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RESEARCH ARTICLE

Optical coherence tomography angiography changes in patients with hemoglobinopathy

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ABSTRACT

Aim: The aim of this study is to evaluate retinal vascular changes in patients with sickle cell disease (SCD) and beta-thalassemia with optical coherence tomography angiography (OCT-A).

Methods: For this purpose, 98 patients with SCD, 75 patients with beta-thalassemia, and 100 healthy controls in Mersin University Hospital between January 1, 2020, and November 1, 2021, were included in this study. OCT-A imaging was performed with ZEISS AngioPlex OCT angiography (Carl Zeiss Meditec, Dublin, CA, USA).

Results: All OCT-A parameters (FAZ area, perimeter, circularity, vessel, and perfusion density) were found to be statistically significantly different in both patients with thalassemia and patients with sickle cell disease when compared to the controls.

Conclusions: In conclusion, retinopathy related to both hemoglobinopathy subgroups can be diagnosed and followed up with OCT-A. It was also found that OCT-A parameters are affected before the development of clinically detectable retinopathy.

Keywords: opptical coherence tomography angiography, retinopathy, sickle cell disease, thalassemia

INTRODUCTION

Hemoglobinopathies, the most common hereditary blood disease in the world, are caused by structural changes in the chains of the hemoglobin. They are divided into two main classes, abnormal hemoglobins and thalassemias. Sickle cell disease (SCD) is a group of inherited hematological diseases in which erythrocytes characteristically distort the biconcave disc shape and take a sickle shape. This situation causes vaso-occlusion and can affect all organs (1).

Retinal hypoxia, ischemia, and neovascularization may develop after microvascular occlusion in patients with SCD. Neovascularization that occurs before the development of vitreous hemorrhage or retinal detachment is the most important precursor (2).

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The most common reasons for vision loss in patients with SCD are proliferative sickle cell retinopathy (PSCR), which is characterized by chronic peripheral retinal microvascular occlusion, and ischemia (3). Retinopathy due to sickle cell disease is divided into proliferative and non-proliferative retinopathy. The grade of proliferative retinopathy is determined by the Goldberg classification (4) (Table 1).

Thalassemia is a genetic disease characterized by a decrease or complete absence in the synthesis of one or more of the globin chains in the structure of the hemoglobin. It is classified according to the reduced or non-synthesized globin chain. The best described types are α-and β-thalassemia (5). The frequency of eye involvement in β-thalassemia was found to range from 41.3% to 85% in various studies (6,7).

In different studies, retinal disorders such as retinal pigment epithelial degeneration and mottling, venous tortuosity, retinal hemorrhage, retinal edema, peripheral and central retinal thinning, cup-to-disk ratio enlargement, and macular scarring have been reported in beta-thalassemia patients. The prevalence of reported retinal disorders varies between studies (8).

The main purpose of this study is to evaluate the retinal changes that may occur in patients with hemoglobinopathy with OCT-A.

MATERIALS AND METHODS

Written informed consent was obtained from all participants in this study. The study protocol was approved by the Mersin University Clinical Research Ethics Committee. At all stages, this study adhered to the principles of the Declaration of Helsinki.

Table 1. Classification of proliferative sickle cell retinopathy (PSCR).

Stage I	Peripheral arterial occlusion
Stage II	Peripheral arteriovenous anastomoses (hairpin loop)
Stage III	Neovascular and fibrous proliferations (sea fan)
Stage IV	Vitreous hemorrhage
Stage V	Retinal detachment

Patients who underwent OCT-A (ZEISS AngioPlex OCT angiography, Carl Zeiss Meditec, Dublin, CA, USA) imaging for beta-thalassemia or sickle cell disease at the Department of Ophthalmology, Faculty of Medicine, Mersin University between 01/Jan/2020 and 01/Nov/2021 were included in this study. Fifty healthy controls without any cardiovascular and/or ophthalmologic diseases were included in the study.

Demographic data, hemoglobin values and OCT-A parameters of the patients included in the study were evaluated. The foveal avascular zone (FAZ) (in square millimeters) is an area of the macula that does not contain capillary structures. The axial length of this area is defined as the FAZ perimeter (in millimeters). FAZ circularity (unitless) indicates the proportion of the shape of the FAZ that resembles an ideal circle. Vessel density (in millimeters per square millimeter) is the total vessel length per unit area in the region. Perfusion density (%) is the total area supplied by the total vessels measured per unit area in the region.

All scans were repeated until an ideal quality was achieved. The data for the FAZ were obtained from a 3×3 mm foveally centered scan area.

Continuous data are expressed as mean ± standard deviation. The Shapiro-Wilk test was used to assess adherence to a normal distribution. The means of two independent groups were compared by Student's t-test and the means of more than two groups were compared using ANOVA. Categorical data were expressed as numbers and percentages and chi-square test was used to compare them. Statistical analysis of the study was performed with SPSS 29,0. The level of statistical significance was accepted as $p < 0,05$.

RESULTS

One hundred healthy controls, 98 patients with SCD and 75 patients with beta-thalassemia were included. The age and gender distribution was similar and is summarized in Table 2.

Table 2. Demographic characteristics of all participants.

	Normal	β-Thalassemia			SCD					
		Total	Major	Minor	No Retinopathy	NPSCR	Stage 1	Stage 2	Stage 3	Homozygous (HbSS)	Heterozygous (HbS variant)
N (%)	**100**	**75 (100%)**	**23 (30,7%)**	**52 (69,3%)**	**61 (62,2%)**	**20 (20,4%)**	**9 (9,2%)**	**5 (5,1%)**	**3 (3,1%)**	**31 (31,6%)**	**67 (68,4%)**
Age (years)	39,8 ± 7,7	40,2 ± 15,2	41,4 ± 14,6	39,7 ± 15,5	38,2 ± 10,4	34,9 ± 12,6	37,1 ± 12,2	37,4 ± 9,8	44,3 ± 7,8	39,4 ± 10,6	36,7 ± 10,8
Male	38 (38%)	26 (34,7%)	5 (21,7%)	21 (40,4%)	25 (41%)	7 (35%)	4 (44,4%)	3 (60%)	2 (66,7%)	7 (22,6%)	34 (50,7%)
Female	62 (62%)	49 (65,3%)	18 (78,3%)	31 (59,6%)	36 (59%)	13 (65%)	5 (55,6%)	2 (40%)	1 (33,3%)	24 (77,4%)	33 (49,3%)

Of the patients with sickle cell disease, 31 (31,6%) were homozygous and 67 (68,4%) were heterozygous. In addition, retinopathy was not detected in 61 (62,2%) patients, non-proliferative sickle cell retinopathy (NPSCR) was found in 20 (20,4%) patients, and proliferative sickle cell retinopathy (PSCR) was found in 17 (17,4%) patients. The distribution of retinopathy in sickle cell patients is shown in Table 3.

The OCT-A parameters and hemoglobin levels of all participants are shown in Table 4. All parameters (FAZ area, circularity, perimeter, vessel and perfusion density) were statistically different across the three groups (for all parameters, $p < 0,05$). When the hemoglobin levels of the all patients and their OCT-A parameters were compared, a statistically significant correlation was found for all parameters in patients with beta-thalassemia major, whereas no statistically significant correlation was found for any parameter in patients with sickle cell disease (Table 5).

When the subgroups of the diseases were compared with the control patients, the difference between the measurements of the patients with thalassemia major and homozygous-sickle cell disease was found to be statistically significant (for all parameters, $p < 0,05$). In addition, no statistically significant difference was found between the measurements of patients with sickle cell disease (for all remaining parameters except vessel density, $p > 0,05$). However, vessel density was statistically different between the patients who had no retinopathy and the control group ($p = 0,038$, $p < 0,05$).

DISCUSSION

This is the largest study using OCT-A imaging in patients with beta-thalassemia and sickle cell disease reported in the literature. There is no standardized imaging protocol yet, but the use of different imaging devices can help in the diagnosis.

Lynch et al. included fifty-two patients with SCR (19 proliferative and 33 non-proliferative) and 20 healthy controls in their study. FAZ perimeter and a circularity index were significantly higher in SCR eyes compared to controls. In addition, vessel density was significantly lower in SCR eyes than in the control group (9).

Table 3. Distribution of retinopathy in sickle cell patients.

	Homozygous (HbSS)		Heterozygous (HbS variant)		Total	
	N	%	N	%	N	%
No Retinopathy	13	41,9	48	71,6	61	62,2
NPSCR	8	25,8	12	17,9	20	20,4
Stage 1	3	9,7	6	9	9	9,2
Stage 2	4	12,9	1	1,5	5	5,1
Stage 3	3	9,7	-	-	3	3,1
Total	31 (31,6%)		67 (68,4%)		98 (100%)	

Zhou et al. included 31 patients with SCR (21 NP-SCR and 10 P-SCR) and 14 healthy controls in their study. All FAZ (area, perimeter, a circularity) measurements were significantly higher in NP-SCR and P-SCR subjects than in healthy controls (10).

Han et al. found in their study of 82 eyes of 46 patients that there was a loss of flow and a decrease in vessel density in patients with sickle cell retinopathy (11).

In another study, the transfusion-dependent thalassemia group (TDT) (thalassemia major) showed a statistically significant decrease in retinal and choriocapillaris vessel density (VD) compared to controls ($p < 0,05$). In our study, vascular density decreased and FAZ area increased in patients in the thalassemia group compared to controls.

This difference is especially more pronounced in the thalassemia major subgroup. This result is consistent with the literature (12).

OCT-A parameters have provided a deeper understanding of retinal involvement, particularly of systemic diseases that produce ischemia and microangiopathy. In a study by Mokrane et al., FAZ area was not significantly different between both genotypes in sickle cell anemia. However, it differed from healthy controls (HbSC $p= 0,034$ and HbSS $p = 0,001$). OCT-A provides useful information about the structural changes associated with microvasculature and retinopathy. It reveals the structural changes in patients who cannot be diagnosed clinically. It is a non-invasive, simple and reproducible imaging technique (13).

Limitations of the study include the relatively small number of patients, reporting from a single center, short follow-up period, lack of evaluation of treatment responses and retrospective design.

In conclusion, it was determined that all FAZ parameters (area, circularity, perimeter) were significantly different in patients with both beta-thalassemia and sickle cell disease, even if retinopathy was not developed clinically. In addition, vessel and perfusion density were found to be lower in both patient groups compared to the healthy controls. However, no significant correlation was found between the severity of retinopathy of the patients and angiography parameters. In addition, a correlation between hemoglobin levels and angiography parameters was observed in patients with beta-thalassemia major.

Ethical approval

This study has been approved by the Mersin University Rectorate Clinical Research Ethics Committee (approval no 146, date 05.02.2020). Written informed consent was obtained from the participants.

Author contribution

Concept: ÖÖ; Design: ÖÖ; Data Collection or Processing: ÖÖ; Analysis or Interpretation: ÖÖ; Literature Search: ESG; Writing: ÖÖ. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Table 4. The OCT-A parameters of all participants.

	Normal	β-Thalassemia			SCD							
		Total	Major	Minor	Total	Homozygous (HbSS)	Heterozygous (HbSvariant)	No Retinopathy	NPSCR	Stage 1	Stage 2	Stage 3
N (%)	**100**	**75 (100%)**	**23 (30,7%)**	**52 (69,3%)**	**98 (100%)**	**31 (31,6%)**	**67 (68,4%)**	**61 (62,2%)**	**20 (20,4%)**	**9 (9,2%)**	**5 (5,1%)**	**3 (3,1%)**
Hb (g/dL)	14,5 ± 3,24	7,6 ± 2,9	4,8 ± 1,1	9,7 ± 1,8	8,26 ± 1,61	7,9 ± 1,45	8,43 ± 1,66	8,36 ± 1,77	8,69 ± 1,09	6,9 ± 1,22	8,12 ± 1,31	7,6 ± 0,72
FAZ area (mm^2)	0,296 ± 0,088	0,327 ± 0,102	0,344 ± 0,09	0,313 ± 0,081	0,315 ± 0,109	0,358 ± 0,124	0,304 ± 0,089	0,299 ± 0,083	0,322 ± 0,105	0,375 ± 0,08	0,384 ± 0,094	0,402 ± 0,153
FAZ circularity	0,84 ± 0,06	0,71 ± 0,13	0,51 ± 0,14	0,8 ± 0,11	0,69 ± 0,12	0,54 ± 0,17	0,77 ± 0,15	0,78 ± 0,14	0,61 ± 0,18	0,46 ± 0,19	0,42 ± 0,11	0,41 ± 0,17
FAZ perimeter	2,05 ± 0,43	2,29 ± 0,54	2,91 ± 0,62	2,02 ± 0,37	2,47 ± 0,55	2,84 ± 0,73	2,01 ± 0,69	2,06 ± 0,50	2,15 ± 0,81	3,09 ± 0,62	3,05 ± 0,53	3,16 ± 0,84
Vessel density	16,07 ± 1,55	14,75 ± 2,86	14,38 ± 3,64	14,94 ± 4,06	14,59 ± 3,53	13,18 ± 2,88	15,92 ± 4,42	14,94 ± 3,11	14,31 ± 2,73	14,11 ± 3,87	12,81 ± 2,61	10,26 ± 0,73
Perfusion density	0,43 ± 0,014	0,38 ± 0,077	0,33 ± 0,062	0,41 ± 0,09	0,36 ± 0,06	0,29 ± 0,068	0,41 ± 0,08	0,38 ± 0,046	0,35 ± 0,082	0,3 ± 0,067	0,24 ± 0,07	0,21 ± 0,02

Table 5. Comparison of hemoglobin levels and OCT-A parameters.

	β-Thalassemia-Major		β-Thalassemia-Minor		SCD	
	Hemoglobin levels					
	r	p	r	p	r	p
FAZ area (mm^2)	-0,866	**0,0023**	-0,013	0,438	-0,122	0,579
FAZ circularity	0,677	**0,021**	0,282	0,599	0,159	0,275
FAZ perimeter	-0,702	**0,037**	-0,035	0,452	-0,265	0,735
Vessel density	0,753	**0,044**	0,288	0,362	0,248	0,469
Perfusion density	0,725	**0,0095**	0,352	0,896	0,062	0,639

Conflict of interest

The authors declare that there is no conflict of interest.

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