Comparison Photo Optical Imaging with Musculoskeletal Ultrasound and Clinical Examination in the Assessment of Inflammatory Activity in Proximal Interphalangeal Joints in Patients with Rheumatoid Arthritis and Osteoarthritis

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ABSTRACT. ***Objective.*** Lightscan is a novel, rapid, low-cost, easily operated and noninvasive imaging technology used to assess inflammatory activity in proximal interphalangeal (PIP) joints. The results are calculated automatically. To our knowledge, this is the first comparative study of photo optical imaging (POI), with clinical examination (CE), disease activity score at 28 joints (DAS28)-erythrocyte sedimentation rate (ESR), and musculoskeletal ultrasonography (US) in healthy subjects and patients with rheumatoid arthritis (RA) or osteoarthritis (OA).

Methods. There were 688 PIP joints of both hands examined in 87 subjects (38 RA, 21 OA, 28 healthy) by Lightscan and compared with CE for clinically swollen and tender joints, DAS28-ESR (only RA), and US.

Results. With US as reference, POI had a sensitivity of 74% and a specificity of 93%. In the receiver-operating curve (ROC) analysis, the Lightscan showed a higher sensitivity and specificity [area under the curve (AUC) 0.879] for the distinction of healthy subjects versus patients (OA, RA) than US in greyscale (GSUS; AUC 0.797) and power Doppler (PDUS; AUC 0.67). POI correlated significantly with GSUS (r 0.473, $p < 0.01$) and PDUS (r 0.486, $p < 0.01$). The agreement rates between POI and GSUS were up to 79%, between POI and PDUS up to 92%, and between POI and CE up to 66%. POI did not correlate with DAS28-ESR.

Conclusion. The Lightscan is a new technology offering sensitive imaging detection of inflammatory changes in subjects with RA and OA with PIP arthritis. POI was more sensitive than CE and correlated significantly to GSUS and PDUS, while presenting a higher sensitivity and specificity for the detection of healthy subjects versus patients (RA, OA) based on the ROC analysis. (J Rheumatol First Release August 1 2015; doi:10.3899/jrheum.150098)

Key Indexing Terms:
MUSCULOSKELETAL ULTRASOUND PHOTO OPTICAL IMAGING
LIGHTSCAN RHEUMATOID ARTHRITIS OSTEOARTHRITIS

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For early diagnosis, estimation of prognosis, and evaluation of therapeutic outcome, imaging plays a major role. For an adequate use of disease-modifying drugs[1,2], sensitive tools for the detection of inflammatory activity in the affected joints are necessary. Clinical examination (CE) is part of the clinical routine, but may miss subclinical inflammation in early disease, as well as in clinical remission under treatment[3,4,5]. Conventional radiography is still used as a standard of reference in detecting disease progression and is therefore used as an indicator of prognosis, but it does not show current inflammatory disease activity. Even though magnetic resonance imaging (MRI) is the gold standard for imaging synovitis and is the strongest independent predictor of radiographic progression in rheumatoid arthritis (RA)[6], in the clinical routine, usage may be limited by availability, costs, and workflow considerations.

Musculoskeletal ultrasonography (US) in greyscale mode (GSUS) and power Doppler mode (PDUS) is a valid and sensitive tool in the detection of synovitis and tenosynovitis, and in scoring the clinical activity in RA[7,8,9]. Compared with the MRI, US is more readily available and less expensive, and therefore it is often used for fast assessment of joint inflammation[10]. However, the limiting factors are the high dependence on the investigator[5,11,12], and time constraints. To overcome these time constraints, the examination procedure is usually limited to a reduced number of joints[13].

US and MRI are each more sensitive in comparison with conventional radiography in detection of soft tissue lesions. PDUS has an especially high sensitivity for the detection of inflammatory activity, such as synovitis and tenosynovitis[14,15,16,17].

In the past, photo optical techniques using light in the visible near-infrared spectral range have been used for diagnostic transillumination of thin tissue layers. Patients with RA and osteoarthritis (OA) have changes in the joint capsule and the synovial fluid, for example, a higher percentage of leukocytes or proteins[18]. This in turn influences the scattering of light and provides completely novel information. Prapavat, *et al* showed for the first time that light scatters differently in healthy tissue compared with pathological tissue in experimental models in 1997[19]. In 2002, Scheel, *et al* examined proximal interphalangeal (PIP) joints of patients with RA in a clinical study[20]. Minet, *et al* further developed this technique by creating a new mathematical algorithm and analysis and colored images for a better visualization of the inflammatory activity[21,22].

PIP joints are usually one of the first and most affected joints in RA and findings in these joints are considered markers of joint damage in patients with RA[23,24].

In the primarily degenerative disease OA, PIP joints are typically involved and also often associated with active joint inflammation[25]. Consequently, a valid tool to assess joint inflammation is of major importance[26].

The aim of our study was to compare the new photo optical imaging system POI ("Lightscan") with US and CE in assessing inflammatory activity in PIP joints in a cohort of patients with RA and OA. Further, we defined the most useful cutoff by also including healthy subjects to distinguish between healthy and pathological conditions and a POI score for each joint, as well as a POI mean sum score of the PIP joints on both sides (n = 8 in each patient) to show the total average activity.

MATERIALS AND METHODS

Patients. There were 87 subjects consecutively recruited from the Rheumatology Outpatient Clinic of the University Hospital Charité Berlin, Germany. Patients with the confirmed diagnosis of RA[27] or OA[28] who agreed to participate in our study were included. The total cohort included 38 patients with RA, 21 patients with OA, and 28 individuals serving as a healthy control group without any clinical and anamnestic evidence for (inflammatory) joint disease. The study was approved by the ethics committee of Georg-August-University in Goettingen, Germany. All of the study's participants were above the age of 18. For inclusion, all participants had to sign consent forms after receiving written and oral information. Clinical and imaging examinations (US and Lightscan) were done on the same day.

Clinical and laboratory assessment. Clinical joint examination and laboratory tests [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] were performed. CRP and ESR, as markers of systemic inflammation, are elevated in almost all patients with RA and are therefore part of the American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for the disease[27]. Further, antibodies were taken (rheumatoid factor and anticitrullinated protein antibodies). Clinical swollen and tender joints were scored for presence and absence (0–1). The Disease Activity Score at 28 joints with ESR (DAS28-ESR) was used to assess disease activity in patients with RA[29]. For patients with OA, only the visual analog scale for disease activity (0–100 mm) was evaluated.

US technique. Musculoskeletal US was used as the standard reference method for the comparison with the Lightscan results. All included subjects were examined by musculoskeletal US using the Esaote Mylab Twice ultrasound machine (Esaote) with high resolution 8–18 MHz linear array transducer. The US examinations were carried out by an experienced ultrasonographer (SO) who assessed the PIP joints according to the EULAR guidelines[30], after OMERACT definitions[31] and German standard scans[32]. PIP joints 2–5 (n = 696) were evaluated semiquantitatively (grades 0–3) for synovitis in greyscale mode and synovial/tenosynovial vascularity in power Doppler mode, each joint from the dorsal and from the palmar view[8,30]. Tenosynovitis was scored for presence and absence (0–1) for a further characterization of the patient cohort (results are not included in our study). Each joint/joint region was considered separately for synovitis in GSUS and PDUS. Further, a semiquantitative sum score for the 8 PIP joints in palmar and dorsal view was calculated (range 0–24), as well as a sum score including all results for palmar and dorsal view (range 0–48) to create an US mean sum score for further comparison with the POI results.

POI (Lightscan). All patients were examined by Lightscan (Figure 1). All Lightscan examinations were carried out by the same health professional (IA). The POI examination follows a standardized procedure: the PIP joints were placed and transilluminated 1 after the other. Examination of 1 PIP joint took, at most, 1 min. Each PIP joint was individually transilluminated by laser diodes with 3 different wavelengths (670 nm, 820 nm, and 904 nm). A charge-coupled device camera was recording the scattered light in a 2-dimensional light pattern. Those black/white bitmaps with a depth of 8 bits were transformed into a false color image[22] and analyzed with a nonlocal image segmentation method[21]. This method minimizes the free energy functional of the picture. A direct-descent method for the free energy was used to separate the components on the image. The range of the POI score for each PIP joint is Grade 1 until Grade 7, where Grade 1 shows no activity and Grade 7 the highest activity. By that score (grade 1–7), each PIP joint was graded for individual activity. The range of 1–7 was raised empirically. For that, a cluster algorithm was used to put the data points into 7 different centers. The color, which is included in the center of the region of interest (box located in the center of POI pictures in Figure 2), shows the score of the individual PIP joint. Yellow was chosen for the lowest score and purple as the color for the highest score (scale is located on the right side of each POI picture). To visualize the different scores better, the colors had been chosen diversely and not in a fluent color scale. For followup studies, a previous image of the PIP joint can be transparently visible over the live picture of the current PIP joint. Because of this overlap of the images, the position of the finger can be reproduced within 1–2 mm. A mean sum score was created. This was done by adding the individual results of each PIP joint and then dividing by the total number of examined joints. This allowed us to compare the results of different patients, even in cases where a specific joint measurement had failed (because of moving artefacts or overexposure, for example). Therefore, 45 of the included 688 PIP joints were excluded

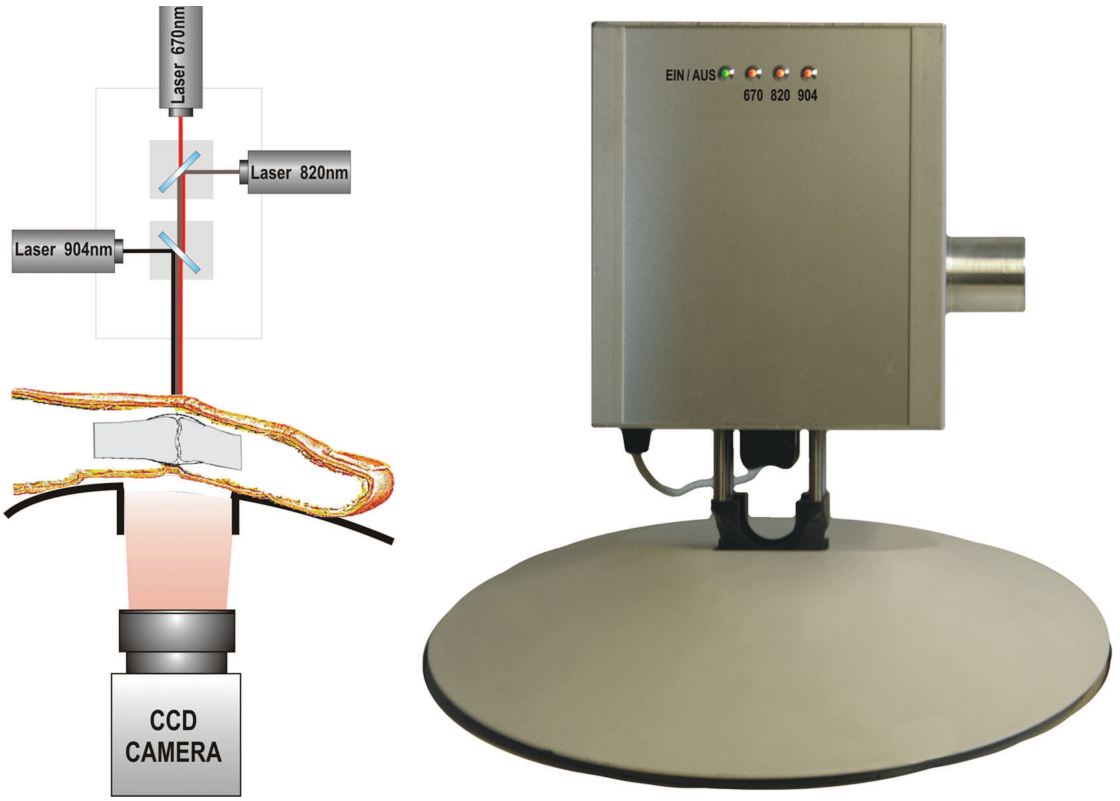

Figure 1. Display of the Lightscan system. The PIP joints are illuminated 1 by 1 by laser diodes with 3 different wavelengths (670 nm, 820 nm, and 904 nm). A CCD camera system records the scattered light in a 2-dimensional light pattern (left). The prototype is shown at right. PIP: proximal interphalangeal; CCD: charge-coupled device.

from the calculation because it was then not possible to continue with the mathematical analysis.

Statistical analysis. Data evaluation and statistical analysis were performed using SPSS version 21 (SPSS). Correlation coefficients were calculated by the 2-sided Spearman ρ test. Further, a receiver-operating characteristics (ROC) analysis was performed by computing areas under the curves (AUC). In a ROC curve, sensitivity is plotted against 1 minus the specificity by varying the threshold value. To compare POI with US and CE, agreement rates were calculated. The level of significance was defined at $\alpha < 0.05$ with a 2-sided p value.

RESULTS

The main clinical, laboratory, POI, and US characteristics are detailed in Table 1.

The Lightscan results can be displayed by 7 different colors according to the increasing inflammatory activity. Figures 2A and 2B present a typical Lightscan image with an increased POI score and the corresponding US result of the PIP joint of a patient with OA. Inflammatory activity in the PIP joint 2 of a patient with highly active RA appears as in Figures 2C and 2D. Images of a normal POI score and the corresponding US result of a healthy subject are shown in Figures 2E and 2F.

POI findings with the Lightscan were compared with clinical findings in 688 joints (118 tender, 110 swollen). POI (Lightscan) agreed well with clinically swollen and tender joints.

POI was compared with US findings in 688 joints. POI displayed positive findings in 257 out of 688 joints, and 45 joints could not be evaluated because of moving artefacts.

Further, in GSUS, 150 joints were positive in dorsal view and 176 joints in palmar view. In PDUS, 54 positive results were found, and in the palmar view of PDUS, 25 joints were positive. Sixty-two joints showed tenosynovitis.

Sensitivity and specificity. Taking US as the gold standard for inflammatory changes (synovitis and tenosynovitis), POI had a sensitivity of 74% and a specificity of 93%. This was computed with the help of ROC analysis. To maximize the number of true-positive results and to minimize the number of false-positive results, thresholds of 1.31 for POI mean sum score were used. Accordingly, Lightscan displayed positive findings in 43 of 59 patients (73%) with RA and OA. Specifically, the Lightscan showed positive findings in 18 of 21 patients (86%) with OA and 25 of 38 patients (66%) with RA. In the healthy control group, 26 of 28 subjects had negative findings. That equaled a specificity of 93% (Table 2).

Further, the Lightscan showed better sensitivity and specificity (AUC 0.879) for the detection of healthy versus disease (OA, RA) compared with GSUS (AUC 0.797) and PDUS (AUC 0.67; Figure 3).

Correlations of POI with US and assessments of disease activity. As shown in Table 3, the POI mean sum score corre-

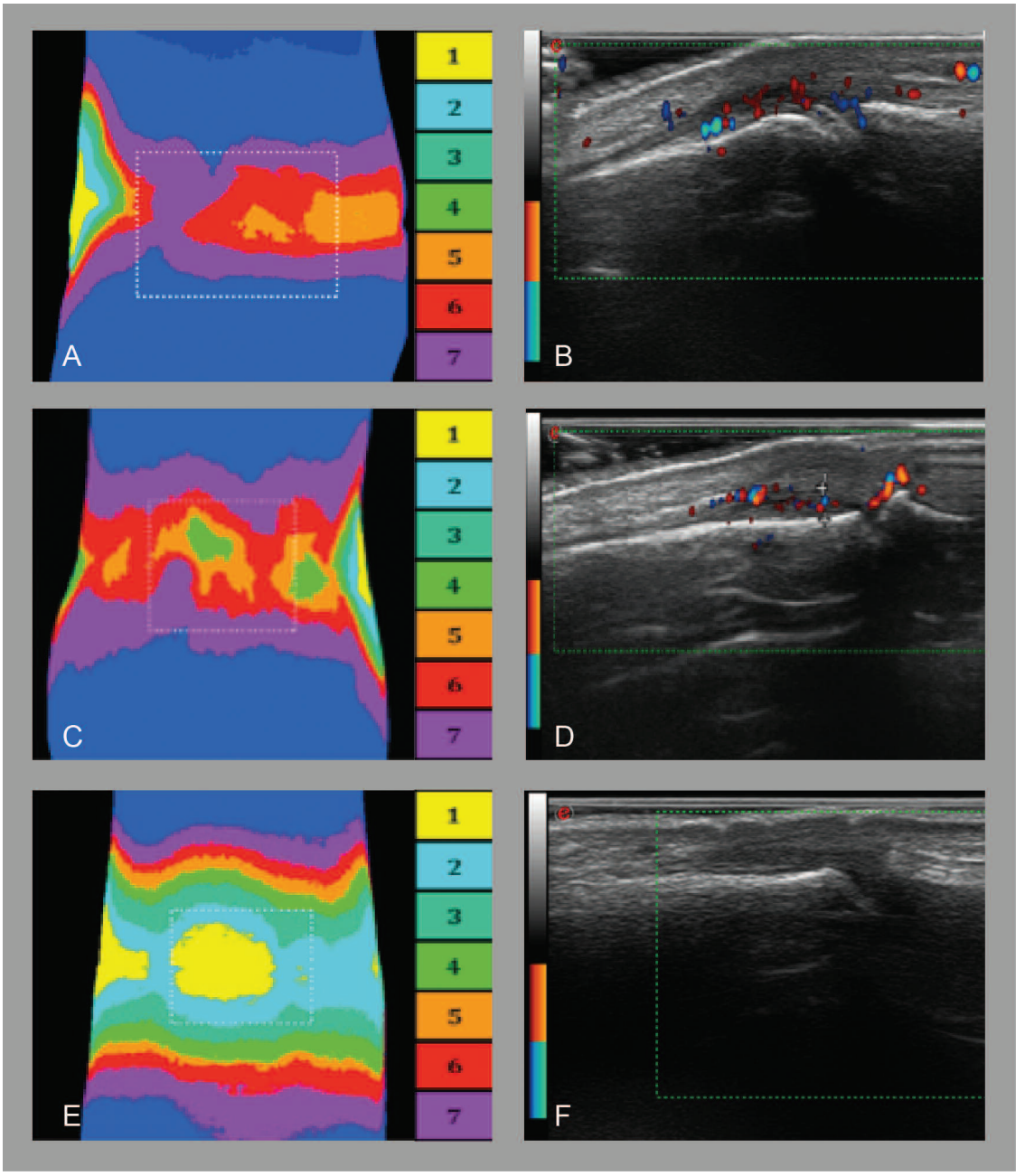

Figure 2. POI and PDUS findings in OA (A + B), active RA (C + D), and a healthy subject (E + F). A. An increased POI score of 5 in the PIP joint 2 of the left hand in a patient with OA. B. PDUS of the PIP joint 2 of the left hand in the same patient with OA, dorsal view with synovitis PDUS Grade 2. C. An increased POI score of 4 in the PIP joint 2 of the right hand in a patient with RA. D. PDUS of the PIP joint 3 of the left hand in the same patient with RA, dorsal view with synovitis PDUS Grade 2. E. A POI score of 1 in a PIP joint 2 of the right hand in a healthy subject. F. PDUS of PIP 2 of the right hand in the same healthy subjects without any inflammatory sign in US, PDUS Grade 0. POI: photo optical imaging; PDUS: power Doppler ultrasonography; OA: osteoarthritis; RA: rheumatoid arthritis; PIP: proximal interphalangeal.

lated significantly with the RA and OA GSUS synovitis mean sum score (r 0.473, $p < 0.01$) and the PDUS synovitis mean sum score (r 0.486, $p < 0.01$). DAS28-ESR did not correlate significantly with the POI mean sum score (r 0.31, $p = 0.09$).

Agreement rates. Agreement rates of POI and greyscale US ranged from 67% to 79% with a mean of 71%. Agreement rates between POI and power Doppler US ranged from 80% to 92% with a mean of 85%.

The results of POI and CE agreed in 52% on average (agreement was calculated for each PIP joint individually; agreement range was 32–66%). Disagreement in 40% of the results (range 28–55%) was because of the high rate of

Table 1. Demographic and clinical data of study population.

Characteristics	Total Cohort, n = 87		RA, n = 38		OA, n = 21		Healthy, n = 28	
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)
n	87		38		21		28	
Age, yrs	49 ± 19	51 (22–86)	56 ± 16	58 (22–80)	64 ± 10	66 (50–86)	28 ± 7	25 (23–51)
Men/women	17/70		5/33		5/16		7/21	
ESR, mm/h*	23 ± 21	16.5 (2–87)	30 ± 22	28 (2–87)	10 ± 7	8 (2–22)	—	—
CRP, mg/l*	7.5 ± 13.7	2.8 (0–73)	9.6 ± 15.6	4.1 (0.3–73)	1.9 ± 1.5	1.7 (0.2–5)	—	—
DAS28, 0–10**	—	—	4.3 ± 1.7	4.4 (1.3–7.3)	–		—	—
SJC, PIP joints	1.0 ± 1.9	0 (0–7)	1.7 ± 2.3	0 (0–7)	1.0 ± 1.5	0 (0–5)	—	—
TJC, PIP joints	1.4 ± 2.4	0 (0–9)	2.2 ± 2.8	1 (0–9)	1.6 ± 2.3	0 (0–7)	—	—
GSUS d + p synovitis	0.38 ± 0.56	0.13 (0–2.4)	0.55 ± 0.63	0.31 (0–2.4)	0.52 ± 0.62	0.4 (0–1.9)	0.05 ± 0.08	0 (0–0.3)
GSUS d synovitis	0.37 ± 0.62	0 (0–2.5)	0.54 ± 0.72	0.13 (0–0.2.5)	0.55 ± 0.64	0.38 (0–15)	0.19 ± 0.05	0 (0–0.1)
PDUS d + p synovitis	0.09 ± 0.25	0 (0–0.13)	0.15 ± 0.29	0 (0–1.3)	0.12 ± 0.29	0 (0–1.3)	0	0
PDUS d synovitis	0.13 ± 0.34	0 (0–1.6)	0.21 ± 0.4	0 (0–1.6)	0.16 ± 0.38	0 (0–1.6)	0	0
POI mean sum score	1.7 ± 0.7	1.3 (1–3.6)	1.7 ± 0.6	1.6 (1–3.6)	2.2 ± 0.7	2.3 (1–3.3)	1.1 ± 0.1	1.1 (1–1.4)

* CRP and ESR were performed for RA and OA. **DAS28-ESR only calculated for RA. RA: rheumatoid arthritis; OA: osteoarthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score at 28 joints; SJC: swollen joint count; PIP: proximal interphalangeal; TJC: tender joint count; GSUS: greyscale ultrasonography; d: dorsal; p: palmar; PDUS: power Doppler ultrasonography; POI: photo optical imaging, "Lightscan"; GSUS d + p synovitis: mean of the sum score of US in greyscale mode in dorsal and palmar view; PDUS d + p synovitis: the mean of the sum score US in power Doppler mode in dorsal and palmar view.

Table 2. Sensitivity and specificity of POI mean sum score compared with the diagnosis.

Diagnosis	POI Mean Sum Score	
	Negative Findings	Positive Findings
Healthy	93% (26/28)	7% (2/28)
RA and OA	27% (16/59)	73% (43/59)
OA	14% (3/21)	86% (18/21)
RA	34% (13/38)	66% (25/38)

POI: photo optical imaging; RA: rheumatoid arthritis; OA: osteoarthritis.

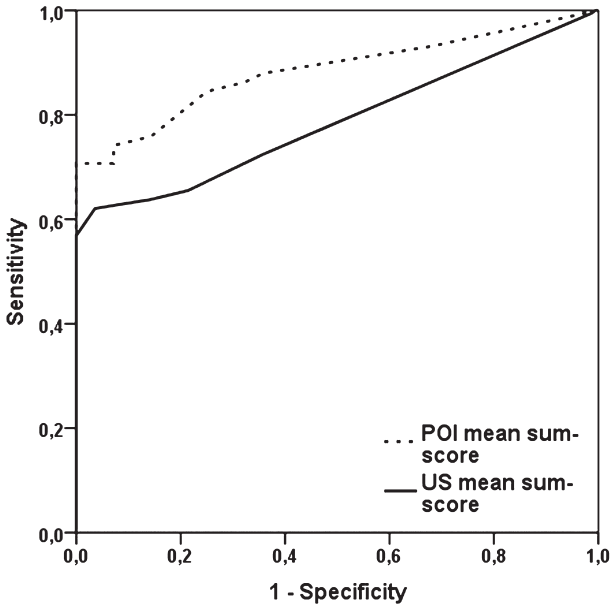

Figure 3. ROC curve of the sensitivity against the false-positive rate (1-specificity) plotted across a range of thresholds. The interrupted line presents the results of the POI mean sum score and the continuous line presents the synovitis mean sum score of GSUS in dorsal and palmar view for the total cohort (healthy, n = 28 and OA/RA, n = 59). ROC: receiver-operating characteristic; POI: photo optical imaging; GSUS: greyscale ultrasonography; OA: osteoarthritis; RA: rheumatoid arthritis.

positive findings in the POI. In 8% of the results (range 2–12.5%), positive findings were found in CE and not in POI. In the individual joint evaluation, the highest agreement was found for the swollen PIP joint 5 of the right hand and the lowest agreement was found for the tender PIP joint 2 of the right hand.

Control group. In 28 subjects (median age 25 yrs, range 23–51 yrs, 21 women), 224 joints were evaluated. POI did not detect positive findings in the POI mean sum score in 92.9% of the subjects. Two of the 28 controls displayed false-positive results in the POI mean sum score with a score of 1.38, while the US synovitis mean sum score was normal. A year after the examination, neither subject showed any clinical activity. They did not have any personal or family history of inflammatory joint disease.

DISCUSSION

The aim of our present study was to validate a novel non-invasive and low-cost POI technology called "Lightscan" in patients with RA and OA using musculoskeletal US as reference. Further, the POI results were compared with clinical joint examination.

One major goal of our study was to develop a scoring system: for each PIP joint individually as well as a sum score

Table 3. Correlations for the POI mean sum score and the GSUS and PDUS mean sum score for the total cohort (healthy, n = 28 and OA/RA, n = 59).

Variables	Coefficient of Correlation with POI, Mean Sum Score, r	Level of Significance
GSUS dorsal synovitis	0.517*	$p < 0.01$
GSUS palmar synovitis	0.391*	$p < 0.01$
GSUS dorsal + palmar synovitis	0.473*	$p < 0.01$
PDUS dorsal synovitis	0.485*	$p < 0.01$
PDUS palmar synovitis	0.365*	$p < 0.01$
PDUS dorsal + palmar synovitis	0.486*	$p < 0.01$

* Coefficient of correlation (r) is significant. POI: photo optical imaging; GSUS: greyscale ultrasonography; PDUS: power Doppler ultrasonography; OA: osteoarthritis; RA: rheumatoid arthritis; GSUS dorsal + palmar synovitis: mean sum score of US in greyscale mode in dorsal and palmar view; PDUS dorsal + palmar synovitis: mean sum score of US in power Doppler mode in dorsal and palmar view; US: ultrasonography.

for all the PIP joints, to see the total inflammatory activity of a patient. Hence, we developed a scoring system for each PIP joint from Grade 1 to Grade 7, in which Grade 1 means no inflammation and Grade 7 the highest inflammatory activity. Therefore, the "regions of interest" were empirically divided into 7 different clusters.

Further, a mean sum score was created. This was done by adding the individual results of each PIP joint and then dividing the sum by the total number of examined joints. This allowed us to compare the results of different patients, even in cases where 1 measurement could have not been used because of moving artefacts, for example.

We used ROC analysis to identify optimal thresholds for distinguishing PIP joints with and without synovitis. The best cutoff to distinguish between "pathological" and "healthy" for the POI mean sum score was 1.31.

Further, it is known that US is more sensitive than the CE[8,30,33,34]. Thus, while showing better results in the ROC analysis, we concluded POI to be more sensitive than US and CE in assessing inflammatory activity in patients with RA and OA.

We found that the POI agreed well with US. POI mean sum scores were more sensitive for detecting synovitis than the US synovitis mean sum scores. POI showed a higher rate of positive findings than the other compared modalities.

In contrast to other novel imaging methods (i.e., fluorescence optical imaging), POI is a noninvasive technique without use of any intravenous agent. Examination of 1 finger joint (only PIP joint examination is possible now) takes, at most, 1 min. It can easily be performed by any medical assistant and the results are calculated automatically. Because of the easy access to the PIP joints, their small size, and the fact that they are often symptomatic in patients with RA and OA, our study, as a pilot project, included only PIP joints. However, in future, the POI technique should be developed to include all the joints of the hands (wrist, metacarpophalangeal) and also other joints for a better evaluation of the disease activity.

It is known that US displays morphological changes (e.g., erosion, osteophytes) and dynamic changes (e.g., hypervascularity, hyperperfusion). The POI, on the other hand, distinguishes inflammatory changes and does not visualize morphological changes. Current studies are merging conventional radiography with Lightscan images to visualize the anatomic structures[35].

By using the Lightscan, it was possible to show inflammatory activity in patients with RA and OA, and to distinguish whether a PIP joint is active. However, it is not possible to distinguish between RA and OA.

Safety. The Lightscan method is a noninvasive method using near infrared light that is completely harmless for the joint transillumination. Further, to avoid any risk to the eye being caused by visual contact with the laser, it is surrounded with a protection layer. Thus, a direct visual contact with the laser is not possible. The procedure is absolutely painless.

Limitations. We are aware of some limitations concerning the image interpretation because of moving artefacts. While the examination procedure itself has been standardized on detail, changes in the amount of light (depending on the thickness of the finger) or the moving artefacts disturbed the interpretation of the images. Further, osteophytes and/or joint space narrowing could have influenced the light scattering. Therefore, 45 of 688 PIP joints were excluded from the calculation. In the cases where the images were too altered, the mathematical analysis was not possible. Nevertheless, excluding measurements from the analysis could have caused an overestimation of validity.

POI is a new imaging technology that allows, in comparison to US, a sensitive and specific assessment of synovial inflammation in PIP joints of patients with RA and OA. POI was comparable to US in detecting synovitis. Thereby, it is a safe, rapid, noninvasive, and low-cost imaging screening tool for patients with arthritis. POI was more sensitive than CE. The Lightscan is easy to use and can be operated by any medical assistant. The interpretation is simple because the results are automatically generated in numbers. After the purchase of the Lightscan, the examinations do not include any more investments (e.g., fluorescence in contrast to fluorescence optical imaging).

However, further investigations are needed for a comprehensive definition of POI results.

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