

Correlations between OCT, OCT angiography and fundus autofluorescence in adults with superficial optic disc drusen: The importance of multimodal imaging

Paulina Szabelska^{1,A–F}, Joanna Brydak-Godowska^{2,B,D,F}, Przemysław Krajewski^{2,B,F}, Radosław Różycki^{1,D,F}, Joanna Gołębiewska^{1,A,B,D–F}

¹ Department of Ophthalmology, Military Institute of Aviation Medicine, Warsaw, Poland

² Department of Ophthalmology, Infant Jesus Clinical Hospital, University Clinical Center, Medical University of Warsaw, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2025;34(11):1959–1968

Address for correspondence

Joanna Gołębiewska

E-mail: joanna.golebiewska@wp.pl

Funding sources

None declared

Conflict of interest

None declared

Received on December 5, 2024

Reviewed on January 15, 2025

Accepted on February 25, 2025

Published online on June 6, 2025

Cite as

Szabelska P, Brydak-Godowska J, Krajewski P, Różycki R, Gołębiewska J. Correlations between OCT, OCT angiography and fundus autofluorescence in adults with superficial optic disc drusen: The importance of multimodal imaging.

Adv Clin Exp Med. 2025;34(11):1959–1968.

doi:10.17219/acem/202319

DOI

10.17219/acem/202319

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Abstract

Background. Optic nerve head drusen (ONHD) are benign calcified deposits that can compress local capillaries, disrupt blood flow and potentially lead to visual loss.

Objectives. The aim of the study was to present the correlations between optical coherence tomography (OCT), OCT angiography (OCTA) results and fundus autofluorescence (FAF) findings in patients with ONHD, and to highlight the importance of multimodal imaging in the diagnosis and management of this pathology.

Materials and methods. This retrospective study included 21 patients (36 eyes) with ONHD, with a mean age of 45.75 years (range: 19–71 years), who had no other ocular pathologies. All participants underwent a full ophthalmic examination and multimodal imaging using the DRI Triton OCT (Topcon). Drusen presence was divided into quadrants based on FAF and correlated with OCT and OCTA results.

Results. Optic nerve head drusen were unilateral in 6 patients (28.57%) and bilateral in 15 (71.43%). Drusen were most common in the nasal and superior quadrants (NQ and SQ) but were significantly more frequent in the inferior (IQ) and temporal (TQ) quadrants in patients with bilateral ONHD. Eyes with drusen located in the IQ and TQ showed a significantly decreased radial peripapillary capillary (RPCP) vessel density (VD). Retinal nerve fibre layer (RNFL) measurements showed the strongest positive correlations with RPCP, especially in the IQ ($r = 0.78$, $p < 0.001$). Ganglion cell layer and nerve fiber layer (GCL++) thickness showed significant correlations with RPCP VD, particularly in the IQ and TQ ($p < 0.001$ for both).

Conclusions. Fundus autofluorescence is a valuable tool for identifying superficial drusen. Optical coherence tomography and OCTA are effective in assessing optic nerve fiber integrity and microvascular changes. Microcirculation assessment using OCTA should focus not only on the radial peripapillary capillaries (RPCP), but also on the macular region. Multimodal imaging plays a crucial role in the accurate diagnosis and comprehensive evaluation of patients with ONHD. Further longitudinal studies are needed to investigate how these correlations evolve over time, particularly in the context of ONHD progression.

Key words: optical coherence tomography, multimodal imaging, fundus autofluorescence, optic nerve head drusen, OCT angiography

Highlights

- The study confirms fundus autofluorescence (FAF) as a sensitive method for detecting superficial optic nerve head drusen (ONHD).
- Optical coherence tomography (OCT) and OCT angiography (OCTA) reveal significant optic nerve fiber and microvascular changes in ONHD.
- Reduced RPCP vessel density (VD) correlates with thinner retinal nerve fibre layer (RNFL), particularly in inferior quadrants, indicating microvascular compromise.
- Macular ganglion cell layer (GCL++) thinning suggest strong associations with superficial capillary plexus (SCP) VD in susceptible superior and inferior quadrants, what should be confirmed in future studies.
- Multimodal imaging is crucial in monitoring ONHD progression.

Background

Optic nerve drusen (OND), also known as optic nerve head drusen (ONHD) or optic disc drusen (ODD), are calcified, acellular deposits that accumulate within the optic nerve head (ONH).^{1,2} These deposits are composed of calcium, amino acids, nucleic acids, and mucopolysaccharides.²

They can be located superficially, where they are visible during an ophthalmologic examination and give the optic disc a lumpy appearance, or buried deeper in the ONH, where they may cause the disc to appear swollen and congested.^{3,4} Recent studies have confirmed that ONHD generally occupy a prelaminar location in the ONH.³ Buried ONHD creates an elevated optic nerve appearance with an irregular, scalloped border, while superficial ONHD appear as hardened yellow deposits on the surface of the optic nerve.⁴

Histological studies, like those by Tso, suggest that ONHD formation may result from disrupted axoplasmic transport, which causes mitochondria to extrude into the extracellular space.⁵ Over time, calcium deposits in the mitochondria lead to the formation of drusen, typically in front of the lamina cribrosa.⁴ Although the exact mechanism of ONHD formation remains unclear, it is thought that a small optic disc and a narrow scleral canal may contribute to their development. These anatomical features can restrict axoplasmic flow, leading to impaired transport within the optic nerve fibers and eventually causing ganglion cell axon degeneration.^{6,7}

The ONHD affect approx. 0.3–2.4% of the general population.^{3,8} They are often bilateral (in about 75% of cases), with a higher preponderance in the nasal, rather than temporal, optic disc quadrants.^{2,4} They are more common in Caucasians and may have a genetic predilection.^{9–11}

Patients with ONHD usually are asymptomatic and unaware of the condition. If occur, visual field defects are the most common symptom, observed in about 51% of children and 75% of all affected individuals, with reported rates ranging from 11.2% to 87%.¹² However, in cases

where symptoms do arise, patients reported peripheral vision loss, reduced night vision, flickering lights, flashes, or brief visual distortions, and increased blind spot size.^{13,14} In rare cases, significant loss of visual acuity can occur due to vascular complications associated with ONHD. Such complications may include secondary conditions like central retinal artery (CRAO) or vein (CRVO) occlusion, anterior ischemic optic neuropathy (AION), or the formation of choroidal neovascular membranes (CNV). These issues are often a result of mechanical pressure exerted by the drusen on nearby blood vessels.^{15,16}

Diagnosing ONHD requires a comprehensive ophthalmic examination and specialized imaging techniques. Multimodal imaging allows proper diagnosis and those used in ONHD diagnostics include, i.a., color fundus photography, fundus autofluorescence (FAF), ultrasound B-scans, optical coherence tomography (OCT), OCT Angiography (OCTA), and visual field testing.¹⁷

Fundus autofluorescence exploits the natural fluorescence emitted by certain components of the drusen, allowing them to be visualized clearly. Autofluorescence imaging is valuable for identifying superficial ONHD.^{17,18}

Optical coherence tomography is a noninvasive imaging technique that uses light waves to create cross-sectional images of the retina. This test can provide detailed images of the ONH and is particularly useful in assessing the location and extent of the drusen.¹⁷

Optical coherence tomography angiography provides detailed images of blood flow in the retina and optic nerve.¹⁹ As drusen accumulate within the ONH, they can crowd this area, compressing the small capillaries that supply blood to the optic nerve. This crowding effect, particularly when drusen are superficial or located near major vessels, can cause disturbances in local blood flow. Such compression can lead to minor ischemia in certain areas, potentially affecting nerve fibers and leading to gradual visual field loss.²⁰ OCTA can show decreased capillary density and areas of peripapillary dropout in patients with ONHD, helping to assess the extent of vascular compromise.¹⁹

Objectives

The aim of the study was to present correlations between OCT and OCTA results and fundus autofluorescence (FAF) findings in patients with superficial ONHD and highlight the importance of multimodal imaging in this pathology.

Materials and methods

This retrospective study enrolled 21 patients (36 eyes) diagnosed with ONHD who attended the Outpatient Clinic of the Military Institute of Aviation Medicine in Warsaw (Poland) between January 2019 and November 2024. The study protocol was approved by the Bioethics Committee at the Military Medical Chamber (approval No. KB 77/2024).

The inclusion criterion was a diagnosis of superficial drusen, determined by their presence observed in FAF. Exclusion criteria included a history of any retinal or choroidal pathology that could have influenced the results, such as glaucoma, diabetic retinopathy, uveitis, or a refractive error greater than ± 3.0 diopters (D).

All patients underwent a complete ophthalmic examination and multimodal imaging using swept-source DRI OCT Triton (SS-OCT; Topcon, Tokyo, Japan), which included color fundus photography, FAF, OCT, en face OCT, and OCTA. The Triton SS-OCT uses a wavelength of 1,050 nm with a scan speed of 100,000 A-scans per second. A 7.0×7.0 mm 3D macula scan centered on the fovea and a 6.0×6.0 mm 3D disc scan centered on the optic nerve head (ONH) were obtained. The RNFL and GCL++ parameters were measured automatically using the built-in OCT software. GCL++ refers to the combination of the ganglion cell layer (GCL) and the nerve fiber layer (NFL) in the macular region. The OCTA was performed using 4.5×4.5 mm images centered on the macula and ONH. Vessel density was automatically calculated by the software as a percentage, based on the area occupied by blood vessels in the superficial capillary plexus (SCP) and radial peripapillary capillaries (RPCP). Macular outcomes were measured in the fovea (0–1 mm) and parafoveally. The parafoveal area, as defined by the 3-mm partial early treatment diabetic retinopathy study (ETDRS) chart provided by the software, corresponds to the region between the 1-mm and 3-mm concentric rings centered on the fovea. This area was further divided into 4 sectors for quadrant analysis: temporal (TQ), superior (SQ), nasal (NQ), and inferior (IQ).

Eyes with low-quality scans (image quality < 60), with motion artifacts or blurred images were excluded from the final analysis.

Statistical analyses

Numerical variables were presented as their mean and standard deviation (SD) values. Categorical variables

were described through integer numbers and percentages. The Shapiro–Wilk W test was performed to verify the normality of distribution. Levene's test was fitted to assess the homogeneity of variances. A multifactor analysis of variance (ANOVA) without replications was carried out for normally distributed numerical traits with homogenic variances when estimating the significance of differences in the investigated traits by prevalence of drusen. Generalized linear models were applied otherwise, when dealing with non-normally distributed variables or heterogenic variances (normal distribution and identity link function were chosen). The parametric models were controlled for age. Their goodness-of-fit was assessed by calculating the Akaike information criterion (AIC) and Bayesian information criterion (BIC), instead of R^2 , which cannot be computed for the Generalized Linear Models used. A special correction method for p-values was used when encompassing family hypotheses if applicable. Model testing was based on one main independent (grouping) variable, i.e., the presence of drusen in the examined eyes, along with participants' age as a control variable. No explicit “family of hypotheses” was established, as the analyses consistently focused on the presence of drusen, controlled for age, and investigated separate and independent retinal areas, which did not naturally infer one another. To estimate linear relationships between pairs of numerical traits, the Pearson's product-moment correlation coefficients were computed. For discrete variables, the significance of references in frequencies were tested by using Fisher's exact test. A level of $p < 0.05$ was considered statistically significant. All the statistical procedures were performed using Statistica v. 13.3 (TIBCO Software Inc., Palo Alto, USA).

Results

The study involved 14 female and 7 male participants. The mean age of the subjects was 45.75 years (range: 19–71 years; SD = 14.81). All participants were Caucasian, in good general health, and had a best-corrected visual acuity (BCVA) ranging from 0.8 to 1.0. Intraocular pressure (IOP) was within normal limits (ranging from 12 mm Hg to 20 mm Hg) in all patients.

Patients' demographic and clinical characteristics were summarized in Table 1. The ONHD occurred unilaterally

Table 1. Demographic and clinical characteristics of patients with ONHD

Characteristics	Patients (n = 21)
Age, range [years]	19–71 (M = 45.75; SD = 14.81)
Sex, n (%)	14 female (66.67), 7 male (33.33)
Race, n (%)	21 Caucasian (100%)
BCVA, range	0.8–1.0

n – integer number, M – mean, SD – standard deviation; BVCA – best-corrected visual acuity; ONHD – optic nerve head drusen.

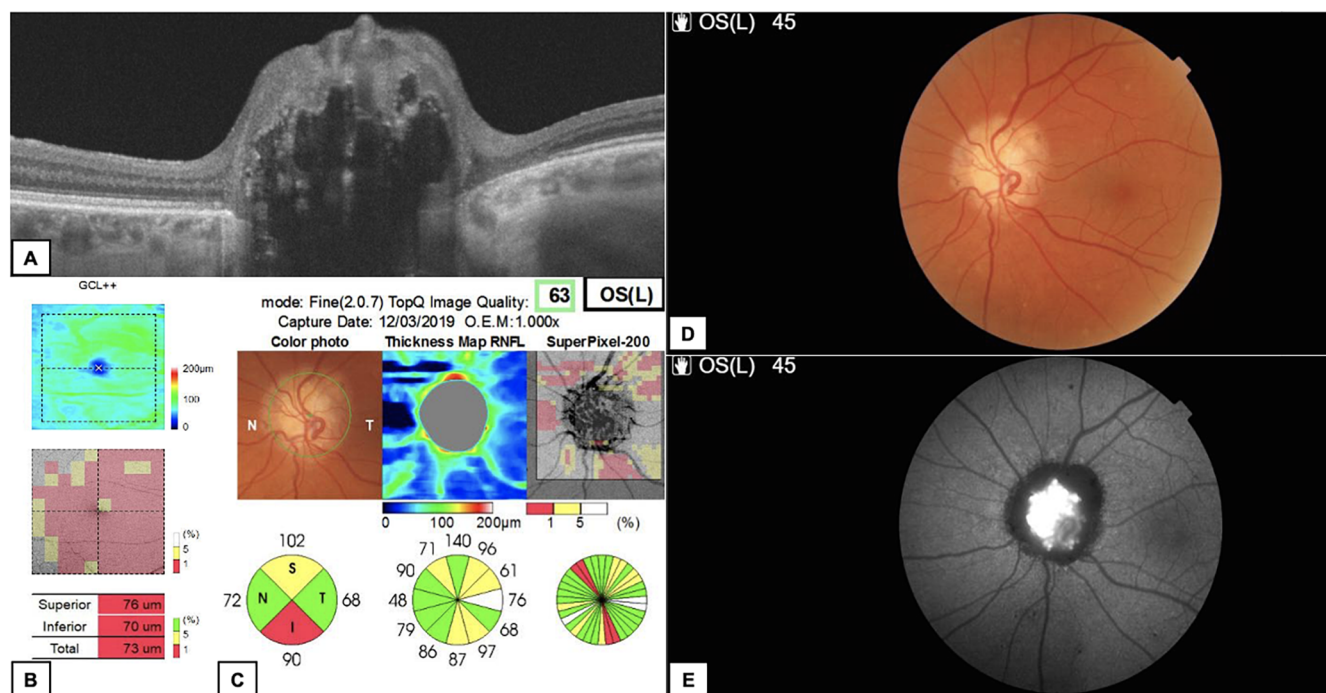


Fig. 1. Multimodal imaging of the left eye (LE) in patient with ONHD. A. SS-OCT B-scan showed hyporeflective core and hyperreflective halo around deposits visible in the ONH; B,C. Decreased RNFL in SQ and IQ and GCL++ values; D. Color fundus photography – indistinct margins and mild swelling of the ONH; E. FAF – irregular hyperautofluorescent round structures with irregular edges were observed in ONH

SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; ONHD – optic nerve head drusen.

Table 2. Baseline characteristics of the study cohort by number of eyes with ONHD

Analyzed trait	Overall	Unilateral drusen	Bilateral drusen	p-value*
Number of participants, n (%)	21 (100.00)	6 (28.57)	15 (71.43)	–
Number of eyes, n (%)	36 (100.00)	6 (16.67)	30 (83.33)	–
Drusen in quadrants, n (%)				
SQ	30 (83.33)	6 (100.00)	24 (80.00)	0.561
IQ	27 (75.00)	2 (33.33)	25 (83.33)	0.024
NQ	32 (88.89)	6 (100.00)	26 (86.67)	>0.999
TQ	15 (41.67)	0 (0.00)	15 (50.00)	0.030
Age [years], M (SD)	45.75 (14.81)	43.83 (19.97)	46.13 (13.97)	F(1,34) = 0.12 Δ = 2.30 partial $\eta^2 < 0.00$ p = 0.734 (Levene's test F(1,34) = 3.78 p = 0.060)

n – integer number, M – mean; SD – standard deviation; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; ONHD – optic nerve head drusen. * Fisher's two-sided test was performed, only p-values are presented. Values in bold are statistically significant.

in 6 (28.57%) and bilaterally in 15 patients (71.43%). Multimodal imaging findings of ONHD were presented in Fig. 1 and Fig. 2.

The FAF imaging technique was used to detect the presence of superficial drusen and to categorize them by their location into specific quadrants. Based on FAF findings, ONHD most frequently occurred in the NQ and SQ. However, we observed that ONHD in the TQ and IQ were more common in patients with bilateral drusen than in those with unilateral drusen, and the differences were statistically significant:

- for TQ ($p = 0.030$), as no eyes in the unilateral group exhibited temporal drusen, while 50% of eyes in the bilateral group did;
- for IQ ($p = 0.025$), with a higher percentage of affected eyes in the bilateral group (83.33%) compared to the unilateral group (33.33%) (Table 2).

The RNFL thickness decreased significantly with age in all quadrants except the TQ ($p = 0.362$). The GCL++ thickness also showed a decreasing trend, but without statistical significance (Table 3).

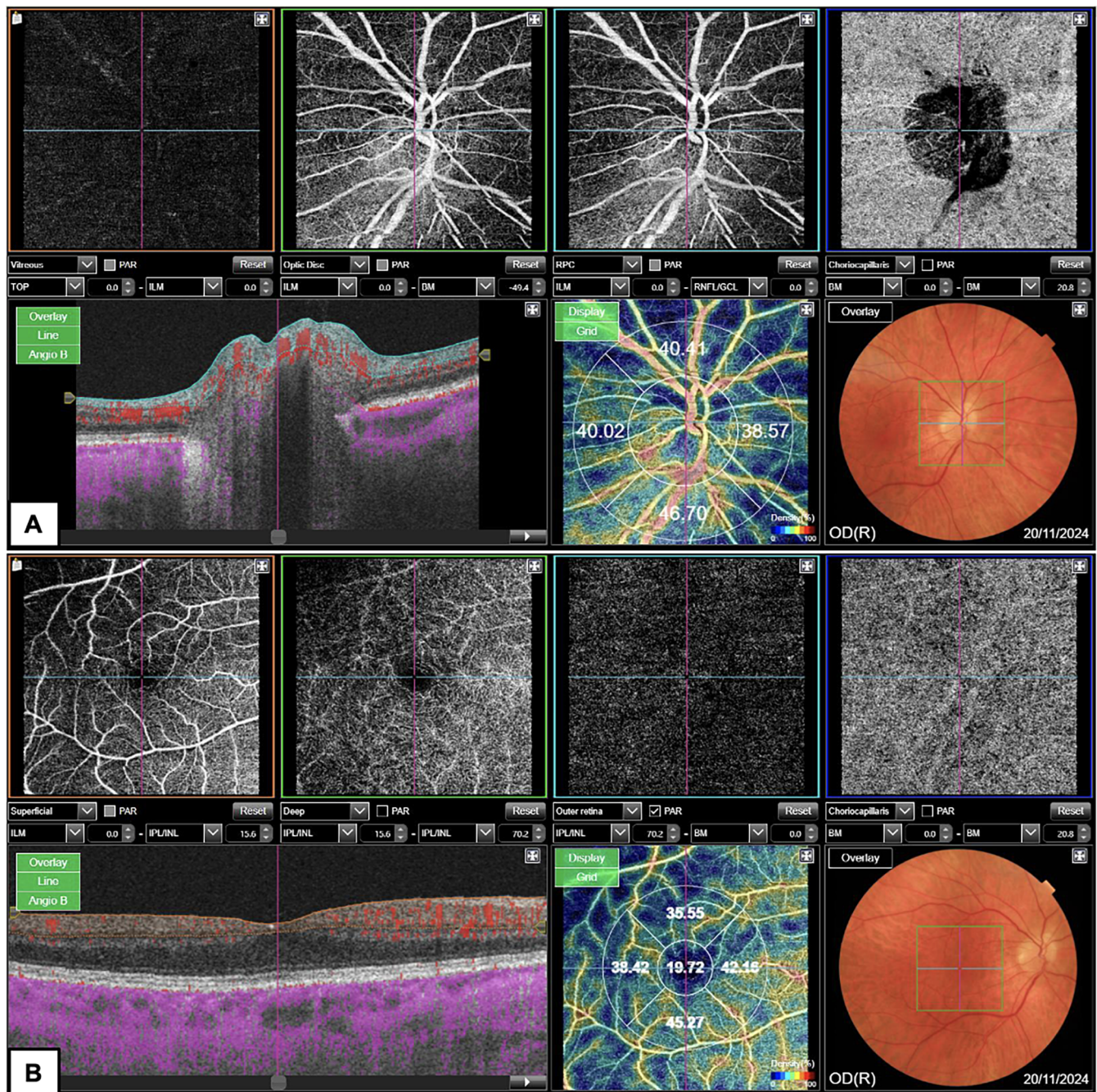


Fig. 2. OCTA of the ONH and macula in patient with ONHD (right eye (RE)). A. VD map of ONH region showed decreased RPCP density (dark blue color) in SQ and NQ; B. VD map of SCP showed decreased VD (dark blue color) in SQ, NQ and TQ of the macula

OCTA – optical coherence tomography angiography; ONH – optic nerve head; VD – vessel density; ONH – optic nerve head; RPCP – radial peripapillary capillaries; SQ – superior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; SCP – superficial capillary plexus.

Age was significantly negatively correlated with RPCP VD in the SQ, IQ, and NQ, indicating reduced capillary density in these areas. The TQ RPCP VD showed a moderate negative trend; however, it did not reach statistical significance ($p = 0.053$). Significant negative correlations were found in the IQ and TQ of SCP VD, suggesting reduced VD with age. However, foveal VD (FVD) increased significantly with age ($r = 0.38$, $p = 0.044$) (Table 4).

A comparison was made between OCTA measurements and other structural parameters, including RNFL and GCL++.

RPCP VD was analyzed by comparing eyes with and without drusen detected by FAF. Eyes with ONHD in the IQ and TQ showed significantly lower RPCP VD compared to eyes without drusen. No significant difference was found in the SQ. While there was a trend for lower RPCP VD in the NQ, the difference was not statistically significant (Table 5).

Optical coherence tomography measurements and RPCP VD were compared. RNFL thickness showed positive correlations with RPCP VD, with the strongest correlation

Table 3. Pearson's product-moment correlation coefficients and corresponding p-values for the investigated OCT measurements vs age in the study participants' eyes

OCT	Age [years]		
	r	n	p-value
RNFL [μm]			
SQ	-0.50	36	0.002
IQ	-0.51	36	0.002
NQ	-0.50	36	0.002
TQ	-0.16	36	0.362
Total	-0.51	36	0.001
GCL++ [μm]			
Superior	-0.25	36	0.146
Inferior	-0.21	36	0.223
Total	-0.25	36	0.147

n – integer number, r – Pearson correlation coefficient; OCT – optical coherence tomography; RNFL – retinal nerve fibre layer; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; GCL++ – ganglion cell layer and the nerve fiber layer. Values in bold are statistically significant.

Table 4. Pearson's product-moment correlation coefficients and corresponding p-values for the investigated OCTA measurements vs age in the study participants' eyes

OCTA	Age [years]		
	r	n	p-value
RPCP VD [%]			
SQ	-0.52	36	0.001
IQ	-0.37	36	0.024
NQ	-0.57	36	<0.001
TQ	-0.33	36	0.053
SCP VD [%]			
SQ	-0.34	36	0.074
IQ	-0.37	36	0.049
NQ	-0.29	36	0.126
TQ	-0.42	36	0.024
FVD	0.38	36	0.044

n – integer number, r – Pearson correlation coefficient; OCTA – optical coherence tomography angiography; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; RPCP – radial peripapillary capillaries; SCP – superficial capillary plexus; FVD – foveal vessel density. Values in bold are statistically significant.

Table 5. RPCP VD values [%] in individual quadrants of the ONH by drusen occurrence in FAF

Quadrant	Drusen occurrence in FAF	Statistical parameter*			
		M	SD	normality	GLZ**
SQ	present	43.76	6.20	W = 0.95 p = 0.156	Wald stat. 0.90 estimate 1.01 ((-1.09)–3.12) $\Delta = 1.48$ AIC = 222.85 BIC = 229.19 p = 0.344 (Levene's test F(1,34) = 4.92 p = 0.033)
	absent	45.24	2.28	W = 0.96 p = 0.838	
IQ	present	44.76	5.74	W = 0.96 p = 0.457	Wald stat. 7.71 estimate 2.42 (0.71–4.13) $\Delta = 4.47$ AIC = 218.82 BIC = 225.16 p = 0.005 (Levene's test F(1,34) = 6.96 p = 0.008)
	absent	49.23	2.46	W = 0.92 p = 0.436	
NQ	present	39.90	6.29	W = 0.93 p = 0.053	Wald stat. 0.93 estimate 1.31 ((-1.36)–3.98) $\Delta = 3.90$ AIC = 227.54 BIC = 233.88 p = 0.335 (Levene's test F(1,34) = 0.14 p = 0.707)
	absent	43.80	6.97	W = 0.91 p = 0.459	
TQ	present	43.46	3.12	W = 0.98 p = 0.960	Wald stat. 7.18 estimate 1.55 (0.42–2.68) $\Delta = 3.38$ AIC = 197.96 BIC = 204.30 p = 0.007 (Levene's test F(1,34) = 0.07 p = 0.789)
	absent	46.84	3.98	W = 0.95 p = 0.285	

*M – mean; SD – standard deviation. **Generalized Linear Models were carried out, controlled for age. AIC – Akaike information criterion; BIC – Bayesian information criterion; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; FAF – fundus autofluorescence; RPCP – radial peripapillary capillaries; VD – vessel density; ONH – optic nerve head; FAF – fundus autofluorescence. Values in bold are statistically significant.

Table 6. Pearson's product-moment correlation coefficients and corresponding p-values for the investigated OCT measurements vs RPCP VD in the study participants' eyes

OCT	RPCP VD, SQ [%]		RPCP VD, IQ [%]		RPCP VD, NQ [%]		RPCP VD, TQ [%]	
	r	p-value	r	p-value	r	p-value	r	p-value
RNFL [μm]								
SQ	0.60	<0.001	0.57	<0.001	0.53	<0.001	0.43	0.009
IQ	0.59	<0.001	0.78	<0.001	0.53	<0.001	0.57	<0.001
NQ	0.42	0.010	0.39	0.017	0.64	<0.001	0.09	0.606
TQ	0.38	0.021	0.51	0.001	0.34	0.043	0.61	<0.001
Total	0.63	<0.001	0.70	<0.001	0.60	<0.001	0.53	<0.001
GCL++ [μm]								
Superior	0.35	0.036	0.50	0.002	0.38	0.023	0.54	<0.001
Inferior	0.44	0.007	0.57	<0.001	0.36	0.033	0.57	<0.001
Total	0.43	0.010	0.57	<0.001	0.39	0.018	0.59	<0.001

Number of correlated pairs of variables was always $n = 36$. n – integer number, r – Pearson's correlation coefficient; OCT – optical coherence tomography; RNFL – retinal nerve fibre layer; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; GCL++ – ganglion cell layer and the nerve fiber layer; RPCP – radial peripapillary capillaries; VD – vessel density. Values in bold are statistically significant.

Table 7. Pearson's product-moment correlation coefficients and corresponding p-values for the VD SCP vs RPCP in the study participants' eyes

SCP VD	RPCP VD, SQ (%)		RPCP VD, IQ (%)		RPCP VD, NQ (%)		RPCP VD, TQ (%)	
	r	p-value	r	p-value	r	p-value	r	p-value
SQ	0.43	0.018	0.37	0.048	0.34	0.068	0.49	0.006
IQ	0.39	0.037	0.44	0.017	0.29	0.132	0.57	0.001
NQ	0.27	0.149	0.31	0.099	0.38	0.041	0.44	0.018
TQ	0.42	0.021	0.28	0.143	0.35	0.060	0.38	0.043
Fovea	–0.31	0.096	–0.33	0.078	–0.37	0.049	–0.21	0.285

Number of correlated pairs of variables was always $n = 36$. n – integer number, r – Pearson's correlation coefficient; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; RPCP – radial peripapillary capillaries; SCP – superficial capillary plexus; VD – vessel density. Values in bold are statistically significant.

observed between the IQ RNFL and RPCP VD ($r = 0.78$, $p < 0.001$). GCL++ measurements also showed moderate positive correlations with RPCP VD, particularly in the IQ and TQ (Table 6). The dependencies of VD in the SCP and RPCP across various quadrants were analyzed. Significant correlations were primarily observed in the SQ and IQ, particularly within their corresponding RPCP regions. The fovea showed weak or negative correlations with RPCP, with 1 significant negative correlation in the NQ (Table 7).

The OCT parameters and VD in SCP in different quadrants and the fovea were examined. The strongest positive correlations were found between total GCL++ and SCP VD in the SQ and IQ ($r = 0.60$ – 0.62 , $p < 0.001$). The weakest and mostly nonsignificant correlations were found between RNFL, GCL++ and SCP VD in NQ (Table 8).

Discussion

The prevalence of ONHD is estimated at 0.2–2% in adults and 0.37–1% in children.^{3,8,21} The patients in our study were between 19 and 71 years old, and age did not appear to have

a significant impact on the distinction between unilateral and bilateral drusen cases. The exact pathogenesis of drusen is still uncertain, but they are believed to harm retinal nerve fibers directly through axonal compression and indirectly by inducing ischemia in the RNFL due to vascular compression.²² Therefore, diagnostic tests are crucial for enhancing the management of patients with ONHD. Previous attempts to investigate the relationship between ONHD severity and optic nerve damage relied on subjective grading systems based on ONH photography, parameters such as ONHD diameter, or imaging techniques like Spectral-Domain OCT (SD-OCT) to assess disease severity.^{14,23}

The FAF is a noninvasive diagnostic technique that detects drusen by utilizing the natural fluorescence emitted by their components, making them easily identifiable. In very young children, ONHD are typically located deeper within the tissue.²⁴ A major limitation of FAF is its reduced ability to detect deeper, buried drusen.²⁵ Nonetheless, drusen often becomes superficial by late childhood.²⁴ Given its capability to detect and map the distribution of drusen, FAF proves to be a valuable tool for diagnosing and managing superficial ONHD,^{17,18} and therefore we chose this method to identify superficial drusen in our group.

Table 8. Pearson's product-moment correlation coefficients and corresponding p-values for the investigated OCT measurements vs SCP VD in the study participants' eyes

OCT	SCP VD, SQ [%]		SCP VD, IQ [%]		SCP VD, NQ [%]		SCP VD, TQ [%]		SCP VD, Fovea [%]	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
RNFL [μm]										
SQ	0.43	0.021	0.33	0.082	0.26	0.171	0.36	0.054	-0.10	0.609
IQ	0.38	0.041	0.44	0.016	0.18	0.351	0.34	0.067	-0.18	0.350
NQ	0.13	0.498	0.11	0.559	0.08	0.676	0.11	0.558	-0.17	0.363
TQ	0.38	0.040	0.45	0.015	0.32	0.093	0.34	0.074	0.13	0.487
Total	0.42	0.022	0.42	0.024	0.26	0.176	0.37	0.048	-0.11	0.577
GCL++ [μm]										
Superior	0.54	0.002	0.50	0.006	0.36	0.054	0.28	0.144	0.25	0.190
Inferior	0.56	0.001	0.65	<0.001	0.46	0.012	0.48	0.009	0.14	0.473
Total	0.60	<0.001	0.62	<0.001	0.45	0.014	0.41	0.029	0.22	0.255

Number of correlated pairs of variables was always $n = 36$, n – integer number, r – Pearson's correlation coefficient; OCT – optical coherence tomography; RNFL – retinal nerve fibre layer; SQ – superior quadrant; IQ – inferior quadrant; NQ – nasal quadrant; TQ – temporal quadrant; GCL++ – ganglion cell layer and the nerve fiber layer; SCP – superficial capillary plexus; VD – vessel density. Values in bold are statistically significant.

Consistent with the available literature, which states that ONHD is often bilateral (in approx. 75% of cases),^{2,4} we found bilateral drusen in 71.43% of our patients. The authors reported that ONHD has a higher prevalence in the NQ compared to the TQ of the optic disc,^{2,4} which was confirmed by our findings. Interestingly, in our study, drusen were significantly more common in TQ and IQ in bilateral than unilateral cases. This suggests that fluorescence in the TQ and IQ, as confirmed by FAF, may serve as an important biomarker for the presence of bilateral drusen and warrants further investigation.

Our research focused on the correlations between FAF, OCT and OCTA. To the best of our knowledge, this is the first study to examine the relationship between those diagnostic methods based on presence of superficial drusen in FAF.

The OCT allows for detailed analysis of both the RNFL and GCC by providing high-resolution images. It allows for the assessment of structural changes in these layers, which are crucial for the diagnosis and monitoring of diseases.¹⁷ Optical coherence tomography-based studies report that both the RNFL and GCC undergo thinning with age.²⁶ These age-related changes were also confirmed in our study group (Table 3).

The OCTA provides detailed images of retinal and optic nerve blood flow, highlighting reduced capillary density and peripapillary dropout in ONHD patients.¹⁹ Additionally, retinal VD declines with age. Previous studies suggest that age-related narrowing of retinal arteries leads to decreased perfusion pressure and lower blood flow, particularly in the peripapillary and parafoveal regions, contributing to reduced vascular function.²⁷ This trend was also observed in our study group (Table 4).

The introduction of OCTA has improved the assessment of the RPCP, overcoming limitations of previous dye-based methods. The RPCP is thought to supply blood to the RNFL in the peripapillary region. Mase et al. found

that RPCP perfusion density is highest in the peripapillary area and decreases toward the macula, with a significant positive correlation to RNFL thickness in healthy eyes.²⁸ Cennamo et al. found that patients with ONHD exhibited a lower flow index and reduced VD in ONH in OCTA compared to the control group.²⁹ In our study, we observed a significant reduction in RPCP VD in all quadrants where drusen were present. We focused on RPCP perfusion within a 700 μm elliptical ring around the optic disc,²⁰ revealing significant VD differences in the TQ and IQ, which can be explained by the fact that the majority of cases were bilateral. Our results were consistent with the available literature, in which RPCP VD in the TQ in ONHD group was found to be lower.³⁰

In the current literature, there are only a few publications addressing vascular changes in the macula in patients with ONHD.^{16,30,31} Turker et al. found no statistically significant differences in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) VD values of the parafoveal and foveal regions between patients with superficial drusen and healthy controls. Therefore, we focused on the SCP VD of the macula to simplify our analysis.³⁰ Yan et al. identified a negative correlation between the presence of drusen and macular flow measurements, suggesting that reduced macular perfusion may serve as a potential early biomarker, based on the analysis of 29 eyes compared to eyes without abnormalities.¹⁶

Based on current studies,³¹ our research revealed a reduction in VD in both SCP and RPCP. Notable correlations were identified in the SQ and IQ of SCP VD, particularly in quadrants overlapping with RPCP regions. This suggests that regions of diminished VD detected via OCTA may be considered predictors for the development of future central scotoma,³¹ confirming the findings of Yan et al. that reduced macular VD serves as an early and valuable biomarker of ischemia.¹⁶ These findings are consistent

with the theory that enlarged ONHD could lead to acute or chronic ischemia by exerting pressure on adjacent nerve fibers or blood vessels. For now, our study represents the largest group of eyes in which vascular abnormalities in the macula have been confirmed among patients with ONHD. Furthermore, it is the first research comparing SCP VD of the macula with RNFL, suggesting strong correlations of these parameters, particularly in the SQ and IQ.

The origin of RNFL damage in ONHD – whether due to direct axonal compression by drusen or indirectly through vascular compromise – remains uncertain. Noval et al. reported that eyes with superficial ONHD exhibited thinner RNFL compared to controls, whereas those with buried ONHD did not show this correlation.³² Similarly, Sato et al. found a significant negative correlation between ONHD diameter and RNFL thickness.⁴ In our study, RNFL thickness demonstrated strong positive correlations with RPCP VD across all quadrants, particularly in the IQ, where the correlation was the highest ($r = 0.78$, $p < 0.001$). In our ONHD cohort, a reduction in RPCP VD was associated with thinner RNFL. These findings align with previous research, suggesting the association between thinner RNFL and decreased peripapillary microvascular circulation, as indicated by lower RPCP VD.³⁰

Notably, total RNFL thickness showed a stronger correlation with RPCP VD than GCC, suggesting that RNFL measurements may serve as a more reliable indicator of microvascular integrity in the ONH. This is particularly relevant in conditions like ONHD, where microvascular changes might precede overt nerve fiber damage.

Advanced OCT technology enables precise macular GCC assessment through automated segmentation. The ganglion cell complex (GCC) encompasses 3 retinal layers: the macular retinal nerve fiber layer (mRNFL), the GCL and the inner plexiform layer (IPL). It is primarily used in assessing the health of the macular region, particularly for early optic nerve damage detection as in glaucoma, monitoring disease progression and advanced-stage evaluation of abnormalities.³³ Notably, asymmetry between macular hemifields in the ganglion cell–inner plexiform layer (GCIPL) can indicate early stages of optic nerve damage, such as in preperimetric glaucoma.³⁴ GCL++ refers to the combination of the GCL and the NFL, focusing on fewer layers than the GCC, and is often used to simplify assessments, particularly for the early detection of neural damage.³³ Based on this, we selected the GCL++ parameter to simplify our analysis and to evaluate early abnormalities in patients with ONHD. To the best of our knowledge, this is the first study to analyze the GCL++ parameter in patients with ONHD.

Our results demonstrated moderate positive correlations between GCL++ measurements and RPCP VD, particularly in the IQ and TQ (Table 6). The relationship between GCL++ and RPCP in these regions aligns with previous research indicating that ganglion cell loss can influence the vascular supply to the retina, particularly

in areas prone to damage like the IQ and TQ. Studies, including those on the “macular vulnerability zone” (MVZ), have shown that GCC thinning in the IQ and TQ regions of the macula corresponds to structural fragility in these areas, particularly involving the lamina cribrosa.³⁴ The initial IQ loss of GCC and RNFL, compared to the SQ, is due to the increased fragility of the inferior lamina cribrosa and the higher fiber density in the inferior segment. This fragility is linked to the weak connective tissue and large pores, which are secondary to the high fiber density in the inferotemporal sector of the ONH.^{35–37} The thinning of the GCC affects vascular supply, suggesting that its loss significantly impacts RPCP VD in susceptible zones. Additionally, as visual field deficits and GCC thinning progress, a more pronounced decline in RPCP VD values may serve as a late-stage biomarker in ONHD cases.¹⁶

This study is the first to compare SCP VD with GCL++. We found a positive correlation between total GCL++ and SCP VD in both the SQ and IQ ($r = 0.60–0.62$, $p < 0.001$), with the SQ being more affected, possibly due to the higher frequency of ONH drusen in this area. Furthermore, GCL++ suggested a stronger association with SCP VD than RNFL. Additional longitudinal research is required to investigate how these correlations develop over the time.

Limitations

The limitations of this study include the small patient cohort and its retrospective design.

Conclusions

This study confirmed that FAF is a useful, sensitive tool for identifying superficial drusen. The OCT and OCTA are valuable methods for assessing the impact of ONHD on optic nerve fibers and microvascular alterations. The assessment of microcirculation using OCTA should include not only the RPCP but also the macula, as we observed attenuation of macular flow, which should be confirmed in a larger study group.

Multimodal imaging plays a crucial role in accurately diagnosing and thoroughly evaluating patients with ONHD. Further longitudinal studies are needed to explore how these correlations evolve over time, particularly in the context of ONHD progression.

Data availability statement

The datasets supporting the findings of the current study are openly available in Zenodo at: <https://doi.org/10.5281/zenodo.14790582>.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

Not applicable.

ORCID iDs

Paulina Szabelska  <https://orcid.org/0000-0002-6216-0646>
 Joanna Brydak-Godowska  <https://orcid.org/0000-0002-7567-4777>
 Przemysław Krajewski  <https://orcid.org/0000-0001-5136-1621>
 Radosław Różycki  <https://orcid.org/0000-0001-7040-026X>
 Joanna Gołębiewska  <https://orcid.org/0000-0002-3013-4363>

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