Original Article

Microvascular and Ultrastructural Changes of the Retina and Choroid in Patients with Sickle Cell Anemia

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Abstract

Objectives: To determine the microvascular changes of the retina and choroid in sickle cell anemia (SCA) patients and to investigate the relationship between the severity of sickle cell retinopathy and sickle cell maculopathy (SCM).

Materials and Methods: In this cross-sectional study, 78 eyes of 39 patients with SCA were included in the patient group and 68 eyes of 34 healthy participants were included in the control group. Differences in foveal avascular zone (FAZ), retinal and subfoveal choroidal thickness (SFCT), and choroidal vascularity index (CVI) between the patient group and the control group were evaluated by swept source optical coherence tomography (OCT) and OCT angiography (OCTA) imaging. In addition, systemic and biological parameters were compared in patients with and without SCM.

Results: SCM was detected in 16 eyes of 8 patients. Proliferative sickle cell retinopathy (PSCR) was present in 10 patients. In logistic regression analysis, PSCR was found to be a risk factor for the development of SCM (p=0.015, odds ratio: 17.25, 95% confidence interval: 1.73-172.02). The temporal inner retinal layers were significantly thinner in the patient group compared to the control group. The patient group also exhibited significantly greater FAZ enlargement in both the superficial and deep capillary plexus when compared with the control group (p<0.001 for both). CVI was higher in the control group than in the patient group (p<0.001). SFCT was significantly thinner in the patient group (p=0.013). There was no significant difference between patients with and without SCM in terms of FAZ enlargement, CVI values, or systemic and biological factors.

Conclusion: In our study, PSCR was found to be a risk factor for the development of SCM. OCT and OCTA provide valuable information about microvascular changes in the retina and choroid in patients with SCM. Structural changes demonstrated by OCTA before the development of SCM are very important for follow-up and treatment in terms of visual prognosis of patients.

Keywords: Sickle cell anemia, sickle cell maculopathy, sickle cell retinopathy, optical coherence tomography angiography

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Introduction

Sickle cell anemia (SCA) affects approximately 400,000 newborns each year.[1] It is more common in Mediterranean countries, including our country, as well as in the Middle East, India, and Africa.[2] The prevalence of SCA in Türkiye is 0.3-0.6%, but it is concentrated in the Çukurova region and this rate reaches up to 44% in some communities.[2,3] The disease is characterized by the formation of hemoglobin S (Hb S), which occurs as a result of the substitution of glutamic acid by valine at the sixth position of the β-globin chain. Hb S is an abnormal form of Hb that assumes a sickle shape under conditions such as hypoxia, hyperosmolarity, and acidosis, which in turn leads to vascular stasis, thrombosis, and ischemia.[4]

In addition to systemic complications, ocular complications also occur in SCA. Ophthalmological complications observed as a result of microvascular occlusion include sickle cell retinopathy (SCR), sickle cell maculopathy (SCM), hyphema, secondary glaucoma, and orbital bone infarctions (especially affecting the sphenoid bone).[4] The main complication that threatens vision in these patients is proliferative sickle cell retinopathy (PSCR).[5] SCR is classified using a severity-based staging system defined by Goldberg.[6] In this classification, the absence of retinopathy is evaluated as stage 0, peripheral arterial occlusions as stage 1, peripheral arteriovenous anastomoses as stage 2, preretinal neovascularizations as stage 3, vitreous hemorrhage as stage 4, and retinal detachment as stage 5.[6]

In SCR, vascular pathologies typically manifest in the temporal peripheral retina and are usually associated with ischemia resulting from arteriolar occlusion.[6] However, central retinal changes such as nerve fiber layer infarcts, foveal avascular zone (FAZ) enlargement, reduced macular vessel density (VD), and microaneurysms may also occur.[7] It has even been suggested that FAZ enlargement and reduction in macular VD can occur over time despite peripheral retinopathy showing no progression.[8]

Optical coherence tomography (OCT) images of the macula in SCA patients have revealed thinning of the inner retinal layers in the temporal quadrant.[9] The patchy areas of the macula corresponding to these areas of thinning are called SCM.[5] Although its exact etiology has not been defined, pre-capillary vascular occlusions in the perimacular area were suggested as a cause of this retinal thinning.[10]

The aim of the present study was to examine the relationship between SCM and peripheral retinal vascular disease in patients followed up for SCA and to determine systemic and biological factors that may be risk factors for SCM. An additional objective was to compare the ultrastructural and microvascular structures of the retina in choroidal and macular sections with swept source (SS) OCT and OCT angiography (OCTA) in SCA patients and a healthy control group.

Materials and Methods

Ethical approval for this cross-sectional study was obtained from the Başkent University Medical and Health Units Research Board and Ethics Committee (project no: KA23/288, decision no: 23/151, date: 20/09/2023). Informed consent was obtained from all participants in the study, and the principles of the Declaration of Helsinki were adhered to during the study period.

A total of 39 patients whose diagnoses were confirmed by Hb electrophoresis and were followed up due to SCA in the Hematology clinic of the Başkent University Adana Application and Research Center were included in the study. Between January 2023 and March 2024, a full ophthalmological examination was performed, best corrected visual acuity (BCVA) was measured with the Snellen chart, intraocular pressures were evaluated, and anterior segment and dilated fundus examinations were performed. For all patients, demographic data such as age, sex, and SCA genotype were recorded, as well as systemic parameters (history of acute chest syndrome, painful crisis, cholelithiasis, cerebrovascular accident, chronic transfusion, anticoagulant use, and hydroxyurea treatment) and biological parameters (Hb, hematocrit, Hb F, platelet, neutrophil, lymphocyte, mean red cell volume, ferritin, total and indirect bilirubin, alanine transaminase, and lactate dehydrogenase values). Exclusion criteria were: age less than 18 years, presence of diabetes, uncontrolled hypertension, retinal vascular occlusions, epiretinal membrane, vitreomacular traction, history of retinal laser photocoagulation or intraocular surgery, spherical equivalent of >3 diopters (D), axial length other than 22-24 mm, and low-resolution OCT images. The control group consisted of 34 age- and sex-matched healthy participants.

All participants were imaged with SS-OCT and SS-OCTA (DRI-OCT Triton Plus; Topcon Corporation, Tokyo, Japan). As described in previous studies, SCM was evaluated as patchy areas of retinal thinning on OCT images and blue areas on color images showing retinal thickness.[5,11] All examinations were performed between 9:00 and 11:00 in the morning to avoid any effect of diurnal changes. Macular images were obtained with the Triton Plus using a linear scan (100 kHz A-scanning speed, 1050 nm wavelength) centered on the foveal center. Inner and outer retinal thicknesses were measured manually using the device software in a total of 7 regions: the fovea and 3 retinal sites at 1-mm intervals nasal and temporal to the foveal center. Inner retinal thickness was measured between the inner limiting membrane and the junction of the inner nuclear layer (INT) and outer plexiform layer (OPT), and outer retinal thickness was measured between the INT/OPT junction and the retinal pigment epithelium layer. Choroidal thickness was measured subfoveally between the outer border of the retinal pigment epithelium and the choroid-scleral junction.

The obtained choroidal images were binarized to calculate the choroidal vascularity index (CVI) (Figure 1). The binarization process was carried out using open-source image J software (version 1.53a; National Institutes of Health, Bethesda, MD, USA; https://imagej.nih.gov/ij/) as defined by Agrawal et al.[12] First, images were obtained from OCT scans using the Image J software. The images were then converted to 8-bit format and the Niblack automatic local thresholding method was applied to visualize the choroid-scleral junction. The region between the retinal pigment epithelium and choroid-scleral junction was scanned using the polygon tool, and this region was selected as the total choroidal area (TCA). The selected region was recorded as a region of interest (ROI). Next, the image was converted to red-green-blue format and saved to the ROI manager after adjusting the brightness. The two fields recorded by the ROI manager were selected and merged using the "AND" tool. Finally, luminal area (LA) and TCA were measured and CVI was calculated as a percentage by dividing the LA by TCA.

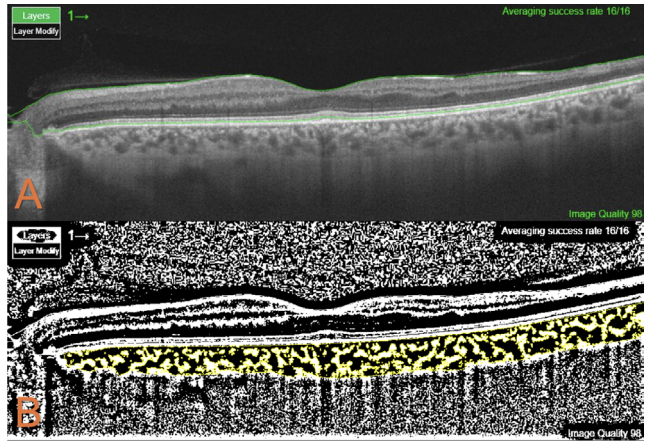

Figure 1. Optical coherence tomography images before (A) and after (B) binarization

OCTA images were measured as 6x6 mm. The superficial capillary plexus (SCP) and deep capillary plexus (DCP) were measured manually on the OCTA images as the regions extending from 2.6 µm below the inner limiting membrane to 15.6 µm below the inner plexiform layer, and from 15.6 µm to 70.2 µm below the inner plexiform layer, respectively. FAZ area (mm^2) in the SCP and DCP was measured manually with the area measurement tool in the device (Figure 2). VD in the SCP and DCP was obtained by the device software.

In patients with signs of SCR, fluorescein angiography (FA) (DRI-OCT Triton Plus; Topcon Corporation, Tokyo, Japan) was performed to determine the stage. SCR staging was done according to the Goldberg classification.[6] The patient group was then divided into 3 subgroups: non-retinopathy (Goldberg stage 0), non-PSCR (Goldberg stages 1 and 2), and PSCR (Goldberg stages 3-5). All image analyses (OCT, OCTA, and CVI) in the study were performed by two different researchers (O.O., A.İ.) and the means of their two measurements were used.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The variables were tested for normal distribution with the Shapiro-Wilk test. Mean and standard deviation values were used to present descriptive analyses. When comparing normally distributed variables between the two groups, independent samples t-test was used, and one-way analysis of variance (ANOVA) with Dunn's Bonferroni post-hoc test was used for comparisons between more than two groups. Frequency and percentage values were used when presenting categorical variables. Relationships between categorical variables were examined with chi-square or Fisher's exact test. Relationships between quantitative variables were examined with Pearson correlation analysis. According to the correlation coefficients (r), correlation strength was evaluated as very strong (0.81-1.0), strong (0.60-0.79), moderate (0.40-0.59), weak (0.20-0.39), or very weak (0-0.19).[13] Parameters that may be risk factors for SCM development were examined by binary logistic regression analysis. Comparisons with p values below 0.05 were evaluated as statistically significant.

Results

The study included a total of 146 eyes of 73 participants (39 patients with SCA and 34 healthy controls). Demographic data of the patient group are presented in Table 1. The control group included 12 females and 22 males and the mean age was 33.44±10.57 years. There was no difference between the patient and control groups in terms of age or sex distribution (p=0.706 and p=1.000, respectively). The most common systemic findings were cholelithiasis (n=21, 53.9%), avascular necrosis (n=19, 48.7%), and painful vaso-occlusive crisis (n=15, 38.5%) (Table 2). There was no significant difference in systemic findings between the sickle cell genotypes. The biological parameters of the patient group are presented in Table 3. There was no difference between patients with and without SCM in terms of systemic or biological parameters. In the patient group, 21 patients (53.9%) had the HbSS and 18 patients (46.2%) had the HbSβ genotype. BCVA was between 20/25 and 20/20 in the patient group and 20/20 for all control subjects.

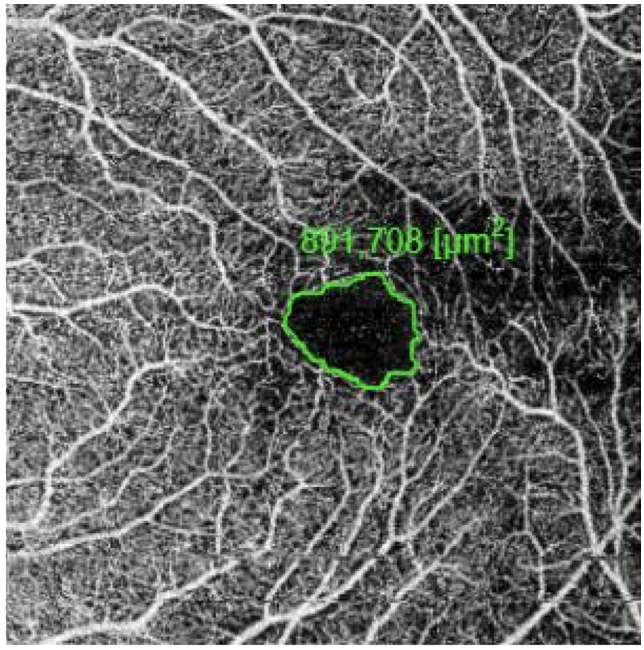

Figure 2. Manual measurement of foveal avascular zone

In the FA examination performed in patients with signs of SCR, 28 eyes (35.9%) had SCR according to the Goldberg classification. Of these, non-PSCR was present in 18 eyes (23.1%) and PSCR was present in 10 eyes (12.8%). Of the eyes with non-PSCR, 10 (12.8%) were stage 1 and 8 (10.3%) were stage 2. Fifty (64.1%) eyes had no retinopathy. There was no significant difference between these groups in terms of age and sex (p=0.463 and p=0.533, respectively). Of the 5 patients with PSCR, the SCA genotype was HbSβ in 4 patients and HbSS in 1 patient.

When OCT images were evaluated, bilateral SCM was detected in 8 (20.5%) of the 39 SCA patients. Of these, 4 patients had the HbSS and 4 had the HbSβ genotype. There was no difference between patients with and without SCM in terms of complete blood count parameters or systemic findings. When we examined the relationship between SCM and SCR, we found that the frequency of SCM increased in patients with PSCR. PSCR was observed in 37.5% (6/16) of the eyes with SCM and 6.5% (4/62) of the eyes without SCM (p<0.001). In the logistic regression analysis, the presence of retinopathy was found to be a risk factor for SCM development (p=0.042). The odds of SCM in patients with PSCR was 17.25 times higher than in patients without retinopathy (p=0.015, odds ratio: 17.25, 95% confidence interval: 1.73-172.016).

In patients with SCA, we found significant thinning of the temporal inner retinal layers in OCT images obtained 1, 2, and 3 mm from the fovea compared to the control group (p<0.001, p=0.006, and p<0.001, respectively) (Table 4). However, there was no difference in temporal inner retinal layer and foveal

thickness in patients without SCM compared to the control group. There was no significant difference between the groups in the inner nasal and outer retinal layers. Subfoveal choroidal thickness (SFCT) was significantly greater in the control group compared to the entire patient group and patients with SCM (p=0.013 and p=0.006, respectively). SFCT did not differ significantly between the control group and patients without SCM (p=0.277) or between patients with and without SCM (p=0.139).

Table 1. Comparison of the patients' demographic data

Parameters		Patient group	Sickle cell maculopathy		p value*
			Yes	No	
Patients/eyes, n		39/78	8/16	31/62	
Age (years), mean ± SD		32.59±8.26	31.13±9.37	32.71±8.12	0.861
Sex (male/female), n		13/26	3/5	10/21	1.000
Retinopathy n (%)	None	50 (64.1)	4 (25.0)	46 (74.2)	**<0.001**
	Non-proliferative	18 (23.1)	6 (37.5)	12 (19.4)	0.124
	Proliferative	10 (12.8)	6 (37.5)	4 (6.5)	**<0.001**
Genotype n (%)	HbSS	21 (53.8)	4 (50)	17 (54.9)	1.000
	HbSβ	18 (4.2)	4 (50)	14 (45.2)	1.000

*Sickle cell maculopathy group vs. non-sickle cell maculopathy group. SD: Standard deviation

Table 2. Comparison of the frequency of systemic parameters in the patient group

Systemic parameters	Patient group (n=39)	Sickle cell maculopathy		p value*
		Yes (n=8)	None (n=31)	
Acute chest syndrome (within last year)	4 (10.3)	2 (25.0)	2 (6.5)	0.180
Avascular necrosis	19 (48.7)	3 (37.5)	16 (51.6)	0.695
Painful crisis (>2 in last year)	14 (38.5)	4 (50.0)	11 (35.5)	0.686
Cholelithiasis	21 (53.9)	3 (37.5)	18 (58.6)	0.432
Cerebrovascular accident	4 (10.3)	2 (25)	2 (6.5)	0.180
Chronic transfusion	10 (25.6)	3 (37.5)	7 (22.6)	0.399
Anticoagulant use	12 (30.8)	3 (37.5)	9 (29.3)	0.682
Hydroxyurea treatment	29 (74.4)	7 (87.5)	22 (71.0)	0.653

All data are presented as number and percentage. *Sickle cell maculopathy group vs. non-sickle cell maculopathy group

Table 3. Comparison of biological parameters in the patient group

Biological parameters	Patient group (n=39)	Sickle cell maculopathy		p value*
		Yes (n=8)	No (n=31)	
Hemoglobin (g/dL)	9.10±1.36	9.74±1.62	8.93±1.26	0.138
Hematocrit (%)	27.87±4.76	27.73±4.61	27.90±4.87	0.926
Hemoglobin F >15%, n (%)	12 (30.8)	1 (12.5)	11 (35.5)	0.394
Platelets (g/L)	400.09±192.43	482.48±167.71	378.84±195.10	0.178
Neutrophils (g/L)	5.46±2.51	5.32±1.65	5.50±2.70	0.860
Lymphocytes (g/L)	3.83±2.06	4.37±1.86	3.69±2.12	0.418
MCV (fL)	92.36±15.93	93.21±17.69	92.14±15.76	0.869
Ferritin (ng/mL)	533.30±552.26	523.6±421.57	535.8±587.21	0.956
Total bilirubin (mmol/L)	2.95±1.67	3.28±1.60	2.87±1.70	0.542
Indirect bilirubin (mmol/L)	2.24±1.67	2.47±1.74	2.18±1.67	0.673
ALT (IU/L)	29.18±23.75	26.88±23.28	29.77±24.21	0.763
LDH (IU/L)	425.59±194.53	424.13±213.96	425.97±193.00	0.881

*Sickle cell maculopathy group vs. non-sickle cell maculopathy group. MCV: Mean corpuscular volume, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

When we examined OCTA parameters, we noted that the FAZ area in both the SCP and DCP was significantly greater in the patient group compared to the control group (p<0.001 for both) (Table 5). In contrast, VD in the SCP and DCP was lower in the patient group than in the control group (p=0.021 and p=0.042). There was no difference between the patients with and without SCM in terms of FAZ area or VD in the SCP and DCP. Figure 3 shows the OCTA, OCT, and retinal thickness maps of patients with and without SCM and one control subject. CVI values were also significantly lower in the patient group than in the control group (p<0.001). The presence of SCM had no effect on CVI.

Discussion

SCA is a common hemoglobinopathy as well as a sight-threatening disease due to the macular damage and retinopathy it causes. In this study, we examined choroidal and foveal microvascular and ultrastructural differences between patients with SCA and healthy volunteers. SCM is a common clinical manifestation in SCA patients that can lead to permanent visual damage; it is therefore important to identify potential risk factors.[14] We determined that PSCR was a risk factor for the development of SCM in patients being followed up for SCA. It has been suggested that this relationship stems from the fact that the macular temporal and peripheral retina are fed by small-diameter terminal arterioles, which are more susceptible to vascular occlusion.[15] Fares et al.[5] also reported that PSCR was

Table 4. Comparison of retinal and choroidal thicknesses in the patient and control groups

			Control group (n=68 eyes)	Patient group (n=78 eyes)	Sickle cell maculopathy		p^1	p^2	p^3	p^4	p^5
					Yes (n=16)	No (n=62)					
Subfoveal choroidal thickness			316.01±53.59	290.49±83.23	259±54.83	298.61±87.62	**0.013**	**0.014**	**0.006**	0.277	0.139
Retinal thickness	Foveal		183.03±15.35	181.85±20.97	181.06±25.76	182.05±19.79	0.142	0.913	1.000	1.000	1.000
	Inner nasal	1 mm	132.22±10.49	130.1±10.06	128.19±13.29	130.6±9.11	0.215	0.328	0.479	1.000	1.000
		2 mm	122.51±11.81	123.03±16.24	120.75±21.26	123.61±14.83	0.830	0.760	1.000	1.000	1.000
		3 mm	87.29±8.04	87.45±21.26	88.88±30.79	87.08±18.35	0.953	0.926	1.000	1.000	1.000
	Inner temporal	1 mm	126.88±12.35	117.21±18.27	99.63±23.41	121.74±13.59	**<0.001**	**<0.001**	**<0.001**	0.078	0.013
		2 mm	119.71±12.94	112.08±18.96	90.69±24.54	117.6±12.44	**0.006**	**<0.001**	**<0.001**	1.000	**<0.001**
		3 mm	99.4±9.24	90.41±17.81	67.81±19.84	96.24±11.63	**<0.001**	**<0.001**	**<0.001**	0.172	**<0.001**
	Outer nasal	1 mm	156.85±11.29	157.24±12.04	153.38±10.44	158.24±12.30	0.841	0.326	0.853	1.000	0.415
		2 mm	143.25±8.86	141.08±10.52	138.06±9.55	141.85±10.69	0.183	0.159	0.503	1.000	0.503
		3 mm	131.19±9.91	128.78±13.66	128.31±12.94	128.9±13.94	0.221	0.481	1.000	0.850	1.000
	Outer temporal	1 mm	157.13±10.17	154.49±11.78	153.06±11.89	154.85±11.83	0.152	0.304	0.566	0.732	1.000
		2 mm	141.96±10.98	142.14±10.60	139.31±9.60	142.87±10.80	0.918	0.498	1.000	1.000	0.721
		3 mm	132.63±8.16	130.9±9.12	131.63±9.30	130.71±9.14	0.230	0.455	1.000	0.632	1.000

p^1: Control vs. patient group (Student t-test), p^2: Control vs. sickle cell maculopathy (SCM) vs. non-SCM group (ANOVA), p^3: Control vs. SCM group (Bonferroni post-hoc), p^4: Control vs. non-SCM group (Bonferroni post-hoc), p^5: SCM vs. non-SCM group (Bonferroni post-hoc). Significance values were adjusted by Bonferroni correction for multiple comparisons

Table 5. Comparison of optical coherence tomography angiography parameters and CVI values in the patient and control groups

	Control group (n=68 eyes)	Patient group (n=78 eyes)	Sickle cell maculopathy		p^1	p^2	p^3	p^4	p^5
			Yes (n=16)	No (n=62)					
FAZ SCP (mm^2)	0.26±0.09	0.42±0.19	0.47±0.26	0.40±0.16	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.333
FAZ DCP (mm^2)	0.28±0.09	0.45±0.19	0.49±0.26	0.44±0.17	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.643
SCP-VD (%)	23.46±3.66 23.61 (13.86-29.56)	21.35±6.94 20.35 (8.63-38.17)	21.58±6.47 23.40 (8.63-31.66)	21.29±7.10 19.65 (10.46-38.17)	**0.021**	**0.009**	0.794	**0.006**	1.000
DCP-VD (%)	21.80±3.62 21.52 (15.21-31.13)	19.97±6.82 18.51 (8.01-36.77)	20.43±6.31 21.57 (8.01-30.42)	19.85±6.98 18.32 (9.23-36.77)	**0.042**	**0.023**	1.000	**0.018**	0.979
CVI (%)	71.02±2.65	68.14±2.20	67.70±2.79	68.25±2.18	**<0.001**	**<0.001**	**<0.001**	**<0.001**	1.000

p^1: Controls vs. patients (Student t-test), p^2: Control vs. sickle cell maculopathy (SCM) vs. non-SCM group (ANOVA [mean ± standard deviation] or median [range]), p^3: Control vs. SCM group (Bonferroni post-hoc), p^4: Control vs. non-SCM group (Bonferroni post-hoc), p^5: SCM vs. non-SCM group (Bonferroni post-hoc). Significance values were adjusted by Bonferroni correction for multiple comparisons. CVI: Choroidal vascularity index, FAZ: Foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, VD: Vessel density

Figure 3. Optical coherence tomography angiography, optical coherence tomography, and retinal thickness analysis images of patients with (A) and without (B) sickle cell maculopathy and a participant from the control group (C)

an independent risk factor for SCM development. In different studies, the prevalence of SCA was found to be higher in patients with PSCR compared to those without PSCR.[11] Mathew et al.[15] detected PSCR in 67% of patients observed to have SCM versus 48% of patients without SCM. In our study, PSCR was observed in 37.5% of the patients with SCM, while this rate was 6.45% in those without SCM. These findings indicate that SCM and PSCR are related.

Some studies have shown SCM to be associated with biological and systemic risk factors such as low Hb and hematocrit level, high reticulocyte, HbSS genotype, clotting disorders, and high total bilirubin level.[5,16] Grego et al.[16] found that patients who developed SCM had hemolysis markers such as low Hb and hematocrit levels and high reticulocytes and total bilirubin. However, there are other studies showing that biological risk factors have no effect on SCM development.[17] We did not find a relationship between biological factors and SCM in the present study. However, the patients' hematological parameters were evaluated on the day they were examined in our clinic, at which point they had already developed SCM. Evaluating these parameters as SCM is developing may reveal a relationship between biological parameters and SCM. Some authors have suggested that SCM is the result of hemolysis-induced endothelial damage rather than vascular occlusion.[18,19]

Thinning of the temporal inner retinal layers in SCA patients has been documented in many previous studies and case reports.[9,10,15] Thinning and atrophy of the inner retinal layers have also been shown in histopathological studies.[20] It has been suggested that atrophy occurs in the temporal region because the temporal arterioles are smaller in diameter than those on the nasal side, but the cause remains inconclusive.[15] In this study, we observed significant thinning in the temporal inner retinal layers in SCA patients compared to controls. However, this difference was not observed between the patients without SCM and the control group. We also found no significant difference in the temporal outer retinal layers or in the nasal quadrant. Dell'Arti et al.[11] reported thinning of both the inner and outer retinal layers in their study, while Hoang et al.[14] reported thinning only in the outer retinal layers. The choriocapillaris vessels that supply the outer retinal layers are larger in diameter than the vessels supplying the inner retina.[14] Since these large vessels are less susceptible to occlusion, the outer retinal layers may be more protected than the inner retinal layers in SCA patients. This may explain the thinning of the inner retinal layers and preservation of the outer retinal layers seen in our study, consistent with many previous studies in the literature.

In our study, SFCT was decreased in the patient group compared to the control group. Reduced choroidal thickness was also reported by Mathew et al.[15] in an adult patient group and by Yılmaz et al.[21] in a pediatric patient group. Decreased choroidal thickness is expected in SCA patients because of sickling and slowed blood flow in the choriocapillaris. Choroidal thickness is known to be affected by changes such as refractive error, diurnal rhythm, and age.[22] Assessing CVI can overcome these limitations of choroidal thickness measurement. As expected, we found that the CVI was lower in the patient group than in the control group. However, there was no difference in CVI between patients with and without SCM. This is consistent with the view that macular microarterial occlusions are not affected by changes in choroidal circulation.[15]

In line with the literature, we observed significant FAZ enlargement in both the SCP and DCP in the patient group. Minvielle et al.[23] and Fares et al.[5] also reported significant enlargement of the FAZ in SCA patients. These findings are also consistent with the FAZ enlargement detected in studies conducted with FA.[24] Fluorescein injection has been suggested to cause painful crises in SCA patients.[25] Therefore, the data obtained with OCTA is invaluable. Minvielle et al.[23] found that VD in both the SCP and DCP was lower in SCA patients compared to the control group. Consistent with their study, we found that VD was decreased in the patient group. We also noted that the FAZ area was significantly larger in patients with SCM compared to controls. Patients with SCM also showed enlargement of the FAZ area compared to those without, but this difference was not reflected in the statistical results. This may be because macular microvascular changes can be detected earlier on

OCTA than OCT. In support of this idea, Fares et al.[5] reported that no flow was detected on OCTA in 36 of 85 eyes without signs of SCM. The fact that macular microvascular changes that are not reflected in OCT images can be detected by OCTA shows that the latter provides useful information in the follow-up and prevention of SCM in SCA patients.

Study Limitations

Our study is the first in our country to evaluate microvascular changes in the retina and choroid in adult SCA patients. Another strength of our study is that all patients in our sample were of the same race. However, there are some limitations that should be noted. These include the cross-sectional nature of the study and the small number of patients for multivariate analyses. In the literature, the prevalence of SCM has been reported between 43% and 60%.[5,26] However, this rate was 20.5% in our study. This may be due to the absence of patients with the HbSC genotype, which is suggested to be more commonly associated with the ocular complications of SCA, although conflicting results have been reported on this subject.[27,28]

Conclusion

In this study, PSCR was identified as a risk factor for the development of SCM in patients being followed up for SCA. In addition, significant differences in both OCTA imaging and CVI values were observed in patients who had not yet developed macular damage compared to healthy individuals. It has been shown previously that there may be FAZ enlargement and reduced VD in the temporal macula even without progression of SCR.[8] OCTA imaging provides essential information in terms of disease course and visual prognosis. Monitoring from an early age is important to facilitate prevention and protect visual function before this damage occurs. More prospective studies with larger patient groups are needed to better understand the course of the disease.

Ethics

Ethics Committee Approval: Ethical approval for this cross-sectional study was obtained from the Başkent University Medical and Health Units Research Board and Ethics Committee (project no: KA23/288, decision no: 23/151, date: 20/09/2023).

Informed Consent: Informed consent was obtained from all participants in the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: O.O., S.A., Ç.G., A.İ., H.C., Concept: O.O., A.P., Ç.G., S.S., C.B., Design: O.O., A.P., S.A., S.S., Data Collection or Processing: O.O., A.İ., H.C., O.Ş., C.İ., Analysis or Interpretation: O.O., A.P., S.A., S.S., Literature Search: O.O., Ç.G., M.K., Writing: O.O.

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