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Research Article

Spectral Domain Optical Coherence Tomography Imaging in Stroke: A Pilot Study

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Abstract

Background/Objectives: The retina is a direct embryologic extension of the central nervous system and, therefore, may offer biomarkers of anatomical changes in the brain due to stroke. Optical coherence tomography (OCT) offers readily available, high resolution, repeatable, non-invasive imaging of retinal anatomy. We sought to determine whether OCT-based measurements of macular thickness (MT), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) thicknesses were associated with stroke.

Methods: In this cross-sectional observational case-control study, individuals with a prior diagnosis of primary stroke and age-matched controls underwent spectral-domain OCT (SD-OCT) imaging. MT, GCL, and RNFL thickness measurements were obtained at a single visit. Fisher exact test (2-tailed) and Mann-Whitney rank-sum or unpaired t-test were used to analyze categorical and continuous variables, respectively. Univariate and multivariate logistic regressions assessed associations between groups.

Results: Fourteen subjects (27 eyes) with prior stroke and 14 age-matched controls (27 eyes) were included for analysis. There was no significant difference in MT between cases and controls. Univariate analyses of GCL thickness showed decreased average and all-sector thickness between cases and controls. Multivariate analyses confirmed a significant reduction in average GCL thickness in cases versus controls, including in those without visual symptoms. Similarly, univariate analyses showed decreased average, superior, and inferior RNFL thicknesses in cases versus controls. Subsequent multivariate analyses confirmed a significant reduction in average RNFL thickness in prior stroke cases.

Conclusion: In this pilot study average GCL and RNFL thickness, but not MT, were significantly reduced in subjects with a history of prior stroke. These OCT-based measures may serve as potential biomarkers of stroke.

Keywords: *Stroke; Imaging; Retina; Optical Coherence Tomography; Biomarker*

Abbreviations

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer; GCL: Ganglion Cell Layer; AV: Arteriovenous; RTSD: Retrograde Trans-Synaptic Degeneration; MT: Macular Thickness; BCVA: Best Corrected Visual Acuity; D: Diopter; RAPD: Relative Afferent Pupillary Defect; IRB: Institutional Review Board; IOP: Intraocular Pressure; SD-OCT: Spectral-Domain Optical Coherence Tomography; ILM: Internal Limiting Membrane; RPE: Retinal Pigment Epithelium; IPL:

Inner Plexiform Layer; VIF: Variance Inflation Factors; SD: Standard Deviation; HS: High School; IQR: Inter-Quartile Range; LHH: Left Homonymous Hemianopsia; RHH: Right Homonymous Hemianopsia; CI: Confidence Interval; OR: Odds Ratio

Introduction

Stroke is the fifth leading cause of death in the United States since 2021, the second leading cause of dementia, and is one of the major contributors to long-term disability [1-3]. Early detection of individuals at high stroke risk and rapid diagnosis of new stroke cases are essential for improving clinical outcomes, enhancing quality of life, and reducing long-term morbidity.

Current clinical diagnostic imaging for cerebrovascular conditions relies primarily on computed tomography (CT) and magnetic resonance imaging (MRI) [4]. These diagnostic modalities, however, require substantial resources to be implemented in clinical care consistently and at scale. In addition, current neuroimaging technologies only identify cerebral injury above a substantial threshold, and do not assess subtle structural and functional changes directly to allow for identification of individuals at high risk of future stroke [4].

Optical coherence tomography (OCT) provides a rapid, non-invasive method for detecting early structural changes in the retina. Given the shared embryological origin, physiological and functional similarities between the retina and the central nervous system, OCT holds promise for assessing cerebral microcirculation and brain function [5]. Studies have shown that retinal vascular morphology, such as vessel caliber, tortuosity, and fractal dimension, can serve as non-invasive biomarkers, reflecting the condition of systemic circulation and offering predictive utility for cerebral vascular pathologies [6-8]. In addition, neuronal retinal abnormalities, such as decreased retinal nerve fiber layer (RNFL) thickness and Ganglion Cell Layer (GCL) thickness have been associated with neurodegenerative disorders and stroke [9-11]. Specifically, alterations in the retinal neuro-vascular unit are being explored to provide diagnostic insight into neurological conditions including Alzheimer's disease, Parkinson's disease and cerebral small vessel disease and their associated cognitive impairment [10,12-16].

To date, exploration of retinal parameters associated with stroke have included vascular assessments of arterial and venular caliber, tortuosity, fractal dimension, and AV-nicking in stroke populations [17,18]. Previous studies also suggest a correlation between retrograde trans-synaptic degeneration (RTSD) of ganglion cells in patients diagnosed with ischemic stroke, identifying associations between RNFL thickness and structural brain changes associated with cerebrovascular disorders [19,20]. Additional findings have demonstrated correlations between macular vessel density, inner retinal thickness, and the severity of cerebrovascular disorders [21]. However, prior studies did not investigate whether specific OCT imaging features can be leveraged to diagnose stroke or identify patients at risk for developing neurodegenerative disorders.

We sought to conduct a pilot study to evaluate neuronal thickness in the ganglion cell layer (GCL), macular thickness (MT) and retinal nerve fiber layer (RNFL) of stroke survivors and stroke-free controls.

Aim of the Study

The aim of the present study was to identify OCT-derived retinal measurements that distinguish stroke cases from controls, in order to inform future studies aimed at implementation in clinical settings.

Materials and Methods

This research was reviewed by an independent ethical review board and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research.

Study participants

Sixteen participants with a clinical diagnosis of ischemic and/or hemorrhagic stroke and seventeen age-matched controls without stroke diagnosis were recruited for the study. We opted to include in our study population survivors of both ischemic and hemorrhagic

stroke to leverage our present pilot study and explore whether heterogeneity exists in the associations between stroke subtypes and retinal imaging markers. Insight from our study would then inform future, larger studies aimed at further characterizing the role of retinal imaging in different stroke subtypes. Patients with a clinical diagnosis of stroke qualified for study inclusion if they had documented evidence of one or more stroke events occurring < 20 years prior to enrollment. Only patients with a history of primary stroke were included in the study; patients with arterio-venous malformation and secondary strokes (motor-vehicle accident, seizure-related, trauma-related, perioperative, etc.) were not included. Control participants were confirmed to be stroke-free by combined study interview and manual review of all available medical records. We opted for 1:1 matching of stroke participants to controls (based on age), as it ensured we had > 80% statistical power to capture a > 20% change in stroke risk associated with differences in retinal measurements. This represented an ideal threshold for a pilot study aimed primarily at informing design of future studies. Exclusion criteria for both stroke and control participants included: 1) diagnosis of multiple sclerosis or other demyelinating disease (with or without optic neuritis); 2) diagnosis of amyotrophic lateral sclerosis or other degenerative motor neuron disorders; 3) diagnosis of glaucoma, retinal venous disease, age related macular degeneration, or congenital/acquired macular disease. Additionally, patients with ocular characteristics suggestive of poor retinal imaging quality such as best corrected visual acuity (BCVA) worse than 20/40, spherical refractive error > +/-6.00 diopters (D), astigmatic refractive error > 2.50D, intraocular pressure > 21 mmHg, or a presence of a relative afferent pupillary defect (RAPD) were ineligible in both the stroke and control participant groups. The study protocol was approved by the New England College of Optometry Institutional Review Board (IRB) and conducted in accordance with the tenets of the Declaration of Helsinki.

Clinical evaluation and OCT imaging

The eligibility of stroke participants and their age matched controls were confirmed by review of medical records, comprehensive eye examination and on-site clinical examination, adhering to the aforementioned inclusion and exclusion criteria. Demographic and systemic medical history were collected. In addition, most recent MRI records were reviewed to verify the type of stroke, date of stroke and residual ocular symptoms. Each participant underwent one in-person study visit during which BCVA of 20/40 or better was confirmed in the habitual spectacle correction or obtained using retinoscopy and refraction, as needed, in the absence of habitual correction. A slit lamp examination including Van Herick estimation was performed to confirm safety for dilation. Intraocular pressure (IOP) estimation was obtained using Goldmann applanation tonometry and only participants with IOP under 21 mmHg were included in the study. Participants then underwent dilated retinal imaging conducted by a trained operator masked to clinical and neuroimaging data.

Zeiss Cirrus 5000 Spectral Domain OCT (SD-OCT) device was used to measure RNFL, MT and macular GCL thickness. Optic disc cube 200 x 200 scans were obtained to calculate RNFL thickness within a predefined circular area centered on the optic disc and extracted from the 6 mm x 6 mm data cube. Macular cube 512 x 128 scans were obtained to calculate macular thickness (the distance between the Inner Limiting Membrane (ILM) to retinal pigment epithelium (RPE)) over the 6 mm x 6 mm cube centered on the fovea. GCL thickness was calculated based on the macular cube 512 x 128 scan and defined as the combined thickness from the innermost limit of the GCL and outermost limit of the inner plexiform layer (IPL).

The order of image acquisition was randomized between each eye and between imaging modalities. All imaging sessions were conducted on both eyes, under dilated conditions, and included two sequential image acquisitions for all modalities. One image of best quality (based on the quantitative and qualitative scan quality assessment) was chosen for analysis for each eye and each imaging modality. Participants with subjective or objective indications of minor tear film disruption during imaging were provided with preservative free artificial tears to improve comfort and image quality [22]. Per manufacturers recommendations, only scans with signal strength ≥6 should be considered for analysis. To optimize image quality, only images with a signal strength of 7/10 or greater were retained for parametrization and analysis. After verification of the inclusion and exclusion criteria, as well as image quality of obtained scans, images from a total of 14 participants (27 eyes) with a history of stroke and 14 stroke-free controls (27 eyes) were ultimately included for analysis.

Statistical methods

Categorical variables were compared using Fisher exact test (2-tailed) and continuous variables using the Mann-Whitney rank-sum or unpaired t test, as appropriate. In order to obtain univariate estimates of effect size we conducted logistic regression for stroke vs. stroke-free control status, with the variable of interest as the only term in the model. We used multivariate logistic regression to identify variables independently associated with stroke vs. stroke-free control status. We utilized OCT imaging data from each eye obtained from all participants as the analysis unit. We evaluated within-individual correlations between eyes for each participant using Bland-Altman plot, and adjustment for within-subject variability between eyes in all analyses [23]. Given differences in imaging acquisition techniques and relevance to different aspects of retinal physiology and anatomy, we created separate models for: 1) MT measurements; 2) GCL retinal measurements; 3) RNFL retinal measurements. For all models, we pre-specified inclusion of terms accounting for age and sex, as well as eye laterality (see above). We also repeated all analyses after stratification of stroke participants based on time (in months) elapsed since stroke (based on quartiles: < 1 year, 1 - 2 years, 2 - 3 years, > 3 years). The presence of heterogeneity due to time elapse since stroke was assessed for significance using the Breslow Day test. Other candidate covariates included variables showing a trend in association with stroke case vs. stroke-free control status in univariate analysis ($p < 0.20$). Backward elimination of nonsignificant variables ($p > 0.05$) was subsequently used to generate minimal models. Potential confounders and predictors were then reincorporated into the resulting minimal models using change-in-effect criteria: all remaining variables were individually added and retained if they improved the overall model fit (as assessed by Harrell's C) by >10%. We assessed multicollinearity by computing variance inflation factors (VIF) for all predictors and removing all variables with VIF >5. Results with $p < 0.05$ (2-tailed) were considered statistically significant. Given the pilot design of the present study, we elected not to apply adjustment for multiple testing. All analyses were performed with STATA v19.0 (StataCorp LLC).

Results and Discussion

Participants' characteristics

We summarized baseline characteristics of study participants in table 1. All participants were appropriately matched 1:1 for age, with no difference between groups ($p > 0.05$). Compared to stroke-free controls, participants diagnosed with stroke were more likely to be male, less likely to consume alcohol at time of enrollment, and more likely to have a prior medical history of hypercholesterolemia and coronary artery disease (all $p < 0.05$). There were no differences in OCT image quality comparing stroke cases and stroke-free controls (all $p > 0.05$).

Variable	Stroke (Cases)	No Stroke (Controls)	p*
No. patients	14	14	-
Age (Mean, SD in Years)	64.2 (8.8)	64.6 (5.1)	0.84
Sex (male %)	10 (71)	6 (42)	0.046
Race/Ethnicity			0.19
White (%)	12 (86)	11 (79)	
Black (%)	1 (7)	1 (7)	
Asian (%)	1 (7)	1 (7)	
Hispanic (%)	0 (0)	1 (7)	
Other	0 (0)	0 (0)	
Education (HS or more), number (%)	14 (100)	14 (100)	0.99
Tobacco smoking (ever), number (%)	3 (21)	7 (50)	0.07

Alcohol use (current), number (%)	10 (71)	13 (93)	0.02
Stroke subtype			
Ischemic (%)	8 (58)	-	-
Hemorrhagic (%)	6 (43)	-	-
Months since stroke (Median, IQR in Months)	32 (14 - 66)	-	-
Stroke-related visual syndrome			
None, number (%)	6 (43)	-	-
LHH, number (%)	7 (50)	-	-
RHH, number (%)	1 (7)	-	-
Hypertension, number (%)	8 (57)	8 (57)	0.99
Diabetes, number (%)	3 (21)	2 (14)	0.73
Hyperlipidemia, number (%)	12 (86)	5 (36)	<0.001
Obesity, number (%)	5 (36)	2 (14)	0.07
Coronary Artery Disease, number (%)	6 (43)	2 (14)	0.02
Physical Inactivity, number (%)	2 (14)	2 (14)	0.99
Family History of Stroke, number (%)	7 (50)	4 (29)	0.11
Multiple Strokes, number (%)	8 (58)	-	-
OCT signal strength (Median, IQR)			
MT	9 (8-10)	9 (8-10)	0.52
GCL	9 (8-10)	9 (8-10)	0.31
RNFL	8 (7-9)	8 (7-9)	0.66

Table 1: *Participant characteristics.*

**p values derived from univariate analyses. Values in bold identify analyses with p < 0.05. Abbreviations: GCL: Ganglion Cell Layer; HS: High School; IQR: Inter-Quartile Range; LHH: Left Homonymous Hemianopia; MT: Macular Thickness; RHH: Right Homonymous Hemianopia; RNFL: Retinal Nerve Fiber Layer; SD: Standard Deviation.*

Macular thickness measurements and stroke risk

OCT-derived measurements of macular thickness for participants diagnosed with stroke and stroke-free controls are shown in table 2. Macular thickness values were derived and analyzed for each individual sector as shown in figure 1A. Univariate analyses demonstrated no associations between OCT-derived measurements of macular thickness and stroke vs. control status (Table 2, all $p > 0.05$). Multivariate analyses (adjusted for age, sex, and medical history of hypercholesterolemia (as per pre-specified statistical methodology, see above) similarly showed no associations between macular thickness and stroke risk (Table 2, all $p > 0.05$). We found no heterogeneity in associations due to time elapsed between stroke and study enrollment (all $p > 0.20$).

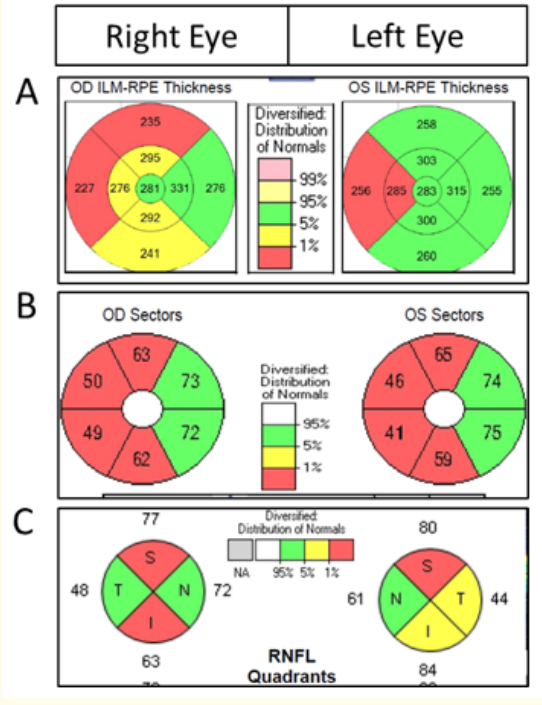

Figure 1: *Example from one of the study participants for sector distribution for A) Macular thickness (MT); B) Ganglion cell layer (GCL) thickness and C) Retinal nerve fiber layer (RNFL) thickness.*

Variable	Stroke Participants*	Controls Participants*	Univariate			Multivariate**		
			OR	95% CI	p	OR	95% CI	p
MT Center	256 (28)	265 (31)	0.99	0.94 - 1.03	0.52	0.97	0.92 - 1.02	0.23
MT Inner Superior	307 (17)	322 (21)	1.26	0.98 - 1.61	0.071	1.28	0.98 -1.68	0.075
MT Inner Nasal	310 (20)	325 (21)	0.85	0.73 - 1.00	0.055	0.88	0.75 - 1.04	0.13
MT Inner Inferior	306 (18)	318 (18)	1.06	0.90 - 1.23	0.50	1.05	0.88 - .125	0.61
MT Inner Temporal	300 (19)	310 (19)	1.00	0.87 - 1.15	0.98	0.99	0.86 - 1.15	0.93
MT Outer Superior	263 (16)	277 (16)	0.92	0.78 - 1.07	0.27	0.90	0.76 - 1.06	0.21
MT Outer Nasal	279 (20)	293 (18)	1.00	0.87 - 1.15	0.97	0.99	0.85 - 1.16	0.97
MT Outer Inferior	254 (18)	266 (15)	1.02	0.93 - 1.13	0.64	1.00	0.90 - 1.11	0.99
MT Outer Temporal	251 (14)	262 (14)	0.83	0.70 - 1.01	0.063	0.87	0.72 - 1.07	0.19

Table 2: *Macular thickness measurements and associations with stroke case vs. control status.*

**Measurements in µm, values presented as mean and standard deviation. **All multivariate models were adjusted for age, sex, and hyperlipidemia. Abbreviations: 95% CI: 95% Confidence Interval; MT: Macular Thickness; OR: Odds Ratio.*

Ganglion cell layer measurements and stroke risk

OCT-derived measurements of GCL thickness are summarized in table 3 for participants diagnosed with stroke vs. stroke-free controls. Average GCL thickness and individual sectors around the macula were analyzed as shown in figure 1B. Univariate analyses demonstrated that individuals diagnosed with stroke displayed lower GCL measurements than controls, both in average and across all regions of interest (Table 3, all $p < 0.05$). Multivariate analyses (adjusted for age, sex, and medical history of hypercholesterolemia as per pre-specified statistical methodology, see above) showed that average GCL thickness was independently associated with stroke risk (Table 3, $p < 0.001$). Because of previously established associations between occipital stroke (causing visual symptoms) and GCL thickness [24], we repeated all analyses among participants diagnosed with stroke but without visual symptoms (n = 6). These stroke participants also had reduced GCL measurements compared to stroke-free controls (mean 73.3, Standard Deviation [SD] 3.1 vs, mean 78.9, SD 1.0). In this subset, greater GCL thickness was still associated with lower stroke risk in both univariate ($p = 0.002$) and multivariate analyses (Odds Ratio [OR] 0.88, 95% Confidence Interval [CI] 0.77 - 0.98, $p = 0.047$). Of note, we found no evidence of heterogeneity in all significant associations due to time elapsed between stroke onset and study enrollment (all $p > 0.20$).

Variable	Stroke Participants*	Controls Participants*	Univariate			Multivariate**		
			OR	95% CI	p	OR	95% CI	p
GCL Average	69.2 (5.1)	78.9 (9.2)	0.81	0.72 - 0.91	<0.001	0.75	0.63 - 0.89	<0.001
GCL Superior	70.7 (8.2)	79.3 (6.3)	0.84	0.76 - 0.93	<0.001	1.32	0.72 - 2.41	0.37
GCL Superior Nasal	69.4 (14.1)	80.6 (5.7)	0.88	0.80 - 0.96	0.003	0.91	0.53 - 1.55	0.73
GCL Superior Temporal	70.3 (10.3)	78.8 (5.8)	0.87	0.79 - 0.95	0.003	1.47	0.69 - 3.12	0.32
GCL Inferior	66.6 (11.4)	77.0 (5.1)	0.83	0.74 - 0.93	0.001	0.97	0.60 - 1.55	0.89
GCL Inferior Nasal	67.1 (15.3)	78.2 (5.6)	0.89	0.82 - 0.96	0.004	1.29	0.69 - 2.40	0.42
GCL Inferior Temporal	71.0 (9.9)	79.6 (4.8)	0.84	0.75 - 0.94	0.002	2.09	0.72 - 6.08	0.18

Table 3: *Ganglion cell layer measurements and associations with stroke case vs. control status.*

**Measurements in µm, values presented as mean and standard deviation. **All multivariate models were adjusted for age, sex, and hyperlipidemia. Abbreviations: 95% CI: 95% Confidence Interval; MT: Macular Thickness; OR: Odds Ratio.*

Retinal nerve fiber layer measurements and stroke risk

Measurements for RNFL thickness derived via OCT imaging for participants diagnosed with stroke and stroke-free controls are shown in table 4. Average RNFL and quadrants around the optic nerve were analyzed as shown in figure 1C. Univariate analyses demonstrated that stroke cases had lower average RNFL thickness than controls, as well as lower measurements in the superior and inferior quadrants (Table 4, all $p < 0.05$). Based on the multivariate analyses (adjusted for age, sex, and medical history of hypercholesterolemia as per pre-specified statistical methodology, see above), higher average RNFL thickness was independently associated with lower stroke risk (Table

4, p =0.032). We found no evidence of heterogeneity due to time elapsed between stroke onset and study enrollment in statistically significant RNFL associations with stroke risk (all p > 0.20).

Variable	Stroke Participants*	Controls Participants*	Univariate			Multivariate**		
			OR	95% CI	p	OR	95% CI	p
RNFL Average	83.3 (11.9)	86.9 (9.2)	0.95	0.92 - 0.99	0.025	0.96	0.93 - 0.99	0.032
RNFL Superior	100.9 (16.8)	104.0 (12.1)	0.98	0.95 - 1.00	0.045	1.02	0.61 - 1.72	0.93
RNFL Inferior	102.3 (19.0)	113.0 (15.7)	0.96	0.93 - 0.99	0.032	0.92	0.54 - 1.55	0.74
RNFL Nasal	69.5 (16.5)	71.1 (12.3)	0.99	0.96 - 1.03	0.67	1.01	0.57 - 1.64	0.97
RNFL Temporal	60.9 (14.0)	59.8 (11.0)	1.00	0.96 - 1.05	0.72	1.05	0.96 - 1.15	0.28

Table 4*: Retinal nerve fiber layer measurements and associations with stroke case vs. control status.*

**Measurements in µm, values presented as mean and standard deviation. **All multivariate models were adjusted for age, sex, and hyperlipidemia. Abbreviations: 95% CI: 95% Confidence Interval; MT: Macular Thickness; OR: Odds Ratio.*

We conducted a pilot case-control study to examine the associations between retinal imaging measurements derived from OCT imaging and risk of stroke. While our conclusions are limited by relatively small sample size, we identified associations between multiple SD-OCT retinal imaging measurements and stroke risk. Our findings expand upon previously reported results, and will serve to inform conduct of future studies aimed at assess the potential role of OCT imaging in: 1) identifying individuals at high risk for first-time or recurrent stroke, to guide preventative interventions; and 2) complementing CT and MRI neuroimaging in evaluation of suspect acute stroke case, especially in lower resource settings.

We report that lower average Ganglion Cell Layer (GCL) thickness was associated with higher stroke risk. Other authors have reported macular GCL thinning in patients who have experienced Retrograde trans-synaptic degeneration (RTSD) of visual pathway neurons in the absence of another neurological or ophthalmological condition [19,25,26]. Following a cerebral infarction of the retrogeniculate visual pathway, thinning of the retinal nerve fiber layer (RNFL) and GCL occur as correlates of retrograde transsynaptic neuroaxonal loss [27]. According to Keller J., *et al*. and Jindahra P., *et al*. there is a progressive thinning of RNFL within the first year of a stroke that tends to remain stable afterwards [26,28,29]. Of note, we found associations between stroke risk and average GCL thickness even among individuals without visual symptoms, i.e. without evidence of direct visual pathway neuronal injury. These findings suggest that the accumulation of low-grade, chronic neurovascular injury that ultimately results in an acute stroke may also be responsible for GCL microstructural damage over time.

We also identified an association between higher average RFNL thickness and lower stroke risk, irrespective of established stroke risk factors in our dataset. Previous studies did report greater RNFL thickness when comparing healthy subjects and patients with ischemic brain injury [30]. However, other studies suggest that RNFL thickness values show lower correlation with visual field defect in stroke patients than GCL thickness [19]. This could be explained by the fact that neuron somas in the macula are more numerous and are topographically organized to coincide with the visual field [31]. In contrast, the distribution of RNFL fibers is anatomically more complex, potentially limiting its relevance as a diagnostic marker of stroke-related injury mediated by trans-synaptic degeneration (especially when

compared to damage related to ocular conditions affecting all RNFL fibers, such as glaucoma) [26,28,29]. There is a general consensus that macular GCL thinning appears to be more sensitive than peripapillary RNFL in detecting retrograde retinal ganglion cell degeneration and its retinotopic pattern in stroke [32]. Despite limited sample size, we did identify associations between average RNFL thickness and stroke risk in a combination of individuals with and without stroke-related visual symptoms. Larger studies are warranted to clarify whether leveraging both GCL and RNFL measurements in combination allows for more precise determination of stroke risk and/or more accurate stroke diagnosis, both with and without associated visual symptoms.

We found no statistically significant differences in macular thickness (MT) when comparing study participants diagnosed with stroke to stroke-free controls. While a larger study of similar design might have uncovered associations between MT and stroke risk owing to greater statistical power [19], our results are consistent with previously published findings of inner retinal thinning in the macular region [33]. In its totality, available evidence suggests that the most of thinning associated with neurovascular injury occurs in the inner retina [9-11,19,26,27,34]. This may represent embryological and pathophysiological differences between the inner and outer retina, resulting in the latter displaying greater similarity to cerebral parenchyma and higher vulnerability to neurovascular injury. Additional studies, both clinical and preclinical are warranted to further elucidate the underlying biological pathways.

Our study had several strengths, including prospective enrollment of highly characterized stroke cases and stroke-free controls. Owing to the availability of detailed information on medical history, vision history, and neuroimaging we were able to test associations between retinal measures and stroke risk among individuals with and without associated visual symptoms. This allowed for exploration of retinal OCT measurements both dependently and independently of direct neuronal visual pathway injuries. We also employed standardized capture and processing of OCT imaging, resulting in availability of high-quality data for the overwhelming majority of study participants. As a result, we were also able to investigate the relevance of regional retinal measurements in determining stroke risk, as compared to averages. This information will be directly informative and crucial for the design of future studies. We must also acknowledge several key limitations of our study. We sought to conduct a pilot study, and accordingly enrolled a small sample size. As a result, we cannot reach definitive conclusions on the associations identified. We were also unable (due to limited statistical power) to combine different OCT measurements (i.e. GCL, RNFL, and MT) to identify retinal imaging "profiles" associated with stroke risk. Finally, our inclusion of survivors of both ischemic and hemorrhagic stroke introduced some degree of heterogeneity given differences in underlying pathophysiology. However, we did not identify substantial heterogeneity in the associations of retinal imaging markers with stroke risk due to subtype, an insight which will be valuable in designing future studies. Indeed, our study will be able to provide crucial guidance for the design and conduct of future investigations aimed at addressing these scientific knowledge gaps.

Conclusion

In summary, in this pilot study we identified associations between OCT retinal imaging measurements and stroke risk. These associations persisted after adjustment for established stroke risk factors, and relevant to survivors of stroke with and without residual visual symptoms. We advocate for the design and conduct of larger studies aimed at validating our findings, potentially employing large sample sizes and advanced analytical techniques to refine diagnostic performance for acute stroke. A large, prospective longitudinal study employing serial OCT imaging to potentially predict future stroke risk would be particularly important to advance current public health policies and clinical care paradigms.

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Conflict of Interest

None of the authors have any conflicts of interest to report.

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