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Central macular thickness in patients with sickle cell disease and no signs of retinopathy: a cross-sectional study of Jordanian patients

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Abstract

Objectives: To measure central macular thickness in Jordanian patients with sickle cell disease who did not have retinopathy and compare the findings with age- and sex-matched controls using spectral domain optical coherence tomography (SDOCT).

Methods: In this cross-sectional study, participants underwent visual acuity testing, slit-lamp biomicroscopy, dilated ophthalmoscopy, and SDOCT imaging to measure central macular thickness. Macular quadrant measurements and thickness difference indexes (TDIs) were compared between groups.

Results: Twenty eyes with sickle cell disease and 20 control eyes were enrolled. The median visual acuity in both groups was 20/20. The mean macular thickness was significantly lower in eyes with sickle cell disease than in matched controls (mean difference, $22.15 \pm 6.44\,\mu m$). Peripheral quadrants were all significantly thinner in eyes with sickle cell disease, especially in superior and temporal quadrants. TDIs were lower in eyes with sickle cell disease than in control eyes.

Conclusions: Eyes with sickle cell disease that had no clinical evidence of retinopathy exhibited significantly lower central macular thickness in all quadrants, compared with eyes in age- and

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sex-matched controls. SDOCT is a non-invasive imaging modality that can detect preclinical changes in eyes with sickle cell disease and can be used to screen and monitor the disease process.

Keywords
Sickle cell disease, hemoglobin SS, retinopathy, central macular thickness, spectral domain optical coherence tomography, cross-sectional analysis, thickness difference index, retinal disease

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Introduction

Sickle cell disease is an inherited red blood cell disorder in which hemoglobin (Hb) A is replaced by Hb S, leading to a wide spectrum of clinical signs.[1] In the Hb SS subtype (i.e., the major disease variant), two alleles harbor a mutation that causes a glutamic acid residue to be replaced by a valine residue at position 6 on the beta-globin chain, thus destabilizing the Hb S molecule and causing red blood cells to assume a sickle shape under metabolic stress. The other major variant is the Hb SC subtype, wherein one Hb S allele and one Hb C allele exist.[1]

The most important ocular finding in patients with sickle cell disease is sickle cell retinopathy; clinical screening is needed to assess its progression among five stages of proliferative sickle cell retinopathy[2] and/or sickle cell maculopathy (i.e., macular thinning secondary to ischemia).[3] The advent of spectral domain optical coherence tomography (SDOCT) as a non-invasive imaging tool has provided invaluable information that extends beyond the clinical classification of sickle cell retinopathy.[4] Previous SDOCT studies have demonstrated retinal thinning in various stages of sickle cell retinopathy.[5] Notably, asymptomatic patients with reduced visual function exhibit corresponding areas of thinning, as measured by microperimetry.[6] This tomographic thinning is more prevalent in patients with the Hb SS variant.[7]

The Hb SS variant is most prevalent in Jordan,[8] but no data have been published regarding retinal thickness in Jordanian patients with sickle cell disease. Furthermore, no protocols have been established to identify those patients in eye clinics. Referrals depend on the clinical experience of treating physicians; in our experience, many patients with minimal symptoms do not attend scheduled visits with ophthalmologists, possibly because of insufficient information regarding visual complications.

This study measured central macular thickness in a group of asymptomatic patients with the Hb SS variant who had no clinically apparent retinopathy, then compared these data with measurements in age-and sex-matched controls. We hypothesized that eyes with sickle cell disease would exhibit early tomographic evidence of subclinical ischemia (i.e., retinal thinning) despite unremarkable examination findings, which might allow SDOCT to be used for non-invasive identification of sickle cell retinopathy.

Methods

Participants

Patients with a confirmed diagnosis of the Hb SS subtype of sickle cell disease were

prospectively recruited from the hematology and ophthalmology clinics at Jordan University Hospital (a tertiary referral center) between January 2020 and March 2020. A control group of age- and sex-matched participants was selected from among all other patients who presented to the eye clinic during that period. Participants in the control group were free of sickle cell disease or risk alleles, thalassemia, systemic cardiovascular disease (e.g., hypertension), and any chronic medical illness (e.g., diabetes mellitus or malignancy). Participants in either group were excluded if they had any ocular disease that might affect retinal thickness including myopia of >3 diopters and/or epiretinal membranes, or a history of intraocular surgery. The study protocol was approved by the University of Jordan ethics committee and the Jordan University Hospital institutional review board (approval #10/2019/25160). All participants provided written informed consent. This study was performed in accordance with the tenets of the Declaration of Helsinki.

Data collection

Detailed data were gathered regarding participant demographics and clinical findings. Information regarding past medical history, ophthalmic medical and surgical histories, and drug history was obtained for each participant and then verified using the hospital's electronic medical records. Each participant underwent a full ophthalmic examination by a single retina consultant, including visual acuity assessment with a Snellen chart, slit-lamp examination, and fully dilated fundus examination. The anterior segment was examined for conjunctival vascular changes; the cornea, anterior chamber, lens, and posterior segment were carefully examined for any abnormalities. Intraocular pressure was measured using a Goldmann tonometer. Only individuals without sickle cell retinopathy (Goldberg stage 0) were included in this study. All participants underwent SDOCT imaging of both eyes using a Revo NX device (OPTOPOL Technology, Zawiercie, Poland). Standard three-dimensional macula scans (width, 6.0×6.0 mm; resolution, 512×128) were acquired and analyzed using ETDRS circles. Macular thickness was assessed using the automated tool in the Revo NX device. Data collection and analysis were performed in accordance with the tenets of the Health Insurance Probability and Accountability Act.

SDOCT images were carefully assessed; those with artifacts were acquired twice. Data were included for both eyes in each of the patients with sickle cell disease and matched controls. Measurements of thickness (central macular, superior, inferior, temporal, and nasal quadrants) were recorded for each participant using MS Excel (Microsoft Corp., Redmond, WA, USA). Because the repeatability of SDOCT is reportedly high, with an interclass correlation coefficient of 0.9–1.0,[9] a single SDOCT examination was performed for each participant. The retinal thickness difference index (TDI) was also determined; this parameter is determined by subtracting foveal thickness from the thicknesses of other macular sectors (for example, TDI of superior macula = superior macular thickness – foveal thickness). Notably, this parameter describes the relative difference in thickness between the macula and the fovea, reflecting the slope in this region of the retina.[10]

Statistical analysis

IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis in this study. Continuous variables were described using means ± standard deviations, while nominal variables were described using counts

(frequencies). Independent samples t-tests were used to analyze differences in mean macular thickness and mean TDI between patients with sickle cell disease and matched controls. These data are described using means, mean differences, and standard deviations. We adopted a p value of 0.05 as a significant threshold.

G-Power software, version 3.1 was used to calculate the power of the primary results by means of post hoc analysis. The effect size was determined using the independent sample mean difference in macular thickness between patients with sickle cell disease and matched controls, using an alpha value of 0.05. Power analysis demonstrated 93% power for the calculated primary result.

Results

Characteristics of patients with sickle cell disease and matched controls

Forty eyes of 20 Jordanian patients were included in this study (mean age, 35.95 ± 9.03 years). The 20 participants included 10 patients with the Hb SS variant of sickle cell disease and 10 age- and sex-matched controls (Table 1). The median binocular best-corrected visual acuity in both groups was 20/20. The detailed demographic characteristics and central macular thickness measurements of the participants are shown in Table 1. The mean IOP values in patients with sickle cell disease were 13.4 ± 3.9 mmHg in the right eye and 13.2 ± 3.5 mmHg in the left eye. Slit-lamp examination findings were within normal limits in all patients. Three patients with sickle cell disease received blood transfusions at 3-month intervals. Only one patient with sickle cell disease had a bone marrow transplant. Five patients with sickle cell disease received hydroxyurea regularly. Retinal thickness tended to be greater in men with sickle cell disease (median= 371 μm) than in women with sickle cell disease (median=222.5 μm), although this difference was not statistically significant.

SDOCT findings

The mean central macular thickness was significantly thinner in eyes with sickle cell

Table 1. Demographic characteristics and macular thickness measurements of patients with sickle cell disease and their age- and sex-matched controls.

	Patients with sickle cell disease			Age and sex-matched controls		
	Mean	Standard deviation	Count (eyes) (%)	Mean	Standard deviation	Count (eyes) (%)
Age (years)	33.70	10.14		38.20	7.61	
Sex						
Male			8 (40.0%)			8 (40.0%)
Female			12 (60.0%)			12 (60.0%)
Eye						
Right			10 (50.0%)			10 (50.0%)
Left			10 (50.0%)			10 (50.0%)
Central thickness	191.40	16.72		213.55	23.46	
Superior quadrant	247.95	26.96		288.30	37.70	
Nasal quadrant	254.35	20.44		279.45	41.03	
Inferior quadrant	250.75	21.37		284.10	41.79	
Temporal quadrant	233.45	24.27		278.60	39.64	

All measurements are shown in micrometers unless otherwise indicated.

disease than in matched control eyes ($p = 0.002$). Power analysis demonstrated 93% power for this finding. Other peripheral quadrants were all significantly thinner in eyes with sickle cell disease, as shown in Table 2. Peripheral measurements were significantly different in superior and temporal quadrants (both $p < 0.001$). Furthermore, eyes with sickle cell disease had lower TDIs, compared with matched control eyes, in superior ($p = 0.045$) and temporal ($p = 0.009$) quadrants (Table 3).

Table 2. Spectral domain optical coherence tomography quadrant measurements of eyes with sickle cell disease (cases) and age- and sex-matched control eyes (controls).

	Mean	Mean difference	Standard deviation	p value
Central thickness				
Cases	191.40	22.15	6.44	0.002
Controls	213.55			
Superior quadrant				
Cases	247.95	40.35	10.36	<0.001
Controls	288.30			
Nasal quadrant				
Cases	254.35	25.10	10.25	0.021
Controls	279.45			
Inferior quadrant				
Cases	250.75	33.35	10.50	0.004
Controls	284.10			
Temporal quadrant				
Cases	233.45	45.15	10.39	<0.001
Controls	278.60			

All measurements are shown in micrometers.

Discussion

Several factors have been reported to affect retinal thickness on SDOCT. Age has been found to significantly correlate with retinal thinning.[11] Compared with women, men tend to have significantly greater retinal thickness; Nieves-Moreno et al.[12] describe a mean thickness difference of 7.113 μm in the central zone. Certain ocular diseases (e.g., myopia) are also associated with macular thinning.[13,14] Retinal nerve fiber layer changes have been used to follow eyes with glaucoma and to identify anatomical and functional deficits in this disease.[15] SDOCT has emerged as a very useful diagnostic and prognostic tool for retinal vascular disease, which can provide clues about retinal perfusion despite the absence of clinical signs.[16]

Table 3. Thickness difference indexes of macular quadrants in eyes with sickle cell disease (cases) and age- and sex-matched control eyes (controls).

	Mean	Standard deviation	Mean difference	Standard deviation	p value
Superior quadrant					
Cases	56.55	33.28	18.20	8.79	0.045
Controls	74.75	20.89			
Nasal quadrant					
Cases	62.95	29.33	2.95	8.34	0.725
Controls	65.90	23.02			
Inferior quadrant					
Cases	59.35	28.84	11.20	8.31	0.186
Controls	70.55	23.44			
Temporal quadrant					
Cases	42.05	30.42	23.00	8.42	0.009
Controls	65.05	22.17			

All measurements are shown in micrometers.

In this study, we analyzed central macular thickness in Jordanian patients with the Hb SS variant of sickle cell disease who had no clinically apparent retinopathy, compared with age- and sex-matched controls. Although our patients with sickle cell disease were asymptomatic and did not exhibit retinopathy, we observed a significant difference in central macular thickness, compared with the matched controls. This relationship was evident in all peripheral macular quadrants; it was most pronounced in the superior and temporal quadrants. These findings are in agreement with previous reports in which ischemia-related retinal structural changes can occur before clinical symptoms in eyes with sickle cell disease.[17,18] Other studies have also shown that thinning of the inner retinal layers can be detected on SDOCT images.[19] Although patients with the Hb SS variant of sickle cell disease experience more frequent occlusive sickling events, compared with patients who have other variants of the disease, the clinical incidence of proliferative retinal complications is lower among patients with the Hb SS variant.[4] The eyes of patients with the Hb SS variant of sickle cell disease might therefore exhibit sufficient ischemia severity to cause cell infarction, which results in tissue loss. Our findings also demonstrated that eyes with sickle cell disease had lower TDIs than matched control eyes; this difference was also most pronounced in temporal and superior macular quadrants. The prognostic value of this finding requires validation in additional studies involving larger numbers of patients with different ethnicities. It would be informative to investigate retinal blood flow by means of optical coherence tomography angiography in eyes with sickle cell disease and determine whether the findings are associated with thickness values. Previous studies have shown that eyes with sickle cell disease may exhibit no remarkable manifestations on fluorescein angiography, despite the presence of microvascular changes on optical coherence tomography angiography.[20,21]

The major limitation of this study was that it included a small number of eyes. Nevertheless, this study had 93% power to detect a difference in mean central macular thickness between patients with sickle cell disease and matched controls. Notably, the patients and controls were young and well-matched to ensure that age and sex could not serve as confounding factors. To the best of our knowledge, this is the first investigation of central retinal thickness measurements in Jordanian patients with sickle cell disease. Although patients with sickle cell disease may exhibit asymptomatic proliferative retinopathy,[7] we included patients without clinically evident retinopathy in this study to investigate potential tomographic changes during early stages of disease in those eyes. Future studies should examine the progression of those changes over time, their relationships with the stages of overall retinopathy, and the effects of disease-modifying agents and/or bone marrow transplantation.

In conclusion, this investigation showed that central macular thickness was thinner in Jordanian patients with the Hb SS variant of sickle cell disease and no signs of retinopathy, compared with age- and sex-matched controls. This difference was most pronounced in the superior and temporal quadrants. Further studies involving larger numbers of Arab patients and patients of other ethnicities are encouraged to explore the relationships between retinal thickness and sickle cell disease subtypes, as well as the progression to new vessel formation. Our findings imply that SDOCT and nascent tomographic technologies can provide non-invasive and accurate assessments of sickle cell disease pathophysiology.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Data availability statement

The datasets generated and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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