"Diagnostic value of optical spectral transmission in rheumatoid arthritis: associations with clinical characteristics and comparison with joint ultrasonography."

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Running head: OST value in RA

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 RA patients and 114 controls. OST difference between the two 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 Spearmann's test 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 (AUC) for all 1,251 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 [DAS28 (*rho=0.313*), swollen joint counts (*rho=0.361*), CRP (*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- (*rho=0.442*; *p=0.001)* and a grey-scale-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

RA patients showed higher OST values in comparison to controls. Moreover, OST associated with clinical, US and laboratory disease activity markers.

INTRODUCTION

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 two very important predictors of sustained disease remission and inhibition of radiographic changes (2). Furthermore, tight clinical control in the course of the disease has proven to be an effective strategy in terms of RA activity suppression and long-term outcomes improvement (3–5). Even though the aforementioned aspects of RA management are crucial, their implementation in the routine rheumatology practice can be difficult (6,7). First of all, tight control disease management strategies could burden the rheumatologist (7). Secondly, clinical activity assessment tools such as the Disease Activity Score 28 (DAS28) are partially subjective and do not always depict the real inflammatory burden (8). Therefore, complementary diagnostic tools such as the ultrasound (US) or magnetic resonance imaging (MRI) are in many cases needed. 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, due to inflammation associated changes of vascularity. For the same reason, transmission of light through the inflamed joint decreases (10,11) and OST promises a non-invasive 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 on this setting: ''HandScan''-Hemics®, the Netherlands) (12–14).

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

In every day clinical pracice we have observed that males and obese patients can have higher OST values in comparison to females and subjects with lower BMI respectively. However, to the best of our knowledge, the effect of anthropometric and epidemiologic patient characteristics on OST has not been established so far. Furthermore, sufficient data regarding the diagnostic value of this new promising tool are missing.

Thus, main objectives of the 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 explore relationships of OST with patient -and not only disease-related characteristics, in order to test for possible confounding of anthropometric and epidemiologic parameters on OST results.

MATERIALS AND METHODS

Study populations

OST and clinical examinations were performed in 168 consecutive RA patients 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 hour interval between examinations). As control subjects served 114 hospital co-workers who freely responded to an open call for study-participation, without underlying inflammatory disease, arthralgias, signs of osteoarthritis 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 and diabetes mellitus in both groups. We calculated Body-Mass-Index (BMI) (kilograms/meters^2) and the size of both hands (% mean surface covered by two hands divided by % mean surface of the two glass hand rests). Tender (TJC) and swollen joint counts (SJC) of RA patients as well as patient disease activity on a visual analogue scale (VAS) were examined and documented by the same trained person (C.H.). 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 cyclic citrullinated peptide antibodies (anti-CCP) were assessed by ELISA. X-rays of the hands in two planes were examined by a Radiology-Specialist in order to control for the presence of RA typical erosions (marginal), osteophytes and calcium pyrophosphate dihydrate crystal depositions (chondrocalcinosis).

Optical spectral transmission

OST examinations were performed by trained study nurse staff using the HandScan diagnostic device (Hemics®, The Netherlands). Study nurses were blinded with respect to clinical examination, laboratory and US results.

During the measurement, patients were asked to put their forearms into the HandScan through two 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 which was transmitted through the hands (Figure 1). A complete measurement lasted approximately 100 seconds and consisted of 3 phases: a. a low cuff pressure phase, b. an increased cuff pressure phase and c. a low cuff pressure phase. During the first phase baseline transmission was measured. In the second phase pressure cuff 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.

A built-in software allowed the automatic identification of ''regions-of-interest'' (ROI: wrists, MCP I-V and PIP I-V) and reference areas which 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'' meaning none hypervascularity and ''3'' standing for the highest possible grade of hypervascularity) (14,17). OST scores were generated automatically by the HandScan software after every OST examination (supplementary document 1).

Ultrasound

US was performed by a blinded experienced examiner [K.T., Rheumatologist, certified by the German Society of Ultrasound in Medicine (D.E.G.U.M.)]. A linear transducer (4-13 MHz) of a MyLab70 US-device (Esaote, Italy) operating at a frequency of 13 MHz was used to examine the same joints examined by OST. US protocol was in accordance with the EULAR guidelines with regard to the positioning of the patient and scanning planes (18). Both Gray Scale-(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.

Colour gain was set at the disappearance of colour 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 colour box were adjusted to include the subcutaneous tissue in order 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) (supplemetary document 1). 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 seath (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 graphical method (quantile-quantile plots). Comparison of categorical variables was performed through Fisher's exact test. As OST values were not distributed normally, the difference between patient and control group was evaluated by Mann-Witney U test. This test was also used to analyse associations between OST and binary categorical variables in both groups and to compare median OST values of patients with different DAS28 cut-off values.

Spearman's correlation coefficient *rho* was used in order to assess correlations of OST and continuous characteristics in the two groups.

All statistical adjustments and examination of OST difference between RA patients 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 of ≥ 10% (assumed as the maximum superior limit) (23).

Finally, to assess OST diagnostic performance, receiver operating characteristics (ROC) were performed at a patient level [1. RA group vs. controls and 2. ''active'' RA subgroup (≥1 swollen joint) vs. controls] and at a joint level (dichotomized US-values vs. nummerical OST-values) for wrist, MCP, PIP and all joints. A probability value of 0.05 was considered to be statistically significant. All statistical explorations were performed using the SPSS software 23.0 (Chicago, USA).

RESULTS

OST measurements were performed in 168 RA patients and 114 control subjects (females: 66.1% vs. 77.2 % respectively; *p=0.044*). Descriptive characteristics of both groups are presented in table 1.

In the RA group, OST could be performed in a total of 3,649 joints (47 joints automatically excluded by the OST software due to anatomic anomalies/missing fingers) and in the control group in 2,508 joints. US examinations of the MCP, PIP and wrist joints were performed in 59 patients (1,298 joints).

Receiver operating characteristics

A ROC was performed to test the diagnostic performance of OST compared to US. A joint was considered inflamed when PDUS-Score≥1 and 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 1,251 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).

In order to compare total OST values between RA and healthy controls, 2 additional ROC were performed [1. RA vs. controls and 2. RA subgroup (≥1 swollen joint) vs. controls]. The AUC of the ROC ''RA vs. 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 cut off of 12.99 (Youden Index: 0.336, positive likelihood ratio (LR+): 2.21, negative 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 cut off 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 (10.49-18.48, IQR) vs. 10.32 (7.68-13.91, IQR), $p<0.001$]. Interestingly, BMI, sex and age were statistically identified as possible confounding factors of OST. On the other hand, arterial hypertension, 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 patients group in comparison to the control group [1.89; 95%CI(0.709– 3.070), $p_{adj=}0.002$)]. Thus, RA patients have higher OST-values than controls.

Associated parameters 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=0.31; p<0.001)*, DAS28-CRP *(rho=0.364; p<0.001)* and 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)*, 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*) (Table 2) and osteoarthritis associated with higher OST values (p=0.022, Table 2). There were no statistically significant relationships between OST and nicotine use, arterial hypertension, diabetes mellitus, rheumatoid factor-/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(-0.51-0.266), $p_{adj=}0.185$], 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 hypertension, 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 RA patients were built using a DAS28-ESR cut-off 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 DA28<2.6 had statistically significant lower median OST in comparison to their counter partners [11.30 (8.10-17.56, IQR) vs. 15.90 (11.19-18.55, IQR) respectively; *p=0.003*]. This difference remained statistically significant even after adjustment for the effect of BMI, age and sex [2.404; 95%CI(0.852–3.956), p_{adj}*=0.002*].

In order to test for the presence of OST overlapping values between healthy subjects and patients in remission or between patients with different DAS28 cut off values, 4 different patient-subgroups were built (a. DAS28<2.6; b. 2.6≤DAS28<3.2; c. 3,2≤DAS28<.5.1; d. 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 2.6≤DAS28<3.2 and RA subgroup with 3.2≤DAS28<5.1, OST values showed statistical differences at the level of at least p<0.001 (Figure 2C, Supplementary Tables 1 and 2). 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-score (*rho=0.591, p<0.001*) (Figure 3).

DISCUSSION

In this study we could show 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 three previous explorations performed in RA cohorts, showing moderate-good diagnostic performances of OST in comparison to clinical examination and US (12–14). In our study, ROC between OST and ultrasound 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 recently reported after the installation of a new light source (14). In our exploration, the most modern HandScan version was used.

Furthermore, 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 decrease the intensity of the transmitted light through the joint. Van Onna et al. found similarly 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 this 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 this 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 lie on this particular methodologic difference (27). Safe conclusions about the possible effects

of chondrocalcinosis on OST cannot be made, due to the small amount of patients included having this pathology concomitantly to RA (3.4%).

Finally, none of the prior OST studies has 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 more robust bony, synovial or tendon structures in males and in subjects with larger hands causing 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.

The present study has some limitations regarding the applied diagnostic methodology to assess presence of erosions. Moreover, no X-rays 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 the fact that OST scores are calculated for individual PIP, MCP and wrist joints and not for their adjacent tendons.

To conclude, herein we showed that OST values of RA patients 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.

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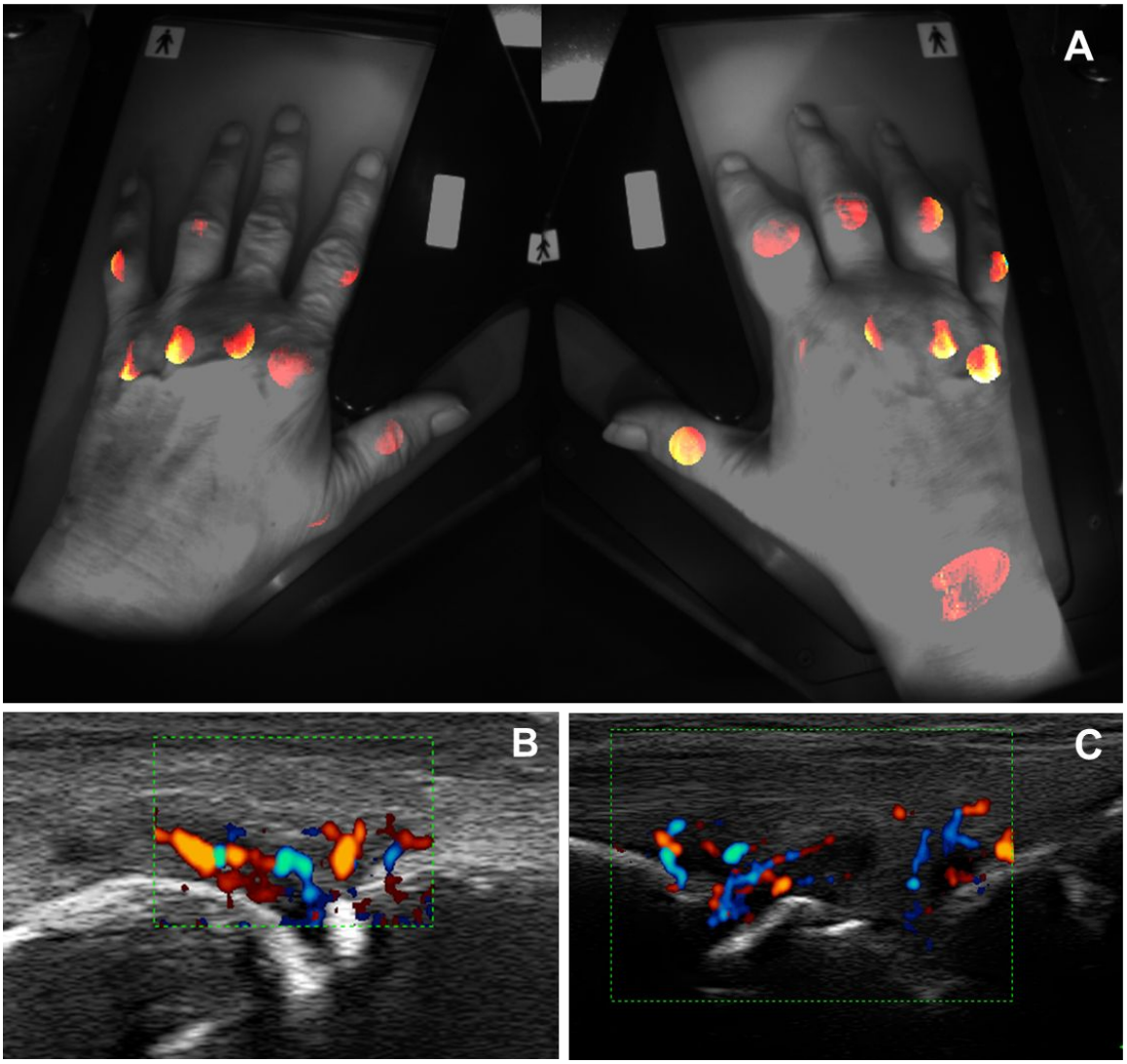

Figure 1. Assessment of inflammation by optical spectral transmission (OST) and ultrasound in the wrists and finger joints of a female patient with rheumatoid arthritis (high disease activity).

A. result of the OST measurement

B. and C. Power Doppler/grey scale ultrasound examination of the left MCP IV and right midcarpal joint respectively (longitudinal views): joint effusions, synovial hypertrophy and increased vascularity.

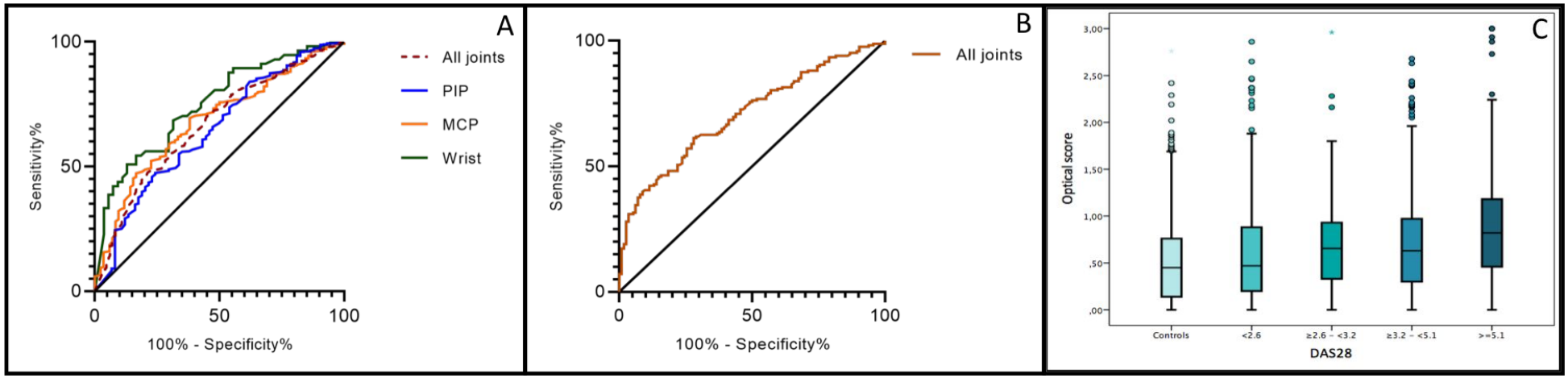

Figure 2. *Receiver Operating Characteristic* curves (ROC) *and Optical Spectral Transmittion (OST) values of patients with different DAS28 cut-offs.*

A. ROC between optical spectral transmission (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 (PIP) joints (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 *b*etween RA and healthy controls at the patient level (''all joints''): Area Under the Curve (AUC=0.71; 95% CI=0.651-0.77).

C. Boxplot graphs regarding median (IQR) optical spectral transmission (OST) single joint values of control group and 4 RA subgroups, according to Disease Activity Score 28 (DAS28) values: a. DAS28<2.6; b. 2.6≤DAS28<3.2; c. 3.2≤DAS28<.5.1; d. DAS28≥5.1

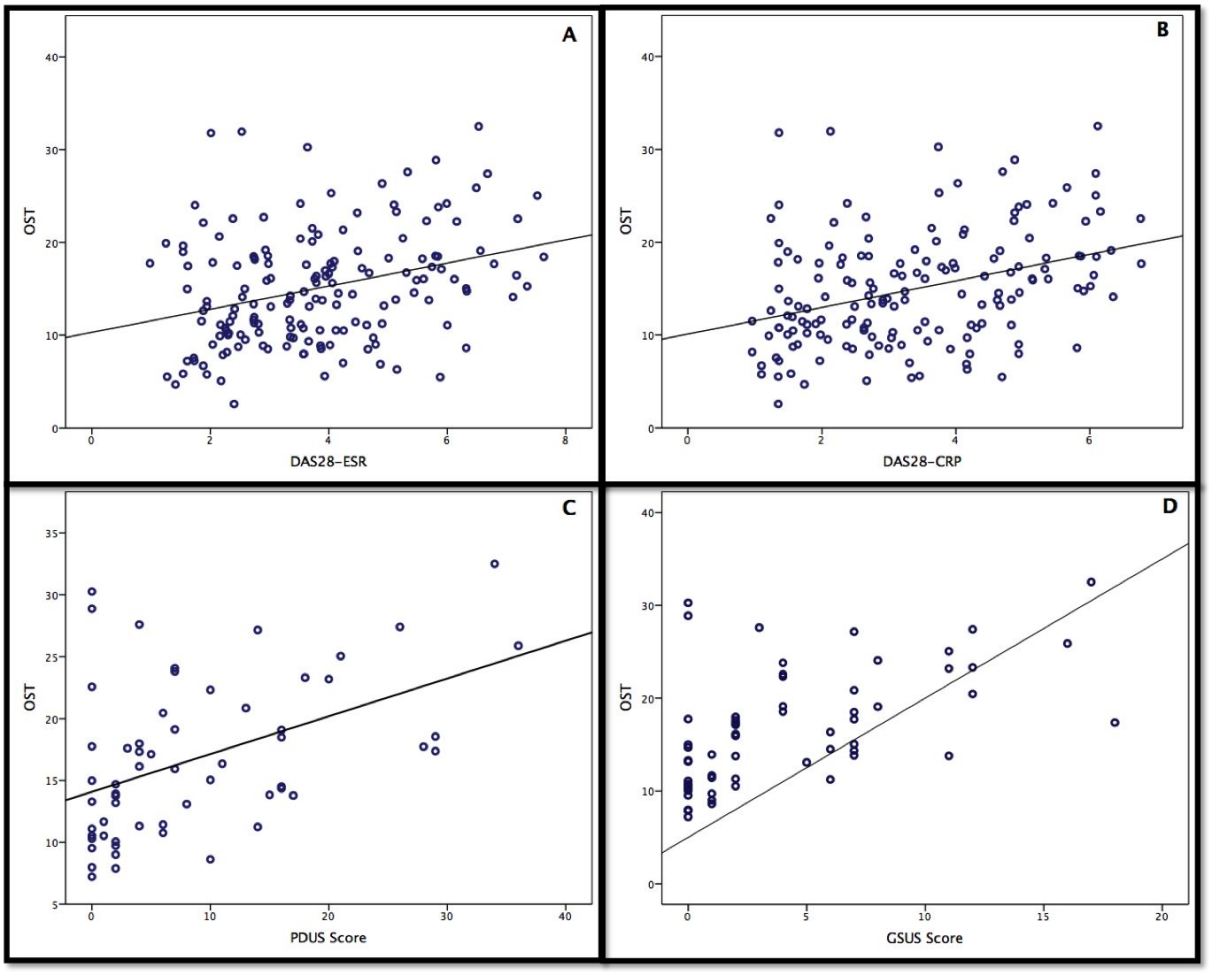

Figure 3. Correlations between optical spectral transmission (OST) and A. Disease Activity Score 28-erythrocyte sedimentation rare (DAS28-ESR) (*p<0.001*), B. DAS28-C-reactive protein (DAS28-CRP) (*p<0.001*), C. power Doppler ultrasound (PDUS) score (*p=0.001*) and D. grey scale ultrasound (GSUS) score (*p<0.001).*

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 *(years)*†	51 (35-57)	60 (54-70)	<0.001*
Sex *(female)*†	77.2%	66.1%	0.047*
Nicotine use *(smokers)*	19.4%	25.7%	0.300
Arterial Hypertension	19.4%	39.9%	<0.001*
BMI†	25.50 (21.72-28.55)	25.94 (24.00-30.72)	0.007*
Diabetes *(yes)*	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)	-
DAS 28 ESR†	-	3.67 (2.53-4.93)	-
DAS 28 CRP†	-	3.20 (2.00-4.66)	-
Disease duration *(years)*†	-	3.00 (1.00-7.00)	-
Erosions *(yes)*	-	33.9%	-

Osteoarthritis *(yes)* ¶	-	14.3%	-
Chondrocalcinosis *(yes)*	-	3.4%	-
Tenosynovitis *(yes)*	-	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%	-

†Data are presented as median (interquartile range) as they are not normally distributed

*$p < 0.05$

¶ Distal intraphalangeal joints excluded, since not examined by OST or Ultrasound

OST optical score total, *BMI* body mass index, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *VAS* visual analog scale, *DAS28 ESR* disease activity score 28 (erythrocyte sedimentation rate), *DAS28 CRP* disease activity score (C-reactive protein), *PDUS score* power Doppler ultrasound score, *GSUS score* grey scale ultrasound score, *sDMARD* synthetic disease modifying antirheumatic drugs, *bDMARD* biologic disease modifying antirheumatic drugs, *JAK* Janus Kinase

‡ combination of different 2 sDMARD or sDMARD with bDMARD or sDMARD with JAK inhibitor

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

	Spearmann's rho	Significance (p)		Median (IQR)	Significance (p)
			Sex		
Age† *(years)*	0.276	<0.001 *	*Female*	12.64 (9.00-16.75)	<0.001 *
			Male	17.75 (14.60-22.44)	
			Nicotine use		
BMI† *(kg/m²)*	0.316	<0.001*	*No*	14.50 (10.76-18.33)	0.584
			Yes	14.51 (8.75-19.12)	
			Hypertension		
ESR† (mm/h)	0.171	0.027* (0.02*)‡	*No*	14.12 (9.00-18.28)	0.053
			Yes	15.93 (11.64-18.55)	
			Diabetes		
CRP† (mg/l)	0.389	<0.001*(0.001*)‡	*No*	14.12 (10.13-18.37)	0.056
			Yes	17.60 (13.66-18.55)	
			RF		
TJC†	0.194	<0.001*(0.005*)‡	*Negative*	14.24 (10.78-17.80)	0.956
			Positive	14.72 (10.17-18.51)	
			Anti-CCP		
SJC†	0.361	<0.001*(0.001*)‡	*No*	14.02 (10.70-17.70)	0.553
			Yes	15.45 (10.11-18.66)	
			Osteoarthritis¶		
VAS† (mm)	0.299	<0.001*(0.001*)‡	*No*	14.1 (9.86-18.23)	0.022 *
			Yes	17.6 (13.22-22.47)	
			Erosions		
DAS28-ESR†	0.313	<0.001*(0.001*)‡	No	14.25 (10.53-18.24)	0.793
			Yes	15.27 (9.61-19.59)	

DAS28-CRP†	0.364	<0.001*(0.001*)‡	**Tenosynovitis**		
			No	14.31 (10.47-20.92)	0.140
			Yes	17.04 (13.16-21.47)	
Hand-size† (%)	0.462	<0.001*(0.185)‡	**Chondro-calcinosis**		
			No	14.46 (10.05-18.49)	0.814
			Yes	14.58 (12.83-17.10)	

Spearmann's († not normal distribution) tests were performed to investigate the relationships between OST and quantitative patients characteristics.

Mann Whitney U test was used to investigate the relationships between OST and qualitative patients characteristics.

‡ in parentheses *p* values adjusted for age, sex, BMI by multiple regression

¶ Distal intraphalangeal joints excluded, since not examined by OST or Ultrasound

*$p < 0.05$

OST optical score total, *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* disease activity score 28 (erythrocyte sedimentation rate), *DAS28-CRP* disease activity score 28 (C-reactive protein)

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

	Spearmann's rho	**Significance (p)**		**Median (IQR)**	**Significance (p)**
			Sex		
Age† *(years)*	0.036	0.702	*Female*	9.45 (6.50-11.91)	<0.001 *
			Male	14.95 (12.41-17.55)	
			Nicotine use		
BMI†*(kg/m²)*	0.240	0.015*	*No*	10.20 (7.24-14.76)	0.755
			Yes	10.63 (9.01-12.00)	
			Hypertension		
Hand-size†(%)	0.477	<0.001*	*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	16.55 (12.64-20.47)	

Spearmann's tests († not normal distribution) were performed to investigate the relationships between OST and quantitative patients characteristics.

Mann Whitney U test was used to investigate the relationships between OST and qualitative patients characteristics.

*$p < 0.05$

OST optical spectral transmission, *BMI* body mass index