DOI:10.14744/bej.2025.48379
Beyoglu Eye J 2025; 10(2): 95-100

Original Article

Evaluation of Retinal Inner Layer Thickness and its Relationship with Visual Prognosis in Multiple Sclerosis Patients with and Without Optic Neuritis

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Abstract

Objectives: The objective is to evaluate retinal inner layer thicknesses in multiple sclerosis (MS) patients with and without optic neuritis (ON) and investigate their relationship with visual prognosis.

Methods: This cross-sectional retrospective study examined 120 MS patients (237 eyes), including 43 with unilateral ON and 26 with bilateral ON. Retinal layer measurements were obtained using Heidelberg Spectralis optical coherence tomography (OCT), including macular retinal nerve fiber layer, ganglion cell layer (GCL), inner plexiform layer (IPL), and peripapillary retinal nerve fiber layer (pRNFL) thicknesses across multiple quadrants defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) grid.

Results: Significant thinning was observed in GCL and IPL across all quadrants except the temporal region in ON patients. The 3 mm nasal GCL thickness showed the strongest correlation with visual acuity ($r=0.725$, $p<0.001$) in the ON group. IPL parameters demonstrated the second strongest correlation, with the 3 mm nasal region showing the highest correlation ($r=0.675$, $p<0.001$). While pRNFL showed significant thinning in all quadrants except the nasal quadrant in ON patients, it exhibited weaker correlations with visual acuity compared to GCL and IPL measurements.

Conclusion: GCL and IPL measurements serve as more reliable and earlier biomarkers for visual prognosis in MS patients compared to pRNFL. The strongest structure-function relationships were observed in the 3 mm nasal and inferior quadrants of the ETDRS grid. These findings support the integration of OCT-based GCL and IPL thickness measurements into routine clinical practice for monitoring MS disease progression and treatment efficacy.

Keywords: Inner retinal layer thickness, optic neuritis, retinal neurodegeneration

Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition marked by demyelination in the central nervous system. Optic nerve involvement is a common finding in MS, with optic neuritis (ON) presenting as the initial manifestation in approximately 20% of patients and occurring at least once in about 50% of patients throughout disease progression (1,2). Following optic nerve injury, retrograde degeneration leads to retinal ganglion cell loss and axonal damage (3).

Spectral domain optical coherence tomography (SD-OCT) has emerged as a significant imaging technique for assessing neurodegeneration in recent years (4,5). This non-invasive method enables high-resolution imaging and quantitative assessment of retinal layers. Using SD-OCT, the

How to cite this article: Kucukiba K, Orman G, Sungur G, Unlu, N, Burcu A. Evaluation of Retinal Inner Layer Thickness and its Relationship with Visual Prognosis in Multiple Sclerosis Patients with and Without Optic Neuritis. Beyoglu Eye J 2025; 10(2): 95-100.

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Submitted Date: December 22, 2024 **Revised Date:** December 28, 2024 **Accepted Date:** May 12, 2025 **Available Online Date:** June 25, 2025

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

thicknesses of the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) can be evaluated independently (6), allowing objective quantification of post-ON neuronal loss.

Studies have demonstrated significant thinning of retinal inner layers in MS patients with a history of ON (7,8). In addition, subclinical retinal neurodegeneration has been observed in MS patients without ON (9,10), suggesting that visual pathway involvement extends beyond clinical ON attacks. While inflammation predominates in early MS, neurodegeneration becomes more prominent in later stages (2). ON holds particular significance as an early manifestation of MS. The assessment of post-ON retinal damage and visual prognosis is crucial for patient monitoring and treatment planning (11,12).

This study aims to evaluate the impact of ON on retinal inner layer thicknesses in MS patients and investigate their relationship with visual function. Furthermore, we assess the potential of retinal inner layer thicknesses as biomarkers for predicting visual outcomes.

Methods

This cross-sectional retrospective study was approved by the Ethics Committee of Health Sciences University (E-24-248/25.09.2024) in compliance with the Declaration of Helsinki principles. Informed consent was obtained from the patients and, when necessary, from their legal guardians. The study examined medical records of 120 patients with relapsing-remitting multiple sclerosis (RRMS) who were followed at the Neuro-ophthalmology Outpatient Clinic of Health Sciences University Ankara Training and Research Hospital Eye Diseases Clinic between November 2022 and December 2024. All patients met the 2017 McDonald diagnostic criteria for MS. The study population was divided into two groups: patients with and without ON.

Inclusion criteria comprised patients aged 18–65 years with RRMS who had been attack free for at least 3 months and whose most recent ON episode occurred more than 6 months before enrollment. Exclusion criteria included progressive MS forms, coexisting ocular diseases (such as glaucoma or uveitis), spherical refractive errors exceeding 4 diopters, cylindrical refractive errors exceeding 2 diopters, OCT signal strength below 7/10, and any history of ocular surgery.

Clinical assessment included measurement of best-corrected visual acuity (BCVA) using Snellen charts, biomicroscopic examination, and fundoscopy with a 90-diopter lens following pupillary dilation with tropicamide. The evaluation encompassed patients' symptoms, clinical findings, and medical histories. All imaging was performed by a single experienced technician using the same device to ensure consistency.

OCT imaging was conducted using the Heidelberg Spectralis device (Heidelberg Engineering, Germany). The scanning protocol included a 30° × 20° macular volume scan comprising 25 sections at 240 µm intervals, centered on the fovea. Segmentation of the retinal layers was conducted utilizing the device's automatic analysis technique (Fig. 1). Measurements included mRNFL, GCL, IPL, and total retinal thickness across nine subfields as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. These measurements were obtained from the central 1 mm zone, 3 mm nasal-temporal-superior-inferior quadrants, and 6 mm nasal-temporal quadrants. pRNFL thickness was calculated by averaging sixteen consecutive B-scans circumscribing the optic disc (3.5 mm diameter, 768 A-scans).

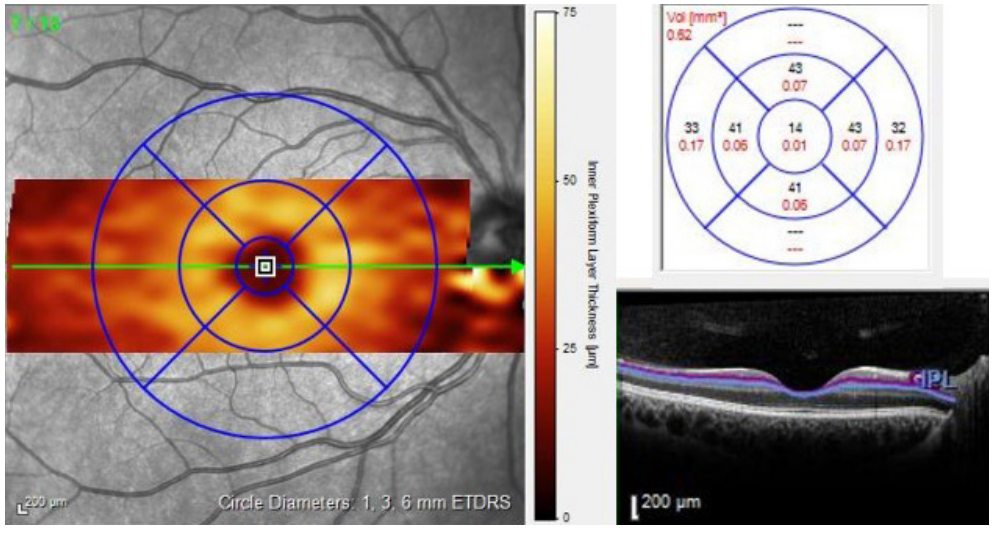

Figure 1. The standard macula protocol of spectral domain optical coherence tomography and automated retinal layer segmentation.

Statistical Analysis

Data analysis was conducted using Statistical Package for the Social Sciences software version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of variables was assessed for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For non-normally distributed variables, between-group comparisons were performed using the Mann–Whitney U test.

Associations between retinal layer thicknesses and visual acuity were evaluated using Pearson's correlation coefficient analysis. Correlation coefficients (r) range from −1 to +1, where the absolute value indicates the strength of the relationship, with values closer to ±1 representing stronger correlations. Statistical significance was defined as $p<0.05$ for all analyses.

Results

The study population comprised 120 MS patients (237 eyes), consisting of 92 females (76.7%) and 28 males (23.3%). Demographic characteristics and clinical parameters, including age, gender, and BCVA for both ON and non-ON groups, are presented in Table 1. The study included 43 patients with unilateral ON and 26 with bilateral ON. While age and gender distributions were comparable between ON and non-ON groups, visual acuity was significantly reduced in the ON group.

Analysis of pRNFL revealed significant thinning in all quadrants except the nasal quadrant in the ON group compared to the non-ON group (Table 2). Although total macular thickness and mRNFL measurements showed no significant differences between groups, both GCL and IPL thicknesses demonstrated significant differences (Table 2).

Correlation analyses revealed that GCL parameters exhibited the strongest associations among all OCT measurements. The 3 mm nasal GCL thickness demonstrated the highest correlation with visual acuity ($r=0.725$, $p<0.001$) in the ON group. While significant correlations between GCL thickness and visual acuity were observed in both groups, the association was more pronounced in the ON group (Fig. 2).

IPL parameters emerged as the second strongest correlate with visual acuity. Within the IPL measurements, the 3 mm nasal region showed the highest correlation ($r=0.675$, $p<0.001$) in the ON group. IPL thickness-visual acuity correlations were substantially stronger in patients with ON.

The pRNFL parameters demonstrated weaker correlations with visual acuity compared to other retinal layers, with the strongest correlation observed in the temporal quadrant ($r=0.675$, $p<0.001$) in the ON group.

Total macular thickness, mRNFL, and pRNFL measurements exhibited the weakest correlations among all parameters studied.

Comprehensive analysis of all OCT parameters revealed three key findings: correlations were consistently stronger in the ON group, measurements from the 3 mm nasal region yielded the most significant results, and GCL parameters demonstrated the strongest relationship with visual acuity. These results suggest that nasal GCL thickness may serve as a valuable marker for assessing visual prognosis.

Discussion

Our study investigated the impact of ON on retinal inner layer thicknesses and visual prognosis in patients with MS. We observed significant thinning of the GCL and IPL across all quadrants, except the temporal quadrant, in patients with ON. These structural changes demonstrated a strong correlation with visual acuity. These findings align with Walter et al.'s (3) research, which demonstrated strong correlations between GCL and IPL neuronal loss and visual function. Although pRNFL thinning has traditionally served as a structural marker for monitoring axonal loss, current evidence suggests that retinal ganglion cell loss plays a fundamental role in the pathogenesis of MS-related visual dysfunction.

Saidha et al. (10) demonstrated that thinning of pRNFL, GCL, and IPL in MS patients correlates with neurodegeneration and brain atrophy. Their research established that GCL and IPL thicknesses exhibit stronger structure-function relationships compared to pRNFL. These observations suggest that OCT serves not only as a clinical monitoring tool but also as a valuable biomarker for evaluating potential neuroprotective and neurorestorative interventions.

Naranayan et al. (13) demonstrated that multifocal visual evoked potential amplitude, latencies, and contrast sensitivity

Table 1. Demographic characteristics and BCVA levels of MS patients with and without ON

	ON (+) eyes (n=95)	ON (-) eyes (n=142)	Total eyes (n=237)	p
Age (year)	38.2±11.4	39.6±10.8	39.0±11.0	0.715
Gender (F/M)	65/30	115/27	180/57	0.673
BCVA (LogMAR)	0.097±0.456	0.013±1.046	0.046±0.620	0.024*

BCVA: Best-corrected visual acuity.

Table 2. Comparison of total macula, GCL, IPL, mRNFL, and pRNFL thicknesses in optic neuritis, non-optic neuritis, and total patient groups

Layers (µm)	ON (+) eyes	ON (-) eyes	Total eyes	p
Macula 1 mm central	245.8±15.4	251.2±14.2	249.2±14.8	0.158
Macula 3 mm temporal	307.2±16.8	314.6±15.9	311.9±16.5	0.727
Macula 6 mm temporal	277.3±15.2	280.5±14.8	279.3±15.0	0.688
Macula 3 mm nasal	318.4±17.9	325.6±16.4	322.9±17.2	0.348
Macula 6 mm nasal	304.2±18.5	308.9±17.2	307.1±17.8	0.511
Macula 3 mm inferior	311.5±20.1	318.2±18.4	315.7±19.2	0.688
Macula 3 mm superior	322.4±19.2	328.6±17.8	326.3±18.5	0.727
GCL 1 mm central	8.5±3.8	10.9±2.8	10.0±3.4	**0.047***
GCL 3 mm temporal	36.2±9.8	41.5±8.2	39.5±9.1	0.051
GCL 6 mm temporal	34.8±7.2	37.5±6.4	36.5±6.8	0.285
GCL 3 mm inferior	40.8±9.4	46.5±7.5	44.3±8.6	**0.003***
GCL 3 mm nasal	42.5±8.9	47.2±7.2	45.4±8.2	**0.001***
GCL 6 mm nasal	36.8±6.5	39.2±5.8	38.3±6.2	**0.038***
GCL 3 mm superior	44.2±8.4	48.6±7.1	46.9±7.9	**0.018***
mRNFL 1 mm central	9.2±2.8	10.1±2.4	9.7±2.6	0.089
mRNFL 3 mm temporal	16.8±2.4	17.2±2.1	17.0±2.2	0.178
mRNFL 6 mm temporal	17.1±2.2	17.4±2.0	17.3±2.1	0.156
mRNFL 3 mm inferior	21.8±3.8	23.5±3.2	22.9±3.5	0.072
mRNFL 3 mm nasal	19.2±3.1	20.1±2.8	19.8±2.9	0.064
mRNFL 6 mm nasal	39.2±8.5	42.4±7.8	41.2±8.2	0.082
mRNFL 3 mm superior	21.5±3.6	22.8±3.2	22.3±3.4	0.134
IPL 1 mm central	16.2±3.8	17.8±3.2	17.2±3.5	**0.028***
IPL 3 mm temporal	35.4±6.9	38.8±4.9	37.5±5.9	0.075
IPL 6 mm temporal	30.2±4.8	31.8±4.2	31.2±4.5	0.688
IPL 3 mm inferior	36.2±5.9	38.4±4.8	37.6±5.4	**0.007***
IPL 3 mm nasal	35.8±6.2	38.2±5.1	37.3±5.7	**0.003***
IPL 6 mm nasal	27.2±4.2	28.4±3.8	27.9±4.0	**0.042***
IPL 3 mm superior	36.8±5.8	38.9±4.9	38.1±5.4	**0.011***
pRNFL mean	91.4±14.3	98.2±13.2	95.7±13.9	**0.002***
pRNFL temporal	58.9±17.1	64.7±12.7	62.5±14.7	**0.011***
pRNFL temporal-inferior	125.9±31.5	134.0±24.1	130.9±27.3	**0.028***
pRNFL nasal-inferior	108.2±24.8	112.4±22.1	110.8±23.2	**0.045***
pRNFL nasal	72.4±12.9	79.0±14.1	76.5±13.9	0.057
pRNFL nasal-superior	108.2±24.5	114.6±22.8	112.2±23.5	**0.042***
pRNFL temporal-superior	134.5±25.8	142.2±23.5	139.3±24.5	**0.033***

GCL: Ganglion cell layer, IPL: Inner plexiform layer, pRNFL: Peripapillary retinal nerve fibre layer, mRNFL: Macular retinal nerve fiber layer..

tests correlate more strongly with GCL and IPL parameters than with pRNFL measurements. Kupersmith's research revealed that GCL and IPL thicknesses show greater resistance to acute inflammation and edema compared to pRNFL. The observation that GCL and IPL thinning occurs within 1 month post-ON, while pRNFL thinning develops over 3 months, suggests that GCIPL thickness represents a more reliable marker for early axonal damage assessment (8).

Our findings corroborate Özbilen et al.'s (14) observations, demonstrating significant alterations in GCIPL lay-

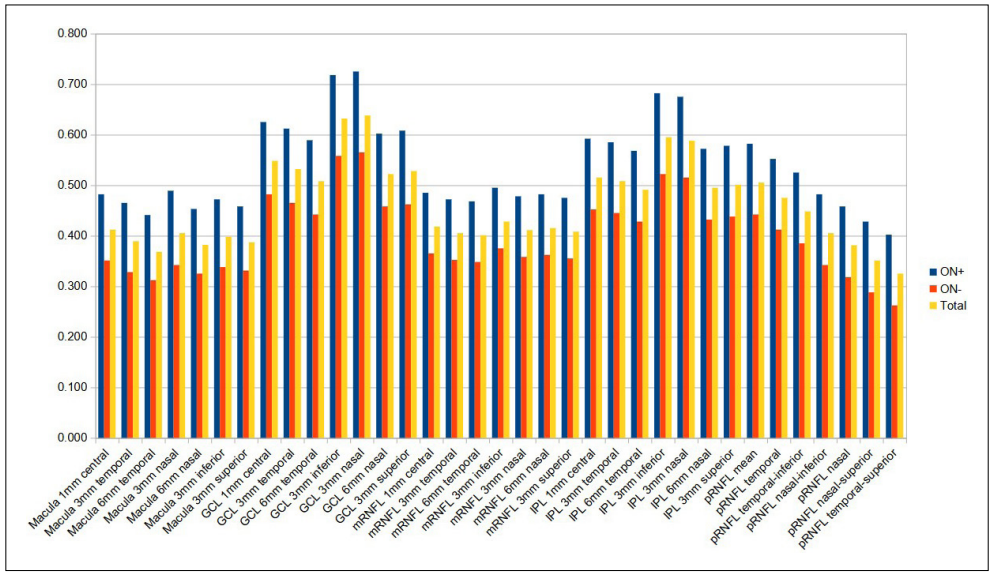

Figure 2. Correlation analysis between Best-Corrected Visual Acuity (BCVA) and retinal layer thicknesses: Total Macula, macular Retinal Nerve Fiber Layer (mRNFL), Ganglion Cell Layer (GCL), Inner Plexiform Layer (IPL), and peripapillary Retinal Nerve Fiber Layer (pRNFL).

ers within the nasal and inferior quadrants of 3 and 6 mm ETDRS grid rings. The strongest correlation was observed in the nasal 3 mm GCL quadrant. Similarly, Kayhan et al. (15) reported significant GCL thickness changes in the 3 mm inferior quadrant in MS patients with ON. In their study, Hood et al. (16) demonstrated that retinal nerve fiber thinning originating from the inferior GCL stratum of the macula, constituting the inferotemporal region of the optic nerve designated as the "macular vulnerability zone," may serve as an early indicator of glaucomatous damage. Concordantly, our data revealed a more pronounced thinning pattern in the inferior quadrant. This topographic distribution exhibits similarities to the inferior macular thinning pattern observed in glaucomatous damage. This phenomenon suggests an enhanced susceptibility to neurodegeneration among retinal ganglion cells within the inferior macular region.

Recent research has demonstrated that post-chiasmal lesions can induce homonymous hemimacular GCL atrophy (17). This thinning pattern, predominantly observed in inferior and nasal regions, represents a more sensitive biomarker of retrograde degeneration than pRNFL measurements. El Ayoubi et al.'s (11) 2024 meta-analysis supports our findings, reporting significant GCL thinning in ON-affected eyes.

A key finding of our study was the observation of significant pRNFL thinning in ON patients, particularly in average, temporal, and temporal-inferior regions. This observation aligns with temporal RNFL thinning patterns reported in the 2017 meta-analysis (4). The pronounced temporal region involvement can be attributed to the anatomical configuration of the papillomacular bundle.

Conclusion

Our investigation of retinal inner layer thicknesses and visual prognosis in MS patients with ON demonstrated that GCL and IPL measurements serve as more reliable and earlier biomarkers compared to pRNFL. We observed significant GCL and IPL thinning across all quadrants except the temporal region, with these changes showing a strong correlation with visual acuity. Notably, alterations in the 3 mm nasal and inferior quadrants of the ETDRS grid demonstrated particular prognostic value.

Our findings establish OCT measurements as objective biomarkers for clinical monitoring and treatment response evaluation. The pronounced thinning observed in the inferior quadrant suggests enhanced neurodegeneration sensitivity of retinal ganglion cells in this region, providing insights into the pathogenesis of MS-related visual dysfunction.

These results support the incorporation of OCT-based GCL and IPL thickness measurements into routine clinical practice for MS patient monitoring. This approach offers clinicians valuable advantages in assessing both disease progression and therapeutic efficacy.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Health Sciences University (E-24-248/25.09.2024) in compliance with the Declaration of Helsinki principles. Informed consent was obtained from the patients.

Peer-review: External peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Author Contributions: Concept – K.K., G.O.; Design – G.O.;

Supervision – N.U., A.B.; Resource – K.K., G.O.; Materials – G.O., G.S.; Data Collection and/or Processing – K.K.; Analysis and/or Interpretation – K.K.; Literature Search – K.K., G.O.; Writing – K.K.; Critical Reviews – G.S., G.O.

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