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Anterior Segment Optical Coherence Tomography Angiography and Optical Coherence Tomography in the Evaluation of Episcleritis and Scleritis

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ABSTRACT

Purpose: To evaluate the feasibility of using anterior segment optical coherence tomography (AS-OCT) and AS-OCT angiography (AS-OCTA) in assessing patients with episcleritis and scleritis.

Methods: Degree of vascularity [vessel density index (VDI)], measured with AS-OCTA, and sclera thickness [conjunctiva epithelium (CE), conjunctiva/episclera complex (CEC), and episclera/sclera complex (ESC)], measured with AS-OCT were compared.

Results: A total of 37 eyes (13 episcleritis, 11 scleritis, 13 controls) were analyzed. VDI was lowest for controls for the various tissue depths (p < .001). Episcleritis versus scleritis revealed a significant difference in VDI at ESC (38.1 ± 11.4% vs 46.4 ± 6.4%; p = .03). Mean sclera thickness was lower in controls for CE (p < .001), CEC (p < .001) but not for ESC (p = .54).

Conclusions: The degree of vascularity and tissue thickness were different between episcleritis, scleritis and controls. AS-OCTA and AS-OCT may potentially be useful in evaluating patients with scleral inflammation.

Keywords: Anterior segment optical coherence angiography, anterior segment optical coherence tomography, episcleritis, inflammation, scleritis

Scleritis is an inflammatory disease that affects the sclera; it can be classified as nodular or diffuse, and may affect one or both eyes. The incidence rates for scleritis have been reported to range between 3.4 and 4.1 per 100,000 person-years.1,2 In anterior scleritis, both the superficial episcleral capillary plexus and the deep episcleral capillary network are affected. In contrast, episcleritis affects only the anterior episcleral tissue without involving the deeper episcleral tissue that underlies the sclera (episclera/sclera complex). The incidence of episcleritis is more difficult to ascertain due to under reporting as not all patients seek medical care but the estimated incidence rates have been reported to range between 21.7 and 41.0 per 100,000 person-years.1,2

Episcleritis is often self-limiting with no underlying systemic association whereas uncontrolled scleritis can progress to ischemia, necrosis, and in some cases, perforation. Clinical examination of the anterior segment is typically performed to differentiate the two conditions; the vascular engorgement in episcleritis tends to produce a distinct red hue whereas in scleritis, the vascular engorgement involves the whole episcleral vascular network resulting in a characteristic bluish-violet hue.3 However, clinical assessment is mainly subjective which makes differentiating the two conditions not always that straightforward, especially in a general ophthalmology setting. Patient symptoms can aid in the diagnosis, globe tenderness and severe pain is often associated with scleritis but not all patients with scleritis present with pain especially in those who take non-steroidal anti-inflammatory drugs.

Anterior segment fluorescein and indocyanine green angiography (ICG) have been shown to produce
distinctive patterns in episcleritis and scleritis but its value is limited by the invasive nature of the procedure. Previous studies have shown that ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) are potentially useful in characterizing scleral inflammation and in differentiating episcleritis from scleritis. However, there are limitations with these technologies including the lack of accurate delineation of the different tissue layers with UBM because of the relatively poorer resolution and the difficulty with penetration of light in opaque, edematous tissue with AS-OCT.

Optical coherence tomography angiography (OCTA), a non-contact imaging system that detects phase variation in reflectivity to detect vascular flow, has been shown to be useful in detecting blood vessels in retina, choroidal and optic nerve conditions. More recently, it has been shown that OCTA, adapted for the cornea, is able to image the cornea and limbal vasculature, serial monitoring of corneal vascularization in clinical evaluation of keratitis, and also comparable to ICG for quantifying area of cornealvascularization. As the degree and depth of vascularity for episcleritis and scleritis are potentially different, we conducted a pilot study to evaluate the feasibility of using anterior segment OCTA (AS-OCTA) in conjunction with AS-OCT in evaluating scleral inflammation.

MATERIALS AND METHODS

Consecutive patients with episcleritis and scleritis, presenting to the A&E and uveitis department, at Moorfields Eye Hospital, were prospectively recruited between March to September 2017. All patients were newly diagnosed and have not had any previous treatment for their ocular inflammation. The inclusion criteria were patients over the age of 18 years with clinical signs of either episcleritis or scleritis. The exclusion criteria were patients with other causes of ocular disease and inflammation including trauma, contact lens associated complication, post-surgery, inflamed pterygium or pinguecula, conjunctivitis, keratitis and uveitis. Clinical diagnosis of either condition was made based on the appearance and on the presenting symptoms for each patient. A diagnosis of episcleritis was made based on mild edema of the episcleral tissue and vascular engorgement of the superficial episcleral blood vessels, associated with mild ocular discomfort. Scleritis was diagnosed on the symptoms of ocular pain that radiate to the brow, jaw or sinuses associated with signs of edema affecting the episclera and scleral regions. Episcleritis was categorized into diffuse or nodular and scleritis was classified into diffuse, nodular, necrotizing without inflammation and necrotizing without inflammation (scleromalacia perforans). The degree of scleral inflammation was defined from 0 to 4+, and if more than one quadrant was affected, the most severe affected region was used for the final grading classification. Age-matched healthy controls, with no history of ocular or systemic disease, were recruited from staff members within the A&E department and one eye from each subject, chosen from random, was selected for imaging. Anterior segment photos in four quadrants were taken in all eyes with a digital camera (Topcon ATE-600, with D1X digital camera, Nikon Corp) with a diffuse illumination, ×10 magnification, flash power 4.5 at 45° angle. The study received local institutional ethics committee approval and adhered to the tenets of Declaration of Helsinki. Informed consent was obtained from all patients.

AS-OCTA and AS-OCT Image Acquisition

AS-OCTA images of the affected eye were performed by one operator (SH) with the AngioVue OCTA system (Optovue Inc., Fremont, California, USA) using the long cornea adaptor module in the Cornea Angio setting. The specification of the machine has been described previously. The 6 mm x 6 mm scan setting was used and only the affected region of the eye was scanned for each patient. To ensure optimum image quality, the instrument was positioned so that the scanning light was directly perpendicular to the region of interest and the images were obtained midway between the limbus and site of insertion of the rectus muscle. For each image acquisition, a series of images were obtained in the coronal plane starting from the superficial conjunctiva all the way to the sclera stroma. Three image composites were acquired for the affected quadrant and the best series of images were used for the blood vessel density or vessel density index (VDI) analysis. In addition, three corresponding AS-OCT line raster cross-sectional images of the affected area were also obtained and the best image showing the full extent of the sclera tissue, with minimal posterior shadowing, was used for scleral thickness measurement. In obtaining the AS-OCT images, care was taken to ensure the scanning light was directly perpendicular to the affected area and that the anterior border of the sclera was as parallel to the horizontal axis as possible. Images where the posterior scleral limit was not clearly seen were excluded from the analysis. If more than one quadrant of the eye was affected, the above imaging acquisition steps were repeated for each quadrant. The machine has a scanning speed of 70 000 scans/second, 840nm wavelength light source, and the optical resolution is 3 µm axial and 15 µm in the lateral direction. The images are processed using the split-spectrum amplitude de-correlation angiography algorithm.
**AS-OCTA and AS-OCT Image Analysis**

Manual segmentations of the images were performed to delineate the different layers of the sclera as detected by the corresponding AS-OCT images. The degree of vascularity was analyzed by dividing each image into the following anatomical layers: conjunctiva epithelium – defined by the border of the most anterior layer; conjunctival/episclera complex – defined by the most anterior layer to the posterior limit of the areas of hyporeflectivity seen within the conjunctival/episclera region; and episclera/sclera complex – defined by the posterior limit of hyporeflectivity to the most anterior layer to the posterior limit of the areas of hyporeflectivity seen within the conjunctival/episclera region. For the corresponding scleral tissue thickness measurements, for each quadrants was affected then one image corresponding to each quadrants was exported and the average vascularity and tissue thickness obtained during image analysis. For control eyes, an image corresponding to each tissue layer of the four quadrants was obtained and then averaged for both vascularity and tissue thickness.

![Figure 1](image1.png)

**FIGURE 1.** Representative anterior segment optical coherence tomography image of a case of anterior diffuse scleritis showing the definition of the different tissue layers for the purpose of manual segmentation: Conjunctiva epithelium (diamond shapes) – defined by the boundary of the most anterior layer of hyporeflectivity; Conjunctiva/episclera complex (dashed two-headed arrow) – defined by the measurement from the most anterior layer to the posterior limit of the areas of hyporeflectivity within the conjunctival/episclera region; Episclera/sclera complex (dotted two-headed arrow) – defined by the posterior limit of hyporeflectivity of the conjunctiva/episclera region to the most posterior edge of the image.

All images were analyzed by one observer (KD) who was masked to the diagnosis. Pre-processing steps to eliminate speckle noise and motion artifacts were performed by applying Gaussian and band-pass filtering. Subsequently, top-hat filtering was done to improve the Signal-to-Noise Ratio while preserving the image features. Local phase-based filter for optimal enhancement of segmented vessels was applied; thereafter, where an infinite perimeter active contour model to partition the enhanced image into a binary image (vessel pixels, 1; background, 0) was performed. The VDI, expressed as a percentage, was then derived as the ratio of the total area of binarized vessel pixels to the total pixel area of the raw image ×100.

**Data Analysis**

Data analysis was performed with SPSS software (IBM SPSS Statistics V24, USA). As this was a pilot study to evaluate the feasibility of using AS-OCTA in assessing scleral inflammation, no prior power calculation was performed to estimate sample size so the results would need to be interpreted with caution and described as exploratory. Descriptive statistics were used for patient demographic data. Normality of the data was checked with the Shapiro-Wilk’s test and inspection of the histograms. One way ANOVA was used to compare the mean VDI values of the various anatomical layers for all the groups followed by the Levene’s test to check for homogeneity of variance, and then post hoc analysis performed with the Bonferroni test. A value of $p < .05$ was deemed statistically significant.

**RESULTS**

A total of 26 consecutive patients (26 eyes) with either episcleritis or scleritis were recruited in this pilot study. Two eyes with scleritis were excluded from the analysis due to the difficulty in delineating the different tissue layers and the posterior scleral margin accurately. The remaining 24 patients (24 eyes) were analyzed. The mean age of the patients was 42 years ± 10.0, and 12 (52.2%) were female. Diffuse scleritis was found in 7 eyes, nodular scleritis in 4, diffuse episcleritis in 11, and nodular episcleritis in 2 eyes. There was a systemic association in three cases of scleritis: one granulomatosis with polyangiitis, one HLAB27-related, and one with C-ANCA related vasculitis. Apart from these three patients, the remaining cases of scleritis and all of the episcleritis were diagnosed as idiopathic. Thirteen normal controls (13 eyes) were recruited; their mean age was 40 ± 8.7 and 6 (46.2%) were female.
VDI Analysis

Figure 2 shows a composite image indicating the vessel density at the conjunctiva epithelium, conjunctival/episcleral complex, and episclera/sclera complex, for diffuse episcleritis (A-D), nodular episcleritis (E-H), diffuse scleritis (I-L), nodular scleritis (M-P), and control (Q-T). AS-OCTA revealed the VDI increased with increasing scleral depth and there was a significant difference in values between the three groups for the various tissue depths, Table 1. Post hoc comparison revealed a significant difference between both episcleritis and scleritis versus control at all the layers: conjunctiva epithelium ($p < .001$), conjunctiva/episcleral complex ($p < .001$) and episclera/sclera complex (episcleritis, $p = .001$; scleritis, $p < .001$). By contrast, post hoc comparison did not reveal any significant difference in AS-OCTA between episcleritis and scleritis at the conjunctiva epithelium ($p = .99$), conjunctiva/episclera complex ($p = .73$) but there was a significant difference in VDI at the episclera/sclera complex ($p = .03$).

For AS-OCT tissue thickness measurement, there was a significant difference between the three groups...
Post hoc analysis revealed a significant difference in tissue thickness between control and scleritis at the conjunctiva epithelium ($p = .02$) but not for control versus episcleritis ($p = .71$) or episcleritis versus scleritis ($p = .37$). Similarly, there was a significant difference in tissue thickness between control versus scleritis at the conjunctiva/episcleral complex ($p = .01$) and episclera/sclera complex ($p = .05$) but not for control versus episcleritis ($p = .21$) or episcleritis versus scleritis ($p = .74$).

**AS-OCT and AS-OCT images for three representative cases:** One diffuse episcleritis, one nodular scleritis, and one control are shown in Figure 3. At the conjunctiva/episcleral layer, pockets of circular or oval shape hyporeflectivities were seen in episcleritis, whereas in scleritis, the hyporeflectivities appeared to be more continuous, thicker and band-like, with the

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**TABLE 1. Comparison of AS-OCTA mean vessel density index and AS-OCT mean thickness measurement between episcleritis, scleritis, and control.**

<table>
<thead>
<tr>
<th>Anatomical layer</th>
<th>AS-OCTA vessel density index (%)</th>
<th>AS-OCT thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episcleritis ($n = 13$)</td>
<td>Scleritis ($n = 11$)</td>
</tr>
<tr>
<td>Conjunctiva epithelium</td>
<td>26.7 (SD 13.9)</td>
<td>27.3 (SD 10.7)</td>
</tr>
<tr>
<td>Conjunctiva/episclera complex</td>
<td>36.8 (SD 9.9)</td>
<td>39.4 (SD 7.6)</td>
</tr>
<tr>
<td>Episclera/sclera complex</td>
<td>38.1 (SD 11.4)</td>
<td>46.4 (SD 6.4)</td>
</tr>
</tbody>
</table>

AS-OCTA, anterior segment optical coherence tomography angiography; AS-OCT, anterior segment optical coherence tomography; SD, standard deviation. *Comparison of the VDI in different anatomical layers with AS-OCTA; **Comparison of tissue thickness in different anatomical layers with AS-OCT.
nodular form showing a much greater tissue thickness (Figure 3b & e). At the episclera/sclera complex, the difference in VDI between episcleritis and scleritis appeared to be the greatest, which suggests the difference in vascularity was highest just anterior to the sclera stroma between the two conditions (Figure 3c & f). The scleral stroma in scleritis showed further bands of hyporeflectivity, indicating probable sclera edema and inflammatory cellular infiltration, which were not present or they were much less prominent in episcleritis. Despite these changes, the episclera/sclera stroma thickness in scleritis was not that much higher compared to episcleritis or controls, Table 1. Indeed, the thickness difference appeared to be the greatest at the conjunctival/episclera complex, where the degree of edema was much more prominent in scleritis (Figure 3e and Table 1). For comparison, the control case did not show any swelling in the conjunctiva/episclera region (Figure 3h). The mean total scleral thickness (MTST) for episcleritis, scleritis, and control was 973.3 µm ± 122.4, 1042 µm ± 128.4 and 749.7 µm ± 84, respectively. There was a statistical significant difference in MTST between control and scleritis (p = .01) but not between control and episcleritis (p = .14) or between episcleritis and scleritis (p = .75). Categorizing the episcleritis and scleritis into nodular and non-nodular form, a slightly higher VDI and tissue thickness measurement at the various anatomical layer were found in the nodular form for both type of scleral inflammation but we did not perform inferential statistics to look for significant difference due to the small sample size, especially with the nodular episcleritis group, Table 2. The MTST for the nodular and diffuse phenotype were nodular episcleritis 988.5 µm, diffuse episcleritis 943 µm, nodular scleritis 1161.5 µm, and diffuse scleritis 962.4 µm.

**DISCUSSION**

AS-OCT has many applications in ophthalmology, whereas by contrast, OCTA is a relatively new technology and currently, most of the OCTA systems are optimized for imaging the retina. Adaptation of the commercial OCTA systems for the anterior segment (AS-OCTA) has been shown to be potentially useful in diagnosing and monitoring corneal neovascularisation and it compares well with anterior segment ICGA in quantifying new blood vessels on the cornea. In the present pilot study, we have shown that it is possible to image the vascular network at various anatomical planes of the sclera with the AngioVue OCTA system. The increase in VDI seen with increasing depth occurred in all eyes and we found the vascular density to be significantly lower in controls than in eyes with episcleritis or scleritis.

| Table 2. Comparison of AS-OCTA mean vessel density index and mean AS-OCT scleral tissue thickness between the nodular and diffuse form for episcleritis and scleritis. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Anatomical layer | Episcleritis | Scleritis | Episcleritis | Scleritis |
| Conjunctiva epithelium | VDI (%) | Thickness (µm) | VDI (%) | Thickness (µm) |
| Nodular (n = 2) | 29.9 (SD 2.3) | 82.5 (SD 38.9) | 26.1 (SD 15.2) | 75 (SD 38.9) |
| Diffuse (n = 11) | 30.1 (SD 33.8) | 36.3 (SD 10.7) | 30.6 (SD 16.1) | 37.4 (SD 12.3) |
| Conjunctiva/episclera complex | VDI (%) | Thickness (µm) | VDI (%) | Thickness (µm) |
| Nodular (n = 4) | 30.1 (SD 33.8) | 36.3 (SD 10.7) | 30.6 (SD 16.1) | 37.4 (SD 12.3) |
| Diffuse (n = 7) | 30.1 (SD 33.8) | 36.3 (SD 10.7) | 30.6 (SD 16.1) | 37.4 (SD 12.3) |
| Episclera/sclera complex | VDI (%) | Thickness (µm) | VDI (%) | Thickness (µm) |
| Nodular (n = 4) | 30.1 (SD 33.8) | 36.3 (SD 10.7) | 30.6 (SD 16.1) | 37.4 (SD 12.3) |
| Diffuse (n = 7) | 30.1 (SD 33.8) | 36.3 (SD 10.7) | 30.6 (SD 16.1) | 37.4 (SD 12.3) |
The sclera stroma is considered to be an avascular tissue and inflammatory cellular migration comes possibly from a combination of three sources, the conjunctival/episcleral capillaries, choroidal circulation, and the vessels that transverse the sclera. In contrast, the episclera is well vascularized, and this reflects the highest VDI values found in the region of the episclera/sclera complex in all three groups. With episcleral/scleral inflammation, the degree of vascularity increases further in all of the anatomical planes resulting in the higher VDI values seen in both episcleritis and scleritis. Although the VDIs were not significantly different between episcleritis and scleritis in the superficial anatomical layers, the greater vascularity detected in the episclera/sclera complex and the comparatively higher amount of edema seen in the conjunctiva/episclera complex with scleritis, suggest these findings may potentially be useful in differentiating the two conditions. These observations are consistent with the fact that the deeper vasculature is more affected in scleritis.

The MTST of the normal controls found in this study (749.7 µm) is similar to those found in previous studies with a range of 747 to 790 µm being reported in the literature. Shoughy et al. found the total transconjunctival sclera is thicker in cases of scleritis compared to episcleritis, whereas Kuroda et al. found the sclera stroma thickness to be similar and it is the conjunctival/episcleral complex that is thickened in scleritis rather than sclera stroma. The reason for the discrepancy is because the total transconjunctival scleral thickness was quoted by Shoughy et al. rather than just the thickness of the sclera stroma, which was quoted by Kuroda et al.

The MTST found in these studies were 822.8 µm, 989.9 µm (difference 167), 825 µm, 882 µm (difference 57) and 952 µm, 1006 µm (difference 54) for episcleritis and scleritis, respectively. The MTST values found in our study are comparable to Axford et al., but slightly higher than in the other studies. Our cohort, similar to Axford et al., had cases of both nodular and diffuse morphology; the nodular form, being greater in values, contributed to the higher overall MTST for both diagnoses. However, different instrumentations such as OCT technology and software, case selection, and segmentation methods could all contribute to the difference in scleral thickness found between studies. The greater tissue thickness found in the nodular form also corresponded to the higher VDI values seen in this phenotype, suggesting a greater degree of vascularity compared to the diffuse type, though the comparison is limited by the small sample size in the nodular episcleritis group in our study. Despite the higher MTST found in scleritis compared to both episcleritis and controls, the mean episclera/sclera complex thickness values for all three groups were not statistically significant. Indeed, these values are comparable to those found in normal uninfamed sclera and it suggests that in scleritis, it is the conjunctival/episcleral complex that is thickened rather than the sclera stroma. Although the scleral stroma did not appear to be significantly thicker in scleritis, we found bands of hyporeflectivity deep into the scleral stroma, probably indicating intra-scleral edema and separation of collagen lamellae, and these findings are consistent with previous findings.

There are several limitations in this pilot study including its small sample size, single assessor with no repeatability assessment of the data performed. However, we mitigated these limitations by performing multiple measurements and followed protocols from previous studies that already established good repeatability. From an imaging perspective, it is important to note that AS-OCT suffers from a greater degree of scatter and posterior shadowing with increasing inflammation and this is reflected in the inability to measure the tissue layer accurately in two eyes. Furthermore, although the AS-OCTA software has been developed for imaging the anterior segment, motion or projection artifacts, limitations with software and a limited field of view may not include the entire lesion in one scan and also affect segmentation for example in nodular scleritis. Moreover, the need for manual segmentation of the different tissue layers, and the reduction in quality of the images on scanning deep into the sclera stroma could all affect the accuracy of measurements obtained in this study. We found a statistically significant difference in VDI at the episclera/sclera complex between episcleritis and scleritis but this would need to be interpreted with caution due to the exploratory nature of the study design. Notwithstanding these limitations, the aim of this pilot study is to evaluate a novel AS-OCTA system and to assess its feasibility and value in imaging the vascular network in patients with scleral inflammation. If established, this technology may potentially be utilized in a general ophthalmological setting to help clinicians in differentiating the different types of scleral inflammation. Further prospective studies with larger sample sizes are needed to evaluate the role of AS-OCTA in such patients.

In summary, our pilot study suggests that, AS-OCTA, in conjunction with AS-OCT, may be useful adjunctive tools in differentiating superficial from deep scleral inflammation by determining the degree of vascularity and tissue thickness of the different tissue layers.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.
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