# Relationship Between Segmented Macular Layers and Visual Field in Primary Open-Angle Glaucoma

*Serdar Bayraktar[1], Gözde Hondur[2], Emine Sen[3], Ufuk Elgin[4]*


## ABSTRACT

**Purpose:** To investigate the relationship between macular nerve fiber layer (mNFL), ganglion cell layer (mGCL), and inner plexiform layer (mIPL) thickness values obtained by spectral domain optical coherence tomography (SD-OCT) segmentation analysis and visual field (VF) mean deviation (MD) values in cases with primary open-angle glaucoma (POAG).

**Materials and Methods:** mNFL, mGCL, and mIPL thickness measurements were performed by SD-OCT in 25 eyes of 25 POAG patients whose intraocular pressures were under medical control. The correlation between the thickness of each segmented layer and VF MD was analyzed by Pearson correlation analysis.

**Results:** The mean age of the patients was 69±9, and the mean VF MD was -8.09±8.21 dB. The mean mNFL thickness was 27.86±4.81 µ, the mean mGCL thickness was 38.12±6.57 µ, and the mean mIPL thickness was 32.09±4.59 µm. Significant positive correlation was found between VF MD and mNFL (r=0.658, p=0.0003), VF MD and mIPL thickness (r=0.718, p=0.00005), and VF MD and mGCL (r=0.789, p<0.00001).

**Discussion:** Strong positive correlations were found between mNFL thickness, mIPL thickness, and mGCL thickness values and VF MD values in the present study. Especially, the changes in IPL that represent dendritic interactions can open new horizons in developing new structural test strategies for early diagnosis of POAG in larger patient populations, when examined longitudinally.


**Keywords:** Ganglion Cell Layer, Inner Plexiform Layer, Macular Nerve Fiber Layer, Optical Coherence Tomography, Primary Open-Angle Glaucoma, Visual Field.

## INTRODUCTION

Glaucoma is a progressive disease that leads irreversible loss of vision due o retinal ganglion cell (RGC) injury.[1-5] The RGC loss is traditionally assessed by thinning of retinal nerve fiber layer (RNFL), optic nerve head (ONH) changes and visual field (VF) defects.[1] However, Visual loss is generally recognized after onset of significant RGC damage, which is irreversible.[2]

Today, optical coherence tomography (OCT) has become a valuable tool aiding the diagnosis of glaucoma and showing its progression.[2,6,7] The OCT is widely used to assess structural properties of RNFL layer around optic disc (cpRNFL) and/or ONH.[2,4-7] However, the reliability of cpRNFL measurements is limited by structural variations seen at optic disc including variable optic disc sizes and optic nerve head inclination angles and several factors such as peripapillary atrophy and papilla edema.[2,8]

In preliminary studies using traditional structural imaging methods, a weak correlation was reported between macular thickness parameters and VF defects in glaucoma.[9] However, innovations in optic coherence tomography (OCT) technology enables reliable and sensitive measurement of perifoveal inner retinal layers.[1-6] Macula is the retinal region with highest concentration of retinal ganglion cells.[10] Thus, in recent years, macula is considered as strategic region in the diagnosis and follow-up of glaucoma.[11] Macular OCT imaging has some advantages over cpRNFL in the diagnosis of glaucoma.[2,6] Because the above-mentioned factors that may affect

1- MD, University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye

2- Assoc. Prof., University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye

3- Prof, University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye

4- Prof., Dünyagöz Eye Hospital, Department of Ophthalmology, Ankara, Türkiye

**Received:** 30.03.2023
**Accepted:** 09.05.2023
*J Glau-Cat 2023; 18: 174-179*
DOİ: 10.37844/glau.cat.2023.18.26

**Correspondence Address:**
Serdar Bayraktar
University of Health Sciences, Ulucanlar Eye Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye
**Phone:** +90 533 655 1134
**E-mail:** drsbayraktar@yahoo.com

reliability of cpRNFL measurements have no effect on macular assessment. In addition, macular ganglion cell layer (mGCL) formed by RGC bodies and inner plexiform layer (mIPL) formed by dendrites of RGC and axons of bipolar cells can be assessed by macular segmentation analysis.[1,6]

In glaucoma patients, macular OCT imaging allows quantification of all components of RGC complex with excellent reproducibility.[1-6] Previous studies showed that GCIPL, formed by combination of mNFL, mGCL, mIPL and mGCL; ganglion cell complex (GCC) formed by combination of mNFL, mGCL and mIPL; and full-layer retinal thickness measurements are thinner in glaucoma patients when compared to healthy population and can be used in the diagnosis and follow-up of glaucoma damage.[2,6,7] In addition, measurements of these layer by OCT were found to be comparable with peripapillary RNFL measurement in distinguishing glaucoma patients from healthy individuals.[2,7,12] However, there is limited number of studies the relationship of glaucomatous damage with mGCL representing macular cell bodies and mIPL representing dendrites separately, with inconsistent results.[1,2,13,14]

In this study, we investigated structural and functional relationship between VF MD and mNFL, mGCL and mIPL thickness values as measured by spectral domain (SD)-optical coherence tomography (OCT) segmentation analysis in patients with primary open-angle glaucoma.

## MATERIALS AND METHODS

This prospective, cross-sectional study was conducted at the glaucoma clinic of a tertiary hospital and included 25 eyes of 25 cases with POAG in which intraocular pressure (IOP) was under control with medical treatment at the glaucoma clinic of a tertiary hospital. All subjects gave written informed consent. All procedures were conducted in accordance to tenets of Helsinki Declaration. The study was approved by Ethics Committee of Ankara Training and Research Hospital.

Detailed medical history was obtained in all subjects; followed by a comprehensive ophthalmological examination including assessment of best-corrected visual acuity, IOP measurement by Goldmann applanation tonometry, gonioscopy, anterior segment and fundus examination by slit-lamp examination, VF assessment (Humphrey Visual Field Analyzer, Carl Zeiss Meditec Inc., Dublin, CA) and SD-OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) measurements.

The diagnosis of primary open-angle glaucoma was made by open anterior chamber angle with gonioscopy, IOP>21 mmHg without treatment, glaucomatous appearance of optic nerve head (thinning of neuroretinal margin, notch, asymmetric cup: disc ratio etc.), RNFL thinning on OCT exceeding 95% confidence interval, glaucomatous VF defect falling out normal limits in 24-2 VF testing, Sweden Interactive Threshold Algorithm (SITA) standard or glaucoma semi-field test.

The study included patients aged >50 years with best-corrected visual acuity ≥20/30, spherical refractive error between +5 and -5 diopters and cylindrical refractive error between +3 and -3 diopters. The patients with previous history of vitreoretinal surgery; those with systemic or ocular disorder which may affect ONH or VF; those with retinal disorders such as epiretinal membrane, age-related macular degeneration or diabetic macular edema; patients with marked cataract or opacity that may affect macular thickness measurements and lead errors in OCT segmentation; patients with refractive errors not fulfilling inclusion criteria; and patients with VF testing not meeting reliability criteria (false-negative>15%, false-positive>15% and fixation loss>20%) were excluded.

### Optical Coherence Tomography and Visual Field:

For optical coherence tomography, horizontal macular OCT scans were obtained by SD-OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) fast macular cube protocol and segmentation was performed in automated manner by SD-OCT automated segmentation software (Figure 1). All OCT scan were performed by same experienced clinician. In each eye, OCT images were carefully evaluated for appropriate segmentation and manually arranged when needed. The scans with inadequate quality (Q<20) were repeated and poor-quality measurements were excluded. The border of retinal layers were defined as margin between inner limiting membrane, RNFL and GCL while border of GCL and IPL was defined

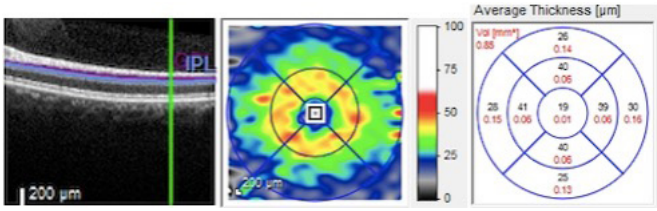



**Figure 1:** *Inner plexiform layer segmentation using Heidelberg Spectralis OCT*

as margin between IPL and inner nuclear layer (INL).

mNFL, mGCL and mIPL thickness values were obtained. Retinal thickness map included 3 concentric circles with diameters of 1, 3 and 6 mm. Two outer circles were divided into 4 identical region by two perpendicular lines. (Figure 1) The outermost circle (6 mm in diameter) was taken into consideration for data collection and analysis. Mean thickness for each layer was obtained by averaging values from 4 inner and 4 outer regions.

Reproducible VF test results (2 or more consecutive testing) were obtained in all subjects. Humphrey VF test using central 24-2 SITA algorithm with spot size of III (Carl Zeiss Meditec, Dublin, CA) was used during standard automated perimetry.

**Statistical analysis:** All statistical analyses were performed using SPSS version 20.0 (SPSS for Windows; SPSS Inc., Chicago, IL). Chi-square test was used to analyze categorical variables. Descriptive statistics are presented as mean±standard deviation. The relationships between thickness values of segmented retinal layers and relevant VF mean deviation (MD) values were assessed using Pearson's or Spearman's regression analyses based on data distribution.

## RESULTS

Mean age was 69±9 years while mean VF MD was -8.09±8.21 dB. Table 1 summarizes demographic and clinical characteristics. Mean mNFL thickness was 27.86±4.81 µm while mean mGCL thickness was 38.12±6.57 µm and mean mIPL thickness was 32.09±4.59 µm. There was significant positive correlation between GA MD and mNFL thickness (r=0.658, p=0.0003), mIPL thickness (r=0.718, p=0.00005) and mGCL thickness (r=0.789, p<0.00001). (Table 2) and (Graphic 1)

## DISCUSSION

In glaucoma patients, visualization of inner macular layers using OCT allows detailed evaluation of all components of RGC complex.[1-6] Anatomically, retinal ganglion cell (RGC) projects across three layers of inner retina. The RGC axons form RNFL while RGC bodies form GCL and dendrites form IPL.[1,6] In experimental glaucoma studies using animal models, it was reported that changes in IPL layers seen at early phases of glaucoma start even before damage occurring at cellular body.[6,15,16] In central nervous system, rather than axons, dendrites respond to injury; de novo dendritic branches are formed following injury and diffusely spread across a larger area.[17] experimental findings in animals with ocular hypertension indicated a numerical increase in the number of synapses between RGC and bipolar cells.[15] However, there is insufficient data regarding clinical translation and relevance of these findings. In this study, it was aimed to evaluate relationship between thickness values of each layer forming macular RGC and VF which is the most important functional test used in the follow-up of glaucoma.

In a study comparing peripapillary RNFL and macular thickness parameters, Medeiros et al.[9] suggested that macular thickness parameters aren't adequate for glaucoma follow-up. However, authors emphasized that, given to technological advances in spectral domain devices, macular thickness will become more important in the glaucoma follow-up.[9] In fact, it has become possible to obtain more sensitive measurements of inner retinal layers over time. Meticulous analysis of the measurements allows more definitive picture of RGC injury in the glaucoma.[6]

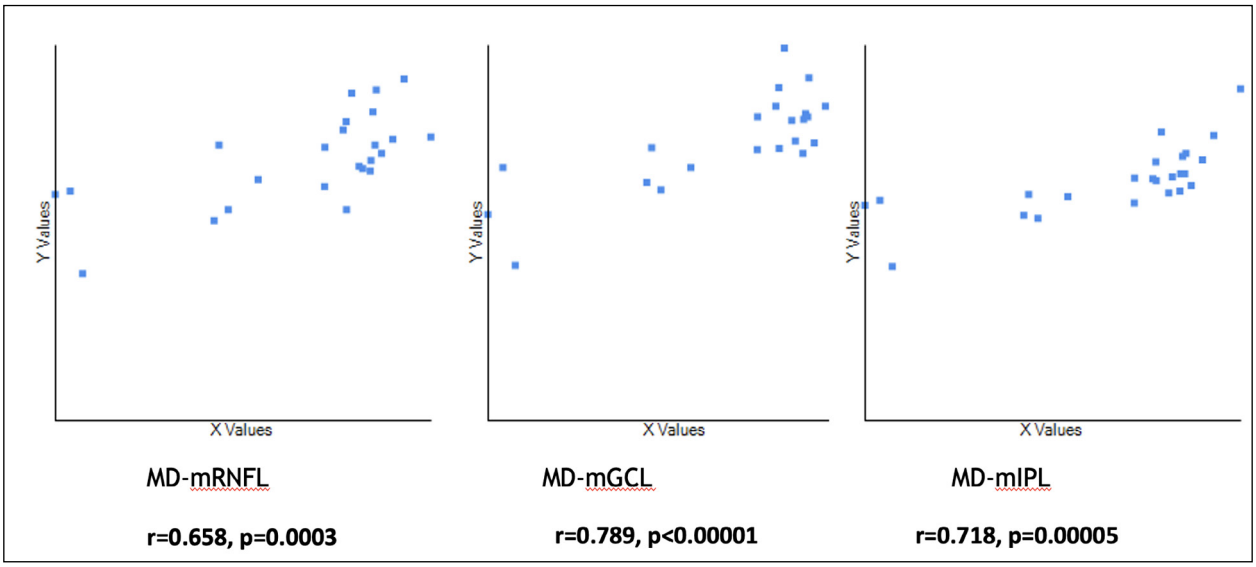
Zeimer et al. were first authors reported that macula can be visualized with potential to assess glaucoma and that macular thickness is decreased in glaucoma patients.[18] In

**Table 1:** *Demographic and clinical data of participants*

| | |
|---|---|
| Age (years) (Mean±SD) | 69±9 |
| Gender (Male/Female) | 11 / 14 |
| Visual Field MD (dB) (Mean±SD) | -8.09±8.2 |
| Intraocular Pressure (mmHg) (Mean±SD) | 14.6±3.2 |
| SD: Standard Deviation | |

**Table 2:** *Correlation between macular layers and visual field mean deviation value*

| Segmented macular layers | | Correlation with MD |
|---|---|---|
| mNFL thickness (µm) (Mean±SD) | 27.86±4.81 | r=0.658, p=0.0003 |
| mGCL thickness (µm) (Mean±SD) | 38.12±6.57 | r=0.789, p<0.00001 |
| mIPL thickness (µm) (Mean±SD) | 32.09±4.59 | r=0.718, p=0.00005 |
| MD: Visual field mean deviation, mNFL: macular nerve fiber layer, mGCL: macular ganglion cell layer, mIPL: macular inner plexiform layer SD: standard deviation | | |




**Graphic 1:** *Correlation between macular layers and visual field mean deviation value*
MD: Visual field mean deviation, mNFL: macular nerve fiber layer, mGCL: macular ganglion cell layer mIPL: macular inner plexiform layer SD: standard deviation

subsequent studies, it was reported that macular thinning detected by OCT had a good diagnostic ability to distinguish glaucoma patients from healthy eyes.[1-4,7,12,19-21]

In preliminary studies on macula using OCT, it was reported that the border between mGCL and mIPL was less prominent when compared remaining macular borders.[3,22] Thus, previous OCT studies focused on GCIPL and GCC rather than mGCL and mIPL.[4,7,12,19-21] Previous studies investigated diagnostic ability of GCIPL formed by mGCL and mIPL[7,14,19,21] as well as GCC formed by mNFL, mGCL and mIPL[4,16] for glaucoma.

There is limited number of studies assessing mGCL and mIPL as isolated layers in glaucoma.[1,2,13,14,23] Moura et al.[13] and Tan et al.[14] showed that GCL and IPL thicknesses were decreased in glaucomatous eyes. However, both studies did not investigated diagnostic ability of mGCL and mIPL in glaucoma. Springelkamp et al.[23] performed macular segmentation using an individually designed segmentation software. In the study, authors reported that, among mGCL, GCC, mNFL and cpRNFL thicknesses, the mean mGCL thickness at inferior half was the macular region with best diagnostic performance regarding sensitivity. Kim et al.[1] found that mIPL thinning was directly related to glaucoma stage. Chien et al.[2] evaluated the diagnostic ability of isolated macular layers using grid with varying size and found that mGCL and GCC had highest diagnostic ability; followed by GCIPL, mNFL and mIPL.[2] Again, Moghimi et al.[3] reported that there is no evidence indicating mIPL thinning provided better result than GCC in the diagnosis of glaucoma. In recent studies, inconsistent results might be due to different methodologies and smaller study populations.

In our study, the finding that there was a strong correlation between VF and thickness values of all three layers (mNFL, mGCL, mIPL) forming RGC confirmed the importance of quantitative measurements of inner retinal layers in the diagnosis of glaucoma.

Kim et al.[1] emphasized that mIPL thickness (or GCIPL thickness) showed stronger correlation with 24-2 VF scores in related areas when compared to mNFL and mGCL thicknesses. In their study, Aydın et al.[5] found substantial local changes in IPL thickness and density in relation with progression of local VA defects in glaucomatous eyes. Authors reported that there was a significant correlation between decrease in mIPL density and progressive VF defects in corresponding areas despite lack of marked worsening in mNFL and mGCL thicknesses.[5] In a study analyzing thickness of RGCL-IPL complex, a similar correlation was reported with loss of local VF sensitivity at a central areas of approximately 8°.[22] In a study investigating effects of glaucoma in different retinal layers, Vianna et al.[24] suggested that IPL was thinner in relation with horizontal semi-field VF defects. In addition, Teixeira et al.[4] reported a strong correlation between GCC parameters and 24-2 GA.

In our study, we found strong positive correlations between VF MD and mIPL thickness as well as VF MD and mGCL thickness representing RGC bodies. The

segmentation analysis of inner retinal layers including IPL may provide valuable information to understand. RGC changes in glaucoma. Our findings should be supported by longitudinal studies and larger series; in particular, clinical relevance of mIPL thickness should be investigated in the diagnosis of early glaucoma.

It is valuable that a direct relationship between VF and inner retinal layers forming RGC was shown in our study. However, this study has also some limitations. Firstly, smaller sample size might have affected our results. In larger series, macular thickness measurements at different stages of glaucoma may reveal relationship between macular thicknesses and VF more definitively. In addition, due to cross-sectional design, we failed to perform longitudinal analysis of structural and functional data. Long-term studies are needed to link inner retinal changes with functional state in glaucomatous optic neuropathy. Secondly, it may be more appropriate to use 24-2c or central 10-2 VF in order to assess relationship between VF sensitivity and macular RNFL, GCL and IPL. It is well-known that 10-2 VF testing provides more valuable information than 24-2 VF testing in patients with parafoveal field defect.[11] In addition, assessment of localized VF defects in areas corresponding to thinning at inner retinal layers will provide valuable information regarding structure-function relationship.

In conclusion, longitudinal assessment of mIPL thickness, representing dendritic interactions, in larger series may open new horizons in developing novel structural testing strategies and directing treatment.

## REFERENCES


1. Kim EK, Park HL, Park CK. Segmented inner plexiform layer thickness as a potential biomarker to evaluate open-angle glaucoma: Dendritic degeneration of retinal ganglion cell. PLoS One. 2017;12:e0182404.
2. Chien JL, Ghassibi MP, Patthanathamrongkasem T, et al. Glaucoma Diagnostic Capability of Global and Regional Measurements of Isolated Ganglion Cell Layer and Inner Plexiform Layer. J Glaucoma. 2017;26:208-15.
3. Moghimi S, Fatehi N, Nguyen AH, et al. Relationship of the Macular Ganglion Cell and Inner Plexiform Layers in Healthy and Glaucoma Eyes. Transl Vis Sci Technol. 2019;8:27.
4. Teixeira IC, Bresciani-Battilana E, Barbosa DT, et al. Correlation between the ganglion cell complex and functional measures in glaucoma patients and suspects. Int Ophthalmol. 2015;35:81-7.
5. Aydın R, Barış M, Durmaz-Engin C, et al. Early localized alterations of the retinal inner plexiform layer in association with visual field worsening in glaucoma patients. PLoS One. 2021;16:e0247401.
6. Chong RS, Martin KR. Retinal ganglion cell dendrites and glaucoma: a case of missing the wood for the trees? Expert Review of Ophthalmology. 2014;9:3, 149-52.
7. Hammel N, Belghith A, Weinreb RN, et al. Comparing the Rates of Retinal Nerve Fiber Layer and Ganglion Cell-Inner Plexiform Layer Loss in Healthy Eyes and in Glaucoma Eyes. Am J Ophthalmol. 2017;178:38-50.
8. Sung KR, Wollstein G, Kim NR, et al. Macula assessment using optical coherence tomography for glaucoma diagnosis. Br J Ophthalmol. 2012;96:1452-5.
9. Medeiros FA, Lisboa R, Zangwill LM, et al. Evaluation of progressive neuroretinal rim loss as a surrogate end point for development of visual field loss in glaucoma. Ophthalmology 2014;121: 100-9
10. Curcio CA. Allen KA. Topography of ganglion cells in human retina. J Comp Neurol. 1990;300:5-25
11. Hood DC. Raza AS. de Moraes CG. Liebmann JM. Ritch R. Glaucomatous damage of the macula. Prog Retin Eye Res. 2013; 32:1-21.
12. Mwanza JC, Durbin MK, Budenz DL, et al. Glaucoma diagnostic accuracy of ganglion cell-inner plexiform layer thickness: comparison with nerve fiber layer and optic nerve head. Ophthalmology. 2012; 119: 1151-8.
13. Moura AL, Raza AS, Lazow MA, et al. Retinal ganglion cell and inner plexiform layer thickness measurements in regions of severe visual field sensitivity loss in patients with glaucoma. Eye. 2012;26:1188-93.
14. Tan O, Li G, Lu AT, et al. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology. 2008;115:949-56.
15. Park HY, Kim JH, Park CK. Alterations of the synapse of the inner retinal layers after chronic intraocular pressure elevation in glaucoma animal model. Mol Brain. 2014; 7: 53-64.
16. Weber AJ, Kaufman PL, Hubbard WC. Morphology of single ganglion cells in the glaucomatous primate retina. Invest Ophthalmol Vis Sci. 1998;39:2304-20.
17. Papadopoulos CM, Tsai SY, Alsbiei T, et al. Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat. Ann Neurol. 2002; 51: 433-41.
18. Zeimer R, Asrani S, Zou S, et al. Quantitative detection of glaucomatous damage at the posterior pole by retinal thickness mapping. Ophthalmology. 1998;105:224-31.
19. Shin HY, Park HL, Jung KI, et al. Glaucoma diagnostic ability of ganglion cell-inner plexiform layer thickness differs according to the location of visual field loss. Ophthalmology. 2014;121:93-9.
20. Tan O, Chopra V, Lu AT, et al. Detection of macular ganglion cell loss in glaucoma by fourier-domain optical coherence

tomography. Ophthalmology. 2009;116:2305-2314.

21. Lee WJ, Kim YK, Park KH, Jeoung JW. Trend-based analysis of ganglion cell-inner plexiform layer thickness changes on optical coherence tomography in glaucoma progression. Ophthalmology. 2017;124: 1383-91.
22. Raza AS, Cho J, de Moraes CG, et al. Retinal ganglion cell layer thickness and local visual field sensitivity in glaucoma. Arch Ophthalmol. 2011; 129: 1529-36.
23. Springelkamp H, Lee K, Wolfs RC, et al. Population-based evaluation of retinal nerve fiber layer, retinal ganglion cell layer, and inner plexiform layer as a diagnostic tool for glaucoma. Invest Ophthalmol Vis Sci. 2014;55:8428-38.
24. Vianna JR, Butty Z, Torres LA et al. Outer retinal layer thickness in patients with glaucoma with horizontal hemifield visual field defects. Br J Ophthalmol. 2019;103: 1217-22.