

Retinal Layer Thickness and Volume Measurements in Traumatic Brain Injury

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Abstract

Purpose: To assess retinal layer thickness and volume by optical coherence tomography (OCT) in patients with prior traumatic brain injury (TBI). **Methods:** Adults (≥ 18 years) with prior TBI were prospectively recruited. 512 $\times$ 128-mm macular cube scans were obtained using Zeiss Cirrus HD-5000 OCT. The previously validated Duke Reading Center's DRCVisualizer semiautomatically segmented (manually corrected) the ganglion cell-inner plexiform (GC-IPL), inner nuclear (INL), outer plexiform (OPL), outer nuclear (ONL), photoreceptors, and retinal pigment epithelium (RPE) layers. Mean thickness and volume were obtained within 3- and 6-mm ETDRS perifoveal rings. Individuals were age- and sex-matched (± 5 years) with controls. **Results:** Thirty-eight patients with TBI (66 eyes; mean $\pm$ SD age 45 ± 19 years) and 37 controls (66 eyes; age 44 ± 18 years) were enrolled. Time from TBI to imaging was a mean $\pm$ SD 136 ± 89 weeks. TBI was categorized by severity (mild without loss of consciousness [LOC] [$n = 25$], mild with LOC [$n = 35$], moderate [$n = 6$]) and injury mechanism (nonpenetrating contact [$n = 54$], acceleration-deceleration [$n = 12$]). Mean GC-IPL was significantly decreased and mean OPL thickness and volume were significantly increased in male TBI patients vs controls. Eyes with moderate TBI had significantly increased mean neurosensory retina, INL, OPL, and RPE thickness and volume vs other TBI severity groups. Eyes with nonpenetrating contact TBI had significantly increased mean neurosensory retina and ONL thickness and volume vs eyes with acceleration-deceleration TBI. All eyes showed a significant correlation for decreasing mean GC-IPL thickness and volume with time from TBI to imaging. **Conclusions:** TBI may impact thickness and volume of the retinal layers, and changes may be progressive over time.

Keywords

traumatic brain injury, retina, neurodegenerative diseases

Introduction

Traumatic brain injury (TBI) is among the leading causes of trauma-related morbidity and mortality worldwide each year.^{1,2} TBI poses a serious health problem: the number of emergency room visits, hospitalizations, and deaths attributed to fall-related TBI in older adults continues to increase yearly.³ Furthermore, the costs associated with TBI can be a large economic burden on healthcare systems. In the United States, overall healthcare costs attributed to nonfatal TBI in 2016 alone were estimated at \$40.6 billion.⁴ It is becoming increasingly important to understand the natural progression of this condition and identify biomarkers that could facilitate timely and cost-effective interventions.

The chronic neurodegenerative findings associated with TBI have become a crucial area of study in this regard. TBI has several neuropathologic consequences, including cerebral hypoperfusion, ischemia, hypoxia, hemorrhage, blood-brain barrier disruption, cerebral edema, and diffuse axonal injury.^{5–7} Ocular neural pathways may serve as a useful surrogate marker for

overarching neurodegenerative changes and cognitive decline.^{8,9} Optical coherence tomography (OCT) has been an effective, noninvasive tool for assessing retinal changes in neurodegenerative conditions.^{10,11} Past studies using OCT have shown that TBI patients may demonstrate significant thinning of the retinal nerve fiber layer (RNFL), even several months after injury.^{12–14} These findings suggest that RNFL thinning

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may serve as a useful biomarker for detection of TBI-associated neurodegeneration.

Few studies have investigated alterations in other retinal layers that may occur after TBI. Changes to the outer nuclear layer (ONL)¹⁵ in experimental animal models and ganglion cell layer (GCL)¹⁶ in human subjects have been reported after TBI. Other studies assessing patients with neurodegenerative disease, cognitive decline, and cerebral atrophy have also noted overall thinning of inner retinal layers, such as the inner plexiform layer (IPL), and thickening of outer retinal layers, such as the retinal pigment epithelium (RPE).^{10,17–19} Examining these retinal layers in human subjects with prior TBI may provide more insight into additional potential retinal imaging biomarkers.

Therefore, the objective of our study was to investigate differences in retinal layer thickness and volume in patients with prior TBI compared with age- and sex-matched control subjects without TBI. We also examined how the time from TBI to retinal imaging and the mechanism and severity of TBI may impact retinal layer morphology.

Methods

Ethics and Consent

This study was approved by the Duke University Health System (DUHS) institutional review board (protocol Pro00111831). Study activities adhered to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Written informed consent was obtained from all eligible individuals before enrollment.

Recruitment and Classification

This was a cross-sectional study of patients age 18 years or older who were diagnosed with TBI and evaluated in adult neurology, sports concussion, and neuro-ophthalmology clinics within DUHS in Durham, North Carolina. A retrospective electronic health record review was conducted using the Duke Enterprise Data Unified Content Explorer (DEDUCE) to identify all patients who were diagnosed as having TBI on the basis of ICD-10 diagnosis codes (S06.0X1; S06.0X2; S06.0X3; S06.0X4) from January 1, 2018 to March 1, 2024. Patients were then contacted by email and/or telephone to gauge study interest. Those providing consent were prospectively enrolled. Patient demographics, including age, sex, and years of education, were collected. Additional information included prior neuroimaging with computed tomography and/or magnetic resonance imaging, history of migraines and/or posttraumatic stress disorder, and number of prior concussions.

Each patient was assigned a TBI severity grade based on the Veterans Affairs TBI severity criteria,²⁰ using categories of mild, moderate, or severe. The mild TBI group was subdivided into categories of mild without loss of consciousness (LOC) and mild with LOC, because LOC has been found to increase the risk of subsequent dementia and result in delayed functional outcomes.^{21,22} TBI was also classified based on the mechanism of injury, in accordance with the American Psychiatric Association

guidelines,²³ with categories of nonpenetrating contact injury or acceleration-deceleration injury.

Age- and sex-matched control subjects with normal cognition and without a history of TBI, migraine, or posttraumatic stress disorder were enrolled. Controls were recruited from the Duke Eye Multimodal Imaging in Neurodegenerative Disease database of patients. Control subjects were age matched to TBI patients within ± 5 years.

Exclusion Criteria

Patient were excluded if they were younger than age 18 years, had a history of penetrating head trauma, Alzheimer's disease, Parkinson's disease, non-Alzheimer's disease dementia, or other preexisting cognitive disorder not related to TBI, or had a current diagnosis of bipolar or psychotic disorder. Those with a secondary brain injury related to alcohol or drug consumption, anoxia, or nontraumatic causes were also excluded. Those with nonpenetrating ocular injury, diabetes mellitus, uncontrolled hypertension, glaucoma, optic neuropathy, any vitreoretinal disorder, best corrected distance visual acuity (BCVA) worse than 20/40, or a refractive error greater than +6 or lower than -6 D were excluded. Any patient with a history of intraocular surgery, other than cataract or refractive surgery, was excluded. If only 1 eye satisfied the inclusion criteria, only that eye was included.

Data Collection

This study used a research and imaging protocol similar to that used in prior studies assessing chronic neurodegenerative disease.^{24,25} At the initial study visit, each participant's BCVA was measured, and a Mini-Mental State Examination (MMSE) score was obtained.

Recruited individuals were imaged by trained study staff using Zeiss Cirrus HD-5000 Spectral-Domain OCT with AngioPlex (version 11.0.0.29946, Carl Zeiss Meditec). Images were assessed for quality, and our prior quality criteria²⁵ were used to exclude poor quality images. We then exported 512×128 macular cube scans. These scans were imported into DRCVisualizer (version number 2.1.1, Duke Reading Center), a previously validated software for segmenting retinal layers.^{26,27} The software resized each image to a fixed resolution. To minimize the impact of ocular magnification from axial length variations, eyes with spherical equivalents greater than 6D were excluded. The impact of axial length below a spherical equivalent of 6D has been shown to be minimal.²⁸ The following retinal layers were then automatically segmented for each OCT scan: neurosensory retina, ganglion cell and inner plexiform layer (GC-IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), photoreceptors layer, and RPE.

After automatic segmentation of the retinal layers, 2 trained readers (N.K. and S.D.P.) reviewed each scan and made manual corrections to segmentation errors, with input from a third adjudicator (D.S.G. or S.C.) as indicated. Measurements of mean thickness (in micrometers) and volume (in cubic millimeters) were exported and reported within the central 1-mm subfield and 3- and

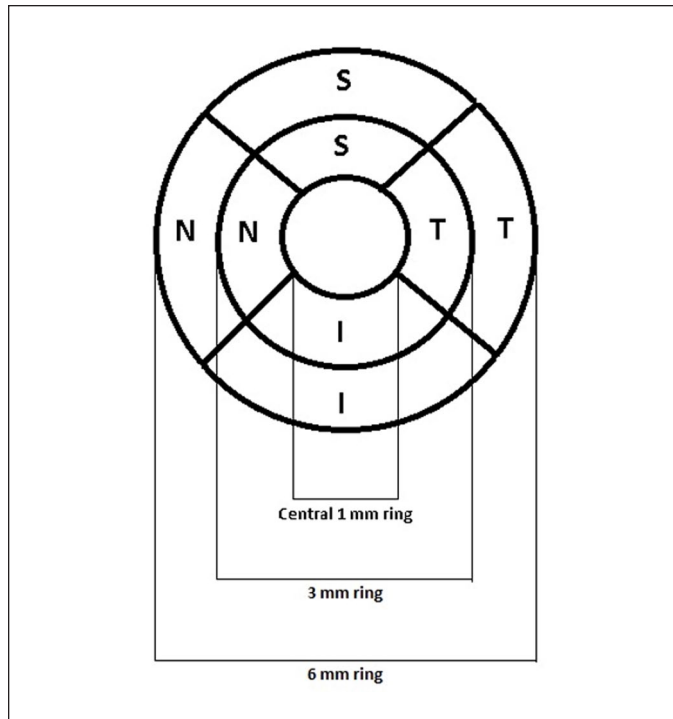


Figure 1. Areas of measurements of retinal thickness and volume on optimal coherence tomography, including the central 1-mm ring, and 3-mm and 6-mm ETDRS perifoveal rings, divided into superior (S), temporal (T), inferior (I), and nasal (N) quadrants.

6-mm perifoveal ETDRS rings. The 3- and 6-mm perifoveal rings were further subdivided into superior, temporal, inferior, and nasal quadrants (Figure 1). Thickness and volume measurements obtained within these quadrants were also collected.

Statistical Analysis

Data analysis was generated using SAS/STAT software, version 9.4 (SAS Institute). Group comparisons of demographics, using patient-level data, were assessed using the Wilcoxon rank-sum test for continuous data and Fisher exact test for categorical data. Continuous outcomes (in the eyes) were compared across groups using the Z-test of difference in mean values between groups, with generalized estimating equations and an exchangeable correlation structure. BCVA was converted from Snellen VA to logMAR notation for analysis. Statistical significance was determined at an α level of .05. Mean values are $\pm$ SD. Correlations between thickness and volume measurements of retinal layers and time from TBI to retinal imaging were determined using Pearson correlation coefficients.

Results

Patient Characteristics

Overall, 66 eyes of 38 participants with TBI were included; 24 of 38 (63.2%) were female, the mean age was 44.7 ± 18.6 years, 36 patients were White (94.7%), and 2 patients (5.3%)

were Black. The mean number of years of education was 16.38 ± 2.97 years. The mean MMSE score at presentation was 29.45 ± 1.37 . Based on TBI severity grading, 25 eyes of 14 patients (37.9%) were classified as mild without LOC, 35 eyes of 20 patients (53.0%) as mild with LOC, 6 eyes of 4 patients (9.1%) as moderate, and 0 patients as severe. The mean time from TBI to OCT imaging was 953 ± 624 days. A total of 23 eyes of 13 patients (34.8%) had a concurrent diagnosis of migraines, and 9 eyes of 5 patients (13.6%) had a concurrent diagnosis of post-traumatic stress disorder. The mean SD BCVA (logMAR) of patients at presentation was 0.050 ± 0.097 (Snellen equivalent 20/20 $\pm$ 5) (Table 1).

In addition, 66 eyes of 37 age- and sex-matched control participants without any prior history of TBI were included; 23 of 37 (62.2%) were female, the mean age was 43.9 ± 17.9 years, 28 patients were White (75.7%), 6 patients were Asian (16.2%), 2 patients were Black (5.4%), and 1 patient was Latinx. The mean SD number of years of education was 17.19 ± 2.39 years. The mean SD MMSE score at presentation was 29.73 ± 0.56 . The mean SD BCVA (logMAR) at presentation was 0.019 ± 0.094 (Snellen equivalent 20/20 $\pm$ 5) (Table 1).

There were no statistically significant differences in age, sex, years of education, or MMSE scores between the TBI and control groups. There was a statistically significant difference in race distributions between the 2 groups ($P = .021$), as shown in Table 1. No significant difference in BCVA (logMAR) was noted between the TBI and control groups (Table 2).

Retinal Layer Thickness and Volume Comparisons

Overall, when comparing retinal layer thickness and volume between patients with TBI and controls, there were no statistically significant differences in the mean thickness and volume for any retinal layer, including the GC-IPL, INL, OPL, ONL, photoreceptors, RPE, and neurosensory retina.

In the eyes of female patients ($n = 41$), there were no statistically significant differences in thickness and volume for any retinal layer.

In the eyes of male patients ($n = 55$), the 1-mm central GC-IPL thickness was significantly decreased in eyes with TBI compared with controls (mean $37.21 \pm 9.74 \mu\text{m}$ vs $45.50 \pm 13.87 \mu\text{m}$), and the volume of the 1-mm central GC-IPL was also significantly decreased in eyes with TBI compared with controls (mean $0.029 \pm 0.008 \text{ mm}^3$ vs $0.036 \pm 0.011 \text{ mm}^3$) (each $P = .013$). Furthermore, the 3-mm nasal OPL thickness and volume were significantly increased (thickness, mean $36.02 \pm 9.53 \mu\text{m}$ vs $30.17 \pm 6.03 \mu\text{m}$; volume, mean $0.057 \pm 0.015 \text{ mm}^3$ vs $0.047 \pm 0.009 \text{ mm}^3$), and the 6-mm nasal OPL thickness and volume were also significantly increased (thickness, mean $28.86 \pm 3.81 \mu\text{m}$ vs $26.34 \pm 3.42 \mu\text{m}$; volume, mean $0.15 \pm 0.02 \text{ mm}^3$ vs $0.14 \pm 0.02 \text{ mm}^3$) (each $P = .031$) (Supplement A).

TBI Severity Comparisons

Eyes with moderate TBI ($n = 4$) had significantly increased 1-mm central neurosensory retina thickness and volume

Table 1. Demographic and Clinical Characteristics of Patients With Prior TBI vs Age- and Sex-Matched Controls.

Variable	TBI	Control	P ^a
Demographic			
Age			
N	38	37	
Mean $\pm$ SD (y)	44.71 $\pm$ 18.64	43.89 $\pm$ 17.91	
Median [Min, Max] (y)	45.5 [19.0, 77.0]	45.0 [19.0, 74.0]	.882
Sex, Male, n/N (%)	14/38 (36.8)	14/37 (37.8)	1.000
Race, n/N (%)			.021 ^b
White	36/38 (94.7)	28/37 (75.7)	
Black	2/38 (5.3)	2/37 (5.4)	
Latinx	0	1/37 (2.7)	
Asian	0	6/37 (16.2)	
Education			
N	37	36	
Mean $\pm$ SD (y)	16.38 $\pm$ 2.97	17.19 $\pm$ 2.39	
Median [Min, Max] (y)	16.0 [12.0, 25.0]	17.0 [12.0, 22.0]	.106
Clinical			
MMSE score			
N	38	37	
Mean $\pm$ SD	29.45 $\pm$ 1.37	29.73 $\pm$ 0.56	
Median [Min, Max]	30.0 [23.0, 30.0]	30.0 [28.0, 30.0]	.718
Time from TBI to OCT imaging			
N	36		
Mean $\pm$ SD (days)	953.2 $\pm$ 623.5		
Median [Min, Max] (days)	764.5 [264.0, 2 967.0]		
MRI, n/N (%)			
0 images	26/38 (68.4)		
1 image	10/38 (26.3)		
2 images	2/38 (5.3)		
OCT, n/N (%)			
0 images	10/38 (26.3)		
1 image	25/38 (65.8)		
2 images	3/38 (7.9)		
Migraine, n/N (%)	13/38 (34.2)		
Posttraumatic stress disorder, n/N (%)	5/38 (13.2)		
Severity of TBI, n/N (%)			
Mild with no LOC	14/38 (36.8)		
Mild with LOC	20/38 (52.6)		
Moderate	4/38 (10.5)		
Concussions, n/N (%)			
0 events	1/38 (2.6)		
1 event	29/38 (76.3)		
2 events	5/38 (13.2)		
3 events	1/38 (2.6)		
4 events	1/38 (2.6)		
5 events	1/38 (2.6)		

Abbreviations: LOC, loss of consciousness; Min, Max, minimum and maximum; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; OCT, optical coherence tomography; TBI, traumatic brain injury.

^aP value based on Wilcoxon rank-sum test for continuous variables, and Fisher exact test for categorical variables.

^bStatistically significant difference in race distributions between the 2 groups.

(thickness, mean $297 \pm 4.89 \mu\text{m}$; volume, mean $0.23 \pm 0.00 \text{ mm}^3$) when compared with eyes with mild TBI without LOC ($n = 14$; thickness, mean $278 \pm 12.3 \mu\text{m}$; volume, mean $0.22 \pm 0.01 \text{ mm}^3$) (each $P < .001$), and when compared with eyes with

mild TBI with LOC ($n = 20$; thickness, mean $277 \pm 23.4 \mu\text{m}$; volume, mean $0.22 \pm 0.02 \text{ mm}^3$) (each $P < .001$).

The 1-mm central INL thickness and volume were significantly increased in eyes with moderate TBI (thickness, mean

Table 2. Best Corrected Visual Acuity at Presentation in Patients With Prior TBI vs Age- and Sex-Matched Controls.

Variable	TBI (N = 66)	Control (N = 66)	P ^a
BCVA, mean $\pm$ SD (logmar)	0.050 $\pm$ 0.097	0.019 $\pm$ 0.094	.069
BCVA, median [Min, Max] (logmar)	0.000 [−0.097, 0.301]	0.000 [−0.097, 0.243]	

Abbreviations: BCVA, best corrected visual acuity; Min, Max, minimum and maximum; TBI, traumatic brain injury.

^aP value based on Z-test of difference between groups using generalized estimating equations to account for correlation between eyes. Differences were not statistically significant.

24.9 $\pm$ 2.94 μ m; volume, mean 0.020 $\pm$ 0.002 mm³) when compared with eyes with mild TBI without LOC (thickness, mean 20.2 $\pm$ 3.10 μ m; volume, mean 0.016 $\pm$ 0.002 mm³) (each P = .003), and when compared with eyes with mild TBI with LOC (thickness, mean 20.5 $\pm$ 4.44 μ m; volume, mean 0.016 $\pm$ 0.003 mm³) (each P = .015). Furthermore, the moderate TBI group had significantly decreased 6-mm inferior INL thickness and volume (thickness, mean 27.0 $\pm$ 2.21 μ m; volume, mean 0.14 $\pm$ 0.01 mm³) when compared with eyes with mild TBI with LOC (thickness, mean 29.8 $\pm$ 2.65 μ m; volume, mean 0.16 $\pm$ 0.01 mm³) (each P = .034).

Eyes with moderate TBI had significantly increased mean thickness and volume in the 1-mm central OPL (P = .037), 3-mm nasal OPL (P = .013), 3-mm superior OPL (P = .029), and 6-mm nasal OPL (P = .018) compared with eyes with mild TBI with LOC.

Furthermore, the moderate TBI group had significantly increased 6-mm temporal RPE thickness and volume (thickness, mean 21.7 $\pm$ 0.72 μ m; volume, mean 0.12 $\pm$ 0.00 mm³) compared with eyes with mild TBI with LOC (thickness, mean 20.2 $\pm$ 2.24 μ m; volume, mean 0.11 $\pm$ 0.01 mm³) (each P = .006) (Supplement B).

There were no statistically significant differences in the mean GC-IPL, ONL, and photoreceptor thickness and volume based on TBI severity.

TBI Mechanism Comparisons

Eyes with nonpenetrating contact TBI (n = 12) had significantly increased mean thickness and volume of the 1-mm central neurosensory retina (P = .049), 6-mm nasal neurosensory retina (P = .011), and 6-mm temporal neurosensory retina (P = .020) compared with eyes that had acceleration-deceleration contact TBI (n = 54). Eyes with nonpenetrating contact TBI had significantly increased mean thickness and volume of the 3-mm temporal ONL (P = .036), 3-mm inferior ONL (P = .009), 6-mm nasal ONL (P = .003), 6-mm temporal ONL (P = .009), and 6-mm inferior ONL (P = .002) compared with eyes that had acceleration-deceleration TBI (Supplement C).

Correlations Between Retinal Layer Thickness and Volume and Time From TBI to Imaging

Overall, there was a significant moderate negative correlation (r = −0.36, P = .004) between the mean thickness and volume of the 3-mm temporal GC-IPL and time from TBI to imaging. No

significant correlations were noted for any other retinal layers (Supplement D).

In the eyes of female participants, there was a significant moderate positive correlation (r = 0.33, P = .04) between the mean thickness and volume of the 6-mm temporal neurosensory retina and time from TBI to imaging. There was a significant moderate positive correlation (r = 0.36, P = .02) between the mean thickness and volume of the 6-mm temporal GC-IPL and time from TBI to imaging. In addition, there was a moderate negative correlation (r = −0.33, P = .04) between the mean thickness and volume of the 6-mm temporal OPL and time from TBI to imaging (Supplement E). No significant correlations were noted between the mean thickness and volume of the INL, ONL, photoreceptor, and RPE layers and time from TBI to imaging.

In the eyes of male participants, there was a significant moderate negative correlation between the mean thickness and volume of the 1-mm central GC-IPL (r = −0.63, P = .002), 3-mm nasal GC-IPL (r = −0.58, P = .01), 3-mm superior GC-IPL (r = −0.64, P = .002), 3-mm temporal GC-IPL (r = −0.69, P = .001), 3-mm inferior GC-IPL (r = −0.63, P = .002), 6-mm nasal GC-IPL (r = −0.44, P = .04), 6-mm superior GC-IPL (r = −0.48, P = .03), and 6-mm temporal GC-IPL (r = −0.44, P = .05) and time from TBI to imaging. In addition, there was a significant moderate positive correlation between the mean thickness and volume of the 6-mm temporal OPL (r = 0.49, P = .03) and 6-mm inferior OPL (r = 0.55, P = .01) and time from TBI to imaging (Supplement F). No significant correlations were noted between the mean thickness and volume of the neurosensory retina, INL, ONL, photoreceptor, and RPE layers and time from TBI to imaging.

Correlation analyses according to TBI severity group showed that in eyes with mild TBI without LOC, there was a significant moderate positive correlation between the mean thickness and volume of the 6-mm superior GC-IPL (r = 0.50, P = .01) and time from TBI to imaging. In these patients, there were significant moderate positive correlations between the mean thickness and volume of the 3-mm superior INL (r = 0.72, P < .001), 6-mm nasal INL (r = 0.51, P = .01), and 6-mm temporal INL (r = 0.49, P = .02) and time from TBI to imaging (Supplement G). In this group, no significant correlations were noted between the mean thickness and volume of the neurosensory retina, ONL, OPL, photoreceptor, and RPE layers and time from TBI to imaging.

In eyes with mild TBI with LOC, there was a significant moderate negative correlation between the mean thickness and volume of the 6-mm nasal neurosensory retina (r = −0.63, P = .002) and time from TBI to imaging. In this same group, there were significant moderate negative correlations between the mean

thickness and volume of the 3-mm nasal GC-IPL ($r = -0.42$, $P = .01$), 3-mm temporal GC-IPL ($r = -0.48$, $P = .01$), and 3-mm inferior GC-IPL ($r = -0.35$, $P = .05$) and time from TBI to imaging (Supplement H). In this group, no significant correlations were noted between the mean thickness and volume of the INL, ONL, OPL, photoreceptor, and RPE layers and time from TBI to imaging.

In eyes with moderate TBI, there were significant strong negative correlations between the mean thickness and volume of the 3-mm temporal OPL ($r = -0.82$, $P = .05$), 3-mm inferior OPL ($r = -0.94$, $P = .01$), and 6-mm inferior OPL ($r = -0.92$, $P < .01$) and time from TBI to imaging (Supplement I). In this group, there were no significant correlations noted between the mean thickness and volume of the neurosensory retina, GC-IPL, INL, ONL, photoreceptors, and RPE layers and time from TBI to imaging.

Correlation analyses according to mechanism of TBI injury showed that eyes with nonpenetrating contact TBI had significant moderate negative correlations between the mean thickness and volume of the 3-mm temporal GC-IPL ($r = -0.42$, $P = .002$) and 3-mm inferior GC-IPL ($r = -0.29$, $P = .04$) and time from TBI to imaging (Supplement J). In this group, no significant correlations were noted between the mean thickness and volume of the neurosensory retina, INL, ONL, OPL, photoreceptors, and RPE layers and time from TBI to imaging.

Eyes with acceleration-deceleration TBI had significant moderate positive correlations between the mean thickness and volume of the 3-mm superior OPL ($r = 0.74$, $P = .01$) and 6-mm superior OPL ($r = 0.61$, $P = .04$) and time from TBI to imaging (Supplement K). In this group, no significant correlations were noted between the mean thickness and volume of the neurosensory retina, INL, ONL, photoreceptors, and RPE layers and time from TBI to imaging.

Conclusions

In this cross-sectional study comparing eyes of patients with prior TBI with eyes of age- and sex-matched control subjects without prior TBI, we noted significant differences in the mean retinal layer thickness and volume based on sex, TBI severity, and mechanism of TBI injury. These changes overall suggest that retinal layer morphology may function as a useful biomarker in diagnosing and monitoring the eye health of TBI patients.

No significant differences in the mean retinal thickness and volume were seen in all eyes of TBI patients when compared with all eyes of control subjects. When categorized by sex, eyes of male TBI patients demonstrated decreased mean thickness and volume of the GC-IPL and increased mean thickness and volume of the OPL. Moreover, eyes of male patients demonstrated a significant correlation of decreasing mean thickness and volume of the GC-IPL with time from TBI to imaging. Prior studies have noted a decrease in RNFL and loss of GCL after TBI.^{12–14,16,29} A study conducted among veterans found that those with mild TBI had OCT evidence of RNFL thinning

over time.¹⁴ The pathophysiology of neural cell loss after TBI has been elucidated.^{30,31} The initial impact from TBI can lead to mechanical damage from shearing, tearing, and/or stretching of neurons, axons, glia, and blood vessels. There is also a secondary wave of biochemical cascades that can consist of excitotoxicity, oxidative stress, mitochondrial dysfunction, blood-brain barrier disruption, and inflammation.³² These processes may explain the correlation of GC-IPL structural loss with length of time since the occurrence of the TBI.

In the eyes of male patients with prior TBI, a significant correlation was observed between increasing mean OPL thickness and volume and time from TBI to imaging. Outer retinal layer thickening after TBI has been previously described. One study involving veterans with a history of blast-induced mild TBI noted thickening of the outer retinal layers on OCT scans, including the ONL.³³ Another study examining retinas in rat models found increased retinal thickness after blast-induced TBI, particularly in outer retinal layers. The thickening was attributed to inflammation, including increased expression of inflammatory chemokines and cytokines such as inducible nitric oxide synthase and aquaporin-4.¹⁵ Inflammatory changes in the outer retinal layers of male patients after TBI may explain our findings.

The eyes of female patients with prior TBI, in contrast, did not show significant differences in mean retinal thickness and volume compared with controls. One theory for sex-based differences in response to TBI includes the functioning of mitochondria after cellular injury.³⁴ Past TBI studies have noted that mitochondria in female patients have reportedly more efficient oxidative phosphorylation³⁵ and lower oxidative stress, owing to greater expression and activity of antioxidant enzymes compared with the mitochondria of male patients.³⁶ Another proposed theory is that female hormones may have a neuroprotective role after TBI.³⁷ In addition, one published review, which compiled several large studies enrolling more than 10 000 TBI patients, showed that 67% of the included studies demonstrated better functional outcomes in the eyes of female patients compared with male patients after TBI.³⁴ These factors may offer an explanation for the lack of significant differences in retinal thickness and volume in female patients with prior TBI compared with controls.

TBI severity also impacted retinal layer morphology in our study. Eyes with moderate TBI had significantly increased mean thickness and volume of the INL, OPL, neurosensory retina, and RPE compared with eyes with TBI of milder severity levels. Furthermore, eyes with moderate TBI showed a significant correlation of decreasing thickness and volume of the OPL with time from TBI to imaging. The previously mentioned study of the retina in rat models found that outer retinal layers were thickened due to increased expression of chemokines and cytokines; furthermore, this correlated with the severity of blast-induced TBI.¹⁵ We postulate that the increased retinal layer thickness and volume seen in eyes with moderate TBI may be attributable to an elevated inflammatory response that subsides with time, as demonstrated by the decreasing mean

thickness and volume of the OPL with time from TBI to imaging in our study.

Eyes with mild TBI with LOC showed a significant correlation of decreasing mean thickness and volume of the neurosensory retina and GC-IPL with time from TBI to imaging. Interestingly, among patients with mild TBI without LOC, there was a significant correlation of increasing mean GC-IPL thickness and volume with time from TBI to imaging. A systematic review of patients with mild TBI found that while there was decreased thickness of the RNFL, no change was seen in the ganglion cell layer.¹³ In prior reports, it has been noted that there are variations in RNFL changes seen in patients with mild TBI, including decreased RNFL thickness over time in some patients but also increased RNFL thickness over time observed in other patients.¹⁴ Our study also noted variations in neuronal layer changes in patients with mild TBI over time, but our findings were noted in the GC-IPL layer as opposed to the RNFL. The GC-IPL region consists of glial cells and axons. Axons can be dynamic and change volume by the level of axoplasmic flow,^{38–40} which potentially explains the opposing trends in GC-IPL thickness and volume with time in the mild TBI with LOC vs mild TBI without LOC group. Furthermore, reactive gliosis occurs after TBI and may be increased based on the severity of TBI.⁴¹ Glial scars are known to inhibit axonal regeneration⁴² and may explain why the more severe TBI group (mild with LOC), with likely greater reactive gliosis and resulting glial scarring, showed a correlation of decreasing GC-IPL with time after TBI.

The mechanism of TBI injury also impacted retinal morphology. Nonpenetrating contact TBI was associated with significantly increased mean neurosensory retina and ONL thickness and volume compared with that in the group with acceleration-deceleration TBI. The literature has noted increased outer retinal thickness in closed globe injury.^{43,44} However, some studies have noted thickening of outer retinal layers in acceleration-deceleration injuries as well.⁴⁵ The acceleration-deceleration group in our study demonstrated a significant correlation of increasing mean OPL thickness and volume with time from TBI to imaging. An explanation for these findings involves the unique inflammatory mediators that are released during TBI events. In mouse models, there has been increased expression of interleukin-6 observed after acceleration-deceleration injury.⁴⁶ Interleukin 6 is a cytokine that has been implicated in inflammation of the inner and outer retinal layers.⁴⁷ Other cytokines and chemokines, similar to interleukin-6, may play roles in the differences in retinal morphology observed between different mechanisms of TBI.

Eyes with nonpenetrating contact TBI showed a significant correlation of decreasing GC-IPL thickness and volume with time from TBI to imaging. One study of patients following closed globe injury noted reductions in the ganglion cell layer after injury, with an average follow-up time of 8 years.⁴⁸ Direct contact injury can cause neuronal cells to undergo apoptosis

and necrosis.⁴⁹ Furthermore, degenerating oligodendrocytes and astrocytes have been observed within injured white matter tracts.⁵⁰ Other mechanisms for cell injury involve excitatory amino acids, increased intracellular calcium, increased free radical production, and/or a shift in the balance between pro- and anti-apoptotic protein factors.⁴⁹ Thus, it becomes important to monitor patients with nonpenetrating contact injury for long-term changes in neuronal cell layers.

Our study has some limitations to note. This was a cross-sectional study with a limited sample size of participants. Furthermore, the racial composition of our study population was primarily White, which limits the applicability of conclusions to other non-White populations. We also obtained images of each patient at different time points after their injury. We strived to address this limitation by looking at correlations between mean thickness and volume of retinal layers based on time from TBI to imaging. However, a longitudinal study of retinal morphologic changes over time in the same patient eye requires further investigation. Additionally, there are inherent limitations with the retinal layer analysis software used. Though this previously validated software semiautomatically segmented retinal layers, each scan still required manual correction from trained graders, which introduces variability. Finally, functional outcomes such as quality of life metrics were not investigated.

Overall, this study demonstrates that patients with prior TBI may have progressive changes in retinal architecture after the injury. These findings may be impacted by sex, TBI severity, and the mechanism of TBI injury. Larger cohort studies with more diverse patient populations are needed to further investigate these findings. Retinal layer morphologic changes after TBI may serve as a useful biomarker to determine patients' long-term prognosis and individualize their care. Further research investigating vision-based quality of life metrics may add insight^{50–52} and help develop predictive models of functional outcomes. With these interventions, we can strive to address the short- and long-term impact that TBI may have on the retina.

Ethical Approval

This study was reviewed and approved by the institutional review board at Duke University Health System, and is registered with ClinicalTrials.gov (NCT03233646). All study activities adhered to the tenets of the Declaration of Helsinki and to regulations outlined in the US Health Insurance Portability and Accountability Act.

Statement of Informed Consent

All patients provided written informed consent, including permission for publication.

Declaration of Conflicting Interests

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental Material

Supplemental material is available online with this article.

References

- Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. 2018;130(4):1080-1097. doi:10.3171/2017.10.JNS17352
- GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):56-87. doi:10.1016/S1474-4422(18)30415-0
- Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66(9):1-16. doi:10.15585/mmwr.ss6609a1
- Miller GF, DePadilla L, Xu L. Costs of nonfatal traumatic brain injury in the United States, 2016. *Med Care*. 2021;59(5):451-455. doi:10.1097/MLR.0000000000001511
- Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. *J Cereb Blood Flow Metab*. 2017;37(7):2320-2339. doi:10.1177/0271678X17701460
- Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013;246:35-43. doi:10.1016/j.expneurol.2012.01.013
- Chen XH, Johnson VE, Uryu K, Trojanowski JQ, Smith DH. A lack of amyloid beta plaques despite persistent accumulation of amyloid beta in axons of long-term survivors of traumatic brain injury. *Brain Pathol Zurich Switz*. 2009;19(2):214-223. doi:10.1111/j.1750-3639.2008.00176.x
- Chen S, Zhang D, Zheng H, et al. The association between retina thinning and hippocampal atrophy in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review. *Front Aging Neurosci*. 2023;15:1232941. doi:10.3389/fnagi.2023.1232941
- Murueta-Goyena A, Romero-Bascones D, Teijeira-Portas S, et al. Association of retinal neurodegeneration with the progression of cognitive decline in Parkinson's disease. *NPJ Park Dis*. 2024;10(1):1-10. doi:10.1038/s41531-024-00637-x
- Wagner SK, Romero-Bascones D, Cortina-Borja M, et al. Retinal optical coherence tomography features associated with incident and prevalent Parkinson disease. *Neurology*. 2023;101(16):e1581-e1593. doi:10.1212/WNL.000000000000207727
- Mejia-Vergara AJ, Restrepo-Jimenez P, Pelak VS. Optical coherence tomography in mild cognitive impairment: a systematic review and meta-analysis. *Front Neurol*. 2020;11:578698. doi:10.3389/fneur.2020.578698
- Kumar Das N, Das M. Structural changes in retina (Retinal nerve fiber layer) following mild traumatic brain injury and its association with development of visual field defects. *Clin Neurol Neurosurg*. 2022;212:107080. Accessed June 12, 2024. <https://pubmed.ncbi.nlm.nih.gov/34883282/>
- Lyons HS, Sassani M, Hyder Y, et al. A systematic review of optical coherence tomography findings in adults with mild traumatic brain injury. *Eye*. 2024;38(6):1077-1083. doi:10.1038/s41433-023-02845-w
- Gilmore CS, Lim KO, Garvin MK, et al. Association of optical coherence tomography with longitudinal neurodegeneration in veterans with chronic mild traumatic brain injury. *JAMA Netw Open*. 2020;3(12):e2030824. doi:10.1001/jamanetworkopen.2020.30824
- Zou YY, Kan EM, Lu J, et al. Primary blast injury-induced lesions in the retina of adult rats. *J Neuroinflammation*. 2013;10:79. doi:10.1186/1742-2094-10-79
- Hepschke JL, Laws E, Bin Saliman NH, et al. Modifications in macular perfusion and neuronal loss after acute traumatic brain injury. *Invest Ophthalmol Vis Sci*. 2023;64(4):35. doi:10.1167/iovs.64.4.35
- Garzone D, Finger RP, Mauschitz MM, Santos MLS, Breteler MMB, Aziz NA. Neurofilament light chain and retinal layers' determinants and association: a population-based study. *Ann Clin Transl Neurol*. 2022;9(4):564-569. doi:10.1002/acn3.51522
- Mutlu U, Bonnemaier PWM, Ikram MA, et al. Retinal neurodegeneration and brain MRI markers: the Rotterdam Study. *Neurobiol Aging*. 2017;60:183-191. doi:10.1016/j.neurobiolaging.2017.09.003
- Ward DD, Mauschitz MM, Bönninger MM, Merten N, Finger RP, Breteler MMB. Association of retinal layer measurements and adult cognitive function: a population-based study. *Neurology*. 2020;95(9):e1144-e1152. doi:10.1212/WNL.00000000000010146
- O'Neil ME, Carlson K, Storzbach D, et al. Definition of mTBI from the VA/DOD clinical practice guideline for management of concussion/mild traumatic brain injury (2009). In: Kansagara D (ed.) *Complications of Mild Traumatic Brain Injury in Veterans and Military Personnel: A Systematic Review*. Department of Veterans Affairs (US); 2013. Accessed June 14, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK189784/>
- Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75(9):1055-1061. doi:10.1001/jamaneurol.2018.0815
- Roy D, Peters ME, Everett AD, et al. Loss of consciousness and altered mental state as predictors of functional recovery within 6 months following mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2020;32(2):132-138. doi:10.1176/appi.neuropsych.18120379
- Textbook of Traumatic Brain Injury. Books. 2005. Accessed June 14, 2024. <https://psychiatryonline.org/doi/book/10.1176/appi.books.9781615372645>

24. Yoon SP, Thompson AC, Polascik BW, et al. Correlation of OCTA and volumetric MRI in mild cognitive impairment and Alzheimer's disease. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50(11):709-718. doi:10.3928/23258160-20191031-06
25. Robbins CB, Thompson AC, Bhullar PK, et al. Characterization of retinal microvascular and choroidal structural changes in Parkinson disease. *JAMA Ophthalmol*. 2021;139(2):182-188. doi:10.1001/jamaophthalmol.2020.5730
26. Lee JY, Chiu SJ, Srinivasan PP, et al. Fully automatic software for retinal thickness in eyes with diabetic macular edema from images acquired by cirrus and spectralis systems. *Invest Ophthalmol Vis Sci*. 2013;54(12):7595-7602. doi:10.1167/iovs.13-11762
27. Chiu SJ, Li XT, Nicholas P, Toth CA, Izatt JA, Farsiu S. Automatic segmentation of seven retinal layers in SDOCT images congruent with expert manual segmentation. *Opt Express*. 2010;18(18):19413-19428. doi:10.1364/OE.18.019413
28. Sampson DM, Gong P, An D, et al. Axial length variation impacts on superficial retinal vessel density and foveal avascular zone area measurements using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2017;58(7):3065-3072. doi:10.1167/iovs.17-21551
29. Kelman JC, Hodge C, Stanwell P, Mustafic N, Fraser CL. Retinal nerve fibre changes in sports-related repetitive traumatic brain injury. *Clin Experiment Ophthalmol*. 2020;48(2):204-211. doi:10.1111/ceo.13673
30. Lozano D, Gonzales-Portillo GS, Acosta S, et al. Neuroinflammatory responses to traumatic brain injury: etiology, clinical consequences, and therapeutic opportunities. *Neuropsychiatr Dis Treat*. 2015;11:97-106. doi:10.2147/NDT.S65815
31. Adams JH, Graham DI, Gennarelli TA. Head injury in man and experimental animals: neuropathology. *Acta Neurochir Suppl (Wien)*. 1983;32:15-30. doi:10.1007/978-3-7091-4147-2_2
32. Kabadi SV, Faden AI. Neuroprotective strategies for traumatic brain injury: improving clinical translation. *Int J Mol Sci*. 2014;15(1):1216-1236. doi:10.3390/ijms15011216
33. Fortenbaugh F, Gustafson J, Zuberer A, et al. Retinal structural changes associated with blast-induced mild traumatic brain injury identified on OCT imaging. *Invest Ophthalmol Vis Sci*. 2021;62(8):2515.
34. Gupte R, Brooks W, Vukas R, Pierce J, Harris J. Sex differences in traumatic brain injury: what we know and what we should know. *J Neurotrauma*. 2019;36(22):3063-3091. doi:10.1089/neu.2018.6171
35. Guevara R, Gianotti M, Oliver J, Roca P. Age and sex-related changes in rat brain mitochondrial oxidative status. *Exp Gerontol*. 2011;46(11):923-928. doi:10.1016/j.exger.2011.08.003
36. Borrás C, Sastre J, García-Sala D, Lloret A, Pallardó FV, Viña J. Mitochondria from females exhibit higher antioxidant gene expression and lower oxidative damage than males. *Free Radic Biol Med*. 2003;34(5):546-552. doi:10.1016/s0891-5849(02)01356-4
37. Roof RL, Duvdevani R, Stein DG. Gender influences outcome of brain injury: progesterone plays a protective role. *Brain Res*. 1993;607(1-2):333-336. doi:10.1016/0006-8993(93)91526-x
38. Fry LE, Fahy E, Chrysostomou V, et al. The coma in glaucoma: retinal ganglion cell dysfunction and recovery. *Prog Retin Eye Res*. 2018;65:77-92. doi:10.1016/j.preteyeres.2018.04.001
39. Abbott CJ, Choe TE, Lusardi TA, Burgoyne CF, Wang L, Fortune B. Evaluation of retinal nerve fiber layer thickness and axonal transport 1 and 2 weeks after 8 hours of acute intraocular pressure elevation in rats. *Invest Ophthalmol Vis Sci*. 2014;55(2):674-687. doi:10.1167/iovs.13-12811
40. Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L. Onset and progression of peripapillary retinal nerve fiber layer (RNFL) retardance changes occur earlier than RNFL thickness changes in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2013;54(8):5653-5661. doi:10.1167/iovs.13-12219
41. Amlerova Z, Chmelova M, Anderova M, Vargova L. Reactive gliosis in traumatic brain injury: a comprehensive review. *Front Cell Neurosci*. 2024;18:1335849. doi:10.3389/fncel.2024.1335849
42. Wanner IB, Deik A, Torres M, et al. A new in vitro model of the glial scar inhibits axon growth. *Glia*. 2008;56(15):1691-1709. doi:10.1002/glia.20721
43. Flatter JA, Cooper RF, Dubow MJ, et al. Outer retinal structure after closed-globe blunt ocular trauma. *Retina Phila Pa*. 2014;34(10):2133-2146. doi:10.1097/IAE.0000000000000169
44. Oladiwura D, Lim LT, Ah-Kee EY, Scott JA. Macular optical coherence tomography findings following blunt ocular trauma. *Clin Ophthalmol*. 2014;8:989-992. Accessed July 18, 2024. <https://www.tandfonline.com/doi/full/10.2147/OPTH.S64082>
45. Pham TQ, Chua B, Gorbato M, Mitchell P. Optical coherence tomography findings of acute traumatic maculopathy following motor vehicle accident. *Am J Ophthalmol*. 2007;143(2):348-350. doi:10.1016/j.ajo.2006.09.024
46. Wang G, Zhang YP, Gao Z, et al. Pathophysiological and behavioral deficits in developing mice following rotational acceleration-deceleration traumatic brain injury. *Dis Model Mech*. 2018;11(1):dmm030387. doi:10.1242/dmm.030387
47. Yang JY, Goldberg D, Sobrin L. Interleukin-6 and macular edema: a review of outcomes with inhibition. *Int J Mol Sci*. 2023;24(5):4676. Accessed July 18, 2024. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10003386/>
48. Cennamo G, Forte R, Reibaldi M, Magli A, de Crecchio G, Cennamo G. Evaluation of retinal nerve fiber layer and ganglion cell complex thickness after ocular blunt trauma. *Eye*. 2013;27(12):1382-1387. Accessed July 18, 2024. <https://www.nature.com/articles/eye2013203>
49. Raghupathi R. Cell death mechanisms following traumatic brain injury. *Brain Pathol*. 2004;14(2):215-222. doi:10.1111/j.1750-3639.2004.tb00056.x
50. Kinnunen KM, Greenwood R, Powell JH, et al. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011;134(2):449-463. doi:10.1093/brain/awq347
51. Tosh J, Brazier J, Evans P, Longworth L. A review of generic preference-based measures of health-related quality of life in visual disorders. *Value Health*. 2012;15(1):118-127. Accessed July 18, 2024. <https://www.sciencedirect.com/science/article/pii/S1098301511015610>
52. Peacock S, Misajon R, Iezzi A, Richardson J, Hawthorne G, Keeffe J. Vision and quality of life: development of methods for the VisQoL vision-related utility instrument. *Ophthalmic Epidemiol*. 2008;15(4):218-223. doi:10.1080/09286580801979417