Diagnostic Value of Optical Spectral Transmission in Rheumatoid Arthritis: Associations with Clinical Characteristics and Comparison with Joint Ultrasonography

Konstantinos Triantafyllias, Caroline Heller, Michele de Blasi, Peter Robert Galle, and Andreas Schwarting

ABSTRACT. ***Objective.*** To examine the value of optical spectral transmission (OST) in detecting joint inflammation in patients with rheumatoid arthritis (RA) and to evaluate whether OST correlates with certain patient characteristics.

Methods. OST measurements were performed in the metacarpophalangeal, proximal intraphalangeal, and wrist joints of 168 patients with RA and 114 controls. OST difference between the 2 groups was statistically examined and subsequently controlled for the effect of possible confounding factors. Diagnostic OST performance was tested by receiver-operating characteristics. Moreover, associations of OST with clinical and serological activity markers (patient group), joint ultrasound (US; patient subgroup) and various anthropometric and epidemiologic parameters (patient and control group) were evaluated by Spearman correlation coefficient and a generalized linear statistical adjustment model.

Results. OST was significantly higher in the RA group than in the control group, even after adjustment for confounding factors (1.89; 95% CI 0.709–3.070, p_{adj} = 0.002). Taking US as a reference, area under the curve for all 1251 joints simultaneously was 0.67 (95% CI 0.631–0.709). In the patient group, correlation and adjustment analyses showed associations of OST with various disease activity markers [28-joint count Disease Activity Score (rho 0.313), swollen joint counts (rho 0.361), C-reactive protein (rho 0.389); all, $p_{adj} = 0.001$], age (rho 0.276, $p < 0.001$), and osteoarthritis ($p = 0.022$). Moreover, OST associated with a power Doppler US score (rho 0.442; $p = 0.001$) and a greyscale US score (rho 0.591; $p < 0.001$). In both groups males had significantly higher OST values than females and OST associated moderately weakly with body mass index (rho patients 0.316, rho controls 0.24; all, $p < 0.001$).

Conclusion. Patients with RA showed higher OST values in comparison to controls. Moreover, OST associated with clinical, US, and laboratory disease activity markers. (First Release August 1 2020; J Rheumatol 2020;47:1314–22; doi:10.3899/jrheum.190650)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
ULTRASONOGRAPHY
INFLAMMATION
DIAGNOSTIC IMAGING

From the ACURA Rheumatology Center Rhineland-Palatinate, Bad Kreuznach; Internal Medicine I, Department of Rheumatology and Clinical Immunology, Johannes Gutenberg University Medical Center; Internal Medicine I, Department of Gastroenterology, University Medical Center of Johannes Gutenberg University, Mainz, Germany.

K. Triantafyllias, MD, ACURA Rheumatology Center Rhineland-Palatinate; C. Heller, Medical Student, Internal Medicine I, Department of Rheumatology and Clinical Immunology, Johannes Gutenberg University Medical Center; M. de Blasi, Medical Informatics Engineer, ACURA Rheumatology Center Rhineland-Palatinate; P.R. Galle, MD, Professor, Internal Medicine I, Department of Gastroenterology, University Medical Center of the Johannes Gutenberg University; A. Schwarting, MD, Professor, ACURA Rheumatology Center Rhineland-Palatinate, and Internal Medicine I, Department of Rheumatology and Clinical Immunology, Johannes Gutenberg University Medical Center.

Address correspondence to Dr. K. Triantafyllias, ACURA Rheumatology Center, Kaiser-Wilhelm-Str. 9-11, 55543, Bad Kreuznach, Germany. E-mail: ktriantafyllias@gmail.com

Accepted for publication March 11, 2020.

Rheumatoid arthritis (RA) is a chronic inflammatory disease typically characterized by polyarticular pain, joint destruction, and functional impairment[1]. Early RA diagnosis and therapy initiation are 2 very important predictors of sustained disease remission and inhibition of radiographic changes[2]. Further, tight clinical control in the course of the disease has proven to be an effective strategy for RA activity suppression and improvement of longterm outcomes[3,4,5]. Even though the aforementioned aspects of RA management are crucial, their implementation in the routine rheumatology practice can be difficult[6,7]. First, tight control disease management strategies could burden the rheumatologist[7]. Second, clinical activity assessment tools such as the 28-joint count Disease Activity Score 28 (DAS28) are partially subjective and do not always depict the real inflammatory burden[8]. Therefore,

complementary diagnostic tools such as ultrasound (US) or magnetic resonance imaging (MRI) are needed in many cases. However, US of multiple joints can be time-consuming, especially when scoring is included, and hand MRI is expensive and frequently performed unilaterally. Thus, there is a need for further diagnostic modalities that could improve RA management.

Optical spectral transmission (OST) is a new diagnostic method based on a technology able to assess the blood-specific absorption of light transmitted through a tissue, without exposure to radiation[9]. In the case of arthritis, speed and magnitude of blood pooling in the joint increases, owing to inflammation-associated changes of vascularity. For the same reason, transmission of light through the inflamed joint decreases[10,11], and OST promises a noninvasive quantification of these blood flow changes. However, clinical data concerning the diagnostic value of this new modality are scarce (3 studies on the only available commercial device: HandScan by Hemics[12,13,14]).

Each study showed a moderate to good OST diagnostic performance in the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist joints. The first study on this topic focused on the internal development of an algorithm to detect joint inflammation by OST in 59 patients with RA comparing a preliminary version of the HandScan with US as a reference[12]. In the second OST study, sensitivity and specificity of OST in detecting joint inflammation were examined in 62 patients using power Doppler US as a reference[13]. The third and last published OST study examined 46 patients with RA using the newest version of the device, with an additional light source that was shown to augment overall diagnostic performance. That study also looked at associations of OST with pathophysiological factors that could lead to under- or overestimation of inflammation[14].

In everyday clinical practice, we have observed that males and obese patients can have higher OST values in comparison to females and subjects with lower body mass index (BMI). However, to the best of our knowledge, the effect of anthropometric and epidemiologic patient characteristics on OST has not been established to date. Further, sufficient data regarding the diagnostic value of this new, promising tool are missing.

Thus, the main objectives of our present study were to validate previous OST study results regarding the diagnostic value of OST in RA, using clinical and US markers, and to examine OST differences between a group of patients with RA and a group of healthy controls. Additionally, we sought to examine relationships of OST between patient-related and disease-related characteristics, to test for possible confounding of anthropometric and epidemiologic variables on OST results.

MATERIALS AND METHODS

Study populations. OST and clinical examinations were performed on 168 consecutive patients with RA during their stay in our inpatient rheumatology clinic. A subset of these patients (n = 59) underwent an additional bilateral US examination of the MCP, PIP, and carpal joints on the same day (> 1 h interval between examinations). Control subjects were 114 hospital co-workers who responded to an open call for study participation, without underlying inflammatory disease, arthralgias, or signs of osteoarthritis (OA) or synovitis in the clinical examination. Exclusion criteria in both groups were age < 18 years, joint protheses/implants, severe hand deformities, pronounced ulnar deviation, recent trauma or surgery, and known photosensitivity.

All included patients met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA[15]. Patients gave their informed consent and the assessment was reviewed and approved by the Standing Committee for Clinical Studies of Rhineland-Palatinate, Germany, in adherence to the Declaration of Helsinki (approval number: 13042).

Data collection. In addition to epidemiological and anthropometric data (sex, age, measured weight and height), we documented cigarette smoking, history of known arterial hypertension (HTN), and diabetes mellitus in both groups. We calculated BMI (kg/m^2) and the size of both hands (% mean surface covered by 2 hands divided by % mean surface of the 2 glass hand rests). Tender (TJC) and swollen joint counts (SJC) of patients with RA as well as patient disease activity on a visual analog scale (VAS) were examined and documented by the same trained person (CH). Inflammation markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] were routinely tested and used for the calculation of DAS28-ESR and DAS28-CRP. Rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies (anti-CCP) were assessed by ELISA. Radiographs of the hands in 2 planes were examined by a radiology specialist to control for the presence of typical RA erosions (marginal), osteophytes, and calcium pyrophosphate dihydrate crystal depositions (chondrocalcinosis).

Details of OST tests. OST examinations were performed by trained study nurse staff. Study nurses were blinded regarding the results of the clinical examination, laboratory, and US.

During the measurement, patients were asked to put their forearms into the HandScan device through 2 frontal openings that held pressure cuffs. Subsequently, the forearms were placed on a glass hand rest. Red and near-infrared laser light at wavelengths of 660 nm and 808 nm illuminated the palmar side of the distal forearm (both wrists, MCP, PIP, and reference areas for every joint). A camera placed at the upper side of the device recorded the light that was transmitted through the hands (Figure 1). A complete measurement lasted about 100 s and consisted of 3 phases: (1) a low cuff pressure phase; (2) an increased cuff pressure phase; and (3) a second low cuff pressure phase. During the first phase, baseline transmission was measured. In the second phase, the cuff pressure increased to 55 mmHg (7.3 kPa), causing blood to pool in the examined areas. During the third phase, cuff pressure decreased, resulting in inversion of venous occlusion and blood pooling.

Built-in software allowed the automatic identification of regions of interest (ROI; wrists, MCP I–V, and PIP I–V) and reference areas that were located distally to the examined joints. A comparison between the blood flow in the ROI and in the reference areas served as a control mechanism for the presence of impaired or increased peripheral blood flow, due to systemic factors such as body temperature, diabetes mellitus, nicotine use, or vasoactive medication.

In accordance with known semiquantitative power Doppler US (PDUS) scoring methods[16], OST assessed joint hypervascularity and translated it to a grade between 0 and 3 (0 = no hypervascularity and 3 = the highest possible grade of hypervascularity)[14,17]. OST scores were generated automatically by the HandScan software after every OST examination (Supplementary Data 1, available with the online version of this article).

Details of US tests. US was performed by a blinded experienced examiner (KT, rheumatologist, certified by the German Society of Ultrasound in Medicine). A linear transducer (4–13 MHz) of a MyLab70 US device (Esaote), operating at a frequency of 13 MHz, was used to examine the

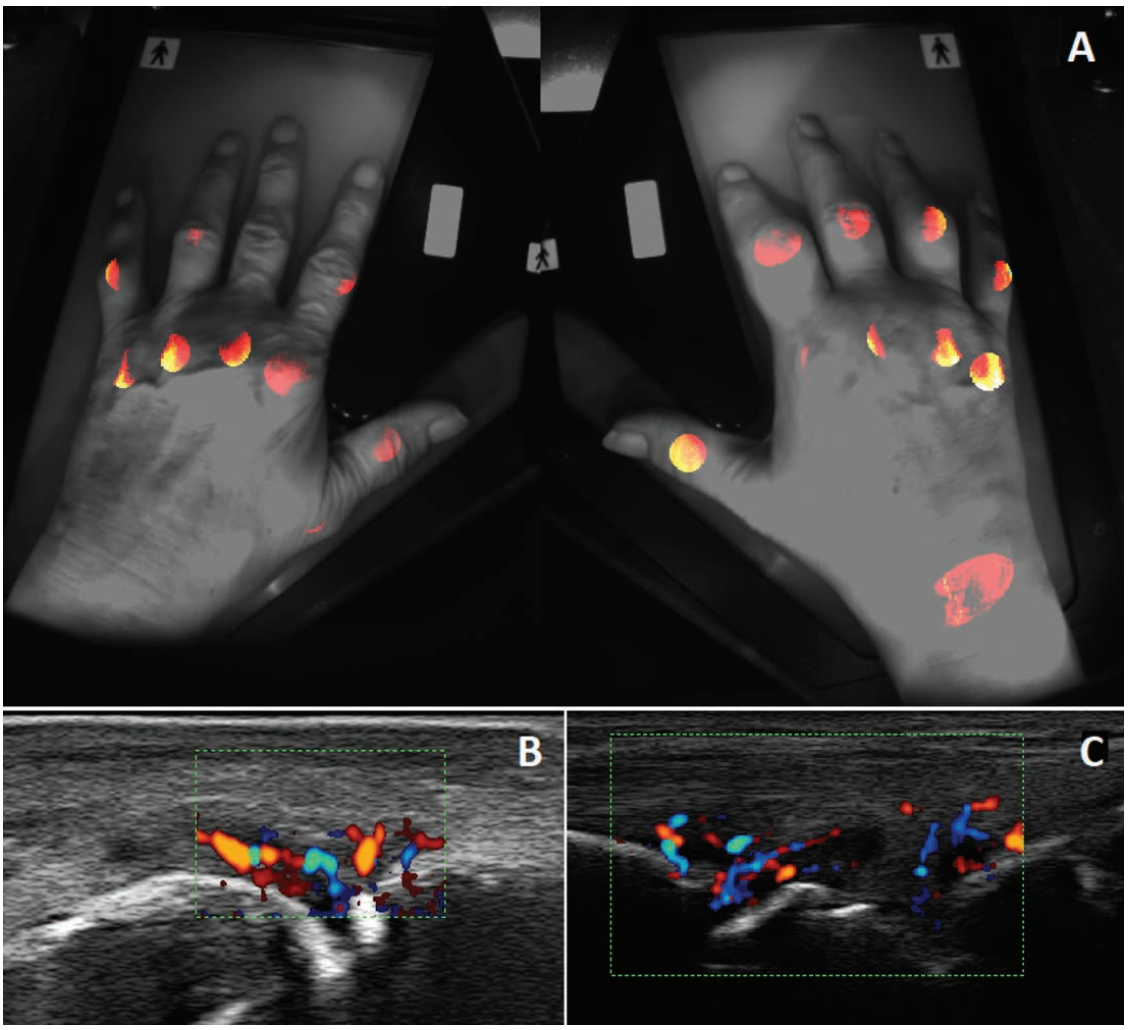

Figure 1. Assessment of inflammation by optical spectral transmission (OST) and ultrasound (US) in the wrists and finger joints of a female patient with rheumatoid arthritis (high disease activity). A. Result of the OST measurement. B, C. Power Doppler/greyscale US examination of the left MCP IV and right midcarpal joint, respectively (longitudinal views): joint effusions, synovial hypertrophy, and increased vascularity. MCP: metacarpophalangeal.

same joints examined by OST. US protocol was in accordance with the EULAR guidelines regarding the positioning of the patient and scanning planes[18]. Both greyscale US (GSUS) and PDUS investigations of the dorsal aspects of MCP I–V, PIP I–V, and the wrists (radiocarpal/midcarpal joint recesses)[12,14] were performed.

Color gain was set at the disappearance of color noise and the pulse repetition frequency (PRF) was set as low as possible to have maximum sensitivity, resulting in a frequency of about 750 Hz. The size and position of the color box were adjusted to include the subcutaneous tissue to detect artifacts caused by vessels above the joint. Doppler activity of the joints was measured in a semiquantitative manner (scoring grades: 0–3) as previously described[16] (Supplementary Data 1, available with the online version of this article). Moreover, a binary US scoring method was applied, documenting GSUS pathology (synovitis/joint effusion)[19,20]. Finally, tenosynovitis of the wrist flexors and extensors was examined in B-mode US and was defined as an abnormal anechoic or hypoechoic widening of the tendon sheath[21]. Its presence or absence was documented in a binary manner[14].

Statistical analysis. The assumption of normality of distribution was evaluated through the Shapiro-Wilk test and a graphic method (quantile-quantile plots). Comparison of categorical variables was performed through Fisher's exact test. Because OST values were not distributed normally, the difference between patient and control groups was evaluated by Mann-Whitney U test. This test was also used to analyze associations between OST and binary categorical variables in both groups and to compare median OST values of patients with different DAS28 cutoff values. Spearman correlation coefficient rho was used to assess correlations of OST and continuous characteristics in the 2 groups.

All statistical adjustments and examination of OST difference between patients with RA and controls were performed by a generalized linear statistical model (GLSM) with a tweedie distribution[22]. To search for confounding factors, we calculated the B coefficient of OST before and after the inclusion of different variables in the multivariate regression analysis model. We considered a variable to be a confounder of OST if its inclusion caused a change of the B coefficient ≥ 10% (assumed as the maximum superior limit)[23].

Finally, to assess OST diagnostic performance, receiver-operating characteristics (ROC) were performed at a patient level [RA group vs controls and active RA subgroup (≥ 1 swollen joint) vs controls] and at a joint level (dichotomized US values vs numerical OST values) for wrist, MCP, PIP, and all joints. A probability value of 0.05 was considered statistically significant. All statistical calculations were performed using the SPSS software 23.0.

RESULTS

OST measurements were performed in 168 patients with RA and 114 control subjects (females: 66.1% vs 77.2%, respectively; p = 0.047). Descriptive characteristics of both groups are presented in Table 1.

In the RA group, OST could be performed in a total of 3649 joints (47 joints automatically excluded by the OST software because of anatomic anomalies/missing fingers) and in the control group in 2508 joints. US examinations of the MCP, PIP, and wrist joints were performed in 59 patients (1298 joints).

Use of ROC. An ROC was done to test the diagnostic performance of OST compared to US. A joint was considered inflamed when the PDUS score was ≥ 1 and the GSUS score > 0. US inflammation status was then compared with OST joint scores. Subsequently, 3 different joint categories (570 MCP, 569 PIP, and 112 wrist joints) were analyzed separately (Figure 2A). The area under the curve (AUC) for all 1251 joints simultaneously was 0.67 (95% CI 0.631–0.709). The best diagnostic performance was seen at the wrist level (AUC 0.75; 95% CI 0.658–0.838), followed by MCP (AUC 0.69; 95% CI 0.634–0.748) and PIP joints (AUC 0.64; 95% CI 0.576–0.713).

To compare total OST values between RA and healthy controls, 2 additional ROC were performed [RA vs controls and RA subgroup (≥ 1 swollen joint) vs controls]. The AUC of the ROC "RA versus controls" was 0.71 (95% CI 0.651–0.77), with a sensitivity of 0.62 and a specificity of 0.72, for an OST cutoff of 12.99 [Youden index 0.336, positive likelihood ratio (LR+) 2.21, LR– 0.53; Figure 2B].

Comparison of the active RA subgroup (n = 98) with controls showed an AUC of 0.76 (95% CI 0.695–0.824), with an improved sensitivity of 0.72 and a specificity of 0.71, for an OST cutoff of 12.74 (Youden index 0.435, LR+ 2.48, LR– 0.39).

Association between group status (RA vs control) and OST. Median OST values were significantly higher in the patients group compared to the control group [14.55, interquartile

Table 1. Descriptive characteristics by group.

	Controls, n = 114	Patients, n = 168	Significance (p)
OST†	10.32 (7.68–13.91)	14.55 (10.49–18.48)	< 0.001*
Age, yrs†	51 (35–57)	60 (54–70)	< 0.001*
Sex (female), %	77.2	66.1	0.047*
Nicotine use, %	19.4	25.7	0.300
Arterial HTN, %	19.4	39.9	< 0.001*
BMI†	25.50 (21.72–28.55)	25.94 (24.00–30.72)	0.007*
Diabetes, %	1.9	11.3	0.004*
Hand size (%)†	60.14 (57.25–65.83)	63.18 (57.73–72.30)	0.013*
RF-positive, %	—	75	—
Anti-CCP–positive, %	—	70.2	—
CRP, mg/l†	—	2.97 (1.56–10.30)	—
ESR, mm/h†	—	18 (10–36)	—
Tender joint count†	—	2 (0–7.75)	—
Swollen joint count†	—	1 (0–3)	—
VAS, mm†	—	40 (20–63.75)	—
DAS28-ESR†	—	3.67 (2.53–4.93)	—
DAS28-CRP†	—	3.20 (2.00–4.66)	—
Disease duration, yrs†	—	3.00 (1.00–7.00)	—
Erosions, %	—	33.9	—
Osteoarthritis**, %	—	14.3	—
Chondrocalcinosis, %	—	3.4	—
Tenosynovitis, %	—	39.3	—
PDUS score†	—	6 (2–15.75)	—
GSUS score†	—	2 (0–7)	—
Immunosuppressants			
sDMARD, %	—	42.8	—
bDMARD, %	—	9	—
JAK inhibition, %	—	4.82	—
Combination therapy‡	—	1.45	—
Glucocorticoids (low dose)	—	78.1 (55.7)	—
No DMARD	100	31.3	—

* p < 0.05. † Data are presented as median (interquartile range) because they are not normally distributed. ** Distal intraphalangeal joints excluded, because they were not examined by OST or ultrasound. ‡ Combination of 2 different sDMARD or sDMARD with bDMARD or sDMARD with JAK inhibitor. OST: optical spectral transmission; BMI: body mass index; RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analog scale; CRP: C-reactive protein; PDUS: power Doppler ultrasound score; GSUS: greyscale ultrasound score; sDMARD: synthetic disease-modifying antirheumatic drugs; bDMARD: biologic DMARD; JAK: Janus kinase; HTN: hypertension; anti-CCP: anticyclic citrullinated peptide antibodies.

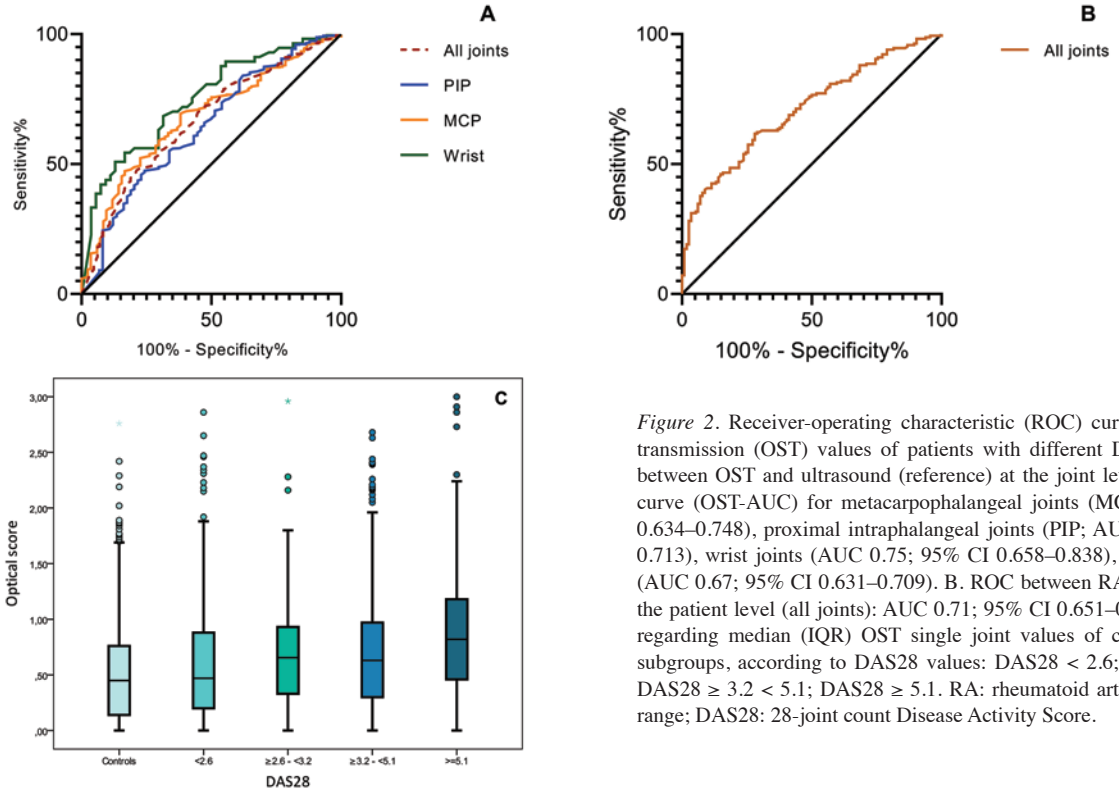

Figure 2. Receiver-operating characteristic (ROC) curves and optical spectral transmission (OST) values of patients with different DAS28 cutoffs. A. ROC between OST and ultrasound (reference) at the joint level: OST area under the curve (OST-AUC) for metacarpophalangeal joints (MCP; AUC 0.69; 95% CI 0.634–0.748), proximal intraphalangeal joints (PIP; AUC 0.64; 95% CI 0.576–0.713), wrist joints (AUC 0.75; 95% CI 0.658–0.838), and all joints combined (AUC 0.67; 95% CI 0.631–0.709). B. ROC between RA and healthy controls at the patient level (all joints): AUC 0.71; 95% CI 0.651–0.77). C. Boxplot graphs regarding median (IQR) OST single joint values of control group and 4 RA subgroups, according to DAS28 values: DAS28 < 2.6; DAS28 ≥ 2.6 to < 3.2; DAS28 ≥ 3.2 < 5.1; DAS28 ≥ 5.1. RA: rheumatoid arthritis; IQR: interquartile range; DAS28: 28-joint count Disease Activity Score.

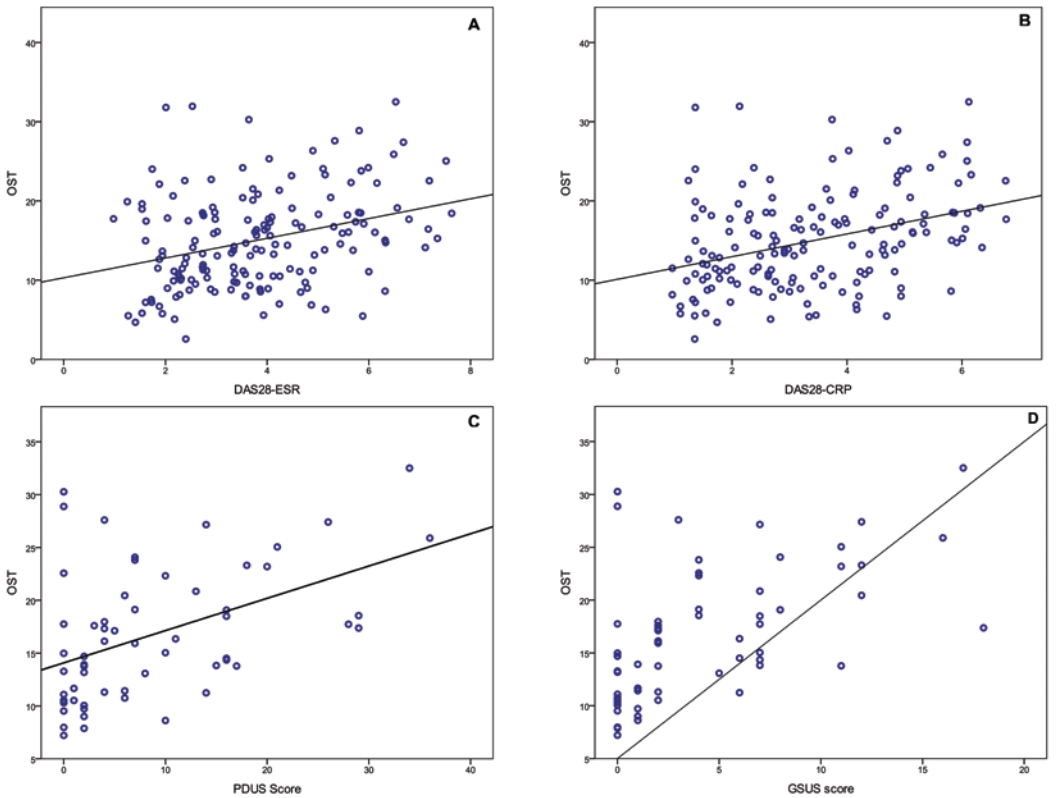

Figure 3. Correlations between optical spectral transmission (OST) and (A) DAS28-ESR ($p < 0.001$), (B) DAS28–CRP ($p < 0.001$), (C) PDUS score ($p = 0.001$), and (D) GSUS score ($p < 0.001$). DAS28-ESR: 28-joint count Disease Activity Score based on erythrocyte sedimentation rate; CRP: C-reactive protein; PDUS: power Doppler ultrasound; GSUS: greyscale ultrasound.

range (IQR) 10.49–18.48, vs 10.32 (IQR 7.68–13.91), $p < 0.001$]. Interestingly, BMI, sex, and age were statistically identified as possible confounding factors of OST. On the other hand, arterial HTN, diabetes mellitus, cigarette smoking, and hand size did not show any confounding effects on the results. After adjustment for BMI, age, and sex, OST remained statistically significantly higher in the patient group in comparison to the control group (1.89, 95% CI 0.709–3.070; $p_{adj} = 0.002$). Thus, patients with RA have higher OST values than controls.

Associated variables of OST within both groups. Among patients with RA, unadjusted statistical correlation analyses showed moderate associations between OST and CRP (rho 0.389, $p < 0.001$), SJC (rho 0.361, $p < 0.001$), DAS28-ESR (rho 0.313, $p < 0.001$), and DAS28-CRP (rho 0.364, $p < 0.001$). The analyses showed poor OST associations with ESR (rho 0.171, $p = 0.027$), TJC (rho 0.194, $p < 0.001$), and VAS (rho 0.299, $p < 0.001$; Figure 3, Table 2).

Moreover, OST correlated moderately with BMI (rho 0.316, $p < 0.001$) and hand size (rho 0.462, $p < 0.001$) and poorly with age (rho 0.276, $p < 0.001$; Table 2). Males had higher OST values than females (all, $p < 0.001$), and OA associated with higher OST values ($p = 0.022$). There were no statistically significant relationships between OST and nicotine use, arterial HTN, diabetes mellitus, RF–/anti-CCP positivity, erosions, tenosynovitis, or chondrocalcinosis (all, $p > 0.05$; Table 2).

To control the established significant correlations of OST in the RA group, we performed a GLSM, adjusting for BMI, sex, and age. With the exception of hand size (0.107, 95% CI –0.51 to 0.266, p_{adj} 0.185), all further statistical relationships of OST remained statistically significant: 0.049, 95% CI 0.006–0.093, p_{adj} 0.02 for OST-ESR; 0.190, 95% CI 0.058–0.322, p_{adj} 0.005 for OST-TJC; and $p_{adj} < 0.001$ for the correlations between OST and CRP (0.091, 95% CI 0.036–0.147), SJC (0.715, 95% CI 0.464–0.965), VAS (0.055, 95% CI 0.028–0.082), DAS28-ESR (1.16, 95% CI 0.693–1.692), and DAS28-CRP (1.148, 95% CI 0.686–1.609), respectively.

Among controls, OST correlated moderately with hand size (rho 0.477, $p < 0.001$) and poorly with BMI (rho 0.24, $p = 0.015$). Moreover, males had higher OST values than females ($p < 0.001$; Table 3). On the other hand, age, nicotine use, arterial HTN, and diabetes mellitus did not show any correlation with OST (all, $p > 0.05$; Table 3).

OST values in patients with different DAS28 values. Two groups of patients with RA were built using a DAS28-ESR cutoff value of 2.6. OST values of patients with DAS28 < 2.6 were statistically compared with OST values of patients with DAS28 ≥ 2.6. Patients with DAS28 < 2.6 had statistically significant lower median OST in comparison to their counter partners (11.30, IQR 8.10–17.56, vs 15.90, IQR 11.19–18.55, respectively; $p = 0.003$). This difference remained statistically significant even after

Table 2. Association between patient characteristics and optical spectral transmission values.

	Spearman rho	Significance (p)		Median (IQR)	Significance (p)
Age, yrs†	0.276	< 0.001*	Sex: Female Male	12.64 (9.00–16.75) 17.75 (14.60–22.44)	< 0.001*
BMI, kg/m²†	0.316	< 0.001*	Nicotine use: No Yes	14.50 (10.76–18.33) 14.51 (8.75–19.12)	0.584
ESR, mm/h†	0.171	0.027* (0.02*)‡	Hypertension: No Yes	14.12 (9.00–18.28) 15.93 (11.64–18.55)	0.053
CRP, mg/l†	0.389	< 0.001* (0.001*)‡	Diabetes: No Yes	14.12 (10.13–18.37) 17.60 (13.66–18.55)	0.056
TJC†	0.194	< 0.001* (0.005*)‡	RF: Negative Positive	14.24 (10.78–17.80) 14.72 (10.17–18.51)	0.956
SJC†	0.361	< 0.001* (0.001*)‡	Anti-CCP: No Yes	14.02 (10.70–17.70) 15.45 (10.11–18.66)	0.553
VAS, mm†	0.299	< 0.001* (0.001*)‡	Osteoarthritis:** No Yes	14.1 (9.86–18.23) 17.6 (13.22–22.47)	0.022*
DAS28-ESR†	0.313	< 0.001* (0.001*)‡	Erosions: No Yes	14.25 (10.53–18.24) 15.27 (9.61–19.59)	0.793
DAS28-CRP†	0.364	< 0.001* (0.001*)‡	Tenosynovitis: No Yes	14.31 (10.47–20.92) 17.04 (13.16–21.47)	0.140
Hand size† (%)	0.462	< 0.001* (0.185)‡	Chondrocalcinosis: No Yes	14.46 (10.05–18.49) 14.58 (12.83–17.10)	0.814

Spearman († not normal distribution) tests were performed to investigate the relationships between OST and quantitative patient characteristics. Mann-Whitney U test was used to investigate the relationships between OST and qualitative patient characteristics. * $p < 0.05$. ‡ p values in parentheses adjusted for age, sex, BMI by multiple regression. ** Distal intraphalangeal joints excluded, because they were not examined by OST or ultrasound. OST: optical spectral transmission; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; VAS: visual analog scale; DAS28-ESR: 28-joint count Disease Activity Score based on erythrocyte sedimentation rate; CRP: C-reactive protein; IQR: interquartile range.

Table 3. Association between characteristics of control subjects and optical spectral transmission values.

	Spearman's rho	Significance, p		Median (IQR)	Significance, p
Age, yrs†	0.036	0.702	Sex: Female	9.45 (6.50–11.91)	< 0.001*
			Male	14.95 (12.41–17.55)	
BMI, kg/m²†	0.240	0.015*	Nicotine use: No	10.20 (7.24–14.76)	0.755
			Yes	10.63 (9.01–12.00)	
Hand size†, %	0.477	< 0.001*	Hypertension: No	10.05 (7.77–14.76)	0.576
			Yes	9.95 (8.15–12.15)	
			Diabetes: No	10.20 (7.91–14.21)	0.104
			Yes	6.55 (12.64–20.47)	

Spearman tests († not normal distribution) were performed to investigate the relationships between OST and quantitative patient characteristics. Mann-Whitney U test was used to investigate the relationships between OST and qualitative patient characteristics. * $p < 0.05$. OST: optical spectral transmission; BMI: body mass index; IQR: interquartile range.

adjustment for the effects of BMI, age, and sex (2.404, 95% CI 0.852–3.956, $p_{adj} = 0.002$).

To test for the presence of OST overlapping values between healthy subjects and patients in remission, or between patients with different DAS28 cutoff values, 4 different patient-subgroups were built (DAS28 < 2.6; DAS28 ≥ 2.6 to < 3.2; DAS28 ≥ 3.2 to < 5.1; DAS28 ≥ 5.1). Median OST values of these 4 subgroups were compared with each other and with the control group. In all cases, except for the comparison between RA subgroup with DAS28 ≥ 2.6 to < 3.2 and RA subgroup with DAS28 3.2 to < 5.1, OST values showed statistical differences at the level of at least $p < 0.001$ (Figure 2C; Supplementary Tables 1 and 2, available with the online version of this article). However, overlap of OST values could be observed in all categories (Figure 2C).

Analysis of US subgroup. In this subset (n = 59), OST correlated moderately with DAS28-ESR and DAS28-CRP (rho 0.476, $p < 0.001$ and rho 0.459, $p < 0.001$, respectively) as well as with SJC (rho 0.448, $p = 0.001$) and VAS (rho 0.402, $p = 0.002$). Moreover, OST correlated poorly with ESR (rho 0.282, $p = 0.037$) and TJC (rho 0.280, $p = 0.039$). Finally, OST showed moderate correlations with both the PDUS (rho 0.442, $p = 0.001$) and the GSUS scores (rho 0.591, $p < 0.001$; Figure 3).

DISCUSSION

In our study we showed that OST values were higher in the RA than in the control group, even after adjustment for confounding factors. Moreover, we found that OST associated with all examined clinical, laboratory, and US disease activity markers.

To our knowledge, this is one of the few validation studies to have examined the diagnostic performance of OST and the first one to show OST correlations with factors not exclusively related to the inflammatory disease. In general, literature lacks adequate data concerning the diagnostic value of OST in patients with inflammatory joint diseases. In particular, we are aware of only 3 previous explorations performed in RA cohorts, showing moderate to good diagnostic performances of OST in comparison to clinical examination and US[12,13,14]. In our study, ROC between OST and US as a reference showed best OST performances at the wrist and MCP joint level. Two previous studies showed a worse OST performance for the wrists in comparison to MCP and PIP joints[12,14]. However, an improvement of diagnostic performance at the wrist level was reported after the installation of a new light source[14]. We used the most modern HandScan version.

Further, OST was found to associate with DAS28. Interestingly, OST associated stronger with SJC than with TJC or VAS. Van Onna, *et al* could similarly show a stronger correlation between OST-SJC than between OST-TJC, strengthening the aforementioned hypothesis[12]. In the same sense, our study showed OST correlations with both inflammation markers. However, OST correlated stronger with CRP than with ESR. A possible explanation for this finding is the confounding effect of factors unrelated to disease activity (i.e., age[24], anemia[25], or immunoglobulins[26]) on ESR. Interestingly, until now only Krabbe, *et al* has showed an association between CRP and OST, which was nevertheless on the edge of statistical significance ($p = 0.047$)[13].

Comparison between median (IQR) OST values of the 4 RA subgroups that were built according to their DAS28 values showed OST overlapping values between the different categories. This result suggests that even if statistical differences among median OST values of the 4 subgroups were significant, differentiation of disease activity was not clear.

Regarding the US subset analysis, established associations of OST with both the GSUS score and the score measuring PDUS activity suggest that not only vascularity changes but also synovial thickening and joint effusion could reduce the intensity of the transmitted light through the joint. Van Onna, *et al* found similar OST correlations with a PDUS joint index and a score examining solely GSUS changes[12]. Thus, GSUS should also be taken into consideration when performing comparisons between OST and US.

Interestingly, we could not find an association between OST and wrist tenosynovitis. Besselink, *et al* described an increased risk of underestimating RA activity through the presence of extensor tendinitis[14]. However, in the Besselink study all tendons of the hands (including finger tendons) were examined by US. Thus, a direct comparison of these results with the results of our study should be avoided. Moreover, chondrocalcinosis and joint erosions did not correlate with OST in our study, whereas osteoarthritis did. Besselink, *et al* found that dorsal erosions and osteophytes can lead to misclassification of inflammation by OST through possible quantitative changes of the light passing through the eroded or osteophytic bone[14]. However, in that study erosions were diagnosed by US, whereas in our study conventional radiologic scans were used. Discordance of the results regarding the effect of erosions could be due to this particular methodologic difference[27]. Safe conclusions about the possible effects of chondrocalcinosis on OST cannot be made, owing to the small number of patients included having this pathology concomitantly to RA (3.4%).

Finally, none of the prior OST studies evaluated the influence of epidemiologic or anthropometric patient characteristics on OST. Nevertheless, our data suggest that they can confound OST and that correct interpretation of OST results presupposes their consideration. The mechanisms that lead to correlation of OST with male sex, high BMI, large hands in both groups, and older age in the patient group are not clear. One could postulate that more robust bony, synovial, or tendon structures in males and in subjects with larger hands cause an increased light absorption and thus higher OST values. Moreover, an effect of increased subcutaneous fat in patients with high BMI influencing light transmission cannot be excluded. Finally, older age could associate with longer disease duration and thus higher OST values through more prominent bone/joint pathology.

Our present study has some limitations regarding the applied diagnostic methodology to assess presence of erosions. Moreover, no radiographs were performed in the asymptomatic control group. However, examination of the main objectives of the study has not been influenced by this methodology. A further possible limitation is the missing US examination of finger tendons. We have nevertheless decided to focus primarily on synovial inflammation, given that OST scores are calculated for individual PIP, MCP, and wrist joints and not for their adjacent tendons.

We showed that OST values of patients with RA were higher than those of healthy controls and that OST associated with clinical, US, and laboratory disease activity markers. Moreover, we report that OST could be influenced by anthropometric and epidemiological patient characteristics. As a limitation, overlap of OST values could be observed in patients with different DAS28 values. Control and confirmation of these results in future studies is important.

ACKNOWLEDGMENT

Special thanks go to the study nurse Martin Rector and the medical assistants Nicole Dirvonskis and Margaret Janson of the ACURA Rheumatology Center Rhineland-Palatinate, Germany. The authors also wish to thank the Dr. Wolfgang and Anita Bürkle Foundation and the Support Association (Förderverein) Rhineland-Palatinate, Germany. Results described in this manuscript are part of the doctoral thesis of Caroline Heller.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;329:1108-11.
2. Raza K, Buckley CE, Salmon M, Buckley CD. Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2006; 20:849-63.
3. Bakker MF, Jacobs JWG, Verstappen SMM, Bijlsma JWJ. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
4. Katchamart W, Bombardier C. Systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis. J Rheumatol 2010;37:1411-15.
5. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
6. van Hulst LT, Hulscher ME, van Riel PL. Achieving tight control in rheumatoid arthritis. Rheumatology 2011;50:1729-31.
7. Schwarting A, Pfeiff B, Amberger C, Pick D, Hesse M, Jendro M, et al. The regional network ADAPTHERA: Rheumatology care through coordinated cooperation: comprehensive, trans-sectoral, covering all health insurance. Initial results. [Article in German] Z Rheumatol 2016;75:999-1005.
8. Fransen J, Stucki G, van Riel PL. Rheumatoid arthritis measures: Disease Activity Score (DAS), Disease Activity Score-28 (DAS28), Rapid Assessment of Disease Activity in Rheumatology (RADAR), and Rheumatoid Arthritis Disease Activity Index (RADAI). Arthritis Rheum 2003;49:214-24.
9. Meier AJ, Rensen WH, de Bokx PK, de Nijs RN. Potential of optical spectral transmission measurements for joint inflammation measurements in rheumatoid arthritis patients. J Biomed Opt 2012;17:081420.
10. Prapavat V, Runge W, Mans J, Krause A, Beuthan J, Muller G. Development of a finger joint phantom for the optical simulation of early stages of rheumatoid arthritis. Biomed Tech 1997;42:319-26.
11. Beuthan J, Zabarylo U, Krause A, Taupitz M, Minet O. RA diagnostics using laser-optical images and conventional X-rays (fused imaging). Med Laser Appl 2007;22:127-33.
12. Van Onna M, Ten Cate DF, Tsoi KL, Meier AJ, Jacobs JW, Westgeest AA, et al. Assessment of disease activity in patients with rheumatoid arthritis using optical spectral transmission measurements, a non-invasive imaging technique. Ann Rheum Dis 2016;75:511-18.
13. Krabbe S, Ammitzbøll-Danielsen M, Østergaard M, Giard MC, Terslev L. Sensitivity and specificity of optical spectral transmission imaging in detecting joint inflammation in rheumatoid arthritis. Ann Rheum Dis 2016;75:632-3.
14. Besselink NJ, van der Meijde P, Rensen WHJ, Meijer PBL, Marijnissen ACA, van Laar JM, et al. Optical spectral transmission to assess inflammation in hand and wrist joints of rheumatoid arthritis patients. Rheumatology 2018;57:865-72.
15. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham

CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
16. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Østergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003;48:955-62.
17. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: A EULAR-OMERACT ultrasound taskforce - Part 1: Definition and development of a standardised, consensus-based scoring system. RMD Open 2017;3:e000428.
18. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641-9.
19. Dougados M, Jousse-Joulin S, Mistretta F, d'Agostino MA, Backhaus M, Bentin J, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. Ann Rheum Dis 2010;69:828-33.
20. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485-7.
21. Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint PV, Filippucci E, et al; OMERACT Ultrasound Task Force. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis 2013;72:1328-34.
22. McNamee R. Regression modelling and other methods to control confounding. Occup Environ Med 2005;62:500-6.
23. Skelly A, Dettori J, Brodt E. Assessing bias: the importance of considering confounding. Evid Based Spine Care J 2012;3:9-12.
24. Hayes GS, Stinson IN. Erythrocyte sedimentation rate and age. Arch Ophthalmol 1976;94:939-40.
25. Ham TH, Curtis FC. Sedimentation rate of erythrocytes: influence of technical, erythrocyte and plasma factors and quantitative comparison of five commonly used sedimentation methods. Med 1938;17:447-517.
26. Talstad I, Haugen HF. The relationship between the erythrocyte sedimentation rate (ESR) and plasma proteins in clinical materials and models. Scand J Clin Lab Invest 1979;39:519-24.
27. Baillet A, Gaujoux-Viala C, Mouterde G, Pham T, Tebib J, Saraux A, et al. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology 2011;50:1137-47.