

Enhanced Optical Imaging of Proximal Human Interphalangeal Joints Using Skin Optical Clearing

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Abstract. In this study we have analyzed the change in the intensity distribution of three-wavelength transillumination images of human interphalangeal joints under the action of the optical clearing agent. RheumaSens medical scanner prototype with the following wavelengths: 660, 850, and 905 nm, has been tested. A water solution of glycerol (70%) and DMSO (5%) has been used as an optical clearing agent, and sonophoresis has been applied for enhance of skin permeability. Eight healthy volunteers and a volunteer with rheumatoid arthritis have been investigated. As a result, we have obtained an increase in the contrast of joint images within 10 min: 1.2 ± 0.14 , 1.16 ± 0.15 , and 1.16 ± 0.02 folds at the wavelengths of 660, 850, and 905 nm, respectively. It has been shown an effect of skin optical clearing on the enhancement of the images of joint with rheumatoid arthritis in the transillumination mode. © 2024 Journal of Biomedical Photonics & Engineering.

Keywords: optical clearing; laser transillumination; optical imaging; proximal interphalangeal joints; rheumatoid arthritis.

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1 Introduction

The most common cause of severe inflammation of the joints is rheumatoid arthritis (RA). RA is a disease of unknown etiology that results in chronic, systemic inflammation that can affect many organs and tissues. This disease can cause inability to move and painful synovial joints, which in turn can lead to significant loss of function and mobility if not treated properly. Thus, it is vital to diagnose and treat this disease early and aggressively before damage ensues [1, 2].

Diagnosing RA requires a physical exam, blood tests and scans like X-ray, MRI, or ultrasound. Testing for serum antibodies to anti-citrullinated protein antibodies and rheumatoid factor continues to be valuable in the diagnostic evaluation of patients with suspected RA, and these antibodies serve as biomarkers of prognostic significance. Advances in imaging modalities assist

clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage [1]. Conventional radiography is still used as a standard of reference in detecting disease progression and is therefore used as an indicator of prognosis, however X-rays may not show anything abnormal in early arthritis and current inflammatory disease activity [2]. MRI is more sensitive in comparison with conventional radiography in detection of early RA, but its usage may be limited by availability, costs, and workflow consideration [3]. Compared with MRI, ultrasonography is more readily available and less expensive, and therefore it is often used for fast assessment of joint inflammation [4].

Synovium is a highly specialized tissue whose main function is to maintain healthy lubrication and nutrition. The process of RA involves an inflammatory response of

the capsule around the joints secondary to swelling (turgescence) of synovial cells, excess synovial fluid (synovia), and the development of fibrous tissue (pannus) in the synovium [1]. Pathological changes lead to changes in the optical properties of the synovium with an increase in both absorption and scattering compared to healthy tissue. The main variations in absorption and scattering coefficients in sinovia and synovial tissues are observed in red and near-IR spectral region [5]. Therefore, optical imaging is one of the perspective methods for diagnostics of the joint pathologies due to its absolutely safety, high sensitivity, and unique specificity in comparison to other biomedical imaging modalities. Some methods of RA optical detection at an early stage are presented in the literature. For example, a method of deconvolution for laser based images was proposed for monitoring RA in Ref. [6]. In Ref. [7] it was offered to improve the diagnostic sensitivity of RA by using overlapped pseudo-colored images at different wavelengths. The techniques of diffuse optical tomography [8], fluorescence optical imaging [9], and fluorometric imaging using bioengineered targeted agents of the blood vessel, bone, and cartilage in combination with the customized optical fluorescence imaging system [10] were also proposed to diagnose RA at an early stage. It was suggested to distinguish septic arthritis patients from other causes of joint effusion by using mid infrared deoxygenated spectroscopy [11]. Authors of Ref. [12] designed a RA system using a ring-array sensor to image human finger vasculature. It was shown that this system has the potential to help visualize abnormal vascularization as an important marker of inflammatory arthritis.

Transillumination can be used successfully for optical imaging of the internal structure of joints. An experimental laser diode based setup for the transillumination of rheumatoid finger joints was described in Refs. [13–15]. However, strong light scattering in tissues causes image blurring. The relatively low contrast and poor spatial resolution of the technique, which do not allow one to find the difference between healthy and pathology joints precisely, could be improved by reduction of skin light scattering at using of optical clearing (OC) technique. Pilot experiments for enhancement of optical imaging of PIP joints were carried out *in vivo* using dehydrated glycerol and hand cream with urea (5%) [16]. It was found that a one-hour glycerol and hand cream topical application resulted in ~1.4 and ~1.1-fold contrast decreasing at 670 nm, respectively. At the wavelengths 820 nm and 904 nm the image contrast increased in ~1.5 and ~1.7 folds, respectively, for glycerol application and in ~1.3 and ~1.1 folds, respectively, for the hand cream application. The contrast rise in the NIR wavelength region was caused by light scattering reduction due to skin optical clearing and, correspondingly, an increase in the intensity of light detected on the opposite side of the finger. Contrast decrease at the wavelength 670 nm during skin optical clearing could be caused by an increase in light absorption by deoxyhemoglobin of venous blood.

As an optical clearing agent (OCA) glycerol is widely used at skin optical clearing [17–22] because of its hyperosmolarity and high refractive index. Glycerol is a highly effective agent providing three major mechanisms of OC: osmotic dehydration of tissue, refractive index matching of scatterers and interstitial fluid, and collagen dissociation [23]. Optical clearing potential of solutions with different concentration of glycerol has been compared theoretically and experimentally [18–22]. Aqueous 70%-glycerol solution has shown the best result due to much low viscosity at dilution by water and still sufficient osmolarity and refractive index.

Dimethyl sulfoxide (DMSO) is an effective enhancer of the diffusion of optical clearing agents through the *stratum corneum* of the epidermis [24, 25]. The mechanism of action of DMSO is due to its ability temporarily and partially dissolve the lipid base of the *stratum corneum* of the epidermis and create pores in it [26]. Due to this property, DMSO increases the rate of transdermal penetration of both hydrophilic and lipophilic agents. For *in vivo* topical applications, low concentration DMSO is preferred because it has no side effects and has been used for many years to reduce inflammation in arthritis [27]. Also, 10%-DMSO solution has been shown to induce skin edema [28]. Thus, the component ratio of 70%-glycerol/5%-DMSO may provide a safe and effective composition for skin optical clearing.

In addition to DMSO application, sonophoresis (US) as an effective physical enhancer of the OCA diffusion in skin [29, 30], can be used. It was shown in Ref. [29] that the combined use of DMSO, US, and OCA reduces the attenuation coefficient of light in skin by about 31% within 4 min, compared with a decrease of 5% achieved when using a combination of DMSO-OCA for 20 min.

The optimization of the device for transillumination imaging of finger joints and development of an approach to the rapid skin OC *in vivo* are important tasks for potential implementation of the method into clinical practice.

The goal of this study is developing the approaches to improve transillumination optical images of human finger capsule synovial structures due to the application of OC technique.

2 Materials and Methods

2.1 Object of Study

The experiments were carried out *in vivo* on proximal interphalangeal (PIP) joint of the middle and ring fingers of the left and right hands of eight healthy volunteers (seven males aged 20 years and a female aged 32 years). Average thickness of the investigated PIP joints was 16.8 ± 0.9 mm. The PIP joint of the middle finger (thickness 16 mm) of the right hand of a female volunteer (age 32) with the first degree of RA was also examined.

An authorization for the human skin studies *in vivo* was obtained from the Saratov State Medical University

Ethical Committee (protocol no. 11 by 7 June 2022). All volunteers gave their informed consent for the study.

2.2 Experimental Setup

To assess the condition of the patient's finger joints a prototype of medical scanner RheumaSens (art photonics GmbH, Berlin, Germany) was used. The RheumaSens (Fig. 1a) consists of transparent spherical hand support (1), set of quickly replaceable adjustable hand holders for different hand sizes (2), three-wavelength laser emitter (660 nm: FP-D-660-40P-C-C, 850nm: FP-D-850-40P-E-C, 905nm: FP-D-905-7P-E-C, FLEXPOINT®, Laser Components GmbH, Olching, Germany) moving around on a 2-axis robotic arm (3 and detailed image is in Fig. 1b), computer controls for emitter and arm positioning, NIR extended CCD camera IDS uEye UI-1240ML-NIR-GL (4) with real-time image display on computer screen, automated image registration on each wavelength.

The power of all lasers was set to 5 mW in order to comply with European safety regulations.

The imaging scheme is shown in Fig. 1c. By adjusting the focus and aperture of the camera lens it was possible to adjust the (vertical) position of the recording zone in the joint and the depth of field.

As a result of the experiment, a set of images was obtained (Fig. 1d), which represent two-dimensional

maps of the scattered light intensity distribution on the underside of the finger.

2.3 OCA and Experimental Design

A mixture of glycerol (70%), DMSO (5%) and distilled water (25%) was used as the OCA for the testing of the possibility of image improvement of the joints. The spectral dependence of the refractive index was measured using an Abbe multiwave refractometer (Atago DR-M2/1550, Japan) in the range 450–1550 nm and approximated to obtain the following refractive index values at the wavelengths used: 1.4409 (660 nm), 1.4371 (850 nm), and 1.4361 (905 nm).

The OCA was applied topically on the investigated skin site and was not subsequently added. The images of the PIP joints were registered before and for 60 min after the OCA application every 5 min.

To enhance the skin permeability for OCA we used the Dynatron 125 ultrasonic (US) device (Dynatronics, USA) for sonophoresis. The following exposure parameters were selected: power density 1.5 W/cm², frequency 1 MHz, exposure time 5 min in pulse mode with a duty cycle of 50%. The diameter of the US probe was 2.2 cm. OCA was used as a contact substance during sonication.

The measurements were obtained before, after the OCA application with sonication, and then for 15 min every 5 min.

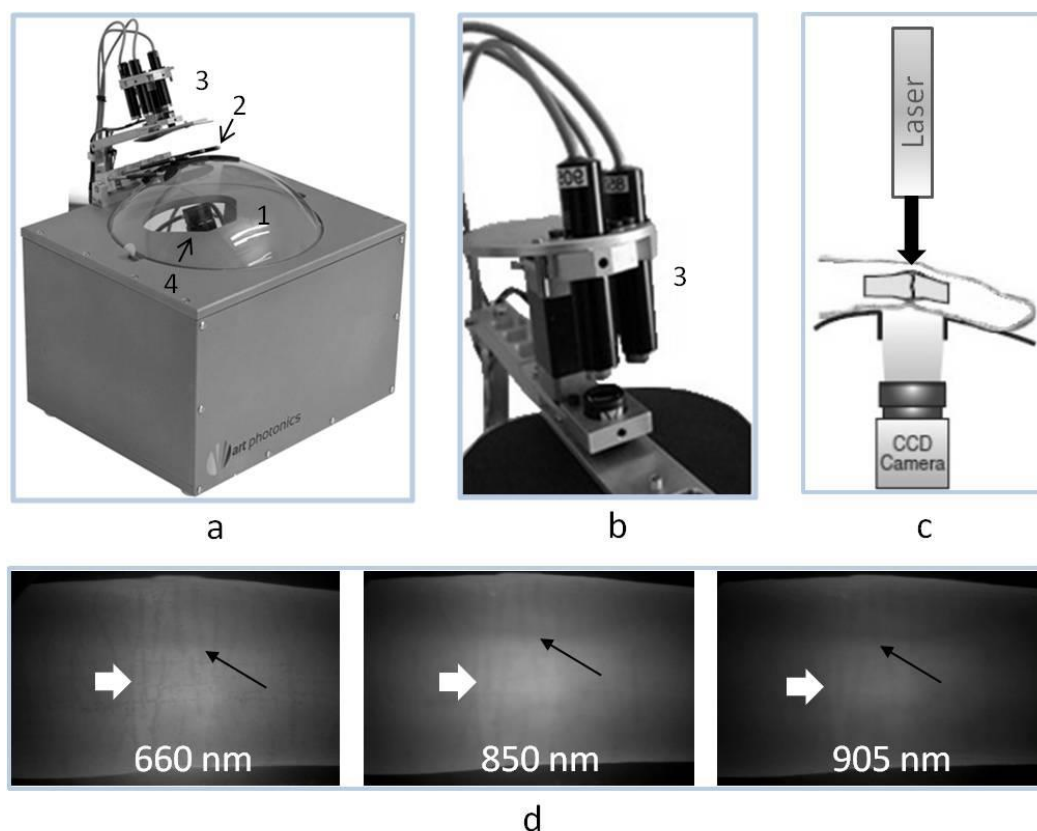


Fig. 1 (a) RheumaSens medical scanner: general view; (b) three-wavelength laser emitter; (c) a scheme for laser illumination of a finger and detection of transmitted light; and (d) images of the interphalangeal joint in transmission mode at three wavelengths: 660 nm, 850 nm and 905 nm. The white arrows point to the joint and the black ones point to the blood vessels.

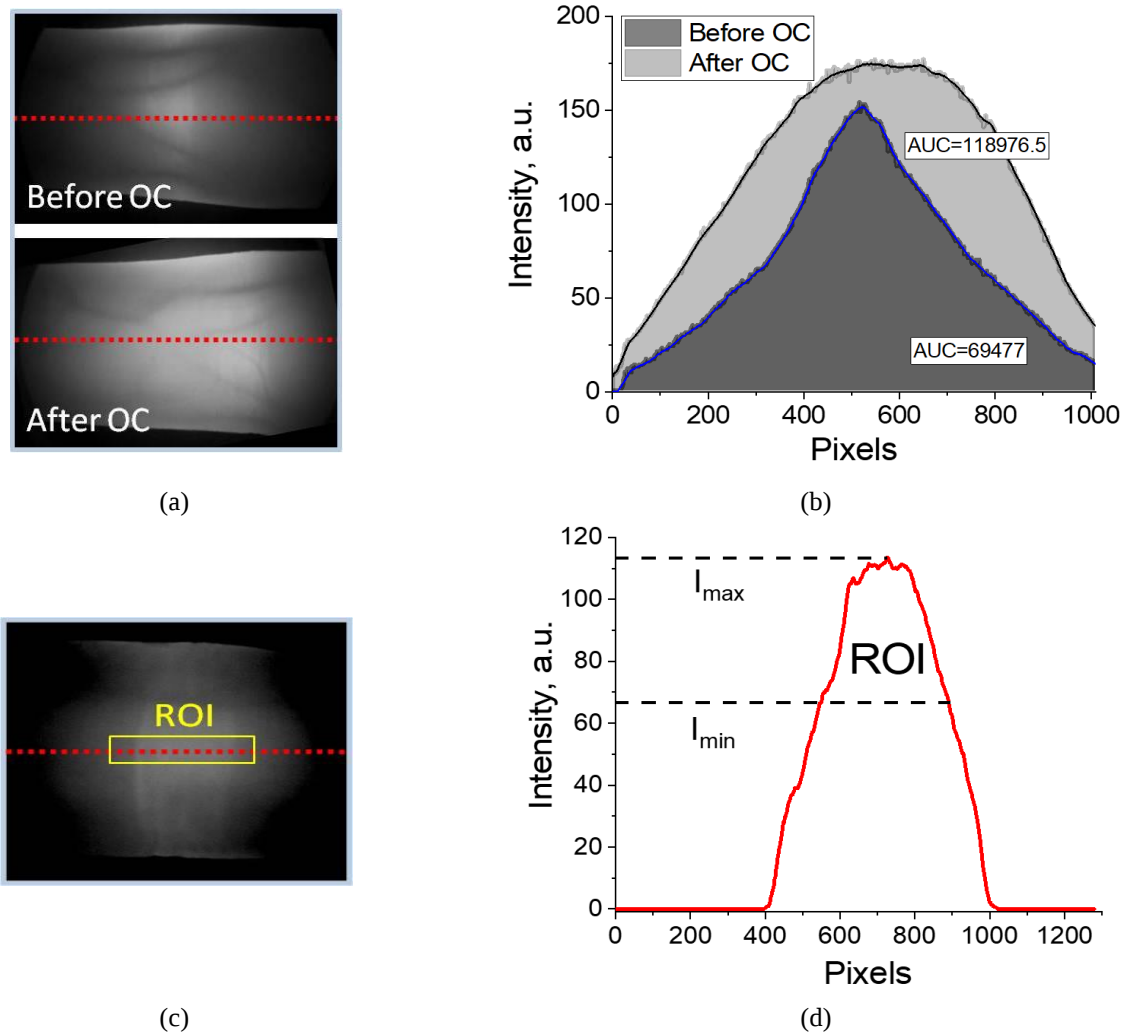


Fig. 2 (a) Images of the finger section in transillumination mode at the wavelength 850 nm and (b) typical profiles of the intensity of the transmitted light with the areas under the curves (AUC), obtained before applying OCA and after 60-min exposure. The parameters were calculated along the red dotted line. (c) The region of interest (ROI) (d) and averaged profile of intensity in the ROI. I_{max} and I_{min} correspond to the maximal and minimal brightness of the pixels in the ROI, respectively.

2.4 Processing of Experimental Data

To evaluate the changes in transillumination images of PIP joint during optical cleaning, the intensity profile of the transmitted light was calculated using the pixel brightness of the finger section images in the range 0–255. The intensity profile was built along the X-axis (red dotted line in Fig. 2a) approximately in the middle of the finger image using the built-in MatLab (The MathWorks, Inc., USA) function. The curves were smoothed by 25 points using the built-in OriginPro (Origin Corp., USA) function “adjacent-averaging”. In addition, the area under the curves (AUC) was calculated, as shown in Fig. 2b. All parameters were calculated for similar experiments, normalized to the initial value and averaged.

Processing of the experimental data allowed calculating the contrast in the region of interest (ROI) near the middle of the finger joint (see Fig. 2c). ROI included the intensity profile corresponding to the image of the joint with the adjacent areas on the right and left to

calculate the contrast of the joint image compared to its immediate surroundings, since the entire observed section of the finger became brighter during the clearing process. The edges of the image were excluded because the pixel brightness in these areas was always almost zero. The calculation of the contrast was performed using the expression $C = (I_{max} - I_{min}) / (I_{max} + I_{min})$, where I_{max} is the maximal brightness and I_{min} is the minimal brightness of the pixels in the ROI (see, Fig. 2d).

3 Results

Fig. 3 shows kinetics of the calculated parameters of the PIP joint images obtained for three wavelengths and normalized on the initial values before OC. It is well seen that 10 min after the OCA application, both the intensity and the AUC lower than in the initial moment. The decrease in both intensity and AUC immediately after application of OCA is apparently explained by a decrease in transmitted light due to an increase in the specularly reflected flow from the skin surface.

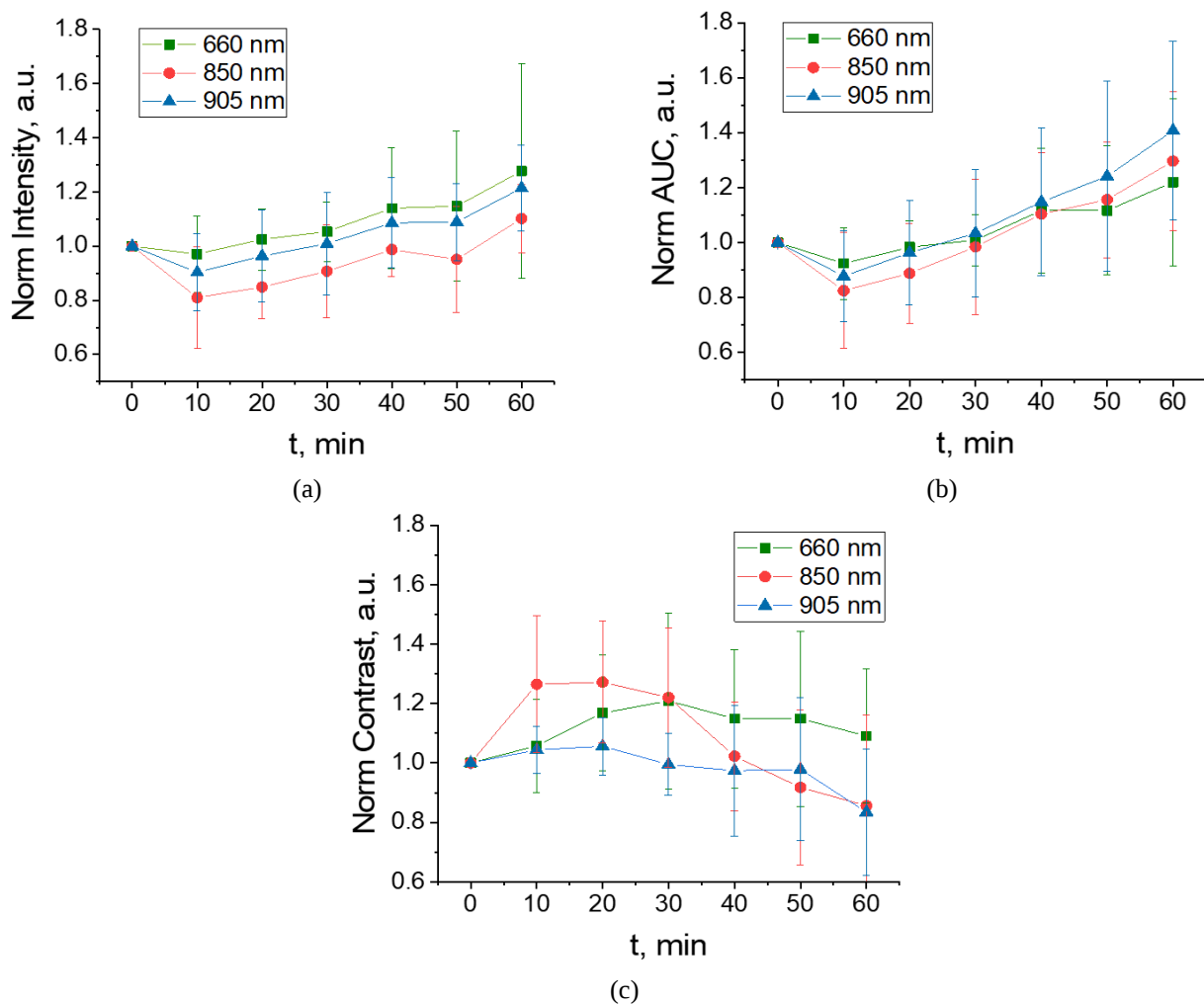


Fig. 3 (a) Kinetics of the normalized maximal intensity of the transmitted light, (b) the area under the curves (AUC) of the intensity, and (c) the contrast of the PIP joint image during optical clearing averaged by seven healthy volunteers.

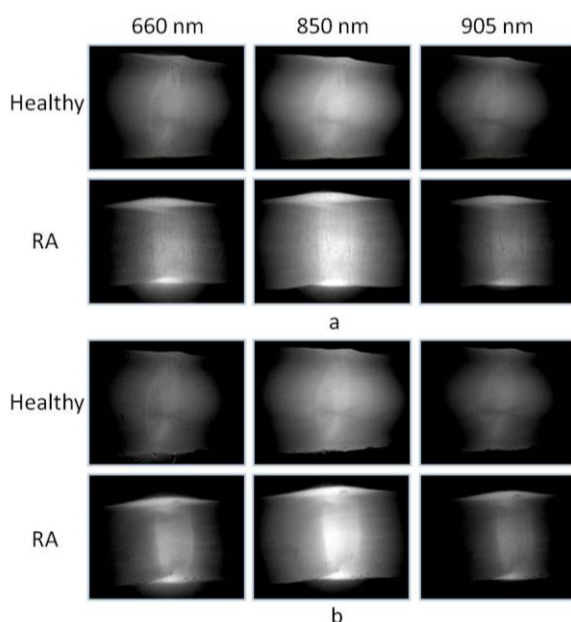


Fig. 4 Images of a healthy joint and an RA joint in the transillumination mode at three wavelengths (a) without optical clearing and (b) 10 min after applying OCA.

However then, the illumination of the opposite surface of the finger gradually increased, which can be seen from an increase in both the brightness of the pixels in the PIP region and the illumination area. The average increase in transmitted light intensity was estimated to be 1.28 ± 0.4 , 1.1 ± 0.1 , and 1.2 ± 0.2 folds at wavelengths of 660, 850, and 905 nm, respectively. The average AUC increased by 1.22 ± 0.3 , 1.3 ± 0.25 , and 1.41 ± 0.3 folds at wavelengths of 660, 850, and 905 nm, respectively. The large standard deviation is caused by significant variation in finger thickness.

Kinetics of the contrast of the PIP joint images, on average, demonstrates complex behavior (Fig. 3c). This is caused by the dependence of contrast on the relation of maximum and minimum pixel brightness within the ROI. Thus, to increase the contrast of the image, it is necessary that the brightness of the image of the joint increases, and the brightness outside the joint decreases. However, from Figs. 3a, b it follows that an increase in illumination intensity as a result of optical clearing of the skin leads to an increase in both the maximum brightness and the illumination area in the ROI, therefore, the brightness of pixels outside the junction region also increases.

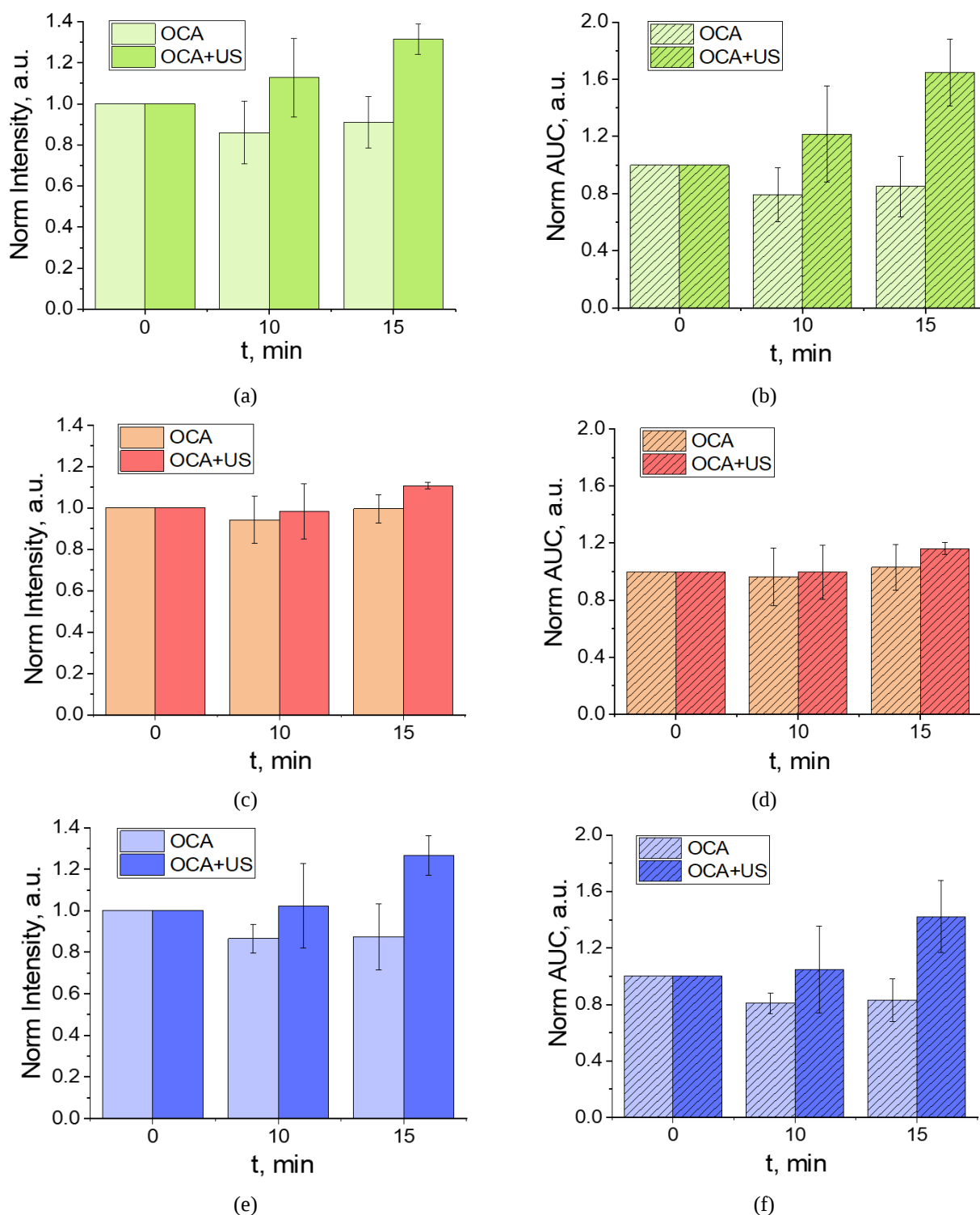


Fig. 5 (a, c, e) Comparative kinetics of the normalized maximal intensity of the transmitted light and (b, d, f) the area under the curves (AUC) of the intensity during optical clearing without/with sonication at the wavelengths: 660 nm (a, b), 850 nm (c, d), and 905 nm (e, f).

The peak contrast value was achieved in different times at the wavelengths used: about 10–20 and 30 min at wavelengths of 850 and 660 nm, respectively. At a wavelength of 905 nm, the contrast tended to decrease within 60 min. On average, the contrast increased by 1.21 ± 0.3 (in 30 min), 1.27 ± 0.2 (in 20 min), and

1.06 ± 0.09 (in 20 min) folds at wavelengths of 660, 850, and 905 nm, respectively.

Fig. 4 presents images of the PIP joints of the middle fingers obtained from a healthy volunteer (female, 32 years) and a volunteer with RA (female, 32 years). The PIP joint looks like a lighter area. The observation time was limited to 10 min, since the images of the joint

with RA had already reached a maximum brightness of 255 pixels at a wavelength of 850 nm. The improvement in the details of the image of the RA joint after the application of OCA is clearly visible. For a healthy joint, the improvement is imperceptible. Apparently, this is caused by differences in the thickness of the fingers in the study area: in healthy volunteers and volunteers with RA, it is 18 and 16 mm, respectively.

For improvement of the joint visualization OCA application was combined with sonophoresis. Fig. 5 shows the normalized intensity and AUC in the group using US to accelerate skin optical clearing. Columns with light shades of color correspond to the values of the

studied parameters when OCA has been applied without sonication. During observation, the parameter values generally decreased. When using US (columns with more saturated colors), they increased immediately after the treatment. The exception was images at a wavelength of 850 nm. In this case, the intensity and AUC of the initial images were quite high, and significant changes in parameters were not noticeable.

The images of the same healthy PIP joint and the contrast values are shown in Fig. 6. It is clearly seen that the best visualization of the joint was achieved after optical clearing with sonophoresis during 10 min. It matches with kinetics of the contrast of the joint images.

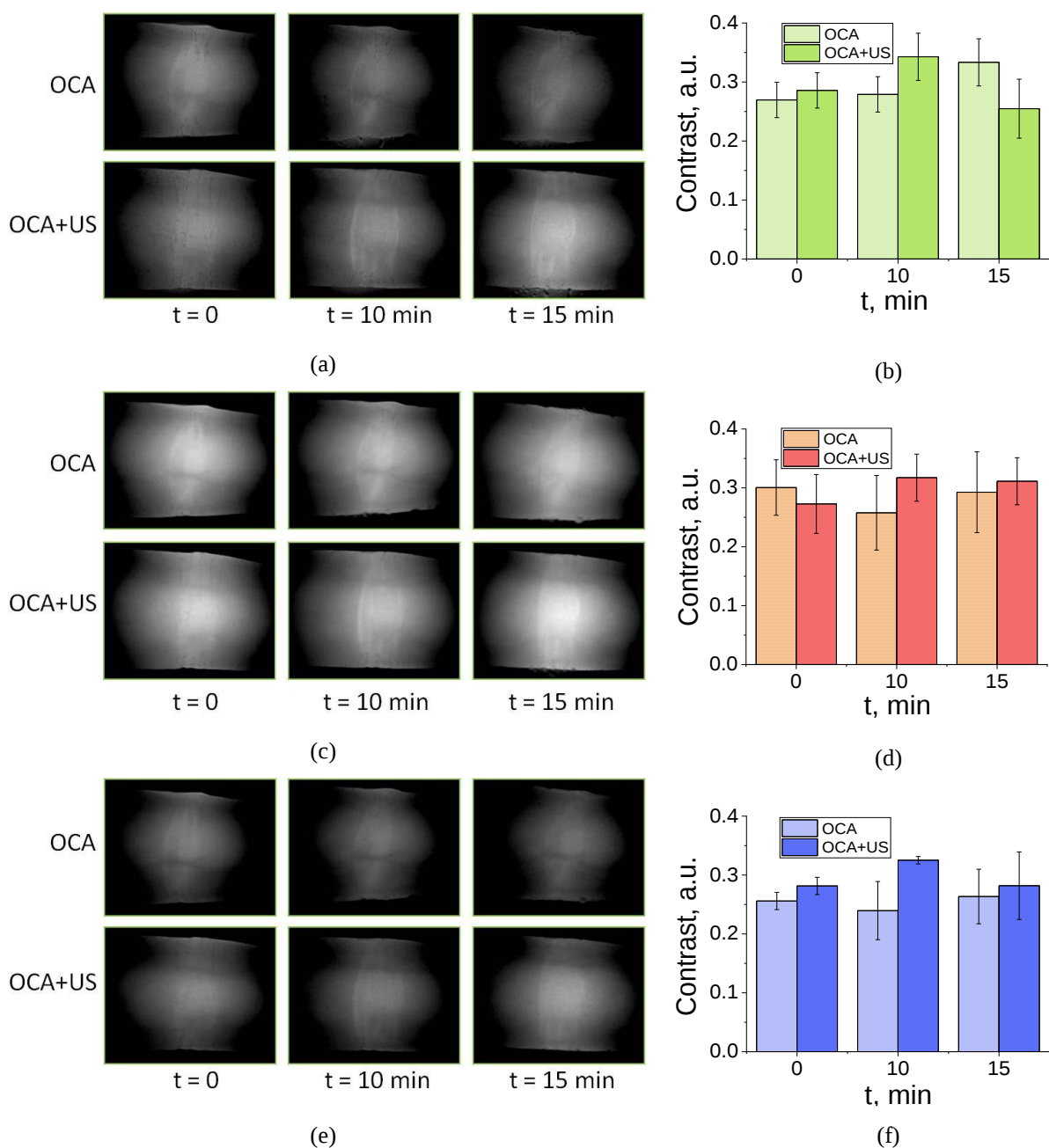


Fig. 6 (a, c, e) Typical images of a healthy joint in transmission mode and (b, d, f) comparative kinetics of the contrast of the joint image during optical clearing without/with sonication at the wavelengths: (a, b) 660 nm, (c, d) 850 nm, and (e, f) 905 nm.

Table 1 Absorption coefficient (μ_a) and reduced scattering coefficient (μ_s') of a healthy and RA diseased human finger joint *ex vivo* at three wavelengths. The data presented in the form of averaged values $\pm$ standard deviation are obtained from Ref. [5].

	μ_a , 1/cm (Healthy/RA)			μ_s' , 1/cm (Healthy/RA)		
	660 nm	850 nm	905 nm	660 nm	850 nm	905 nm
Synovia	(0.04 $\pm$ 0.015)/ (0.11$\pm$0.1)	(0.025 $\pm$ 0.02)/ (0.09 $\pm$ 0.07)	(0.065 $\pm$ 0.01)/ (0.09 $\pm$ 0.01)	(0.06 $\pm$ 0.01)/ (0.13$\pm$0.06)	(0.1 $\pm$ 0.03)/ (0.135 $\pm$ 0.06)	(0.055 $\pm$ 0.006)/ (0.085 $\pm$ 0.012)
Synovial tissues	(0.16 $\pm$ 0.03)/ (0.25$\pm$0.03)	(0.1 $\pm$ 0.01)/ (0.13 $\pm$ 0.1)	(0.17 $\pm$ 0.04)/ (0.14 $\pm$ 0.01)	(6.0 $\pm$ 0.5)/ (11.5$\pm$4.5)	(5.0 $\pm$ 0.8)/ (6.0 $\pm$ 1.5)	(3.5 $\pm$ 0.8)/ (6.3$\pm$1.8)

Relative increase in the contrast for the group with US treatment was estimated as 1.2 ± 0.14 , 1.16 ± 0.15 , and 1.16 ± 0.02 folds at the wavelengths of 660, 850, and 905 nm, respectively. During this time interval in the group without sonophoresis the following increased contrast was achieved: 1.06 ± 0.16 , 1.26 ± 0.2 , and 1.04 ± 0.08 folds at the wavelengths of 660, 850, and 905 nm, respectively. Thus, significant enhancement in the visualization of the PIP joint due to sonophoresis was observed only for the wavelengths 660 and 905 nm.

4 Discussion

The development of optical methods of RA diagnostics requires knowledge of optical parameters of healthy and pathological PIP joints. Lichter et al. measured the transmission of a set of wavelengths by a healthy finger joint: 650, 710, 730, 830, and 930 nm using a multispectral diffuse optical tomographic imaging system [15]. These wavelengths were chosen as optimal for differentiation of main chromophores, which are oxyhemoglobin, deoxyhemoglobin, water, and lipids [31]. The maximum transmission in the center of the joint was obtained at a wavelength of 830 nm [15].

The affected joints of patients with RA are characterized by increased metabolism, which manifests itself in lower local oxygenation (hypoxia) compared to healthy joints [32]. To meet this increased metabolism, the regulation of blood vessel formation (synovial angiogenesis) is also enhanced [33]. The absorption coefficient of deoxygenated blood is an order of magnitude higher than that of oxygenated blood at a wavelength of 660 nm [34]. These pathological changes lead to a significant change in the absorption of the synovium compared to healthy tissue in this spectral range. Spectra of absorption and reduced scattering coefficients of synovialis in a healthy and a pathological state in the range of 630–1100 nm are presented in Ref. [5]. Table 1 shows the values for three wavelengths used in our study.

It is clearly seen that the minimum absorption of healthy joints occurs in the spectral range of about 850 nm. Thus, it is possible to visualize the structure of the joint. However, changes in absorption and scattering caused by the development of pathological processes in the synovial and synovial tissues are insignificant in this area due to the large deviation of values for RA tissues.

A significant increase in both absorption and reduced scattering coefficients in the synovia, as well as in synovial tissues, is observed at a wavelength of 660 nm due to the presence of deoxyhemoglobin. A registered increase in scattering is also observed in pathological synovial tissues at a wavelength of 903 nm.

In RA, bone edema (i.e., free water in tissues), detected by MRI, is a marker of inflammation [3, 4, 35]. A prolonged inflammatory process reduces scattering in tissues since the presence of additional water leads to swelling of the collagen fibers of connective tissue and reduces the relative refractive index. Thus, the intensity of red-NIR light transmitted through the joint with RA may be higher than in a healthy joint. This can be seen in Fig. 4a.

However, reliable differentiation of healthy and pathologically altered joints using variations in optical properties and, thus, accurate optical diagnosis of RA is difficult due to the high scattering of surrounding tissues, including skin and muscles. For example, the depth of light penetration into the skin was estimated from 2 to 2.5 mm in the range of 660–900 nm [36]. A comparison of images of healthy joints and RA joints in the transillumination mode shows that the RA joint is visualized worse without optical clearing than a healthy joint. Apparently, this may be caused by increased absorption and scattering of the synovial membrane. Increasing the contrast of images due to optical clearing provides improved visualization of joint details. Using US to accelerate the penetration of OCA into the skin allows achieving maximum contrast within 10 min (Fig. 6).

However, too high illumination of the surrounding tissues can interfere with clear visualization of the joint. Therefore, the use of a specific approach depends on the thickness of the fingers. In particular, in a volunteer with RA, the maximum contrast at the wavelength of 850 nm was obtained after 10 min without the use of sonophoresis (Fig. 4b).

5 Conclusions

In this paper we have demonstrated that topical application of OCA (e.g. water solution of glycerol (70%) with DMSO (5%)) to human skin in area of finger joint allows one to improve the contrast of joint optical transillumination images. It has been found that one-hour

OCA application on the human skin results in the contrast increasing by 1.21 ± 0.3 (in 30 min), 1.27 ± 0.2 (in 20 min) and 1.06 ± 0.09 (in 20 min) folds at wavelengths of 660, 850, and 905 nm, respectively. Further application of the OCA leads to the contrast reducing due to the growth of the illumination of the surrounding tissues. Combination of OCA with sonophoresis accelerates achievement of maximum contrast within 10 min: 1.2 ± 0.14 , 1.16 ± 0.15 , and 1.16 ± 0.02 folds at the wavelengths of 660, 850, and 905 nm, respectively.

In this study, we only focused on the effect of optical clearing on the joint transillumination images. Although the study involved only one volunteer with early-stage rheumatoid arthritis, the results reliably showed the effect of skin optical clearing on improving transillumination images of such joints. In the future, we plan to expand the group of volunteers with different degrees of rheumatoid

arthritis, age and gender to develop a methodology for differentiating pathology. It can be assumed that the combination of all wavelengths accompanied by optical clearing will provide the most complete information about the joint condition and will allow differentiating between diseased and healthy joints using machine learning.

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Disclosures

The authors declare that they have no conflict of interest.

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