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ANALYSIS OF RETINAL THINNING USING SDOCT IMAGING OF SICKLE CELL RETINOPATHY EYES COMPARED TO AGE- AND RACE-MATCHED CONTROL EYES

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Abstract

Purpose—To determine whether the retina is thinner in sickle cell patients than in race- and age-matched controls, and if it is thinner, whether there is any association with systemic diseases.

Methods—Sickle cell and control (age- and race-matched) patients were prospectively enrolled from a university retina clinic into this observational study. Participants underwent visual acuity testing, slit-lamp biomicroscopy, dilated ophthalmoscopy, and spectral domain optical coherence tomography imaging. Sickle cell retinal lesions, degree of vascular tortuosity, caliber of arteriovenous anastomosis, and stage of retinopathy were noted. Early Treatment Diabetic Retinopathy Study (ETDRS) subfield measurements were compared between sickle cell and control subjects and also among sickle cell hemoglobin subtypes. Associations between ETDRS subfield measurements and hemoglobin subtype, retinopathy stage, and systemic diseases were assessed.

Results—A total of 513 sickle cell eyes (260 patients) and 75 control eyes (39 patients) had median visual acuities of 20/20. ETDRS central (P=.002), inner (nasal P=.009, superior P=.021, temporal P<.001, inferior P=.017), and temporal outer (P=.012) subfield measurements were thinner in sickle cell eyes compared to control eyes. Hemoglobin SS eyes had significantly thinner inner ETDRS subfield measurements compared to SC and SThal eyes. Retinal thinning in all subfields was associated with age (P=.017) for sickle cell and control eyes. No association was found between retinal thinning and hydroxyurea use or arteriovenous anastomosis caliber.

Conclusions—The macula is thinner in sickle cell eyes compared to control eyes; retinal thickness decreases with increasing age and sickle cell retinopathy stage and is most severe in hemoglobin SS subtypes.

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INTRODUCTION

Sickle cell retinopathy is one of the protean manifestations of sickle cell disease. Goldberg[1] created the classification system for proliferative sickle cell retinopathy over 40 years ago. Since then, advances in ocular imaging have essentially enabled a “live biopsy” of the retina to be performed. Specifically, modern ocular image technology, such as spectral domain optical coherence tomography (SDOCT), allows visualization of the anatomical changes and may help to further classify the stages of sickle cell retinopathy beyond what is visible clinically. Prior research in this area by our group has shown evidence of subclinical disease.[2–4] In one study, a significant proportion (60%) of sickle cell patients with normal visual acuity and without any ocular complaints was noted to have retinal thinning in the Early Treatment Diabetic Retinopathy Study (ETDRS) central subfield locations.[3] In another study, the central and other ETDRS subfields were noted to be thinned in sickle cell patients, and microperimetry testing showed decreased visual function corresponding to these areas of retinal thinning.[4]

This current study is performed to determine whether SDOCT may be a useful biomarker of sickle cell retinopathy severity and/or systemic sickle cell–related disease severity in a large cohort of sickle cell patients. Currently, patients with sickle cell disease may receive disease-modifying medications, such as hydroxyurea, to attempt to diminish the number and severity of sickle cell crises. In patients with more severe sickle cell retinopathy with retinal thinning noted by SDOCT imaging, such intervention may also be warranted. The purpose of this study is to evaluate (1) whether the stage of sickle cell retinopathy is correlated with SDOCT parameters and (2) whether the presence of sickle cell disease–related systemic complications is associated with SDOCT findings.

Based on prior work in this area, we hypothesize that eyes with sickle cell retinopathy will show evidence of subclinical ischemia manifested as retinal thinning on SDOCT imaging and that these SDOCT abnormalities will be correlated with the stage of the disease. Measurements of the central and other ETDRS subfields are postulated to be thinner in sickle cell eyes compared to age- and race-matched controls. Also, the ETDRS subfield area thickness measurements are postulated to correlate with sickle cell stage and disease severity.

In addition, we hypothesize that eyes of patients with more severe systemic disease have more severe ocular findings on SDOCT imaging. The thickness measurements are postulated to correlate with the presence and severity of systemic complications related to sickle cell disease.

METHODS

CLINICAL PROTOCOL

Sickle cell patients were prospectively recruited into this study from the sickle cell clinic at the University of Illinois at Chicago and underwent a full dilated ocular examination by a retina specialist (J.I.L.). Participants in the control group were chosen from race- and age-matched patients from the retina and general eye clinics. Controls were required to be free of

sickle cell disease, sickle cell trait, prior retinal disease, or any acute or chronic ocular disease except for mild refractive errors or mild lens opacities. In addition, controls were required to be free of systemic cardiovascular disease (except controlled hypertension) and any chronic illness or malignancy. Approval from the Investigational Review Board (IRB) of the University of Illinois at Chicago was obtained prior to the start of this project. Each study participant was required to sign a written, IRB-approved, informed consent form. The patients were then evaluated and enrolled into the study.

All patients underwent a full ophthalmic examination consisting of Snellen visual acuity, slit-lamp examination, and dilated fundus examination. The Goldberg classification system for proliferative sickle cell retinopathy was used to determine the sickle cell disease stage based on the dilated fundus examination findings.[1] The anterior segment was examined to look for conjunctival vascular changes; the cornea, anterior chamber, and lens status were examined thoroughly and intraocular pressure was measured. The presence and degree of vascular tortuosity and vascular narrowing were noted, and each was graded on a scale of 1 (mild) to 3 (severe). In the posterior segment, the presence or absence and location of a foveal depression sign, pigmentary abnormality, vascular occlusion, sunburst lesion, iridescent spot, salmon-patch hemorrhage, arteriovenous anastomosis, retinal neovascularization (sea fan), retinal hemorrhage, vitreous hemorrhage, or retinal detachment were noted during the dilated fundus examination. The cup-disc ratio was approximated during the examination and recorded into the chart. All patients underwent SDOCT imaging (Spectralis, Heidelberg Engineering Inc) of each eye. SDOCT images were taken using standard and enhanced depth imaging with 6-mm scans.

During the clinical evaluation, a thorough review of systems was performed for sickle cell and control patients. In addition, patients were asked to self-report the use and duration of hydroxyurea or whether they were receiving any experimental sickle cell disease–modulating drugs. Also, patients were queried regarding current or prior use of tobacco. The electronic medical records from the sickle cell clinic were reviewed to verify the information given for type of medication and duration of use. Patients were asked to return for annual examinations. Data collection and analyses complied with the Health Insurance Portability and Accountability Act (HIPPA). The SDOCT images were reviewed, and images were included if the scans were free of artifacts. Segmentation boundaries were adjusted as needed. Then, SDOCT measurements of the central and surrounding ETDRS subfield areas were recorded for each eye and for each visit of each patient onto an Excel database. The SDOCT subfield measurements were recorded as central, nasal inner, superior inner, temporal inner, inferior inner, nasal outer, superior outer, temporal outer, and inferior outer from the SDOCT maps for each eye for each patient for each visit. Visual acuities, intraocular pressures, anterior segment findings, cup-disc ratios, and posterior segment findings based on clinical records were also recorded onto an Excel database.

The electronic medical records of all patients (sickle cell and controls), available online from the University of Illinois Cerner Electronic Health Record system, were extensively reviewed to determine the types and severity of systemic diseases. The records were searched to determine the presence of medical conditions and surgical procedures related to sickle cell disease. Specifically, medical records were searched for presence of acute chest

syndrome, avascular necrosis of any joint, joint replacement, gallstones, cholecystectomy, hypertension, liver disease, renal disease, pulmonary embolism, deep venous thrombosis, pulmonary hypertension, seizure disorder, splenectomy, stroke, and transient ischemic attack. In addition, major systemic diseases, including the presence of cancer, cardiac disease, infectious disease, inflammatory conditions, and surgeries, were also recorded for each patient. Records from internal medicine, hematology, cardiology, orthopedics, renal, pulmonary, and ophthalmology clinics were reviewed electronically to obtain the data on past and current medical history for each patient at the time of the baseline SDOCT.

DATA ANALYSIS

The SDOCT subfield measurements for the control group of eyes were compared to those of the sickle cell group of eyes. The SDOCT central and surrounding subfield measurements were expressed as group mean and standard error (SE). These mean central and subfield ETDRS thicknesses were compared between sickle cell patients and age- and race-matched controls or within the sickle cell hemoglobin group subtypes using repeated-measures analysis of variance (ANOVA) to account for correlations between two-eye measurements from the same individuals. Demographic and clinical characteristics were compared using ANOVAs for continuous variables or chi-square tests for categorical variables. The effect of age, concomitant systemic diseases, or hydroxyurea use on ETDRS subfield thickness was analyzed using repeated-measures ANOVA, with sickle cell types controlled. The *P* values were corrected using Bonferroni method for multiple comparisons.

RESULTS

DEMOGRAPHICS

The study had a total of 513 eyes in 260 sickle cell patients and 75 control eyes in 39 control patients. Among the sickle cell group, there were three subtypes: 318 Hgb SS eyes (161 patients), 133 Hgb SC eyes (68 patients), and 62 Hgb SThal eyes (31 patients). Ages ranged from 18 to 70 years. The demographic data are shown in Table 1. Mean age, gender, and smoking status did not significantly differ between the groups. The mean visual acuities were 20/22 (median 20/20; SD = 4.2) for controls and 20/24 (median 20/20; SD = 19.8) for sickle cell patients (20/24 [median 20/20; SD = 22.4] for Hgb SS eyes, 20/26 [median 20/20; SD = 17.5] for SC eyes, and 20/22 [median 20/20, SD = 4.6] for SThal eyes).

Compared to controls, sickle cell patients were *less* likely to have hypertension (P=.025) and *more* likely to have kidney disease (P<.001), liver disease (P=.026), avascular necrosis of a joint (P=.001), pulmonary hypertension (P<.001), acute chest syndrome (P<.001), stroke (P<.001), and a history of prior cholecystectomy (P<.001) or hip replacement (P=.006). Among the sickle cell disease patient subtypes, those with Hgb SS subtype were more likely to have liver disease (P=.012), kidney disease (P=.001), pulmonary hypertension (P=.001), acute chest syndrome (P<.001), and stroke (P=.001). More Hgb SC patients had systemic hypertension than Hgb SS or SThal (P=.022) patients. In the multivariate analysis, using the Bonferroni correction, hypertension, liver disease, and hip replacement did not differ between sickle cell and control patients (Table 2).

The sickle cell patients differed in their current use of hydroxyurea: 49.4% of sickle Hgb SS subtypes, 17.3% of Hgb SC, and 21% of Hgb SThal currently using hydroxyurea ($P<.001$), whereas 19.2% of Hgb SS, 6.8% of Hgb SC, and 12.9% of Hgb SThal patients had previously used hydroxyurea (see Table 1). Mean duration of hydroxyurea use was 6 years for Hgb SS, 4 years for Hgb SC, and 2 years for Hgb SThal patients ($P<.001$).

SICKLE CELL STAGING

The sickle cell retinopathy stages ranged from 0 to 5 (Table 3), with stage 2 as the predominant type of proliferative sickle cell retinopathy for eyes with Hgb subtype SS (267 of 318, 84 %) and SThal (48 of 62, 77.4 %). Stages 2 and 3 were about equal in Hgb SC eyes (stage 2: 64 of 133, 48.1%; stage 3: 55 of 133, 41.4%). Hgb SS had the highest degree of tortuosity among the subtypes: 1.57 for Hgb SS, 0.89 for Hgb SC, and 0.63 for Hgb SThal ($P<.001$). Mean grade of arteriovenous anastomosis was 1.62 for Hgb SS eyes, 1.79 for Hgb SC eyes, and 1.04 for Hgb SThal eyes ($P<.001$). Occlusions were found on average in about 25 % of all sickle cell eyes, iridescent spots in 5%, pigmentary changes in 10%, and sunburst lesions in 31%, with no significant differences between the Hgb subtypes. In contrast, presence of sea fans ($P<.001$) and hemorrhage ($P<.001$) differed among the Hgb subtypes, with 38.3% of Hgb SC eyes having sea fans (vs 11.3% for Hgb SS and Hgb SThal eyes) and 13.5% of Hgb SC having hemorrhage (vs 4.4% for Hgb SS and 1.6% for Hgb SThal eyes).

SDOCT FINDINGS

Compared to control eyes, sickle cell eyes had lower retinal thickness measurements on SDOCT for the central subfield ($P=.002$) and the nasal inner ($P=.009$), superior inner ($P=.021$), temporal inner ($P<.001$), inferior inner ($P=.017$), and temporal outer ETDRS subfields ($P=.012$) (see Table 4A for mean subfield measurements). With multivariate analyses, using the Bonferroni correction, the central subfield and temporal inner subfields remained significantly lower in the sickle cell eyes compared to the control eyes. Secondary analyses showed that the thickness measurements were lower for Hgb SS and Hgb SThal eyes compared to Hgb SC eyes for the central subfield ($F_{3,580}=7.65$, $P<.001$). The retinal thickness measurements were also significantly lower for SS vs SC eyes for nasal inner ($F_{3,580}=3.41$, $P=.017$), superior inner ($F_{3,580}=3.45$, $P=.017$), and temporal inner ($F_{3,580}=5.58$, $P<.001$) ETDRS subfields (see Table 4B for mean subfield measurements for Hgb subtypes). With multivariate analyses, using the Bonferroni correction, the central subfield remained significantly lower in the Hgb SS and Hgb SThal eyes compared to Hgb SC eyes. In addition, the temporal inner subfield remained significantly lower in the Hgb SS eyes compared to the Hgb SC and SThal eyes.

SDOCT measurements of the inner ETDRS four subfields were inversely correlated with age (repeated-measures ANOVA, $P<.001$) (Table 5) for all eyes. The ETDRS central subfield and nasal inner thickness were significantly lower in females than males. The ETDRS inferior inner subfield and the nasal, superior, and inferior outer subfields were associated with tortuosity. Thinning of temporal inner ETDRS subfield significantly associated with stage of sickle cell retinopathy ($P=.016$). The presence of a sea fan correlated with thinning in superior inner ($P=.024$), temporal inner ($P<.001$), inferior inner

(*P*=.024), and temporal outer (*P*=.003) ETDRS subfields. The presence of hemorrhage correlated with thinning in nasal inner (*P*=.012), superior inner (*P*=.008), temporal inner (*P*=.021), nasal outer (*P*=.043), and superior outer ETDRS subfields (*P*=.022). The presence of a sunburst lesion was associated with thinning in superior inner (*P*=.047), temporal inner (*P*=.020), superior outer (*P*=.014), temporal outer (*P*=.006), and inferior outer (*P*=.024) ETDRS subfields. No association between SDOCT thickness measurements and severity of arteriovenous anastomoses or hydroxyurea use was seen (Table 5).

Repeated-measures ANOVA was used to determine the association between SDOCT subfield measurements of sickle cell eyes and systemic diseases or surgical procedures in sickle cell patients. SDOCT ETDRS subfield thinning was associated with the presence of avascular necrosis of any joint, hypertension, seizure disorder, and history of pulmonary embolism or deep vein thrombosis. For these systemic diseases, more than half of the ETDRS subfields showed an association (Table 6). With multivariate analyses, using the Bonferroni correction, hypertension, seizure disorder and a history of deep vein thrombosis remained significant.

Retinal thickness is significantly related to both age and hypertension. However, when controlling for hypertension, age is still significantly associated with retinal thinning. In the sickle cell eyes, a comparison of averaged inner and outer subfields showed that the temporal retinal subfields had much more thinning as compared to the nasal subfields (temporal vs nasal: 293.19 ± 25.41 μm vs 320.19 ± 21.34 μm; *P*<.001). In control eyes, the temporal subfields were also thinner than the nasal subfields. However, sickle cell eyes had more severe thinning in temporal vs nasal subfields than that in control eyes (*P*=.01). In sickle cell patients, on average, the temporal subfield had 26.99 μm ± 0.8 μm more thinning than the nasal subfield, whereas in control eyes, that value was 21.57 ± 0.74 μm.

DISCUSSION

This study of 513 sickle cell eyes in 260 patients is the largest study to date evaluating eyes with sickle cell disease with SDOCT imaging. In this study, the majority of patients had no symptoms of ocular disease except for mild refractive errors and had median visual acuities of 20/20. Despite the lack of symptoms, our results show that subclinical ultrastructural changes are present in sickle cell eyes as compared to age- and race-matched controls. Specifically, the inner ETDRS subfields are significantly thinner than in control eyes. Moreover, the temporal watershed zone appears to be the most affected subfield across all sickle cell subtypes. These findings support the earlier smaller study by our group, which first showed evidence of central subfield thickness thinning in asymptomatic sickle cell patients.[3] These results also support the hypothesis that retinal ischemia is sufficient to cause tissue loss even before the patient is symptomatic.[5–9] The association of thinning in the temporal ETDRS subfield with more advanced sickle cell stages, such as sea fan formation or hemorrhage, suggests that it could be a biomarker for advancing disease. In fact, a recent study showed that proliferative sickle cell retinopathy was more prevalent in eyes with temporal thinning on SDOCT than in eyes without temporal thinning.[9] Our current study found additional areas of thinning associated with advanced stages of sickle cell retinopathy and also expanded on the association of the subtypes.

Our current study also showed that the amount of retinal thinning in each ETDRS subfield uniformly correlates with age. This association with aging is not unexpected, as recurrent sickling episodes that contribute to ischemia would be expected to result in tissue destruction over time. This is similar to the systemic effects seen over time in patients. Sickling episodes that occur throughout the capillary beds in the body also take place in the retinal and choriodal vessels. Since there are no pain fibers in the retina, these ischemic episodes result in loss of retinal tissue without pain. Theoretically, the higher metabolic demands of the posterior pole would increase its vulnerability to ischemia. The finding of SDOCT foveal splaying in sickle cell eyes correlates nicely with the foveal depression sign.[6–8] Indeed, the transition from infarction of the posterior pole to thinning of the inner macular layers 5 weeks later has been captured on SDOCT.[10] Histopathology of sickle cell eyes supports this selective infarction of inner retinal layers.[11] Our group and others have reported SDOCT thinning of the inner retinal layers, including the nerve fiber layer.[3,9,10,12]

Our study shows that more severe retinal thinning occurs in Hgb SS eyes as compared to Hgb SC and SThal eyes. It is well established that Hgb SS patients experience more occlusive sickling episodes than other Hgb subtypes, resulting in more severe retinal nonperfusion and loss of tissue. Hgb SS eyes less often have retinal complications of neovascularization or hemorrhage.[13–15] In the Hgb SC eyes, milder degrees of ischemia that result in incomplete retinal destruction would be expected to generate more angiogenic factors and result in higher rates of stage 3 sickle cell retinopathy. In our study, the rates of stage 3 sickle cell retinopathy in the Hgb SC subtype eyes were four times greater than in HgSS eyes and five times greater than in Hgb SThal eyes. Our study supports prior work showing Hgb SC eyes to have more severe degrees of sickle cell retinopathy (stages 3 and 4) compared to Hgb SS and SThal subtypes.[13–16] This finding suggests that the levels of ischemia are sufficient enough to cause neovascularization but not enough to infarct the retina. Recent work has shown that indeed this is the case.[17] Thus it is postulated that the viable, although ischemic, Hgb SC retina produces vascular endothelial growth factor, whereas the Hgb SS retina suffers ischemia severe enough to cause cell death, and hence more severe thinning is found on the SDOCT.

Our results also support prior research that has shown Hgb SS sickle cell patients to have more severe systemic disease than patients with Hgb SC or SThal subtypes. In the baseline evaluations, the systemic diseases associated with sickle cell disease were more prevalent in the Hgb SS patients, even though the ages of patients in the subtypes were similar. It is possible that SDOCT imaging in patients with these associated systemic diseases may be of benefit. SDOCT imaging may detect early signs of retinal thinning in some patients, who would then be considered for systemic disease sickle cell–modifying agents in an attempt to avert future retinal loss. It is important to try to prevent tissue loss, as our prior work has also shown that loss of function accompanies these areas of SDOCT thinning.[4] A prospective study looking at hydroxyurea use over time is needed. Our patients are being followed up prospectively, and hopefully this question will be addressed.

The finding of varying degrees of retinal thinning based on the ETDRS subfield location, despite the same level of stage of sickle cell retinopathy, supports the assertion that SDOCT imaging adds information to the clinical staging of sickle cell retinopathy. Whether this will

prove to have prognostic information in terms of future visual loss or retinal complications remains to be seen. The longitudinal portion of this study is currently continuing and will evaluate this factor over time. In one study, temporal macular atrophy as noted on SDOCT had a sensitivity of 27%, a specificity of 67%, a positive predictive value of 83%, and a negative predictive value of 13% for identifying neovascularization in sickle cell eyes.[18] Another study has also found significant macular temporal thinning in sickle cell retinopathy eyes.[19] Unlike in our study, the investigators did not analyze stage of disease or systemic disease associations. They did find that more severe thinning was seen in the more severe genotypes.

The finding that retinal thinning is associated with age is important. This association is probably a correlate for duration of disease and suggests worsening ischemia over time. The longitudinal portion of this study will investigate this aspect. Perhaps patients in whom progressive retinal thinning is seen would be helped by disease-modifying agents, such as hydroxyurea. Whether one can halt the progression of the disease remains to be seen. In our study, 10 patients (3.8%) underwent a sickle cell transplant and were theoretically cured of sickle cell disease. Continued monitoring of these patients will show whether the retinal thinning is halted or whether retinal tissue loss progresses for some time.

Finally, the association of ETDRS subfield thinning with seizure disorder, avascular necrosis of any joint, hypertension, and history of pulmonary embolism or deep vein thrombosis identifies patients who may suffer higher risk of retinal thinning. These systemic diseases themselves do not cause retinal thinning. Hypertension may be associated with a retinal vascular event that could result in retinal infarction and thinning. Note that the prevalence of hypertension was 31% in our controls but only 21% in our sickle cell patients. Prior reports do not show retinal thinning in hypertension alone. Those patients in whom these systemic diseases are present perhaps should be followed up more carefully and should receive therapy with disease-modifying agents to try to offset retinal thinning.[17,20–22] Disease-modifying agents have recently been shown to attenuate key endothelial cell angiogenic mechanisms that are activated in sickle cell disease.[17] Prior work has shown halting of sickle cell retinopathy with exchange transfusion or with disease-modifying agents.[20–22] Further work is needed to determine whether patients with significant systemic disease requiring disease-modifying agents indeed will suffer retinal vascular infarcts and loss of retinal function compared to those sickle cell patients without these findings.

In conclusion, SDOCT imaging adds information to the clinical staging of the disease and potentially can serve as a biomarker of more severe retinopathy. The sickle cell classification system in general is correlated with retinal thinning. However, the amounts of retinal thinning that occur are variable even within a sickle cell disease stage. Not all stage 2 sickle cell retinopathy eyes are equivalent. Some will have normal or close to normal ETDRS subfield measurements, whereas others may have marked thinning of the retinal subfields. The SDOCT can differentiate further within each sickle cell retinopathy stage by detecting these subclinical areas of thinning. The association of more severe retinal thinning suggests that it may be useful as a biomarker of more severe disease and a patient who therefore needs closer ophthalmologic and systemic disease monitoring. Further work is needed to see if continued thinning of the ETDRS measurements indeed continue to progress over time.

Analysis of retinal bloodflow using OCT angiography (OCTA) would also be useful in these patients. Recent work in this area shows microvascular changes visible on OCTA that are not seen on fluorescein angiography.[23–25] The patients in our study are undergoing OCTA in addition to SDOCT imaging for their annual examinations as part of the study.

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Table 1

Baseline demographic and clinical characteristics of sickle cell patients compared to controls *

CATEGORY	Controls	Sickle Cell (All subtypes)	*P* value Sickle Cell vs Controls	Hgb SUBTYPES			*P* value ALL Hgb subtypeS
				SS N (%)	SC N (%)	SThal N (%)	
Number of patients	39	260		161 (62)	68 (26)	**31** (12)	
Age, years (mean ± SD)	42.1 ± 2.0	37.7 ± 0.8	.045	35.40 ± 1.0	42.5 ± 1.6	38.8 ± 2.3	**.005**
Gender male	13 (33%)	93 (40%)	.779	64	18	11	.157
Smoking status			.476				.967
Never	32 (82.1%)	194 (74.6%)		121 (75.2%)	49 (72.1%)	24 (77.4%)	
Past	1 (2.6%)	18 (6.9%)		10 (6.2%)	6 (8.8%)	2 (6.5%)	
Current	6 (15.4%)	49 (18.8%)		30 (18.6%)	13 (19.1%)	6 (19.4%)	
Hydroxyurea †			**<.001**				**<.001**
Never	75 (100%)	242 (47.2%)		100 (31.4%)	101 (75.9%)	41 (66.1%)	
Past	0 (0%)	193 (37.6%)		61 (19.2%)	9 (6.8%)	8 (12.9%)	
Current	0 (0%)	78 (15.2%)		157 (49.4%)	23 (17.3%)	13 (21.0%)	

Hgb, hemoglobin; SC, sickle cell Hgb SC subtype; SS, sickle cell Hgb SS subtype; SThal, sickle cell Hgb SThal subtype.

* *P* values less than .0125 (ie, 0.05/4) are considered significant based on Bonferroni correction and are in bold type.

† Based on number of eyes.

Table 2

Comparison of prevalence of systemic diseases and surgical procedures in sickle cell patients and controls (ANOVA)*

CATEGORY	Controls N (%)	Hgb subtypes			SC vs Control
		SS N (%)	SC N (%)	SThal N (%)	
Number of patients	39	161	68	31	260 vs 39
Systemic disease					**ANOVA *P* value**
Acute chest syndrome	0	81 (50)	19 (28)	10 (31)	**<.001**
Avascular necrosis of any joint	0	42 (26)	19 (28)	13 (41)	**.001**
Pulmonary hypertension	0	37 (23)	5 (7)	1 (3)	**<.001**
Stroke	0	36 (22)	4 (6)	1 (3)	**<.001**
Kidney disease	0	35 (22)	4 (6)	1 (3)	**<.001**
Hypertension	12 (31)	27 (16)	22 (32)	5 (16)	.025
Liver disease	2 (5)	17 (11)	1 (1)	0	.026
Pulmonary embolism	0	15 (9)	5 (7)	3 (9)	.262
Deep venous thrombosis	0	15 (9)	3 (4)	1 (3)	.11
Seizure disorder	1 (3)	15 (9)	2 (3)	0	.068
Gallstones	0	13 (8)	2 (3)	3 (9)	.139
Diabetes	3 (8)	4 (2)	5 (7)	2 (6)	.283
Surgical procedure					
Cholecystectomy	2 (5)	76 (47)	16 (24)	6 (19)	**<.001**
Hip replacement	0	19 (12)	5 (7)	8 (25)	.006
Tonsillectomy	0	16 (10)	2 (3)	2 (6)	.069

ANOVA, analysis of variance; Hgb, hemoglobin; SC, sickle cell Hgb SC subtype; SS, sickle cell Hgb SS subtype; SThal, sickle cell Hgb SThal subtype.

**P* values <.003 (ie, 0.05/16) are considered significant based on Bonferroni correction and are in bold type.

Table 3

Baseline stage of sickle cell retinopathy and retinal findings of sickle cell eyes compared to control eyes (ANOVA)*

CATEGORY	Control Eyes No. (%)	All Sickle Cell Subtypes No. (%)	Hgb subtypes			ANOVA *P* value comparing sickle cell subtypes
			SS No. (%)	SC No. (%)	SThal No. (%)	
Number of eyes	75	513	318	133	62	
Stage 0	75 (100%)	13 (2.5%)	5 (1.6%)	2 (1.5%)	6 (9.7%)	**<.001**
Stage 1	0 (0%)	8 (1.6%)	5 (1.6%)	3 (2.3%)	0 (0.0%)	
Stage 2	0 (0%)	379 (73.9%)	267 (84.0%)	64 (48.1%)	48 (77.4%)	
Stage 3	0 (0%)	95 (18.5%)	34 (10.7%)	55 (41.4%)	6 (9.7%)	
Stage 4	0 (0%)	17 (3.3%)	7 (2.2%)	9 (6.8%)	1 (1.6%)	
Stage 5	0 (0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
Pigment	0 (0%)	52 (10.1 %)	35 (11.0%)	12 (9.0%)	5 (8.1%)	.692
Sea fan	0 (0%)	94 (18.3%)	36 (11.3%)	51 (38.3%)	7 (11.3%)	**<.001**
Sunburst	0 (0%)	159 (31.0%)	105 (33.0%)	33 (24.8%)	21 (33.9%)	.199
Hemorrhage	0 (0%)	33 (6.4%)	14 (4.4%)	18 (13.5%)	1 (1.6%)	**<.001**
Retinal finding		**Mean Severity grading (SD)**				**ANOVA *P* value comparing grading among subtypes**
Tortuosity severity	N/A	1.34 (0.07)	1.57 (0.08)	0.89 (0.13)	0.63 (0.12)	**<.001** (ST, SC) <SS
Caliber of anastomosis	N/A	1.58 (0.06)	1.62 (0.07)	1.79 (0.14)	1.04 (0.14)	**<.001** ST< (SS, SC)

ANOVA, analysis of variance; Hgb, hemoglobin; N/A, not applicable; SC, sickle cell Hgb SC subtype; SS, sickle cell Hgb SS subtype; SThal, sickle cell Hgb SThal subtype.

**P* values <.007 (ie, 0.05/7) are considered significant based on Bonferroni correction and are in bold type.

Table 4

A. Comparison of SDOCT subfield measurements for sickle cell eyes with control eyes (ANOVA)*			
Subfield location	**SDOCT thickness (μm)**		**ANOVA *P* VALUE**
	Control Eyes, Mean ± SE	**Sickle cell (all subtypes) Eyes, Mean ± SE**	
Central	262.8 ± 2.42	253.7 ± 1.05	**.002**
Nasal inner	339.8 ± 2.26	332.1 ± 1.07	.009
Superior inner	338.4 ± 2.23	331.4 ± 1.13	.021
Temporal inner	325.0 ± 2.08	313.3 ± 1.20	**<.001**
Inferior inner	335.9 ± 2.30	328.6 ± 1.11	.017
Nasal outer	310.2 ± 2.08	308.3 ± 0.93	.461
Superior outer	294.6 ± 1.88	292.7 ± 0.89	.428
Temporal outer	281.7 ± 1.78	273.1 ± 1.28	.012
Inferior outer	287.1 ± 1.89	284.5 ± 0.90	.286

B. Spectral domain optical coherence tomography subfield measurements for sickle cell eyes compared to control eyes using ANOVA*						
ETDRS subfield	**SDOCT thickness measurements (μm) Mean ± SE**					**Statistical test among sickle cell subtypes and control and post hoc comparison**
	Control eyes	**Sickle Cell (All subtypes) eyes**	**Hgb Subtypes**			
			SS eyes	**SC eyes**	**SThal eyes**	
Central	262.8 ± 2.42	253.7 ± 1.05	252.1+/− 1.33	259.8+/− 2.02	249 +/− 3.06	**<.001** SS,ST<C,SC
Nasal inner	339.8 ± 2.26	332.1 ± 1.07	330.7 ± 1.39	335.1 ± 1.68	333.1 ± 3.86	.017
Superior inner	338.4 ± 2.23	331.4 ± 1.13	329.5 ± 1.55	334.8 ± 1.60	333.7 ± 3.32	.017
Temporal inner	325.0 ± 2.08	313.3 ± 1.20	311.6 ± 1.58	315.8 ± 2.12	316.7 ± 3.43	**<.001** SS<SC, ST
Inferior inner	335.9 ± 2.30	328.6 ± 1.11	327.7 ± 1.47	330.1 ± 1.76	329.9 ± 3.82	.08
Nasal outer	310.2 ± 2.08	308.3 ± 0.93	308.5 ± 1.16	309.2 ± 1.74	305.3 ± 3.19	.559
Superior outer	294.6 ± 1.88	292.7 ± 0.89	292.4 ± 1.18	294.1 ± 1.55	291.3 ± 2.67	.631
Temporal outer	281.7 ± 1.78	273.1 ± 1.28	272.3 ± 1.84	273.4 ± 1.92	276.3 ± 2.47	.061
Inferior outer	287.1 ± 1.89	284.5 ± 0.90	286.1 ± 1.11	282.1 ± 1.66	281.7 ± 3.04	.093

ANOVA, analysis of variance; SDOCT, spectral domain optical coherence tomography.

** P* values <.006 (ie, 0.05/9) are considered significant based on Bonferroni correction and are in bold type.

ANOVA, analysis of variance; ETDRS, Early Treatment Diabetic Retinopathy Study; Hgb, hemoglobin; SC, sickle cell Hgb SC subtype; SDOCT, spectral domain optical coherence tomography; SS, sickle cell Hgb SS subtype; SThal, sickle cell Hgb SThal subtype.

** P* values <.006 (ie, 0.05/9) are considered significant based on Bonferroni correction and are in bold type.

TABLE 5

Association between SDOCT subfield measurements and demographic or clinical findings using repeated-measures ANOVA, with sickle cell types controlled (513 eyes in 260 patients) *

SDOCT Subfield	Patient Age	Smoking	Stage	Hydroxy urea use	Caliber of Anastamoses	Tortuosity	Sea fan	Hemorrhage	Sunburst
Central	.017	.214	.051	.256	.327	.312	.455	.434	.320
Nasal inner	**<.001**	.281	.445	.885	.950	.072	.105	.012	.287
Superior inner	**<.001**	.165	.164	.502	.846	.105	.024	.008	.047
Temporal inner	**<.001**	.069	.016	.760	.464	.761	**.001**	.021	.020
Inferior inner	**<.001**	.162	.509	.670	.711	.019	.024	.184	.107
Nasal outer	**<.001**	.049	.435	.503	.829	.016	.097	.043	.164
Superior outer	**<.001**	.260	.515	.413	.384	.037	.450	.022	0.014
Temporal outer	.010	.175	.061	.125	.494	0.520	**.003**	.521	.006
Inferior outer	**<0.001**	.064	.666	.149	.667	.025	.106	.485	.024

ANOVA, analysis of variance; SDOCT, spectral domain optical coherence tomography.

* *P* values <.006 (ie, 0.05/9) for the associations are considered significant based on Bonferroni correction and are in bold type.

Table 6

Association between SDOCT subfield measurements of sickle cell eyes and systemic diseases or surgical procedures in sickle cell patients based on repeated-measures ANOVA *

CATEGORY	No. of patients				ANOVA *P* values	Association between Systemic Condition and SDOCT Measurements (*P* values from repeated-measures ANOVA)								
	Control N=39	SS N=161	SC N=68	S-Thal N=31										
Systemic disease	**N %**	**N %**	**N %**	**N %**	**SCD vs Control SCD only**	**CST**	**Nasal Inner**	**Superior Inner**	**Temporal inner**	**Inferior Inner**	**Nasal Outer**	**Superior Outer**	**Temporal Outer**	**Inferior Outer**
Acute chest syndrome	0 0	81 50.3	19 27.9	10 31.3	**<.001** **<.003**	.881	.072	.067	.391	.148	.579	.249	.867	.805
Avascular necrosis of any joint	0 0	42 26.0	19 27.9	13 40.6	**.001** .248	.358	.028	.086	.015	.008	.017	.011	.323	.006
Pulmonary hypertension	0 0	37 23	5 7.4	1 3.1	**<.001** **.001**	.419	.185	.281	.59	.55	.065	.072	.048	.154
Stroke	0 0	36 22.4	4 5.9	1 3.1	**<.001** **.001**	.176	.056	.252	.023	.026	.05	.47	.161	.228
Kidney disease	0 0	35 21.7	4 5.9	1 3.1	**<.001** **.001**	.8	.061	.077	.308	.124	.017	.014	.152	.072
Hypertension	12 30.8	27 16.8	22 32.4	5 15.6	.025 .022	.045	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**
Avascular necrosis of the hip joint	0 0	17 10.6	13 19.1	5 15.6	.023 .205	.035	.4	.993	.269	.263	.877	.947	.857	.453
Liver disease	2 5.1	17 10.6	1 1.5	0 0	.026 .012	**.004**	.567	.682	.885	.65	.227	.382	.575	.737
Pulmonary embolism	0 0	15 9.3	5 7.4	3 9.4	.262 .885	**<.001**	.011	.014	.06	.046	.042	.309	.971	.084

CATEGORY	No. of patients				ANOVA *P* values	Association between Systemic Condition and SDOCT Measurements (*P* values from repeated-measures ANOVA)								
	Control N=39	SS N=161	SC N=68	S-Thal N=31										
Systemic disease	N %	N %	N %	N %	SCD vs Control SCD only	CST	Nasal Inner	Superior Inner	Temporal inner	Inferior Inner	Nasal Outer	Superior Outer	Temporal Outer	Inferior Outer
Deep venous thrombosis	0 0	15 9.3	3 4.4	1 3.1	.11 .268	. **0 01**	**<.001**	**<.001**	**<.001**	**.003**	**.001**	**.003**	.01	.026
Seizure disorder	1 2.6	15 9.3	2 2.9	0 0	.068 .057	. 3 2 7	.062	**.002**	.13	.035	.021	**.001**	**.003**	**.002**
Gallstones	0 0	13 8.1	2 2.9	3 9.4	.139 .315	. 5 49	.119	.056	.021	.106	**.004**	.01	.156	.049
Diabetes mellitus	3 7.7	4 2.5	5 7.4	2 6.3	.283 .204	.596	.197	.259	.486	.14	.266	.932	.871	.822
Surgical procedure	**N %**	**N %**	**N %**	**N %**	**SCD vs. Control SCD only**	**CST**	**NASAL Inner**	**SUPERIOR inner**	**TEMPORAL Inner**	**INFERIOR INNER**	**NASAL Outer**	**SUPERIOR Outer**	**TEMPORAL Outer**	**INFERIOR OUTER**
Cholecystectomy	2 5.1	76 47.2	16 23.5	6 18.8	**<.001** **<.001**	.779	.908	.699	.752	.807	.417	.974	.613	.605
Tonsillectomy	0 0	16 9.9	2 2.9	2 6.3	.069 .182	. 7 14	.491	.863	.611	.896	.887	.805	.609	.637

ANOVA, analysis of variance; CST, central subfield thickness; SC, sickle cell hemoglobin SC subtype; SCD, sickle cell disease; SDOCT, spectral domain optical coherence tomography; SS, sickle cell hemoglobin SS subtype; SThal, sickle cell hemoglobin SThal subtype.

*P values <.003 (ie, 0.05/15) for the associations are considered significant based on Bonferroni correction for group comparison. For the association between the systemic disease or surgical procedure and SDOCT subfield measurements, P values <.006 (ie, 0.05/9) are considered significant based on Bonferroni correction and are in bold type.