	65.1	86.0	27.3	65.9		47.7	61.4	
	3	44.2	83.7	51.2	86.0	39.5	67.4	55.8	79.1	29.5	52.3		40.9	59.1	
	4	51.2	90.7	65.1	93.0	60.5	88.4	76.7	88.4	50.0	75.0		56.8	84.1	
	5	67.4	93.0	74.4	90.7	46.5	83.7	55.8	83.7	45.5	72.7		52.3	70.5	
Sum	1–5	23.3	41.9	37.2	55.8	9.3	34.9	46.5	60.5	15.9	31.8	0.41 (0.14, 0.62)	20.5	38.6	0.39 (0.10, 0.61)
Wrist		34.9	76.7	30.2	79.1	37.2	83.7	39.5	83.7	25.0	63.6	0.15 (−0.12, 0.41)	27.3	52.3	0.23 (−0.05, 0.48)
Total		7.0	14.0	4.7	7.0	7.0	18.6	7.0	34.9	4.5	9.1	0.31 (0.01, 055)	4.5	15.9	0.38 (0.10, 0.6)

PEA expresses the percentage of the patients receiving the same score by FOIE-GRAS and US and PCA is the percentage of the patients where the scores differ no more than one between FOI and US. Inter-reader agreement on sum scores were assessed using single measure ICCs. An ICC ≥0.50 was considered moderate, an ICC ≥0.75 was considered good and an ICC ≥0.90 was considered excellent. CD: Colour Doppler; FOIE-GRAS: fluorescence optical imaging Enhancement-Generated RA Score; GS: grey scale; ICC: intraclass correlation coefficient; MCP: metacarpophalangeal; PIP: proximal interphalangeal (including first interphalangeal); PEA: percentage of exact agreement; PCA: percentage of close agreement; total: total sum joint score for both hands; US: ultrasound.

ICCs were good to excellent for all scores, except for the wrist at 3 months for reader 1. Corresponding good to excellent ICCs were seen for baseline inter-reader scores. For the inter-reader change scores, ICCs were moderate to good, with the wrist joint performing slightly less well than other joint regions. This may be explained by the anatomical complexity of the wrist joint and by potential enhancement from inflammation in dorsal tendon sheaths, interfering with the assessment of the carpal joints. This inter-reader agreement was in line with previously demonstrated agreement for ultrasound [3].

A change greater than the SDCs may be considered a true change in inflammation. More than 60% of the patients showed a change ≥SDC at 6 months, documenting that the FOIE-GRAS allows reliable detection of change over time.

The inter-reader agreement in this study was slightly better than in the previously reported study by Maugesten *et al.* [25], which may be explained by better reader training and calibration. In the same study, FOIAS phase 1 had a lower total joint sum score, but with a slightly higher inter-reader agreement compared with FOI-GRAS.

Ultrasound is a commonly used imaging method for synovitis assessment in routine care, and in this study we found a poor to moderate (0.30–0.54) ICC for total sum scores between FOIE-GRAS and ultrasound. The best ICC with ultrasound was found for CD change at 6 months, which may be explained by the fact that both imaging modalities

Table 5 Baseline and change in score for FOIE-GRAS, ultrasound grey scale and colour Doppler, swollen and tender joint count, DAS28-CRP, VAS Global, CRP and HAQ and their standardized response means, during 3 and 6 months of follow-up, for all patients

All sites imaging modality ($n = 46$)	Baseline	Δ 0–3 month	*P*	SRM	Δ 0–6 month	*P*	SRM
FOIE-GRAS reader 1							
Median	11 (6, 19)	−5 (−9, −1)	<0.01	0.6	−6.5 (−13, −3)	<0.01	0.85
Mean (S.D.)	12 (7.8)	−5.1 (8.5)			−7 (8.3)		
FOIE-GRAS reader 2							
Median (IQR)	11 (6, 19)	−5 (−13, −4)	<0.01	0.8	−9 (−13, −4)	<0.01	0.9
Mean (S.D.)	12.6 (8.0)	−6.9 (8.3)			−8.7 (8.3)		
Grey scale ultrasound							
Median (IQR)	9.2 (8, 22)	−5 (−11, −1)	<0.01	0.8	−9 (−15, −3.5)	<0.01	0.98
Mean (S.D.)	15.6 (14.5)	−7.2 (9.1)			−9.1 (9.3)		
Colour Doppler ultrasound							
Median (IQR)	8 (3, 14)	−4 (−10, 0)	<0.01	0.7	−5.5 (−11.0, −0.5)	<.0.01	0.82
Mean (S.D.)	9.5 (8.0)	−5.48.1			−6.6 (8.0)		
Swollen joints							
Median (IQR)	6 (3, 14)	−3 (−6, −1)	<0.01	1.0	−4.0 (−7, −4)	<.0.01	1
Mean (S.D.)	5.7 (3.3)	−3.9 (4.0)			−4.2 (4.1)		
Tender joints							
Median (IQR)	6 (3, 9)	−4 (−6, −4)	<0.01	0.8	−3.0 (−6, −3)	<.0.01	0.9
Mean (S.D.)	6.6 (4.3)	−3.3 (4.2)			−3.7 (4.0)		
DAS28-CRP							
Median (IQR)	5 (4.4, 5.4)	−1.5 (−2.6, −0.6)	<0.01	0.8	−2 (−2.85, −075)	<.0.01	1
Mean (S.D.)	4.7 (1.3)	−1.3 (1.7)			−1.7 (1.8)		
VAS Global							
Median (IQR)	68.5 (38, 83)	−1 (−11, 5)	<0.01	0.9	−30 (−52, −6.5)	<0.01	1
Mean (S.D.)	62.7 (24.0)	−4.1 (18.2)			−30 (31.2)		
CRP							
Median (IQR)	13 (07, 29)	−3 (−15, 0)	<0.01	0.5	−6.5 (−19, 0)	<0.01	0.5
Mean (S.D.)	22.6 (29)	−12.7 (26.3)			−15 (29.5)		
HAQ							
Median (IQR)	1.1 (0.8, 1.4)	−0.3 (−0.9, −0.1)	<0.01	0.3	−0.4 (−0.9, −0.1)	<0.01	0.2
Mean (S.D.)	1.6 (3.6)	−1 (3.8)			−0.8 (4)		

SRM interpretation: trivial <0.20; small 0.20–0.49; moderate 0.50–0.79; good ≥0.80. *P*-value shown for Wilcoxon–Pratt test for paired data (change between two time points). DAS28: Disease Activity Score for 28 joints, using CRP; FOIE-GRAS: fluorescence optical imaging Enhancement-Generated RA Score; IQR: interquartile range; *n*: number of patients; SRM: standardized response mean; VAS Global: patient global visual analogue scale.

assess hyperaemia in joints. The agreement between FOIE-GRAS and ultrasound was also illustrated in the Bland–Altman plots and by PEA and PCA. The Bland–Altman plots indicated that most total sum scores were in the same range, but with a few outliers. At joint level, PEA for change between FOIE-GRAS and CD ultrasound was above 48% and the PCA above 81.5%. Similar values were seen for status (baseline, 3 and 6 month) PEA and PCA agreement scores. Overall, the agreement with ultrasound was acceptable, considering different imaging techniques and scoring systems with different cut-off values for synovitis assessment, while previous studies using other FOI scoring systems showed variable or low agreement with ultrasound [13, 14, 26]. The FOIE-GRAS demonstrated a good responsiveness, which is in line with GS and CD ultrasound scores, but also other established outcome measures, e.g. clinical joint evaluation and DAS28-CRP. Furthermore, FOIE-GRAS demonstrated a moderate correlation with clinical joint evaluation, DAS28-CRP and HAQ for change. This result is in contrast to Glimm *et al.* [26], where limited sensitivity to change (only FOIAS phase 1) and no correlation between change and DAS28 among RA patients (<2 years disease duration) initiating DMARDs were found using FOIAS.

Our study clearly shows the discriminatory ability of the scoring system, as healthy controls had a markedly lower FOIE-GRAS score than RA patients. The FOIE-GRAS in healthy controls was compared with ultrasound and showed acceptable agreement. However, we found a slightly higher score in MCP and PIP joints for FOIE-GRAS than by ultrasound, mostly driven by one healthy control who accounted for around 50% of the positive scores. Only two healthy controls had a single joint FOIE-GRAS score above 1 and none had a score above 2. It is well known that ultrasound score increases with age in healthy controls [27], but no data existed for FOI. In our study we found that 87.2% of the positive FOIE-GRAS were powered by healthy female controls under 38 years, the opposite to the ultrasound scores. The ultrasound assessment was not blinded for participant type, contrary to the reading of the FOI examinations, which may have contributed to a lower ultrasound score in younger healthy controls.

FOI has some limitations. The use of a contrast agent can very rarely cause allergic reactions. Furthermore, disease activity on the palmar aspect of the hands is only partly assessed due to the limited penetration of infrared light. Development and implementation of different camera angles may provide a potential solution of this problem and may further facilitate future imaging of other joint regions. Notably, this study identifies important pitfalls such as that very dry skin, eczema or a small wound located over the joint region can mimic synovitis, which is important since FOI only offers information about blood flow in a specific region and not its anatomical location, in contrast to ultrasound, MRI or X-rays.

Even though FOIE-GRAS appears to be valid for detecting synovitis and for monitoring of RA patients, FOI may also potentially be useful or helpful in other inflammatory diseases such as psoriasis or psoriatic arthritis, and systemic sclerosis [28, 29], where diagnosing and monitoring may be more difficult with the currently available methods.

In conclusion, the FOIE-GRAS system for synovitis assessment has been proven to be reliable, responsive and feasible as an outcome measure in RA, with a moderate correlation with ultrasound and DAS28 for change over time. The FOIE-GRAS may have a future role in monitoring RA patients in clinical trials and practice.

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Data availability statement

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

Supplementary data

Supplementary data are available at *Rheumatology* online.

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