Available online at www.sciencedirect.com

ScienceDirect

Journal of Current Ophthalmology 31 (2019) 275–280
http://www.journals.elsevier.com/journal-of-current-ophthalmology

Original research

Spectral domain optical coherence tomography findings in Turkish sickle-cell disease and beta thalassemia major patients

Mahmut Oğuz Ulusoy [a,*], Hakan Türk [b], Sertaç Argun Kıvanç [c]

[a] *Department of Ophthalmology, Başkent University, School of Medicine, Konya Research Hospital, Konya, Turkey*
[b] *Department of Ophthalmology, Tarsus State Hospital, Mersin, Turkey*
[c] *Department of Ophthalmology, Uludağ University, School of Medicine, Bursa, Turkey*

Received 4 December 2018; revised 21 January 2019; accepted 30 January 2019
Available online 14 February 2019

Abstract

Purpose: To assess probable structural changes using spectral domain optical coherence tomography (SD-OCT) on sickle-cell disease (SCD) and beta thalassemia major (B-TM) patients, without any retinal abnormalities.
Methods: This cross-sectional study included 32 B-TM, 34 SCD patients, and 44 healthy controls. One of the eyes of all participants was evaluated for SD-OCT and choroidal thickness, retinal nerve fiber layer (RNFL) thickness, central macular thickness (CMT), ganglion cell complex (GCC).
Results: Age, gender, and intraocular pressure (IOP) were not statistically different between the three groups. Hemoglobin (Hgb), hematocrite (Htc), and ferritin levels were not statistically different between the SCD and B-TM groups. Choroidal thickness at the subfoveal region was statistically higher in the control group (353.79 ± 71.93) than in the B-TM (317.41 ± 53.44) and SCD (283.21 ± 63.27) groups. In addition, it was statistically higher in the B-TM group than the SCD group ($P = 0.05$). CMT did not differ among the three groups, average RNFL was only significantly thinner in SCD than in controls, and GCC thickness was significantly thinner in SCD than in controls and B-TM.
Conclusion: In both diseases, we can show early structural changes even if proliferative or non-proliferative retinopathy or other ocular manifestations were not developed yet.

Keywords: Beta thalassemia major; Choroidal thickness; Sickle-cell disease; Spectral domain optical coherence tomography

Introduction

Hemoglobinopathies are disorders caused by mutations in specific globin genes such as a or b, leading to ineffective erythropoiesis. Beta thalassemia major (B-TM) is an autosomal recessive disorder characterized by genetic mutations and results in the reduced synthesis of A globin chains.[1] The prevalence of this disease is 2.1% in Turkey, and it affects considerably large populations in other Mediterranean countries.[2] One of the treatment options of these patients to survive is regular red blood cell (RBC) transfusions. As a result of these transfusions, iron accumulates in the body, and chelation therapy is used to prevent the toxic effects of iron. Some ocular abnormalities have previously been reported due to chelation therapy toxicity or the nature of the disease that affects the microvasculature of systems.[3,4] In addition, there are some reports about the thinning of retinal nerve fiber layer (RNFL) and choroid from our country.[5,6] However, in these reports, the authors did not specify the retinopathy situation of the patients, and they did not evaluate both the RNFL and choroid in each study.

Competing/Conflicts of interest: None.
Funding sources: None.
This manuscript was presented as poster at ARVO 2017.
* Corresponding author. Başkent Üniversitesi Hastanesi, GözHastalıkları, Hoca Cihan Mahallesi Saray Caddesi No. 1, Selçuklu, Konya, Turkey.
E-mail address: drmoguz@gmail.com (M.O. Ulusoy).
Peer review under responsibility of the Iranian Society of Ophthalmology.

https://doi.org/10.1016/j.joco.2019.01.012

Another severe hemoglobinopathy is sickle-cell disease (SCD), which leads to the development of vaso-occlusions with intravascular sickling, hemolysis, hemostasis, and thrombosis.[7] The interactions between sickled RBCs, vascular endothelium, vasoactive factors, and other blood cells lead to vaso-occlusion and tissue ischemia.[7] These occlusions can develop anywhere in the body including retina. Vascular changes of the peripheral retina are classified into non-proliferative and proliferative sickle-cell retinopathy (PSR).[8] Besides the peripheral retinopathy, some macular lesions have been reported by fluorescein angiography or spectral domain optical coherence tomography (SD-OCT).[9]

Not only do B-TM and SCD directly affect the vascular system but also severe anemia and long-term multiple blood transfusions. Therefore, in this study, we aimed to evaluate the potential effects of these diseases and their treatments on the retina and choroid by SD-OCT.

Methods

This cross-sectional study adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients. The study protocol was approved by the local Ethics Committee of the Çukurova University School of Medicine. The study group comprised 32 B-TM and 34 SCD patients without clinical retinopathy and retinal or systemic ischemia or stroke and 44 control patients (age and sex match) without any systemic diseases. The participants with B-TM were diagnosed using clinical, hematological, and electrophoretic studies, and the SCD patients were diagnosed using electrophoretic confirmation of SCD, sickle-cell hemoglobin C disease, or sickle-cell thalassemia. Forty-four patients with a hemoglobin level of >12 g/dl, serum ferritin level of >12 lg/l, and serum transferrin saturation of >15% were selected in the control group after a routine examination at the ophthalmology clinic.

Hemoglobin, serum ferritin, and hematocrit levels were recorded for all patients. B-TM and SCD patients received RBC transfusions every 3 or 4 weeks and used only oral iron chelators (Deferiprone-75 mg/kg/day) as treatment.

All patients underwent a detailed ophthalmic examination, including visual acuity testing using the Snellen chart, refraction assessment, anterior segment examination using slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using non-contact tonometry, dilated fundus examination using 90 diopter (D) lens, and choroidal thickness measurement using SD-OCT. Only measurements of the right eye were used for statistical analysis. All basal SD-OCT scans were performed at the same time of the day (in the morning) to avoid diurnal fluctuations.[10] Patients with a history of ocular surgery, ocular trauma, anterior or posterior segment disease, glaucoma, uveitis, systemic hypertension, diabetes mellitus, neurodegenerative disease, or any other rheumatologic disease were excluded from the study. In addition, to obtain clear images and minimize the effect of axial length on choroidal thickness, patients with best corrected visual acuity worse than 20/20 and a refractive error >±1 D were excluded from the study.

All participants were examined with SD-OCT (retina scan, RS-3000; Nidek, Gamagori, Japan) after pupillary dilation with tropicamide 1% (Tropamid 1%; Bilim İlaç, Istanbul, Turkey).

Three images were taken from each participant, and the one with the strongest signal (at least 8) was chosen for analysis. To improve choroidal visualization, each image consisted of 50 averaged B-scans in a single raster line scan, and the optical coherence tomographic (EDI OCT) device was positioned close to the eye in order to visualize the image on the top of the monitor (to be in closer proximity to the zero-delay line) in a standard manner (uninverted image). The advanced speckle noise reduction system, by averaging images, provided 4-mm optical coherence tomography (OCT) digital resolution. To obtain a better image quality, "the toggle switch" option was also used. This function allows one to get closer to the eye without moving the scan out of the monitor, obtaining a significantly better in-depth penetration (by adjusting the z position). Moreover, increasing the luminosity of the images and monitor and decreasing the contrast of the monitor allowed the graders to better visualize choroidal details. The choroidal thickness was measured as the perpendicular distance between the hyperreflective outer border of the retinal pigment epithelial (RPE)–Bruch membrane layer (automatically detected by the SD-OCT device). The choroidal thickness was measured at 7 different points: at the subfovea; at 500 μm, 1000 μm, and 1500 μm temporal to the fovea; and at 500 μm, 1000 μm, and 1500 μm nasal to the fovea.

Mapping a wide area (9 mm × 9 mm) enables the ganglion cell complex (GCC) status to be observed, even in peripheral regions. The OCT scanning position was precisely matched with the scanning laser ophthalmoscope (SLO) fundus image. The macula map x-y, and disc map x-y scanning protocols were performed for all subjects in this study. Superior and inferior hemiretinal GCC, macular thickness and global, inferior, superior, nasal, and temporal RNFL values were included for the analysis. Submitted scans were assessed for signal strength index, image centration, and color cross section. Signal strength index greater than 50 were included. Scans that were decentered or had poor color cross-sections were excluded. All SD-OCT measurements were obtained by two masked physicians (M.O.U. and H.T.).

Statistical analysis

Statistical data were analyzed using SPSS version 21.0 (SPSS, Chicago, IL, USA). Values were expressed as mean ± standard deviation. The normality of the values was analyzed using the Kolmogorov-Smirnov test. Student *t*-test was performed in comparison of the control group and the hemoglobinopathies group. ANOVA test and post hoc analysis with the Tukey test were performed according to the Kolmogorov-Smirnov test results. Differences were considered

significant at $P \leq 0.05$. Correlations between the variables were investigated based on the multiple regression analysis.

Results

A total of 110 patients (110 eyes) were recruited in this study. The mean age of the patients was 24.45 years (range, 15–40 years) in the B-TM group, 26.33 years (range, 16–45 years) in the SCD group, and 25.42 years (range, 17–42 years) in the control group. There was no significant difference in age among the three groups. ($P = 0.80$) Similarly, gender status, refractive status, and IOP were similar among the groups. Finally, there was no statistical difference between the B-TM and SCD groups regarding hemoglobin (Hgb) level, hematocrite (Htc) level, and ferritin level. ($P = 0.10$, $P = 0.94$, and $P = 0.40$, respectively) (Table 1).

In comparison to the hemoglobinopathies and control group, we found that all choroidal levels were significantly thinner in the patient's group. In addition, all peripapillary RNFL quadrants were thinner in the patient's group, except temporal quadrant. However, there were no statistically difference in CMT and macular average GCC (Table 2).

Choroidal thickness at the subfoveal region was statistically higher in the control group (353.79 ± 71.93) than in the B-TM (317.41 ± 53.44) and SCD (283.21 ± 63.27) groups ($P < 0.05$). In addition, it was statistically higher in the B-TM group than in the SCD group ($P = 0.05$) (Table 2).

In the SCD group, the average RNFL was significantly thinner than in the control group. However, there was no significant difference between the B-TM and control or SCD groups. Regarding the GCC layer, that of the SCD patients was significantly thinner than that of the other two groups' patients. But there was no difference between the B-TM and control groups. CMT values were not significantly different among the three groups (Table 3).

We did not find a correlation between the choroidal, RNFL, CMT, and GCC thicknesses and Hgb, Htc, ferritin, and other demographic characteristics in either of the diseases (Tables 4 and 5).

Discussion

B-TM and SCD are autosomal recessive disorders that are the world's most common forms of inherited anemia. Both of them cause severe transfusion-dependent anemia, and the patients can suffer from iron overload conditions in addition to the nature of diseases.[11] These effects can be seen in various parts of the patients' bodies, including the retina. Some of these changes have already been identified by other authors.[12,13] Although the mechanism of the manifestations in these diseases seems different, vascular changes can be seen in both of them. Therefore, we evaluated and compared the SD-OCT results of these diseases.

Survival of patients with thalassemia necessitates long-term blood transfusions with consequent iron overload of vital organs, for which chelation therapy is mandatory. Probable toxic effects to RPE, choroid and layers of retina, of iron chelators were reported in several previous studies. Especially in Wu

Table 1
Demographic and ocular characteristics of the groups.

	SCD	B-TM	P^a	Control	P^b
Sex (M/F)	16/18	14/18	0.94	20/24	0.80
Age (years)	26.33 ± 10.94	24.45 ± 9.25	0.72	25.42 ± 8.84	0.69
IOP (mmHg)	13.46 ± 1.17	12.86 ± 2.10	0.62	13.25 ± 2.02	0.53
Hgb (g/dl)	8.75 ± 1.94	9.77 ± 2.18	0.10	14.2 ± 0.97	<0.001
Htc	30.02 ± 6.90	29.64 ± 6.31	0.84	46.6 ± 2.31	<0.001
Ferritin (ng/ml)	848.98 ± 301.61	942.70 ± 451.40	0.40	28.29 ± 4.15	<0.05
Mean RBC Transfusion/year	15.12 ± 1.67	15.09 ± 1.54	0.94	0	

SCD: Sickle-cell disease; B-TM: Beta thalassemia major; M: Male; F: Female; IOP: Intraocular pressure; Hgb: Hemoglobin; Htc: Hematocrite; RBC: Red blood cell; $P < 0.05$.
[a] Student *t*-test.
[b] ANOVA.

Table 2
Comparison of the choroidal thickness measurements of the beta thalassemia major (B-TM), sickle-cell disease (SCD), and control groups.

	SCD	B-TM	Control	*P*		
				SCD vs. B-TM	SCD vs. control	B-TM vs. control
N 1500	209.00 ± 43.94	239.09 ± 68.25	314.04 ± 73.79	0.24	**<0.05**	**<0.05**
N 1000	258.29 ± 64.06	309.77 ± 50.48	334.63 ± 72.76	**0.002**	**<0.05**	0.47
N 500	270.33 ± 60.90	319.59 ± 53.83	342.92 ± 79.03	0.36	**0.003**	0.71
Subfoveal	283.21 ± 63.27	317.41 ± 53.44	353.79 ± 71.93	**0.014**	**<0.05**	**0.013**
T 500	245.92 ± 64.23	306.23 ± 52.81	332.88 ± 91.68	**0.016**	**<0.05**	0.42
T 1000	222.13 ± 66.72	289.86 ± 55.97	357.38 ± 72.99	**0.002**	**<0.05**	**0.003**
T 1500	205.00 ± 39.04	241.00 ± 82.48	343.38 ± 78.57	0.18	**<0.05**	**<0.05**

SCD: Sickle-cell disease; B-TM: Beta thalassemia major; N: Nasal; T: Temporal; $P < 0.05$.
Statistically significant *P* values are marked bold.

Table 3
Comparison of the retinal nerve fiber layer (RNFL), central macular thickness (CMT), and ganglion cell complex (GCC) measurements of the beta thalassemia major (B-TM), sickle-cell disease (SCD), and control groups.

	SCD	B-TM	Control	*P*		
				SCD vs B-TM	SCD vs Control	B-TM vs Control
Average RNFL	108.13 ± 10.80	116.14 ± 14.36	123.88 ± 9.77	0.061	**<0.05**	0.073
Superior RNFL	134.25 ± 17.19	150.32 ± 15.53	162.63 ± 21.52	**0.011**	**<0.05**	0.067
Inferior RNFL	137.71 ± 17.07	146.68 ± 22.09	153.08 ± 8.29	0.16	**0.006**	0.39
Nasal RNFL	85.38 ± 18.52	87.73 ± 21.86	99.58 ± 26.89	0.93	0.08	0.18
Temporal RNFL	72.17 ± 13.00	75.82 ± 17.86	76.50 ± 19.71	0.75	0.65	0.99
CMT	265.79 ± 14.87	274.68 ± 29.96	275.00 ± 23.75	0.41	0.36	0.99
GCC	98.62 ± 8.46	104.88 ± 8.90	105.33 ± 7.19	**0.03**	**0.01**	0.98

SCD: Sickle-cell disease; B-TM: Beta thalassemia major; RNFL: Retinal nerve fiber layer; CMT: Central macular thickness; GCC: Ganglion cell complex; $P < 0.05$.
Statistically significant *P* values are marked bold.

Table 4
Correlation of the parameters of beta thalassemia major (B-TM) patients.

	Hgb (r/p)	Htc (r/p)	Ferritin (r/p)
N1500	−0.289/0.19	−0.477/0.25	−0.621/0.2
N1000	0.078/0.72	0.059/0.79	0.101/0.65
N500	0.052/0.81	0.051/0.82	0.087/0.69
Subfoveal	0.026/0.9	0.005/0.98	0.012/0.95
T500	0.067/0.76	0.054/0.81	0.068/0.76
T1000	0.021/0.92	−0.006/0.97	0.005/0.98
T1500	0.13/0.56	−0.052/0.81	−0.131/0.56
Av. RNFL	−0.347/0.11	−0.276/0.21	−0.086/0.7
Superior	−0.362/0.09	−0.228/0.3	−0.086/0.7
Inferior	−0.349/0.11	−0.142/0.52	0.026/0.9
Temporal	−0.351/0.11	−0.422/0.06	−0.228/0.3
Nasal	−0.109/0.62	−0.174/0.43	−0.071/0.75
CMT	−0.273/0.22	−0.139/0.53	−0.082/0.71
Av. GCC	−0.3/0.17	−0.424/0.49	−0.268/0.22

Hgb: Hemoglobin; Htc: Hematocrite; N: Nasal; T: Temporal; RNFL: Retinal nerve fiber layer; CMT: Central macular thickness; GCC: Ganglion cell complex.

Table 5
Correlation of the parameters of sickle-cell disease (SCD) patients.

	Hgb (r/p)	Htc (r/p)	Ferritin (r/p)
N1500	0.429/0.37	0.194/0.36	−0.304/0.14
N1000	−0.124/0.56	0.212/0.31	0.222/0.29
N500	−0.204/0.34	0.091/0.67	0.183/0.39
Subfoveal	−0.183/0.39	0.094/0.66	0.148/0.49
T500	−0.123/0.56	0.047/0.82	0.057/0.79
T1000	−0.134/0.53	−0.094/0.66	−0.068/0.75
T1500	0.186/0.38	−0.156/0.46	0.036/0.86
Av. RNFL	−0.044/0.83	0.254/0.23	0.240/0.25
Superior	0.064/0.76	0.237/0.26	0.212/0.32
Inferior	−0.174/0.41	0.181/0.39	0.286/0.17
Temporal	−0.203/0.34	0.065/0.76	0.121/0.57
Nasal	0.294/0.16	0.474/0.19	0.116/0.58
CMT	0.417/0.43	0.304/0.14	−0.019/0.92
Av. GCC	0.036/0.86	0.197/0.35	0.024/0.91

Hgb: Hemoglobin; Htc: Hematocrite; N: Nasal; T: Temporal; RNFL: Retinal nerve fiber layer; CMT: Central macular thickness; GCC: Ganglion cell complex.

et al.'s study, the authors hypothesized that hyper-reflective deposits detected by means of SD-OCT may represent a primarily involvement of RPE–Bruch membrane–photoreceptor-choroid complex in deferoxamine toxicity which correlated with previous histologic findings.[14] However, in one study where the choroidal thickness was evaluated in B-TM patients, the authors did not find any correlation between iron chelator treatment and choroidal thickness.[15] Besides this, long-term blood transfusions may affect the retinal layers and choroid of the patients. Although frequent red cell transfusions were reported to reduce thrombogenesis and vascular remodeling, in some reports authors suggested that blood products that are not fresh may have proinflammatory potential to the vascular system and negative acute impact on microvascular endothelial function.[16,17] Consistent with these reports, we found choroidal thinnings in the hemoglobinopathies group compared with the controls. However, when we separated the patients into two groups as SCD and B-TM, SCD patients choroid values were thinner than B-TM. Although mean transfusion rate and age of the patients were statistically similar, minimal highness of the age and duration of transfusion period according to higher age of SCD patients and the more aggressive nature of the disease can play a role in the difference of choroid values between these groups.

In our study, we mainly demonstrated that the choroid of the patients with B-TM and SCD was thinner than that of those in the control group at all levels. Also in the SCD group, the choroid was thinner than that in the B-TM group. Another study previously reported on the thinning of the choroidal thickness in patients with SCD and found no correlation between choroidal thickness and retinal thinning.[18] In patients with SCD, these results can be explained by the sickling of RBCs in the choriocapillaris. According to Eaton et al., following deoxygenation, there is a 'delay time' for RBCs before sickling and escape from microcirculation.[19] However, the low flow velocity of the choroid can facilitate the sickling period and vascular occlusions.[20] In patients with B-TM, the mechanism can be even more complicated. It has been previously reported that the choroid can be affected by various situations, including hypoxia and reperfusion episodes.[21] In the study by Şimşek et al., choroidal thickness in children with B-TM was found to be thinner than in control patients.[6] Retinal abnormalities of this disease were separated by the authors into two groups: pseudoxanthoma elasticum (PXE)-like abnormalities and non-PXE-like abnormalities.[13] PXE is characterized by calcium mineralization of elastin, and similar ocular manifestations have been

demonstrated by previous studies in B-TM and PXE.[22] The elastin degeneration in patients with B-TM may be the result of hypoxia, an oxidative process caused by the denaturation of Hb products and free iron.[23] Another study reported that these elastin defects may develop due to vaso-occlusive impairment in the retinal vasculature.[4]

We also evaluated RNFL thickness in these groups. On average, the RNFL segment thickness in the SCD group was thinner than in the other groups. The temporal horizontal raphe presents a watershed area and is particularly at risk for terminal arteriolar occlusions. A previous study reported that the peripapillary RNFL thickness was thinner in patients with SCD than in controls and also more prominent in patients with macular thinning.[24] A study which evaluated RNFL and GCC thickness reported that only the nasal sector of RNFL was thinner and only in patients with SCD who had proliferative retinopathy.[25] However, in another study there was no RNFL difference in patients with SCD.[25] In this study, we did not find any difference in CMT values among the three groups; therefore, we did not evaluate the association between CMT and RNFL thicknesses. Patients with SCD are known for having dilated and tortuous vessels.[26] One study examined the possible effects of tortuosity of the retinal vessels on peripapillary RNFL thickness and reported that patients with vessel tortuosity had thicker RNFL. This situation can cause underestimations in RNFL measurements. In our study, we did not observe marked tortuosity in our SCD group, but the RNFL thicknesses were already thinner than in the other groups. In patients with B-TM, RNFL thickness was thinner than the control group, but it was not statistically significant. Aksoy et al. showed that children with B-TM have significantly thinner RNFL thickness than the control group.[27] There was a positive correlation between RNFL thickness and mean Hgb value in this study. However, the authors were unable to determine if the thinning was a result of disease itself or side effects of the iron chelators. RNFL thickness imaging is more important in glaucoma patients.[28] An association between SCD and glaucoma has not been shown before. In addition, to the best of our knowledge, there have been no prevalence studies looking at glaucoma in patients with both SCD and B-TM.[29] Although there was no evidence of glaucoma in patients with B-TM in previous studies, miscellaneous optic nerve head changes and visual field (VF) defects were reported in these patients.[3] One of these studies suggested that the cause of the VF defect is the dose of iron chelators; however, another report could not find any correlation between VF defects and iron chelators. In our study, none of the patients' IOP measurement was above 21 mmHg, and there was no difference among the three groups. In addition, we did not observe glaucomatous optic disc head appearances in any of the patients, and we did not evaluate the perimetry of the patients. In a previous study, the authors reported that non-diabetic hemodialysis patients have thinner RNFL than healthy patients. This patient group may need blood transfusions similar to hemoglobinopathies patients. According to this knowledge, thinning RNFL of hemoglobinopathies can be associated with long-term transfusions.[30]

As suggested above, we could not find any difference in CMT among the three groups. A previous study reported that patients with SCD had thinner temporal total and inner retinal thicknesses than healthy controls. Yet most patients that showed macular thinning had proliferative PSR, as well.[18] In a recent study, the authors suggested that ischemic events usually start in the deeper capillary plexus of temporal macular region; therefore, this is not reflected in the CMT until late in the course of the disease.[31]

None of our patients had PSR, which may have affected our results. Another study which showed the CMT thinning in patients with SCD also found thinning of the outer retinal thickness. The authors suggested that this result indicated that the choriocapillaris can be more prone to occlusions than retinal capillaries.[9] Perhaps the choroidal thinning that we revealed is the result of this probable pathology. Foveal thinning in patients with B-TM was examined in a previous study where the authors found a positive correlation between chelators and this finding.[15]

In the present study, we found that the GCC layer thickness was thinner in the SCD group than in the others, which is consistent with previous studies. These results can be indicative of ischemia of the macular region in patients with SCD like peripheral retina, even before PSR develops. In patients with B-TM, the GCC layer was thinner than in the control group, but it was not statistically significant. To the best of our knowledge, there have been no previous studies that evaluated GCC in patients with B-TM. However, it has been previously reported, that chelator-related retinopathy primarily affects the RPE layer.[13] Therefore, the GCC layer of the retina may be affected due to the disease's ischemic potential.

As in many metabolic processes, iron is needed in the retina, especially in phototransduction cascade; however, appropriate regulation is necessary to prevent toxicity.[32] Patients with SCD and B-TM require regular blood transfusions to survive. To prevent iron overload, these individuals must use iron chelators. Unfortunately, the iron chelators are toxic to the retina, as reported in previous studies.[3,4] According to these data, El-Shazly et al. reported that chelation therapy used by B-TM patients can cause a significant decrease in foveal thickness.[15] In patients with B-TM, previous studies have separately found a negative correlation between ferritin and choroidal thickness and RNFL.[6,27] On the other hand, some authors reported that higher ferritin levels were associated with RPE degeneration, retinal vascular tortuosity and retinal pigment mottling.[3,22] However, we did not find any correlation between choroidal, RNFL, CMT, and GCC thicknesses and Hgb, Htc, ferritin, and other demographic characteristics in either of the diseases.

One of the limitations of our study was the small sample size. In addition, we did not perform VF testing, especially microperimetry for macular functional changes. Finally, we did not evaluate inner and outer macular thickness changes.

In conclusion, choroidal thicknesses of the hemoglobinopathy patients that must have multiple long-term blood transfusion were found to be thinner than in controls. Also, in patients with SCD, RNFL, and GCC, the choroid was thinner

than that in patients belonging to the other two groups. These values can be the results of the ischemic effect of these diseases, result of long-term blood transfusions, side effects of the iron chelators, or additive effect of all these, and furthermore, it is important to see that they are not limited to the periphery of the retina. In addition, we concluded that these effects on SCD patients are more prominent than in those with B-TM, even if the prolipherative or non-prolipherative changes are not seen. To the best of our knowledge, this is the first study that compared SD-OCT findings in patients with SCD and B-TM. Although additional studies with larger sample sizes are needed to confirm these results, we recommend routine ophthalmologic examinations to these patients, based on our findings.

References

1. Cao A, Galanello R. Beta-thalassemia. *Genet Med*. 2010;12:61−76.
2. Arcasoy A. Hemoglobinopathies in Turkey. *Hematol Rev*. 1992;6:61−67.
3. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. *Indian J Ophthalmol*. 2010;58(2):125−130.
4. Eleftheriadou M, Theodossiadis P, Rouvas A, Alonistiotis D, Theodossiadis G. New optical coherence tomography fundus findings in a case of beta-thalassemia. *Clin Ophthalmol*. 2012;6:2119−2122.
5. Şimşek A, Tekin M, Bilen A, Ş Bilak, Turgut M. The assessment of retinal nerve fiber layer thickness in children with thalassemia major. *Turkiye Klinikleri J Ophthalmol*. 2015;24(4):211−216 [Article in Turkish].
6. Simsek A, Tekin M, Bilak S, Karadag AS, Konca C, Almis H. Choroidal thickness in children with beta thalassemia major. *Optom Vis Sci*. 2016; 93(6):600−606.
7. Nagpal KC, Goldberg MF, Rabb MF. Ocular manifestations of sickle zemoglobinopathies. *Surv Ophthalmol*. 1977;21(5):391−411.
8. Elagouz M, Jyothi S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. *Surv Ophthalmol*. 2010;55(4):359−377.
9. Hoang QV, Chau FY, Shahidi M, Lim JI. Central macular splaying and outer retinal thinning in asymptomatic sickle cell patients by spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2011;151(6): 990−994.
10. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53(1):261−266.
11. Senol SP, Tiftik EN, Unal S, Akdeniz A, Tasdelen B, Tunctan B. Quality of life, clinical effectiveness, and satisfaction in patients with beta thalassemia major and sickle cell anemia receiving deferasirox chelation therapy. *J Basic Clin Pharm*. 2016;7(2):49−59.
12. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol*. 1971;71(3):649−665.
13. Bhoiwala DL, Dunaief JL. Retinal abnormalities in β-thalassemia major. *Surv Ophthalmol*. 2016;61(1):33−50.
14. Wu CH, Yang CP, Lai CC, Wu WC, Chen YH. Deferoxamine retinopathy: spectral domain-optical coherence tomography findings. *BMC Ophthalmol*. 2014;14:88.
15. El-shazly AA, Elkitkat RS, Ebeid WM, Deghedy MR. Correlation between subfoveal choroidal thickness and foveal thickness in thalassemic patients. *Retina*. 2016;36(9):1767−1772.
16. Hyacinth HI, Adams RJ, Voeks JH, Hibbert JM, Gee BE. Frequent red cell transfusions reduced vascular endothelial activation and thrombogenicity in children with sickle cellanemia and high stroke risk. *Am J Hematol*. 2014;89(1):47−51.
17. Parviz Y, Hsia C, Alemayehu M, et al. The effect of fresh versus standard blood transfusion on microvascular endothelial function. *Am Heart J*. 2016;181:156−161.
18. Mathew R, Bafiq R, Ramu J, et al. Spectral domain optical coherence tomography in patients with sickle cell disease. *Br J Ophthalmol*. 2015; 99(7):967−972.
19. Eaton WA, Hofrichter J. Hemoglobin S gelation and sickle cell disease. *Blood*. 1987;70(5):1245−1266.
20. Wajer SD, Taomoto M, McLeod DS, et al. Velocity measurements of normal and sickle red blood cells in the rat retinal and choroidal vasculatures. *Microvasc Res*. 2000;60(3):281−293.
21. Bayhan HA, Aslan Bayhan S, İntepe YS, Muhafiz E, Gürdal C. Evaluation of the macular choroidal thickness using spectral optical coherence tomography in patients with obstructive sleep apnoea syndrome. *Clin Exp Ophthalmol*. 2015;43(2):139−144.
22. Barteselli G, Dell'arti L, Finger RP, et al. The spectrum of ocular alterations in patients with beta-thalassemia syndromes suggests a pathology similar to pseudoxanthoma elasticum. *Ophthalmology*. 2014;121(3): 709−718.
23. Aessopos A, Samarkos M, Voskaridou E, et al. Arterial calcifications in beta-thalassemia. *Angiology*. 1998;49(2):137−143.
24. Chow CC, Shah RJ, Lim JI, Chau FY, Hallak JA, Vajaranant TS. Peripapillary retinal nerve fiber layer thickness in sickle-cell hemoglobinopathies using spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2013;155(3):456−464.
25. Brasileiro F, Martins TT, Campos SB, et al. Macular and peripapillary spectral domain optical coherence tomography changes in sickle cell retinopathy. *Retina*. 2015;35(2):257−263.
26. Ahmad A. Retinopathy in ophthalmologically asymptomatic patients with abnormal hemoglobins. *Ann Ophthalmol*. 1979;11(3):365−369.
27. Aksoy A, Aslan L, Aslankurt M, et al. Retinal fiber layer thickness in children with thalessemia major and iron deficiency anemia. *Semin Ophthalmol*. 2014;29(1):22−26.
28. Leung CK, Chiu V, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a comparison between spectral-domain and time-domain optical coherence tomography. *Ophthalmology*. 2011; 118(8):1558−1562.
29. Steinmann W, Stone R, Nichols C, et al. A case-control study of the association of sickle cell trait and chronic open-angle glaucoma. *Am J Epidemiol*. 1983;118(2):288−293.
30. Demir MN, Eksioglu U, Altay M, et al. Retinal nerve fiber layer thickness in chronic renal failure without diabetes mellitus. *Eur J Ophthalmol*. 2009;19(6):1034−1038.
31. Ghasemi Falavarjani K, Scott AW, Wang K, et al. Correlation of multimodal imaging in sickle cell retinopathy. *Retina*. 2016;36(Suppl 1): S111−S117.
32. Moiseyev G, Chen Y, Takahashi Y, Wu BX, Ma JX. RPE65 is the isomerohydrolase in the retinoid visual cycle. *Proc Natl Acad Sci USA*. 2005; 102(35):12413−12418.