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Retinal thickness and microvascular alterations in the diagnosis of behcet's disease: a case-control study

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Abstract

Background In the current study optical coherence tomography angiography (OCTA) was used to compare retinal thickness (RT) and superficial vascular density (SVD) in patients with Behcet's disease (BD) and healthy controls.

Methods The study included 17 BD patients (34 eyes) and 17 healthy participants (34 eyes). Each eye had an en-face OCTA scan. Macular RT and SVD were assessed in both groups after segmenting each image into 9 subregions.

Results BD patients and controls had significantly different visual acuity ($p < 0.001$). Compared to the control group, BD patients had increased inner RT in the inner superior, inferior, temporal, outer superior, inferior, and center regions, and increased full RT in the inner inferior, outer inferior and superior regions ($p < 0.05$). RT was positively correlated with visual acuity in the outer and full retina at outer temporal regions ($p < 0.05$). Also, c-reactive protein was positively correlated with full and outer RT in the center region in patients with BD ($p < 0.05$). The area under the receiver operating characteristic curve for the outer nasal region of the SVD was 0.913 (95% confidence interval: 0.835–0.991).

Conclusion The OS region of full RT and the II region of inner RT in the macular region may serve as a diagnostic marker for BD, and has clinical significance for auxiliary imaging diagnosis.

Keywords Behcet's disease, Optical coherence tomography angiography, Retinal thickness, Vascular density

Introduction

Behcet's disease (BD) is a chronic, recurrent palliative vasculitis of unknown etiology. It can affect practically all organ systems and cause substantial organ-compromising morbidity and mortality because it can affect arteries and veins of any diameter [1]. Due to its high prevalence along the historic "silk road", which connected East Asia to the Mediterranean basin, BD is also known as the "silk road disease" [2]. It is more common in men in most Mediterranean, Middle Eastern, and Asian countries, whereas it is more common in women in the United States, Northern Europe, and East Asia [3]. BD usually arises between the ages of 18 and 40 years [4]. Recurrent oral and vaginal ulcers, skin manifestations, and ocular

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symptoms are all characteristics of BD, but clinical signs and symptoms differ between nations and ethnic groups [5]. Behcet's referral center patients may present with various and possibly atypical signs, which greatly complicate the diagnostic process [6]. The categorization of BD has been continuously modified since its discovery in 1937. Recurrent mouth ulcers (at least three times per year) and one or more of recurrent genital ulcers, eye lesions, or skin lesions are used to make the diagnosis [7].

Patients with BD frequently experience substantial ocular involvement, which is often bilateral and quickly impairs visual function [2]. Recurrent non-granulomatous uveitis that affects the anterior and posterior parts of the eye and impairs vision is the hallmark of ocular involvement in BD. Repeated inflammatory episodes can harm the retinal vascular system permanently, and result in blindness if they cause injury to the back of the eye [8]. A genetic component of BD has been validated [9, 10], and HLA-B51 is the most significant genetic risk factor. HLA-B51 is reportedly present in between 40% and 80% of BD patients but only 10% to 30% of healthy controls. The eastern areas of Eurasia that are not in Europe, along the historic silk road, have a comparatively high proportion of HLA-B51^{+} BD patients who develop ocular symptoms [11]. It is important to investigate ocular alterations in BD.

Fluorescein angiography (FA), a technique for detecting blood flow, has been used for more than 50 years in clinical settings. It can only monitor the superficial plexus, however, because it cannot photograph multiple layers of significant arteries in the eye [12]. Optical coherence tomography angiography (OCTA) is almost as accurate as histology. The retinal vascular system can be visualized via OCTA in a dependable, high-resolution, and non-intrusive manner, which has facilitated the development of numerous scientific and clinical research applications [13]. Fine structures of the retina and choroid can be measured via OCTA [14, 15], which is crucial for diagnosing diseases such as diabetic retinopathy [16], glaucoma [17], and systemic lupus erythematosus [18].

Although OCTA's role in the quantitative evaluation of fundus illnesses has been extensively investigated, only a few studies have used OCTA to identify BD. In the current study OCTA was used to investigate the optic health of BD patients, and compare the thickness and vascular density of their retinas with that of healthy controls (HCs). We present the following article in accordance with the STROBE reporting checklist.

Methods

Subjects

A cross-sectional study was conducted at the Department of Ophthalmology and Rheumatology of Nanchang University's First Affiliated Hospital (Nanchang, China) in 2022. The study included 17 BD patients, and 17 HCs with no ocular abnormalities. The same retinal expert assessed all study participants.

Recruitment criteria

All patients in the BD group met the International Criteria for Behcet's Disease [11], and those with scores of 4 (active BD) were recruited. The scoring system is as follows:

1. Oral ulcers a minimum of three times every year—2 points.
2. Recurrent genital ulcers—2 points.
3. Ocular diseases (uveitis, retinal vasculitis, choroidal retinitis, papillitis)—2 points.
4. Cutaneous lesions (papulo-pustular rash, erythema nodosum)—1 point.
5. Lesions of the central nervous system (parenchymal central nervous system involvement, venous sinus thrombosis)—1 point.
6. Vascular signs and symptoms (arterial thrombosis, venous thromboembolism, superficial thrombophlebitis, and aneurysms, particularly aortic and pulmonary)—1 point.
7. Positive pathology test—1 point.

Patients ages ranged from 24 to 56 years. None of the patients exhibited retinal vasculitis, choroidopathy, or optic neuropathy symptoms or signs.

Exclusion criteria

Exclusion criteria were (1) autoimmune conditions besides BD and medical conditions that affect the microvasculature (e.g. hypertension, diabetes); (2) eye surgery within the previous year; (3) pregnant or lactating; (4) pre-existing fundus lesions (e.g., macular edema, macular degeneration, etc.) and (5) long-term use of hormonal eye drops.

Clinical examinations

The following fundamental clinical and ophthalmological examinations were performed in all individuals:

1. Tests for aortic endothelial cell antibodies (Fasting blood tests).
2. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) assessment (Fasting blood tests).
3. T-SPOT. TB tests (Fasting blood tests).
4. Intraocular pressure assessment (Goldmann tonometry) and visual acuity determination (Snellen chart)
5. OCTA (Angio OCT Optovue RTVue Avanti XR system (Optovue, Fremont, USA))

OCTA

The Angio OCT Optovue RTVue Avanti XR system (Optovue, Fremont, USA) was used to perform OCTA on all participants. The scanning parameters were 70,000 A-scans per second, 840-nm central wavelength, 45-nm bandwidth, 5-μm axial resolution, and 22-μm horizontal resolution rate. An acquisition period of 3.9 s and 5 repeat angiography scans in 216 grating positions along the y-axis were utilized, and a B-scan focused on the posterior pole was performed along the x-axis in 6 × 6-mm scanning mode. Three-dimensional 6 × 6-mm en-face OCTA images were obtained from each eye while simultaneously taking 1080 B-scans at 270 frames per second [13]. Ensure that the signal strength index is > 70 when operating the equipment. Carefully check and manually adjust to ensure that each stratified line on the B-scan is accurate. The same ophthalmologist reviews and manually removes OCTA images with obvious motion artifacts and inferior quality. Each retina was scanned then divided into nine Early Treatment Diabetic Retinopathy Study (ETDRS) subareas comprised of three concentric circles with radii of 0.5, 1.5, and 3 mm. The thicknesses of each of these subareas were then determined. The layers of the retina include the full retina which stretches from the inner limiting membrane (ILM) to the retinal pigment epithelium, and the inner retina which runs from the ILM to the inner plexiform layer. The distinction between full retinal thickness (RT) and inner RT is based on how outer RT was defined, and vascular density is defined as the percentage of vascular perfusion area in the measured region. The threshold method was used to determine vascular density via two-dimensional surface images of the superficial retina (the layer between the vitreoretinal interface and the anterior boundary of the ganglion cell layer). Each background pixel was assigned the value of the image block, either 1 or 0. The vascular density of the macular center of the 6 × 6-mm edge brightness gradient image was determined using the average value of the skeleton plate in the region of interest based on pixel size scaling (512 pixels/3 mm). RT and the SVD of the macula were calculated. First, each participant focused their right eye. It was essential to obtain information on the right eye's mirror image. The information for the left eye was switched around to create a mirror copy of the right eye. Averaging and in-depth analysis of the data from the left and right eyes was then performed (Fig. 1A). All OCTA image segmentation was performed using the fully automated algorithm provided by the AngioAnalytics™ software without manual intervention to ensure objectivity and reproducibility.

Statistical analysis

The data were analyzed using GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA) and SPSS version 22 (IBM Corp., Armonk, NY, USA). They were then collated as means ± the standard deviation, and compared using the *t*-test for independent samples. Linear correlational analysis of RT (full, inner, and outer) and visual acuity was conducted in each group. Statistical analysis of binocular data was performed due to the small sample size. To reduce the repeated confounding effect of independent statistical analysis of binocular data and enhance the statistical power of the results, an additional sensitivity analysis was conducted specifically for the right eye as a supplementary analysis. Receiver operating characteristic (ROC) curves were used to analyze OCTA parameters, and the area under the curve and critical point for each parameter were identified. ROC curves for RT and SVD were used to evaluate differentiation between HCs and BD patients. $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

All data were collected at the First Affiliated Hospital of Nanchang University. Seventeen patients and 17 HCs were included. The mean ages were 47.06 ± 8.99 years in the BD group and 47.00 ± 9.85 years in the HC group ($p = 0.986$). Each group contained 9 females and 8 males ($p = 1.0$). Visual acuity in the BD group was significantly worse than that in the HC group ($p < 0.001$) (Table 1).

Macular RT

Subregional RTs in the BD and HC groups are shown in Table 2; Fig. 1B. The superior and inferior quadrants of the outer ring (superior: $p < 0.001$; inferior: $p < 0.001$), all regions of the inner ring except the nasal region ($p < 0.001$), and the foveal center ($p = 0.001$) all exhibited significantly higher inner RT in the BD group than in the HC group. The nasal ($p = 0.859$) and temporal ($p = 0.710$) portions of the outer ring did not differ significantly in the two groups. There was no significant difference in outer RT between the BD group and the HC group (Fig. 1C, D). In the outer superior, outer inferior, and inner inferior regions, the full RT in BD individuals was substantially greater than that of the HC group (OS: $p < 0.001$; II: $p = 0.002$; OI: $p = 0.002$). There were no significant differences between the groups at any other locations ($p > 0.1$) (Fig. 1E).

Macular retinal SVD

SVDs at various retinal subregions in the BD and HC groups are shown in Table 3; Fig. 1B. Both nasal (inner ring: $p < 0.001$; outer ring: $p < 0.001$) and superior (inner ring: $p < 0.001$; outer ring: $p < 0.001$) SVDs were substantially lower in the BD group than in the HC group (Fig. 1F).

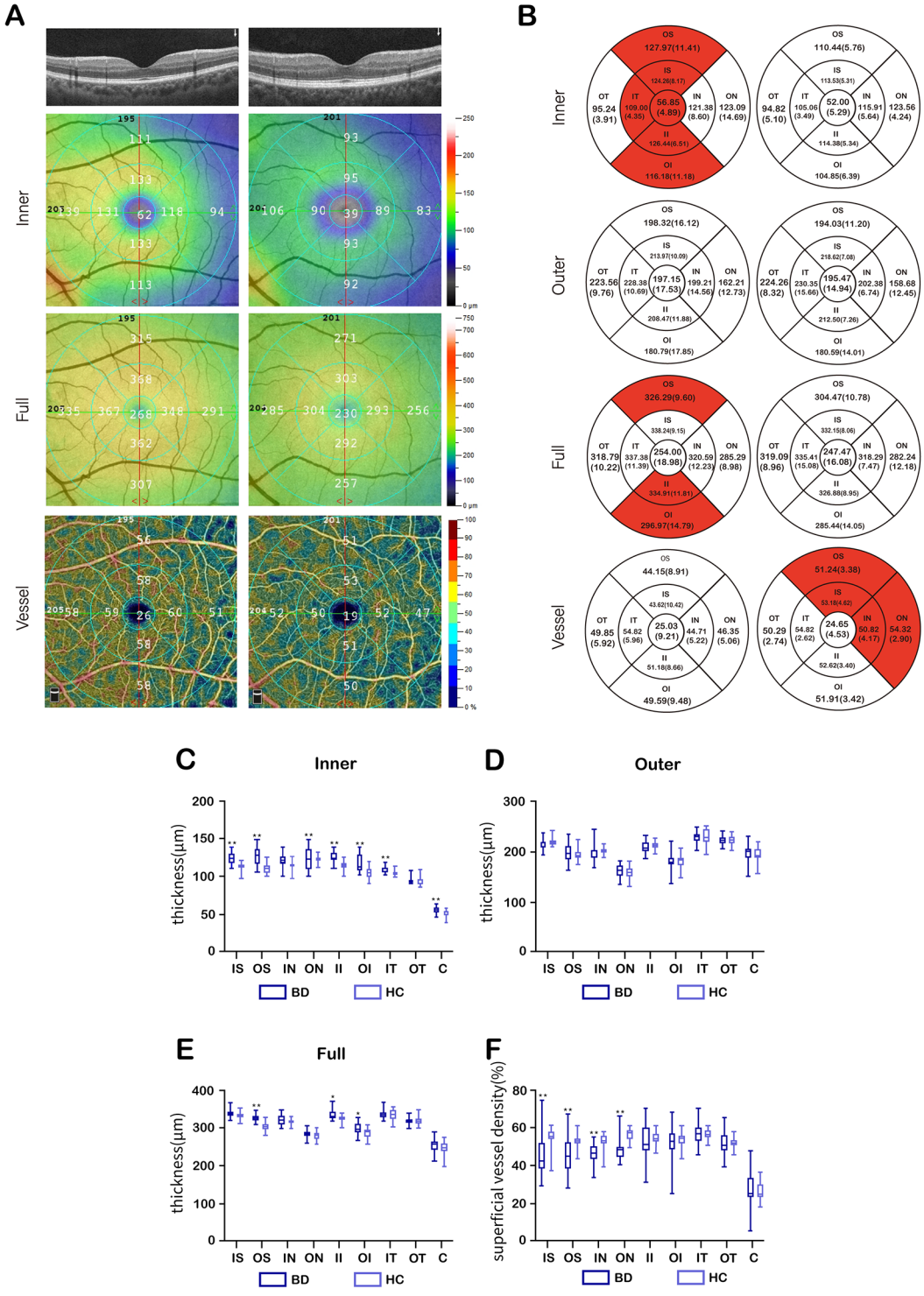

Fig. 1 The OCTA images and RT and SVD analysis of BD and control groups. (**A**) Cross-sectional view of retinal thickness in the BD and control group under OCTA. The inner RT, full RT, and SVD were measured by ETDRS. (**B**) The data presents the mean values ± standard deviations of the inner RT, outer RT, full RT, and SVD in the ETDRS for both the BD group and HC group. The red areas highlight regions where statistically significant differences ($p<0.05$, H-B corrected) were observed between the two groups. (**C**-**E**) Analysis of RT results in the BD group and control group. The vertical coordinate is the value of RT, and the horizontal coordinate is the retinal subregions. (**F**) Analysis of SVD results in the BD group and control group. The vertical coordinate is the value of SVD, and the horizontal coordinate is the retinal subregions. Abbreviations: OCTA, optical coherence tomography angiography; BD, Behcet's Disease; RT, retinal thickness; SVD, superficial vessel density; ETDRS, early treatment of diabetic retinopathy study; IS, inner superior; OS, outer superior; IN, inner nasal; ON, outer nasal; II, inner inferior; OI, outer inferior; IT, inner temporal; OT, outer temporal; C center. *, $P<0.05$, after H-B corrected; **, $P<0.01$, after H-B corrected

Table 1 General information of patients with BD and healthy subjects

	BD (*n* = 17, 34 eyes)	HC (*n* = 17, 34 eyes)	t	*P*-value	H-B corrections
Age (y)	47.06 ± 8.99	47.00 ± 9.85	0.018	0.986	1.000
Gender (female: male)	9:8	9:8		1.000	1.000
VA (logMAR)	0.38 ± 0.19	0.05 ± 0.07	9.147	< 0.001*	0.011#
Mean IOP (mm Hg)	15.31 ± 1.45	15.33 ± 1.71	-0.053	0.958	1.000
Duration of BD (y)	1.73 ± 2.14	N/A			
ESR (mm)	20.59 ± 18.08	N/A			
CRP (10 mg/L)	8.12 ± 4.11	N/A			
ANA, n(%)	1(5.89)	N/A			
ANAs, n(%)	0(0)	N/A			
Systolic blood pressure (mm Hg)	122.41 ± 13.75	124.24 ± 5.82	-0.506	0.618	1.000
Diastolic blood pressure (mm Hg)	82.53 ± 7.98	83.06 ± 6.12	-0.217	0.829	1.000
BUT (s)	6.79 ± 2.11	13.97 ± 1.77	-15.187	< 0.001*	0.011#
OSS	1.71 ± 0.68	0	14.725	< 0.001*	0.011#
SIT (mm)	9.35 ± 2.70	12.94 ± 1.37	-6.920	< 0.001*	0.011#
TMH (mm)	0.18 ± 0.33	0.57 ± 0.12	-18.010	< 0.001*	0.011#
HADS	7.65 ± 3.16	2.82 ± 1.07	5.957	< 0.001*	0.011#

*, statistically significant at P value < 0.05. #, statistically significant after Holm-Bonferroni correction (Family Wise Error Rate 0.05)

BD, behcet's disease; HC, healthy control; VA, visual acuity; MAR, minimum angle of resolution; IOP, intraocular pressure; ANA, antinuclear antibody; ANAs, antinuclear antibody spectrum; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; BUT, tear breakup time; OSS, ostaining score; SIT, schirmer test; TMH, tear meniscus height; HADS, hospital anxiety and depression Scale; N/A, not applicable

RT and SVD analysis of right eyes in BD and control groups

To enhance the statistical power of binocular data, independent sample t-tests were performed solely on the right-eye data from the HC and BD groups for the macular retinal thickness (inner, outer, and full layers) and retinal vascular density. The results were consistent with the trend observed in binocular data (Fig. 2). However, minor differences were present due to the small sample size.

ROC analysis of RT and SVD

To determine the specificity and sensitivity of RT and SVD as diagnostic indicators of BD-related alterations, data from OCTA were investigated (Fig. 3). There were significant differences in full OS, II, OI, and the whole inner RT except the ON, IN and OT regions between the two groups. The area under the curve for full OS was 0.933 (95% confidence interval: 0.873–0.993), inner OS was 0.908 (95% confidence interval: 0.840–0.976), and inner II was 0.938 (95% confidence interval: 0.878–0.998), suggesting a moderate to high BD diagnostic sensitivity range (Fig. 3A). The IS, OS, IN, and ON regions of the SVD differed significantly between the two groups. The area under the ROC curve for the ON region of the SVD was 0.913 (95% confidence interval: 0.835–0.991), indicating that it has high diagnostic sensitivity for BD (Fig. 3B).

Relationship between RT and visual acuity

Full ($r = 0.6849$) and outer ($r = 0.6109$) RT and visual acuity in the OT region had positive relationships in BD patients (Fig. 4). These findings suggested that decreased visual acuity may be linked to increased RT.

Relationships between RT and ESR and CRP

In the full and outer retina in the C area, there were significant correlations between RT and CRP in patients with BD (full: $r = 0.6277$; outer: $r = 0.5691$). There was no significant association between RT and ESR ($p > 0.05$) (Fig. 5).

Discussion

Nearly all organ systems can be affected by BD [1]. Recurrent oral ulcers, vaginal ulcers, cutaneous signs, and eye problems are predominant clinical characteristics of BD [5], and the eyes are the most frequently affected organ. Ocular involvement (Behcet's uveitis) is characterized by occlusive retinal vasculitis and non-granulomatous panuveitis [19]. It typically involves a number of consequences, the most frequent of which are retinal degeneration and optic nerve atrophy, which can lead to permanent vision loss [20]. In the current study, alterations in RT and superficial vascular density were evident in BD patients, in conjunction with much lower visual acuity than healthy people. This finding may serve as a foundation for the early diagnosis of BD.

Arteries and veins of all diameters can be affected by BD [1]. Ocular symptoms can directly indicate changes in blood vessels, making them crucial indicators of disease activity [21]. According to the ETDRS partitioning approach used in the present study, SVD is significantly reduced in the IS, OS, IN, and ON regions. This is

Table 2 Comparison of macular retinal thickness at different locations between patients with BD and healthy subjects

Location (%, mean ± SD)	BD (*n* = 17, 34 eyes)	HC (*n* = 17, 34 eyes)	*P*-value	H-B corrections
Macular inner retinal thickness (μm, mean ± SD)				
IS	124.26 ± 8.17	113.53 ± 5.31	< 0.001*	0.027#
OS	127.97 ± 11.41	110.44 ± 5.76	< 0.001*	0.027#
IN	121.38 ± 8.60	115.91 ± 5.64	0.003*	0.054
ON	123.09 ± 14.69	123.56 ± 4.24	0.859	1.000
II	126.44 ± 6.51	114.38 ± 5.34	< 0.001*	0.027#
OI	116.18 ± 11.18	104.85 ± 6.39	< 0.001*	0.027#
IT	109.00 ± 4.35	105.06 ± 3.49	< 0.001*	0.027#
OT	95.24 ± 3.91	94.82 ± 5.10	0.710	1.000
C	56.85 ± 4.89	52.00 ± 5.29	< 0.001*	0.027#
Macular outer retinal thickness (μm, mean ± SD)				
IS	213.97 ± 10.09	218.62 ± 7.08	0.032*	0.512
OS	198.32 ± 16.12	194.03 ± 11.20	0.207	1.000
IN	199.21 ± 14.56	202.38 ± 6.74	0.252	1.000
ON	162.21 ± 12.73	158.68 ± 12.45	0.252	1.000
II	208.47 ± 11.88	212.50 ± 7.26	0.097	1.000
OI	180.79 ± 17.85	180.59 ± 14.01	0.958	1.000
IT	228.38 ± 10.69	230.35 ± 15.66	0.547	1.000
OT	223.56 ± 9.76	224.26 ± 8.32	0.749	1.000
C	197.15 ± 17.53	195.47 ± 14.94	0.673	1.000
Macular full retinal thickness (μm, mean ± SD)				
IS	338.24 ± 9.15	332.15 ± 8.06	0.005*	0.085
OS	326.29 ± 9.60	304.47 ± 10.78	< 0.001*	0.027#
IN	320.59 ± 12.23	318.29 ± 7.47	0.354	1.000
ON	285.29 ± 8.98	282.24 ± 12.18	0.243	1.000
II	334.91 ± 11.81	326.88 ± 8.95	0.002*	0.040#
OI	296.97 ± 14.79	285.44 ± 14.05	0.002*	0.040#
IT	337.38 ± 11.39	335.41 ± 15.08	0.545	1.000
OT	318.79 ± 10.22	319.09 ± 8.96	0.900	1.000
C	254.00 ± 18.98	247.47 ± 16.08	0.131	1.000

*, statistically significant at P value < 0.05. #, statistically significant after Holm-Bonferroni correction (Family Wise Error Rate 0.05)

BD, Behcet's Disease; HC, healthy control; IS, inner superior; OS, outer superior; IN, inner nasal; ON, outer nasal; II, inner inferior; OI, outer inferior; IT, inner temporal; OT, outer temporal; C, center

Table 3 Comparison of superficial vessel density at different locations between patients with BD and healthy subjects

Location (%, mean ± SD)	BD (*n* = 17, 34 eyes)	HC (*n* = 17, 34 eyes)	*P*-value	H-B corrections
IS	43.62 ± 10.42	53.18 ± 4.62	< 0.001*	0.009#
OS	44.15 ± 8.91	51.24 ± 3.38	< 0.001*	0.009#
IN	44.71 ± 5.22	50.82 ± 4.17	< 0.001*	0.009#
ON	46.35 ± 5.06	54.32 ± 2.90	< 0.001*	0.009#
II	51.18 ± 8.66	52.62 ± 3.40	0.371	1.000
OI	49.59 ± 9.48	51.91 ± 3.42	0.186	0.930
IT	54.82 ± 5.96	54.82 ± 2.62	1.000	1.000
OT	49.85 ± 5.92	50.29 ± 2.74	0.694	1.000
C	25.03 ± 9.21	24.65 ± 4.53	0.829	1.000

*, statistically significant at P value < 0.05. #, statistically significant after Holm-Bonferroni correction (Family Wise Error Rate 0.05)

BD, Behcet's Disease; HC, healthy control; IS, inner superior; OS, outer superior; IN, inner nasal; ON, outer nasal; II, inner inferior; OI, outer inferior; IT, inner temporal; OT, outer temporal; C, center

concordant with previous reports that eyes with BD had much lower rates of macular whole-face VD, foveal VD, and parafoveal VD [22]. There was also increased RT in all full and inner areas in the current study, in conjunction with notable thickening of the IS, OS, II, OI, IT, and C regions in the inner RT as well as the OS, II, and OI regions in the full RT. In linear correlational analysis, there was a strong link between RT and visual impairment. This is consistent with a previous report of swelling of the retinal nerve fiber layer in BD [23]. There are no previous reports of OCTA measurements of the entire RT in BD patients.

The choroid is a highly vascular structure and thus it can be affected by a variety of systemic diseases, including hematological, neurological, and systemic inflammatory conditions [24]. Choroidal neovascularization membrane development, which may cause a change in choroid thickness, can be induced by inflammation [25]. The choroid is particularly susceptible to subclinical disease activity. Choroid thickness may reflect the intensity of systemic inflammation, which could be an indicator of ocular inflammation in BD patients [26]. This subclinical alteration may also be present in the retina.

Similar to the brain, the retina has a high metabolic rate and high energy needs. Until relatively recently in evolutionary terms, choroidal capillaries supplied blood to the retinas of practically all species [27]. Retinal neurons are susceptible to excitatory toxic cell death, which can result in visual impairment or loss [28]. The pathological changes that arise when this happens in blood vessels that supply the retina may affect the entire choroidal retinal vascular network. In the current study, SVD in BD patients exhibited decline in almost all subregions, with statistically significant declines in the IS, OS, IN, and ON areas. Similar changes have also been observed in patients with diabetes [29] and systemic lupus erythematosus [30], and microcirculation changes in these patients may precede clinically detectable retinopathy. So we postulate that these subclinical changes also exist in individuals with BD. Although capillaries were lost throughout the body [31], the temporal area of the retina exhibited the most noticeable thinning. Choroid vessels may be involved in BD patients in addition to retinal vascular injury, and this may be the major focus or it may be subsequent to retinal inflammation. Retinal structure and function can be severely affected by persistent inflammation, which can ultimately result in blindness [32].

In BD patients, the HLAB51 allele may be linked to a high level of neutrophil activation. Neutrophils coordinate inflammatory activity by generating a variety of chemokines and cytokines, especially CXCL8 (also known as

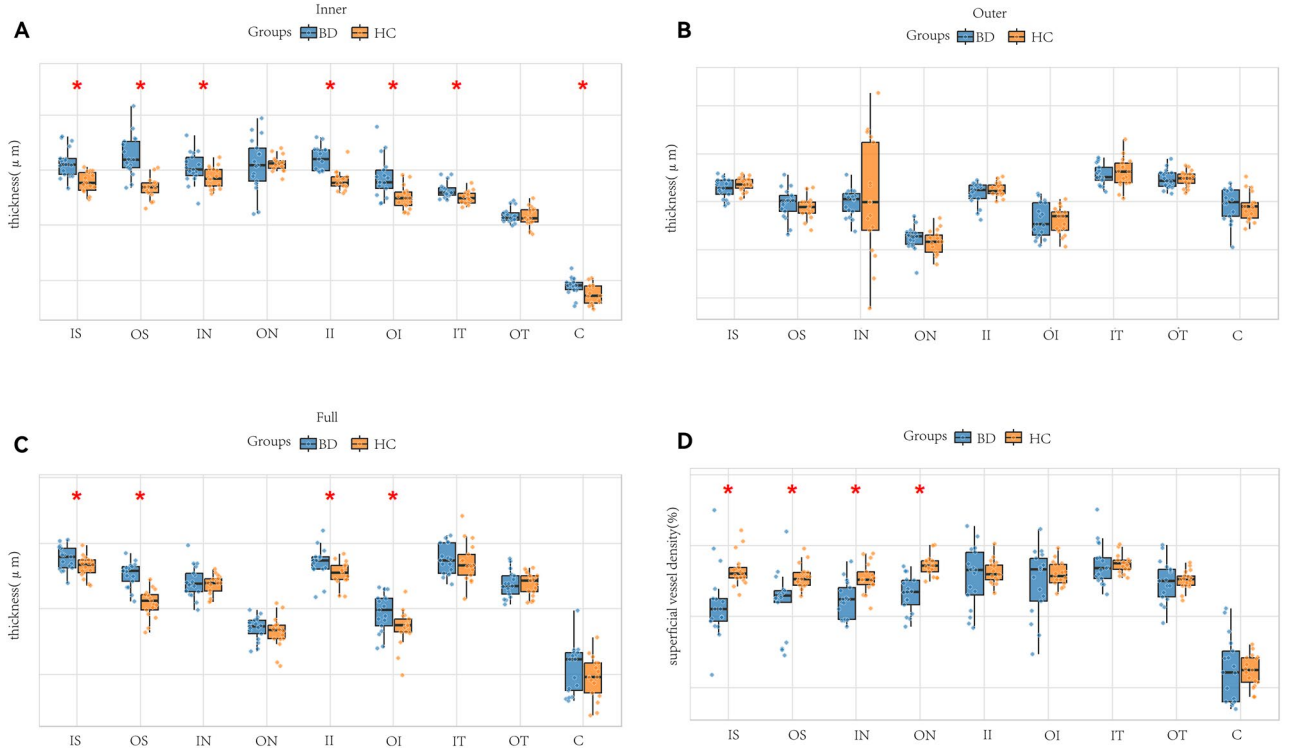

Fig. 2 RT and SVD analysis of right eyes in BD and control groups. (**A-C**) Analysis of RT results in the BD group and control group. The vertical coordinate is the value of RT, and the horizontal coordinate is the retinal subregions. (**D**) Analysis of SVD results in the BD group and control group. The vertical coordinate is the value of SVD, and the horizontal coordinate is the retinal subregions. Abbreviations: OCTA, optical coherence tomography angiography; BD, Behcet's Disease; RT, retinal thickness; SVD, superficial vessel density; ETDRS, early treatment of diabetic retinopathy study; IS, inner superior; OS, outer superior; IN, inner nasal; ON, outer nasal; II, inner inferior; OI, outer inferior; IT, inner temporal; OT, outer temporal; C center. *, $P < 0.05$, after H-B corrected

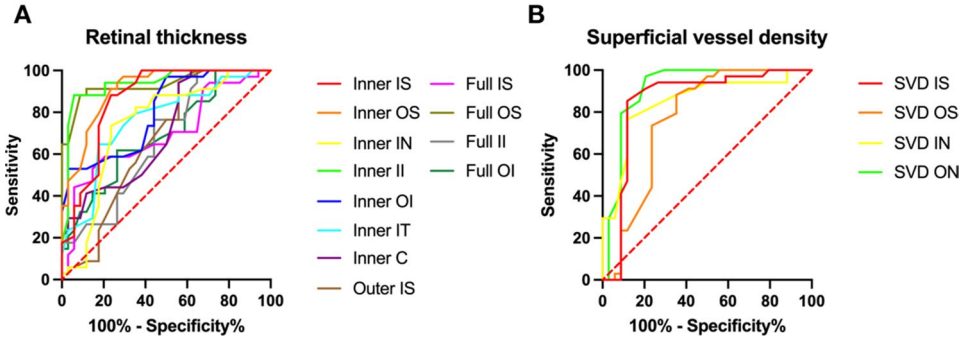

Fig. 3 ROC curve analysis of RT and SVD. The area under the ROC curve was 0.862 for inner IS (95% CI: 0.771 to 0.953), 0.908 for inner OS (95% CI: 0.840 to 0.976), 0.742 for inner IN (95% CI: 0.618 to 0.866), 0.938 for inner II (95% CI: 0.878 to 0.998), 0.801 for inner OI (95% CI: 0.698 to 0.904), 0.759 for inner IT (95% CI: 0.643 to 0.875), 0.702 for inner C (95% CI: 0.579 to 0.826), 0.665 for outer IS (95% CI: 0.532 to 0.798), 0.694 for full IS (95% CI: 0.567 to 0.822), 0.933 for full OS (95% CI: 0.873 to 0.993), 0.668 for outer II (95% CI: 0.538 to 0.797), and 0.691 for full OI (95% CI: 0.566 to 0.815). (**B**) The area under the ROC curve was 0.856 for SVD IS (95% CI: 0.750 to 0.962), 0.771 for SVD OS (95% CI: 0.651 to 0.891), 0.849 for SVD IN (95% CI: 0.753 to 0.945), 0.913 for SVD ON (95% CI: 0.835 to 0.991). Abbreviations: ROC, receiver operating characteristic; RT, retinal thickness; SVD, superficial vessel density; IS, inner superior; OS, outer superior; IN, inner nasal; ON, outer nasal; II, inner inferior; OI, outer inferior; IT, inner temporal; OT, outer temporal; C, center

interleukin 8) and interleukin 17, which causes thrombosis and affects arteries throughout the body [33]. Patients with BD have aberrant hematological and biochemical markers, leading to impaired stability and elevated CRP due to systemic inflammation and inappropriate immunological responses [34]. In the present study, there was a significant association between full and outer RT in the C area and higher CRP, suggesting that RT may be affected by an aberrant immunological status, and that BD is a reflection of systemic inflammation. ESR is another general indicator of inflammation. Like CRP, ESR is frequently used to assess the level of inflammation in BD patients. In the current study however, there was no significant relationship between RT and ESR.

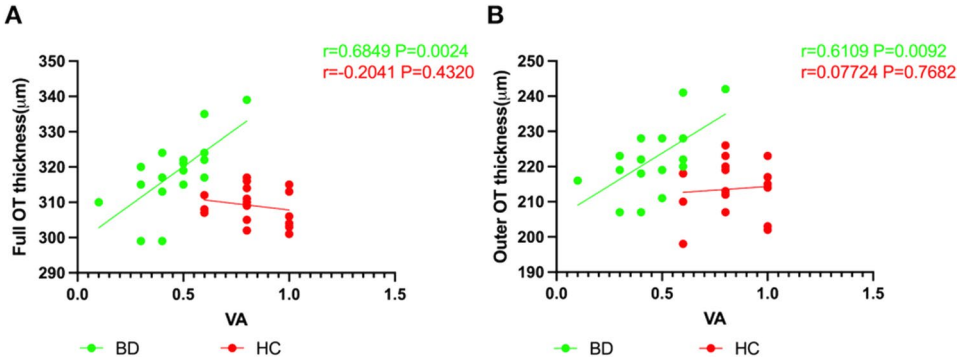

Fig. 4 The correlation between RT and VA in control and BD patients. The vertical coordinate is the value of RT, and the horizontal coordinate is the value of VA. (**A**) A positive correlation was found between RT and VA in the full retina in the C region ($r = 0.6849$; $P = 0.0024$). (**B**) A positive correlation was found between RT and VA in the outer retina at C region ($r = 0.6109$; $P = 0.0092$). Abbreviations: BD, Behcet's Disease; RT, retinal thickness; VA, visual acuity; OT, outer temporal

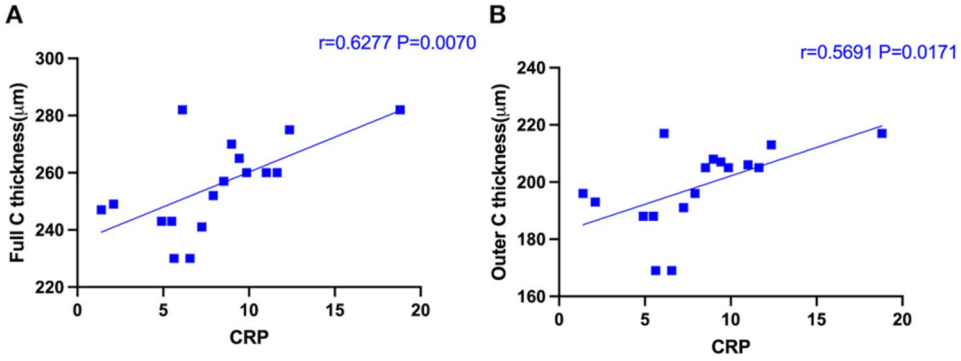

Fig. 5 The correlation between RT and CRP in BD patients. The vertical coordinate is the value of RT, and the horizontal coordinate is the value of CRP. (**A**) A positive correlation was found between RT and CRP in the full retina in the C region ($r = 0.6277$; $P = 0.0070$). (**B**) A positive correlation was found between RT and CRP in the outer retina at C region ($r = 0.5691$; $P = 0.0171$). Abbreviations: BD, Behcet's Disease; RT, retinal thickness; CRP, C-reactive protein; C, center

ROC curves for SVD in the IS, OS, IN, and ON regions revealed that ON region may be useful diagnostic indicators of BD. Early diagnosis and evaluation of BD are essential for effective therapy and a favorable prognosis. However, only clinical criteria can not support a diagnosis of BD, thus other diseases must be ruled out based on clinical symptoms [2]. A non-invasive imaging method called OCTA can be used to generate images for volumetric ocular angiography. Clinically discernible retinopathy may be preceded by microcirculation abnormalities in BD. Healthy eyes can be distinguished from BD eyes via OCTA, and RT measurements obtained via OCTA may be useful for diagnosing BD. Notably however, further investigation is required to establish a foundation for future clinical applications. With high-resolution images, OCTA can reveal the supporting band capillary beds and their subtle changes that are not detected with fluorescence angiography (FA) [35].

At present, the new research field of artificial intelligence (AI) and image joint diagnosis of diseases is being developed and applied in a vigorous way, which is also a new translational research direction of combining AI and OCTA images to diagnose lung cancer in the future. Extensive research has demonstrated the remarkable advantages of AI in disease diagnosis, treatment, and prediction. AI can accurately detect conditions such as diabetic retinopathy, macular degeneration, glaucoma, and cataracts through fundus imaging and slit-lamp examinations [36]. By integrating machine learning, deep learning, and image analysis, numerous intelligent detection systems for various diseases have been developed. Tang et al [37] established deep learning combined with ultra-wide field of view fundus (UWF) image detection for diabetic retinopathy (DR), and the accuracy rate was up to 90%. Li et al [38] established a deep learning system for glaucoma optic neuropathy detection from fundus images, achieving an AUC of 0.986 and a sensitivity of 95.6%. Zhang et al [39–41] constructed a new unbalanced image classification model (ADSR-Net) to better identify salient and small lesions. In the future of healthcare, AI will serve the battle for human health with solid basic theoretical research and robust clinical transformation results.

The present study had some limitations. (1) A variety of variables including age and prescription drugs are not considered, which can affect RT and SVD. (2) The

study did not incorporate comparisons of different illness stages. (3) The study did not include the apparent characteristics and genetic history of BD as indicators to analyze the correlation. (4) The data from both eyes of the same patient were analyzed independently and their correlation was not considered in the statistical model, which may increase the risk of type I error. The reason for this is that (5) the sample size is small and the results are not robust. (6) While the current study did not perform intra- or inter-observer reproducibility assessments for the segmentation, the automated algorithm employed (AngioAnalytics™) has been previously validated and demonstrated excellent reproducibility in prior studies [42].

Conclusion

RT and SVD were investigated in BD patients via OCTA imaging in the study. In comparison to HCs, BD patients exhibited thickening of the inner and entire retina as well as considerably lower SVD in the IS, OS, IN, and ON areas. The study also suggested that vision could be affected by the center region of the retinal macula thickness. OCTA assessment of the ON region of SVD, full OS and inner II region of RT may be useful for supplementary imaging diagnosis of BD.

Abbreviations

OCTA	Optical coherence tomography angiography
RT	Retinal thickness
SVD	Superficial vascular density
BD	Behcet's disease
FA	Fluorescein angiography
HCs	Healthy controls
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
ETDRS	Early Treatment Diabetic Retinopathy Study
ILM	Inner limiting membrane
ROC curves	Receiver operating characteristic curves
AI	Artificial intelligence
UWF	Ultra-wide field of view fundus
DR	Diabetic retinopathy
AUC	Area under the curve
VA	Visual acuity
MAR	Minimum angle of resolution
IOP	Intraocular pressure
ANA	Antinuclear antibody
ANAs	Antinuclear antibody spectrum
BUT	Tear breakup time
OSS	Ostaining score
SIT	Schirmer test
TMH	Tear meniscus height
HADS	Hospital anxiety and depression Scale
N/A	Not applicable
IS	Inner superior
OS	Outer superior
IN	Inner nasal
ON	Outer nasal
II	Inner inferior
OI	Outer inferior
IT	Inner temporal
OT	Outer temporal
C	Center

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Author contributions

ZM X and C C participated in Writing – Original Draft, Review & Editing, Formal Analysis, Methodology and Fig. 2; L Z, JY H and YM Z participated in Tables 1, 2 and 3, Writing – Review & Editing and Data Curation; XY W, LQ H, QM G and Q L participated in Figs. 1, 3, 4 and 5 and Writing – Review & Editing; X C and YX W participated in Conceptualization, Validation and Project Administration; Y S participated in Funding Acquisition, Resources, Software and Validation.

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Data availability

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Medical Ethics Committee of the First Affiliated Hospital of Nanchang University approved the study's methodology (cdyfy 2021039), and the study adhered to the Declaration of Helsinki. All participants provided written informed consent after being fully informed of the study objectives, protocols, procedures, and associated risks, thereby agreeing to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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