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High resolution imaging of acne lesion development and scarring in human facial skin using OCT-based microangiography

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Abstract

Background and Objective—Acne is a common skin disease that often leads to scarring. Collagen and other tissue damage from the inflammation of acne give rise to permanent skin texture and microvascular changes. In this study, we demonstrate the capabilities of optical coherence tomography based microangiography in detecting high-resolution, three-dimensional structural and microvascular features of *in vivo* human facial skin during acne lesion initiation and scar development.

Materials and Methods—A real time swept source optical coherence tomography system is used in this study to acquire volumetric images of human skin. The system operates on a central wavelength of 1310 nm with an A-line rate of 100 kHz, and with an extended imaging range (~12 mm in air). The system uses a handheld imaging probe to image acne lesion on a facial skin of a volunteer. We utilize optical microangiography (OMAG) technique to evaluate the changes in microvasculature and tissue structure.

Results—Thanks to the high sensitivity of OMAG, we are able to image microvasculature up to capillary level and visualize the remodeled vessels around the acne lesion. Moreover, vascular density change derived from OMAG measurement is provided as an alternative biomarker for the assessment of human skin diseases. In contrast to other techniques like histology or microscopy, our technique made it possible to image 3D tissue structure and microvasculature up to 1.5 mm depth *in vivo* without the need of exogenous contrast agents.

Conclusion—The presented results are promising to facilitate clinical trials aiming to treat acne lesion scarring, as well as other prevalent skin diseases, by detecting cutaneous blood flow and structural changes within human skin *in vivo*.

Keywords

Swept-source optical coherence tomography; optical microangiography; acne vulgaris

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Disclosure

The authors state no conflict of interest.

Introduction

Acne is a common chronic skin inflammatory disease affecting about 27% of early adolescents and up to 93% of late adolescents [1]. It targets to the pilosebaceous unit, consisting of the hair shaft, the hair follicle, the sebaceous gland that makes sebum. Acne is mainly located in areas where sebaceous glands are abundant like face, chest and upper arms and back, and is clinically illustrated as comedones, inflammatory papules, pustules, nodules and cysts and scarring [1, 2]. Although there has been significant research for enlightening the pathogenesis of acne, the exact aetiopathogenesis of the disease has yet to be completely understood. However, the main mechanisms in the pathogenesis of acne can be summarized as the increased sebum production with prominent androgen activity, the hyperkeratinization of the follicle and proliferation of propionibacterium acnes within the follicle, and inflammatory reaction [3]. Although there are grading and lesion counting techniques to assess the severity of acne [4], no grading system has been accepted universally. New research tools are needed to better understand the natural history, subtypes, and triggers of acne and to compare and improve the therapeutic efficacy of treatment products.

Various non-invasive techniques have been developed to aid in the assessment of cutaneous diseases. Capillaroscopy has been used to directly visualize vascular disorder in the capillaries beneath nailfold [5]. However, being a traditional light microscopy, capillaroscopy has a very limited light penetration, especially for subjects with darker skin, therefore, unable to visualize 3D microvascular network and tissue structure. In addition, confocal microscopy [6] can provide a very high resolution compared to capillaroscopy but again suffers from a limited light penetration through skin. Optical polarization-sensitive imaging, which measures the reflected light orthogonal to the polarized incident light, is used in applications such as in the assessment of sublingual microcirculation in critical care patients with severe sepsis [7], however, it does not allow for the detailed studies of microvascular changes in skin. Laser Doppler imaging utilizes the Doppler effect and provides a direct measure of blood perfusion [8], which has been previously used to evaluate burns [9], dermal inflammation [10], wound healing [11], and cutaneous ulceration [12]. Although they can provide relative changes in skin blood perfusion with a large field of view, they have a limited imaging resolution to resolve capillaries. In addition to these methods, high-resolution ultrasound imaging tools can penetrate deeper into tissue with a 50–100 μm resolution [13], but still cannot resolve the capillaries that are typically smaller than 30 μm .

Optical coherence tomography (OCT) is a real-time, non-invasive 3D imaging technique that overcomes the weaknesses of existing techniques by producing cross-sectional morphological images of tissue microstructures in vivo with a reasonable field of view (millimeters) and a micron-level imaging resolution analogous to histology [14]. OCT detects the light signals backscattered from tissue features. The imaging contrast is originated from the magnitudes in the measured signal intensity due to the variation in refractive index distribution within heterogeneous tissue [15]. Due to its relatively high resolution (up to 1 μm), deep imaging depth (1–3 mm), and the real-time image acquisition, OCT has gained more and more attention in the field of dermatology. It can accurately

delineate wound re-epithelialization, reformation of the dermoepidermal junction, thickening of newly formed epidermis and dermal remodeling [16]. So far, OCT has been successfully used to study non-melanoma basal cell carcinoma [17], actinic keratosis [18], inflammatory diseases [19], to quantify structural changes in skin and monitor therapeutic effects [20], and cutaneous wound healing in human [21]. However, traditional OCT does not provide blood vessel imaging, therefore, preventing it from studying blood perfusion status. Fortunately, by analyzing OCT spectral interferograms, a new technique named optical microangiography (OMAG), has been developed to provide 3D blood perfusion map in microcirculatory tissue beds in vivo [22]. To further increase the blood flow sensitivity, ultrahigh-sensitive OMAG was proposed [23, 24], allowing to image intact microvasculature network down to capillary level. Over the last few years, OMAG technique has been intensively used to study microvasculature of a variety of biological tissues in vivo. For example, it has been used to investigate the vascular abnormalities in a psoriasis patient [25], and cutaneous wound healing in rodents [26]. It has also been used to study cerebral microvasculature in mice [27, 28], to image capillary morphology in human finger [29, 30] and to study microvascular response to inflammation induced by tape stripping on human skin *in vivo* [31].

Based on these previous results, OMAG technique can be an excellent alternative in the monitoring of acne lesion development and scarring by providing functional microvasculature within cutaneous tissue beds. In this paper, we propose to utilize OCT based microangiography to track microvascular and structural changes during acne lesion development and scarring *in vivo* in humans. Our aim is to explore the feasibility of OMAG in detecting changes in microvasculature during acne lesion progress and to introduce a microvasculature-based biomarker in evaluating the treatment and grading of acne.

System and Methods

We used a commercial OCT system (SL1310V1-10048, Thorlabs Inc.) to implement the OMAG scanning protocol to achieve the purposes of imaging tissue morphology and microcirculation within acne lesions in human. The OCT system uses a swept light source containing a MEMS-tunable vertical cavity surface-emitting laser (VCSEL) (Fig. 1). This VCSEL source is able to sweep the lasing wavelength across a broad spectral range near 1310 nm at a fixed repetition rate of 100 kHz, giving a long coherence length (>50 mm) with 15 μm axial resolution in tissue and an extended imaging range (nominally ~12 mm in air) [32]. The output beam (28 mW in power) exiting from the VCSEL laser was fiber-coupled into a Mach-Zehnder interferometer built in the imaging module, where the light was evenly split into two beams by a 50:50 broadband fiber coupler that were directed to a reference arm and a sample arm, respectively. The sample arm was consisted of a probe imaging head (including a fiber collimator and X-Y galvanometric scanners) and a 5 $\times$ objective lens (LSM03, working distance = 25.1 mm, Thorlabs Inc.), giving 22 μm lateral resolution. The probe was attached to an articulating arm to make it easy to access to a sample (Fig. 1a). A detachable head band was employed to secure the volunteer's head to the imaging probe in order to reduce the artifacts due to the involuntary body movement. Acne lesion on the right cheek of a 27-year-old male volunteer was targeted. In order to mitigate strong specular reflection from the skin surface, a mineral oil was topically applied

to the skin surface. The optical power of incident light upon the sample was ~5.2 mW well below the American National Standards Institute (ANSI) standards (Z136.1) for the safe use of near infrared light at 1310 nm [33].

For vascular mapping of the skin tissues, we utilized the algorithms of ultrahigh-sensitive optical microangiography (OMAG) [23] and correlation mapping OCT (cmOCT) [34] by combining the two angiograms obtained from each algorithm with the same OCT data set [35]. To implement the algorithm, the OMAG scanning protocol [24] has to be used in the OCT system to acquire the volumetric dataset. Briefly in this scanning protocol, 3D OCT imaging was performed on acne lesion (3 mm × 3 mm) using a raster scanning of the galvanometric scanners. For fast B-scan (in X direction), a B-frame contained 256 A-lines. In the slow C-scan (in elevational Y direction), total of 2048 B-frames were captured with 8 repetitions at the each location, which took ~20 s with a 100 frames/s imaging rate. A cross-correlation-based image registration method was applied for the adjacent B-frames in the 3D amplitude data set to compensate axial displacement induced by possible tissue bulk motion [36]. Then, magnitude subtraction algorithm as detailed in [37] was applied to 8 consecutive B-frames at the same location to obtain a cross-sectional blood flow intensity image. To acquire a large field of view, this imaging protocol was repeated to create a mosaic image. Same procedure was repeated seven times over five weeks to monitor the targeted acne's development and scar formation.

Acquired 3D datasets were visualized through volume rendering and Gaussian filter is applied for noise reduction. Maximum intensity projection (MIP) of the OMAG blood flow image and average intensity projection (AIP) of the OCT structural image were produced. To produce en-face MIP of the OMAG blood flow image, the maximal value in each A-line was mapped on to an en-face 2D plane. En-face MIP images from volumetric OMAG are used to visualize only the blood vessel connections and depth-encoded en-face MIP images are used to visualize the depth distribution of microvasculature around the acne lesion. Similarly, the average value of each A-line for up to 1 mm depth was mapped on to an en-face 2D plane for AIP of the OCT structural image. En-face AIP images from volumetric OCT structure images are used to distinguish the acne lesion from the healthy tissue.

Results

Structural and microvasculature imaging on acne lesion

The selected acne region is photographed before experiments to match the OMAG (Fig. 2a). The volumetric MIP en-face view OMAG data shows the vessels in the acne region are coarse and less organized than those in the surrounding normal tissue as shown in Fig. 2b. Structural image (Fig. 2c) is merged with the microvasculature and shown in Fig. 2d with depth-encoded en-face MIP and in Fig. 2e with 3D volume rendering. Moreover, cross sectional images of OMAG and structure from the center of the acne lesion are presented in Fig. 2f–g and overlaid image of those shown in Fig. 2h.

OCT structural image (Fig. 2c) is used to better visualize and locate the acne lesion borders compared to the photograph. OCT can differentiate alterations in optical properties of the skin induced by collagen or other tissue damage induced by inflammation. In Fig. 2c, region

with a lighter color in the middle represents the area affected by the inflammation. Disturbance of the epidermal layer exposes the light to edema region which is mostly consisted of inflammatory cells and water, as pointed out in Fig. 2f–h with red dashed line. Since there is less light scattering in this region compared to surrounding tissue, it looks lighter on the en-face AIP of OCT image.

Monitoring acne lesion development and scarring

Acne scarring involves microvascular changes and fibrosis in the initial acne lesion. To detect these changes, OCT imaging was applied to the acne lesion two weeks after the acne development stage shown in Fig. 2, and presented in Fig 3. Similar to Fig. 2, the selected acne region is photographed before the experiment to match the OMAG images (Fig. 3a). This time, larger field of view is acquired by mosaicking 9 images and the MIP of OMAG and structural images surrounding the acne region are presented in Fig. 3b–c. Structural image (Fig. 3c) is merged with microvasculature and shown in Fig. 3d with MIP and in Fig. 3e with 3D volume rendering. Thanks to the large field of view (5 mm × 7 mm after truncation into a rectangle shape), cross sectional images provided great detail of re-constitution process of epidermal-dermal junction and new vessel development. To be able to compare the scarring process with the healthy state, another healthy area with previous acne lesions are imaged using the same procedure and shown in Fig 4.

To understand the transition from acne lesion initiation to scarring, longitudinal changes in a selected acne lesion is monitored using OMAG. Fig. 5 shows the structural and microvasculature changes in the acne lesion throughout 51 days. In Fig. 5, the results from each day are arranged in clusters, in which photograph image (upper left), en-face AIP (upper right), depth-encoded en-face MIP of microvasculature (lower left) and MIP of microvasculature (lower right) of the acne lesion are given and compared to those from the other days within the natural development of the acne lesion and scarring.

Moreover, to provide quantitative biomarker about acne scarring, vessel density is calculated for each day and plotted in Fig 5. To calculate the vessel density changes, vessel segmentation algorithm [38] is applied to each en-face MIP blood flow image. Briefly in this method, MIP images of microvasculature are binarized, and vessel density is calculated by dividing the number of ones with the total pixel number. Consistent with the wound healing process, after the damage caused by the inflammation, vascular density in the acne region increases at the early development stage and then decreases at the later stage.

Discussion

The *in vivo* OCT imaging results clearly demonstrate the acne lesion development stages from initiation to scarring in great detail. As shown in Fig. 2, acne lesion deteriorates the microcirculation network in the inflammation stage. It can be explained by edema formation inside the epidermal layer, which in return blocks or damages the microvasculature in dermis. Breakage of dermal balance naturally leads to hypertrophic scarring observed with dense microvasculature in Fig 3. At the end of the acne healing process, the microcirculation network becomes less dense as in the healthy tissue but fibrosis can be observed in structural images of Fig. 4. In addition to the detailed demonstration of each stage of acne

development, we also presented the longitudinal monitoring of the same acne lesion over 51 days and calculated the vascular density changes in the ROI.

These results can be useful in facilitating several clinical trials in the treatment of acne lesion scarring. Laser based acne treatment methods modify the subdermal microvasculature [39]. OMAG can play an important role in guiding and improving these treatment methods. Moreover, vascular density in the acne lesion can be used as a biomarker for grading acne severity and the assessment of the effectiveness of the treatments. For example, instead of applying irritating and potentially dangerous topical drugs on a larger portion of patient's skin, drugs can be applied to a small area to see the drug's effectiveness on a specific patient.

Furthermore, there are several reports discussing the involvement of microvasculature or angiogenesis in the etiopathogenesis of acne. It has been suggested that local changes in the peripheral blood vessels at the dermal papilla or in the interfollicular region may be a factor in development of acne vulgaris, by supplying proinflammatory cytokines controlling the inflammatory and proliferative processes [40]. IL-8, expressed by endothelial cells, has been suggested as a potential endothelial cell growth factor [40]. An increased expression of IL-8 in endothelial cells and increased dermal blood vessels in the skin biopsies of inflammatory acne patients have been observed in a recent study [41].

Moreover, the reports suggest that during bevacizumab treatment an acneiform eruption clinically and histopathologically may be observed as the cutaneous adverse effects [42]. Retinoids have also been used in the systemic and topical treatment of various disorders, ranging from acne vulgaris to several types of cancer. It has been established that inhibiting or decreasing angiogenesis is one of main mechanism of actions of these drugs [43].

Similarly, in the disease rosacea, where the vascular pathogenesis is predominately observed, OCT was used to monitor the effectiveness of brimonidine topical gel, on human skin in vivo [44]. Correspondingly, OMAG can also be used as a pre-treatment measurement device to define the possible morphologic features in the skin for the disease susceptibility and enable monitoring the treatment modalities in acne with a non-invasive prospect.

From the results in the current study, it seems reasonable to hypothesize that the vascular density derived from OMAG measurement may be used as a biomarker in the monitoring, therapeutic treatment and management of other prevalent skin diseases in general, e.g. port wine stain (PWS), psoriasis, skin burn, and skin cancer. For instance, vascular malfunction in superficial dermal capillaries in PWS [45] can easily be characterized with vascular density derived from OMAG. Moreover, replacing a standard visual inspection of the skin burn, the scar vascular density can be a potential indicator to assess the scar progression, providing diagnosis and proper treatment of pathological scarring.

In summary, acne vulgaris is a distressing skin disease, prevalent in the majority of the population aged between 11 and 30, which can affect the quality of life for those affected. OMAG can be a promising technique for the monitoring of acne lesion development and scarring by providing functional microvasculature within cutaneous tissue beds. The results demonstrated significant advantages of utilizing OCT-based microangiography compared to

alternative imaging methods. If this is being systematically tested, OMAG can become a major tool to facilitate clinical trials in the treatment and diagnosis of various skin diseases. Further well-designed studies will be required to systematically investigate and establish the benefits of this technique and these will be able to help clarify the complex pathogenesis of acne and contribute to the clinical management and improve new treatment alternatives.

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Figure 1.

Photographs of the swept-source OCT (SS-OCT) system for acne imaging. (a) Picture of the probe attached to the articulating arm. (b) User interface of the SS-OCT system. (c) Portable bench top SS-OCT system on the wheeled cart.

Figure 2.

Images from the inflammation stage of an acne lesion. (A) Photograph of the acne lesion where imaged area is delineated with a blue dashed line. (B) OMAG MIP of microvasculature at 0–1 mm depth. (C) AIP of OCT structural image of the same area. (D) Overlay of B and C. (E) Overlay of 3D rendered OCT structural image (orange) with the 3D OMAG (green). (F–G) Cross sectional view of OMAG and structural images, respectively, at a location delineated by a dashed yellow line on B–C. (H) Overlay of F and G. Scale bar represents 0.4 mm.

Figure 3.

Images from the scarring stage of an acne lesion. (A) Photograph of the imaged acne lesion. (B) OMAG maximum intensity projection (MIP) of microvasculature at 0–1 mm depth. (C) AIP of OCT structural image of the same area. (D) Overlay of B and C. (E) Overlay of 3D rendered OCT structural image (orange) with the 3D OMAG (green). (F–G) Cross sectional view of OMAG and structural images, respectively, at a location delineated by a dashed blue line on B–C. (H) Overlay of F and G. Scale bar represents 1 mm.

Figure 4.

Images from a healthy skin with previous acne lesions. (A) Photograph of the imaged area. (B) OMAG maximum intensity projection (MIP) of microvasculature at 0–1 mm depth. (C) AIP of OCT structural image of the same area. (D) Overlay of B and C. (E) Overlay of 3D rendered OCT structural image (orange) with the 3D OMAG (green). (F–G) Cross sectional view of OMAG and structural images, respectively, at a location delineated by a dashed blue line on B–C. (H) Overlay of F and G. Scale bar represents 1 mm.

Figure 5. MIP of microvascular and structural changes during over days. Bottom right figure shows the vascular density change in the MIP images of microvasculature over time. Scale bar represents 1 mm.