Original Article

DOI: 10.4274/haseki.galenos.2022.7540
Med Bull Haseki 2022;60:138-144

Optic Nerve Head and Macular Vascular Density Changes in Different Stage Glaucoma

Turker Oba*, Nilgun Solmaz**, Baris Komur***, Feyza Onder**

*Karaman Training and Research Hospital, Clinic of Ophthalmology, Karaman, Turkey

**University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Ophthalmology, Istanbul, Turkey

***Kastamonu Training and Research Hospital, Clinic of Ophthalmology, Kastamonu, Turkey

Abstract

Aim: The vascular theory is thought to have an important place in the pathophysiology of glaucoma. In the present study, we aimed to analyze the structural and vascular changes in both eyes of patients with glaucoma at different stages and to investigate the relationship between structural and vascular structures.

Methods: In this prospective cross-sectional study conducted between 2018 and 2019, 54 eyes of 27 patients with bilateral asymmetric glaucoma were included. Eyes with glaucoma were evaluated into 2 groups: an earlier stage and an advanced stage. All data is provided from the optical coherence tomography angiography (OCTA) device. The retinal nerve fiber layer (RNFL), ganglion cell inner plexiform layer (GCIPL) thickness, and rim area (RA) were measured using optical coherence tomography (OCT). The optic nerve head total (tVD), peripapillary (ppVD), intradisc (idVD), macular superficial (msVD), parafoveal (pasVD), perifoveal (pesVD), and deep macular vascular density values were compared with using OCTA. The correlation was investigated between thinning in the structural parameters and a decrease in the vascular density parameters.

Results: There was a significant difference in both optic nerve head vascular density parameters (tVD, ppVD) and superficial macular vascular density parameters between the eyes with asymmetric glaucoma ($p<0.001$). The thinning of macular GCIPL, which was very strongly correlated with the change in optic nerve perfusion (tVD, ppVD) ($r=0.899$ and 0.892, $p<0.001$), was well correlated with the change in msVD and pesVD ($r=0.642$ and 0.574). The correlation of RNFL with tVD and ppVD was high ($r=0.741$ and 0.813), and the correlation with msVD and pesVD was moderate ($r=0.480$ and 0.494). Macular pasVD, deep vascular density, and idVD showed no correlation with changes in structural parameters.

Conclusion: As the stage progresses, both the optic nerve head and macular perfusion are impaired in glaucoma. Macular superficial vascular density is affected more than deep vascular density. Thinning in the structural parameters correlates mostly with optic nerve head tVD and ppVD parameters.

Keywords: Optical coherence tomography angiography, glaucoma, microvascular density, angiography

Introduction

Glaucoma, which is a progressive group of optic neuropathies, is characterized by progressive degeneration of retinal ganglion cells (RGC) and axons, accompanied by optic disc changes and vision loss (1-3). The etiology of primary open-angle glaucoma (POAG) is multifactorial, and no single mechanism adequately describes the susceptibility to glaucomatous damage and variations in damage patterns (4). The vascular theory is based on the notion that abnormal perfusion of the optic nerve head (ONH) and this ischemia play an important role in glaucomatous damage (5). In previous studies, using methods such as fluorescein angiography, color Doppler imaging, confocal laser ophthalmoscopic angiography, and laser Doppler flowmetry, evidence has been shown of decreased peripapillary optic nerve perfusion in glaucoma patients (6-9). However, it has not been proven due to difficulties in accurately measuring ocular blood flow and ONH perfusion.

Optical coherence tomography angiography (OCTA), which has been developed recently, is a noninvasive

Address for Correspondence: Turker Oba
Karaman Training and Research Hospital, Clinic of Ophthalmology, Karaman, Turkey
E-mail: turkeroba89@hotmail.com ORCID: orcid.org/0000-0002-8694-5982
Received: 16.06.2021 **Accepted:** 27.01.2022

imaging method that can visualize and quantitatively evaluate vascularity in the retina, ONH, and peripapillary region with motion contrast created by erythrocytes and does not require a contrast agent injection (10). OCTA can evaluate the vascular density and blood flow of the ONH, the peripapillary retina, and macula (11). It has been shown that OCTA parameters such as blood flow index and capillary density of the ONH, the peripapillary retina, and macula are decreased in patients with glaucoma (12,14). Whether the reduction in vascular density is the effect or the cause of glaucoma is not fully known (15). Previous studies have focused more on papillary and peripapillary perfusion, and macular perfusion has received less attention in these studies. Additionally, these studies were conducted on the eyes of different patients at different stages and are subject to individual differences and the effects of the drugs used on vascular density.

This study aimed to evaluate the correlation between structural parameters [retinal nerve fiber layer (RNFL), ganglion cell complex, and rim area] and vascular parameters and to compare the ONH and macular perfusion between the two eyes of individuals with glaucoma at different stages to avoid systemic effects.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (number: 1648) and conducted between November 2018 and June 2019 in the glaucoma unit of the ophthalmology clinic and was performed in line with the principles of the Declaration of Helsinki. Informed consent for participation in the study was obtained from the patients.

Study Participants

This was a cross-sectional, prospective observational study that included 54 eyes of 27 POAG patients with glaucoma at different stages in both eyes according to at least two reliable visual field (VF) tests performed in the last month were included in the study. Eyes with glaucoma were evaluated into 2 groups: the early stage and the advanced stage. Patients with glaucomatous optic nerve change, structural damage on optical coherence tomography (OCT), IOP >21 mmHg, and without VF defects were defined as having preperimetric glaucoma. Glaucoma staging was applied according to the Hodapp-Anderson-Parrish classification (16). Patients were excluded from the study if they had any retinal or optic nerve disease other than glaucoma, were taking drugs that affect the macula or optic nerve, had hypertensive retinopathy, diabetes, visual acuity of 0.6, refractive error of >3.0 spherical, >2.5 astigmatism, ocular media opacity, or had undergone any intraocular surgery other than uncomplicated phacoemulsification surgery.

All patients included in the study had visual acuity, refraction, biomicroscopy, fundus examination, gonioscopy, Goldman applanation tonometry, ultrasonic pachymetry, standard automatic perimetry, OCT, and OCTA scans performed on them. VF assessment was performed using the SITA-standard 24-2 VF test (Humphrey Instruments, Model 740, San Leandro, CA). VF tests with a loss of fixation, false positive, and negative response of 20% were considered reliable.

Optical Coherence Tomography Imaging

For OCT measurements, Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA) was used for OCT imaging. Only shots with a signal strength of 6 or above were evaluated. Macular ganglion cell inner plexiform layer (GCIPL) (Macular 512x128 Cube protocol), RNFL, and ONH analysis (Optic Disc 200x200 Cube protocol) were performed. Mean RNFL, GCIPL thickness, and rim area were evaluated.

Optical Coherence Tomography Angiography Imaging

OCTA measurements; OCTA was examined with an AngioVue (RTVue-XR, Optovue, Inc.; Fremont; California, USA; software version 2016.2.035) device. Shots with a signal strength of ≥ 6 were evaluated. Optic nerve vascular density measurements were made in the 4.5x4.5 mm area where the ONH was centered, and macular vascularity measurements were made in the fovea-centered area of 6x6 mm. Peripapillary vascular density was measured between the inner surface of the inner limiting membrane (ILM) and the outer surface of the RNFL. Macular superficial vascular density (msVD) was evaluated between the inner surfaces of the ILM and the outer surface of the inner plexiform layer (IPL). The macular deep vascular density (mdVD) was automatically measured between the outer surface of the IPL and the outer surface of the outer plexiform layer. Parafoveal vascular density was calculated through a 1-mm-wide circular ring with an inner diameter of 1 mm and an outer diameter of 3 mm in the fovea-centered area, and perifoveal vascular density was calculated through a 1.5-mm-wide circular ring with an inner diameter of 3 mm and an outer diameter of 6 mm.

The OCTA parameters of the optic nerve and macula in eyes at different stages of glaucoma were compared and correlations with OCT parameters (mean RNFL, mean GCIPL, rim area) were investigated. Optic nerve parameters, which were total vascular density (tVD), peripapillary vascular density (ppVD), intradisc vascular density (idVD), and macular parameters, which were

msVD, parafoveal superficial vascular density (pasVD), perifoveal superficial vascular density (pesVD), mdVD, parafoveal deep vascular density (padVD), and perifoveal deep vascular density (pedVD), were evaluated.

Statistical Analysis

The data analysis was performed using SPSS statistical software (version 15.0; SPSS Inc., Chicago, Illinois). For categorical variables, descriptive statistics were expressed as a number and a percentage, while numerical variables were expressed as a mean, standard deviation, minimum, and maximum value. Dependent group analyses were performed with the Paired t-test when the differences in numerical variables met the normal distribution condition. Relationships between numerical variables were analyzed using Pearson Correlation analysis when the parametric test condition was met, and with Spearman Correlation analysis when the parametric test condition was not met. The statistical significance level of alpha was set at $p<0.05$.

Results

The study consisted of 27 patients, 12 females, and 15 males. The age range of the patients is between 42 and 81. There were 18 POAG (33.3%) and 9 pseudoexfoliative (PEX) (66.7%) glaucoma patients. The glaucoma stages were determined as in nine patients, one eye was preperimetric and the fellow eye was at the early-moderate stage, ten patients had one eye at the early stage and the fellow eye at a moderate-advanced stage, and eight patients had one eye at a moderate stage and the fellow eye at an advanced stage. While seventeen of the patients were using beta-blocker and dorzolamide combinations and brinzolamide, ten of them were using prostaglandin analog and beta-blocker combinations. There was no significant difference between the two eyes of the patients in terms of drug use.

The mean deviation (MD) values in earlier and advanced stage eyes with asymmetric stage glaucoma were -4.4±3.6 and -13.2±9.0, respectively, while pattern standard deviation (PSD) values were -3.7±2.9 and 6.9±2.9, respectively (Table 1). We observed that the measurements were significantly lower in the eyes of patients with more advanced stage glaucoma (Table 2).

When the optic nerve perfusion was evaluated between eyes with asymmetric glaucoma, it was observed that the total and peripapillary vascular density were statistically significantly decreased in the more advanced eyes ($p<0.001$) (Table 3).

When msVD was examined; msVD, pasVD, and pesVD were significantly lower in the more advanced stages ($p<0.001$). When mdVD was examined, there was a statistically significant difference between mdVD, padVD, and pedVD in eyes at different stages ($p<0.05$) (Table 3).

The relationship was examined between thinning in structural parameters and changes in vascular parameters among eyes with asymmetric glaucoma. We observed that the structural parameter of GCIPL had the strongest correlation with tVD, ppVD, and pesVD ($r=0.899$, 0.892, and 0.674, respectively, $p<0.001$). RNFL and rim area, which correlated highly with tVD and ppVD, correlated moderately with msVD and pesVD (Table 4).

Discussion

Recent studies have shown that peripapillary vascular densities measured by OCTA are as sensitive as RNFL in the diagnosis of glaucoma (17-19). Moreover, the relationship between peripapillary tVD, ppVD, and functional loss has been reported to be stronger than the relationship between structural loss and functional loss, and vascular density better reflects ganglion cell function than structural loss (20,21). There are also studies reporting that OCTA detects pre-perimetric glaucoma better than OCT (21-23). It has also been suggested that as the stage of glaucoma progresses, while the benefit of OCT parameters decreases due to the basal effect, the decrease in vascular density can be followed with OCTA. The new and noninvasive technology seems to be promising and useful for the early diagnosis, staging, and follow-up of glaucoma patients (23-26).

In this study, similar to the literature, it was found that as the stage of glaucoma progressed, ONH perfusion decreased. In the same patient's eye with more advanced glaucoma, a significant reduction was observed in both tVD and ppVD values compared to the earlier stage eye. Like these findings, Lommatzsch et al. (27) found significantly lower tVD values in patients with glaucoma compared to the control group. In the same study, ppVD was examined on average and in 6 sectors (superior-nasal, superior-temporal, nasal, inferior-nasal, inferior-temporal, and temporal), and a significant decrease was determined in both the average value and in all sectors.

Yarmohammadi et al. (23) investigated the diagnostic capacities of vascular density (VD) parameters in studies of healthy eyes with suspected glaucoma and glaucoma and stated that tVD has a better diagnostic value compared to ppVD. This was attributed to the fact that the device used a larger measurement area during tVD measurement and was better able to detect changes in axons located eccentrically along the temporal vessels. Chen et al. (28) found a significantly lower rate of idVD in glaucomatous eyes compared to healthy eyes. The same finding was reported in the study by Lommatzsch et al. (27). Hou et al. (29) reported that they found a decrease in peripapillary vessel density in the POAG group, but they did not observe a statistical difference in the inner disc. Although there was a significant difference in idVD values between eyes with

Table 1. Ocular and systemic findings of the cases			
	Earlier stage	**Advanced stage**	**P-value**
Age, mean ± SD	64.1±11.1	64.1±11.1	-
Gender (male/female)	15/12	15/12	-
Spherical equivalent (D), mean ± SD	-1.25 (-0.5 to -2.25)	-1.5 (-0.75 to -2.25)	0.391
SAP MD (dB), mean ± SD	-4.4±3.6	-13.2±9.0	**<0.001**
SAP PSD (dB), mean ± SD	-3.7±2.9	6.9±2.9	**<0.001**
Systolic BP (mmHg)	130 (120 to 140)	130 (120 to 140)	1.000
Diastolic BP (mmHg)	75 (60 to 95)	75 (60 to 95)	1.000
Use of topical glaucoma medication, n (%)	100	100	-
IOP (mmHg)	16 (13 to 18)	15 (13 to 18)	0.867
CCT (µm)	530 (524 to 552)	534 (520 to 557)	0.741

SAP: Standard automated perimetry, MD: Mean deviation, PSD: Pattern standart deviation, BP: Blood pressure, IOP: Intraocular pressure, CCT: Central corneal thickness, SD: Standart deviation

asymmetric glaucoma in the current study, this difference was not as statistically significant as tVD and ppVD.

In this study, superficial and deep macular perfusion parameters were also evaluated together with optic nerve perfusion. In the comparisons of eyes with asymmetric glaucoma, the msVD, pasVD, and pesVD values were significantly lower in eyes with more advanced glaucoma. Other studies in the literature have reported different results regarding the change in macular vascular density in glaucoma patients. Penteado et al. (30) reported that the VD of the perifoveal area of the macula scan performed better than the parafoveal area of either scan size when differentiating between healthy and mild glaucoma. Khayrallah et al. (31) found that the pasVD and msVD were decreased in glaucoma proportionally to its severity. Unlike this study, Triolo et al. (13) found that there was no statistically significant difference between the groups in the mean or sectorial values of msVD in healthy, suspected glaucoma, and POAG patients and reported that msVD was not useful in the diagnosis of glaucoma (16). In the same study, although there was a statistically significant difference in the superior, inferior, and temporal sector ppVD values between the groups, there was no difference in the mean ppVD. This situation could be explained in two ways. The first is that structural damage occurs first and vascular damage later, and the second theory is that OCTA is not as sensitive as OCT in detecting early changes. Yarmohammadi et al. (25) also reported that msVD did not differ in glaucoma patients with unilateral VF defects, although there was a difference in VF, structural parameters, and ppVD between the two eyes. This was partly attributed to the smaller difference in mean vessel density measurements in the macular region compared to the peripapillary region. In contrast to those studies, Chen et al. (18) reported that the diagnostic performance of msVD was as good as ppVD (17).

Table 2. Optical coherence tomography parameters in eyes with asymmetric glaucoma			
OCT parameters	**Earlier stage**	**Advanced stage**	**P-value***
RNFL (µm)	88.8±14.1	68.3±15.0	**<0.001**
GCIPL (µm)	81.2±9.5	66.3±12.3	<0.001
Rim Area (mm^2)	1.36±0.31	0.91±0.33	**<0.001**

RNFL: Retinal nerve fiber layer, GCIPL: Ganglion cell inner plexiform layer
*Comparison was performed by using Paired t-test

Of the deep macular vascular density parameters examined in the current study, the mdVD, padVD, and pedVD values were also decreased in more advanced eyes compared to earlier stage eyes. Although this difference was statistically significant, it was not as significant as the superficial vascular density. Similarly, Takusagawa et al. (32) examined the superficial and deep capillary plexus vascularity in the macular area and stated that glaucoma affects the superficial plexuses rather than the deep plexuses. Some studies showed that the glaucoma diagnostic capabilities of superficial parafoveal and perifoveal vascular density were significantly better than those of deep perifoveal and parafoveal vascular density, regardless of the glaucoma stage (33,34).

When the correlations were examined between the thinning in structural parameters and the decrease in ONH and macular vascular density parameters due to glaucoma, there was a strong positive correlation between the decrease in RNFL, rim area, GCIPL thickness, and the decrease in tVD and mean ppVD values. While the correlation between GCIPL and tVD and ppVD was compelling, the correlation of RNFL and rim area with tVD and ppVD was also high. There was no correlation between structural parameters and changes in idVD. A statistically significant correlation was determined between the msVD parameters, such as msVD and pesVD, and the RNFL, GCIPL, and rim area. There was a high correlation of GCIPL with msVD and pesVD, while the

Table 3. Optic nerve and macular perfusion in eyes with asymmetric glaucoma

Optic nerve head and retinal vascular density (%)	Earlier stage	Advanced stage	P-value*
tVD	46.9±5.1	37.8±7.4	**<0.001**
ppVD	49.2±6.2	38.4±9.5	**<0.001**
idVD	48.7±4.3	44.5±7.3	**0.003**
msVD	47.7±5.2	40.4±6.0	**<0.001**
pasVD	49.7±6.0	44.7±6.2	**<0.001**
pesVD	48.5±5.2	40.9±6.3	**<0.001**
mdVD	50.3±5.3	46.8±5.9	**0.008**
padVD	54.6±3.7	52.5±4.8	**0.021**
pedVD	51.6±6.3	48.2±6.2	**0.009**

tVD: Total vascular density, ppVD: Peripapillary vascular density, idVD: Intradisc vascular density, msVD: Macular superficial vascular density, pasVD: Parafoveal superficial vascular density, pesVD: Perifoveal superficial vascular density, mdVD: Macular deep vascular density, padVD: Parafoveal deep vascular density, pedVD: Perifoveal deep vascular density
*Comparison was performed by using Paired t-est

Table 4. The correlation between thinning in structural parameters and decreasing vascular parameters in eyes with asymmetric glaucoma

Optic nerve head and retinal vascular density (%)	RNFL		Rim Area		GCIPL	
	r	p*	r	p*	r	p*
tVD	0.749	**<0.001**	0.773	**<0.001**	0.899	**<0.001**
ppVD	0.741	**<0.001**	0.813	**<0.001**	0.892	**<0.001**
idVD	-0.255	0.199	-0.202	0.313	-0.165	0.420
msVD	0.480	**0.011#**	0.494	**0.009#**	0.642	**<0.001#**
pasVD	-0.058	0.775	0.005	0.981	0.159	0.438
pesVD	0.487	**0.010#**	0.499	**0.008#**	0.674	**<0.001#**
mdVD	-0.020	0.923	0.119	0.553	-0.114	0.580
padVD	-0.071	0.726	0.073	0.718	-0.207	0.311
pedVD	0.066	0.742	0.092	0.650	-0.101	0.624

RNFL: Retinal nerve fiber layer, GCIPL: Ganglion cell inner plexiform layer, tVD: Total vascular density, ppVD: Peripapillary vascular density, idVD: İntradisc vascular density, msVD: Macular superficial vascular density, pasVD: Parafoveal superficial vascular density, pesVD: Perifoveal superficial vascular density, mdVD: Macular deep vascular density, padVD: Parafoveal deep vascular density, pedVD: Perifoveal deep vascular density
*Comparison was performed by using Pearson correlation analysis
#Comparison was performed by using Spearman correlation analysis

correlation of RNFL and rim area with msVD and pesVD was moderate. It is not surprising that there is a statistically significant positive relationship between GCIPL and msVD and pesVD, due to the feeding of the macular GCIPL from the superior capillary plexus (12) and the concentration of RGC in the perifoveal region. Interestingly, the correlation of GCIPL with tVD and ppVD was seen to be stronger than its correlation with msVD and pesVD. There are conflicting findings in the literature about the relationship between OCTA and structural parameters. Most studies have shown a high correlation between tVD and ppVD with structural parameters (26-28,35-37). Mansoori et al. (38) reported that sector-based ppVD reduction correlated with RNFL thinning in the same sector, but mean ppVD did not correlate with mean RNFL and rim area. However, that study included patients with early glaucoma, and compared with the control group, ppVD differed only in the superotemporal and inferotemporal sectors. While Triolo et al. (13) found a strong correlation between mean RNFL and ppVD values in glaucoma patients, no correlation was determined for either GCIPL or RNFL with msVD (16). Richter et al. (39) also reported that peripapillary vascular density has slightly better diagnostic performance than macular superficial density and that msVD correlates with functional parameters rather than structural parameters.

These results, both in the current study and in similar studies in the literature, point to a significant relationship between vascular and structural parameters and support the vascular theory of the pathogenesis of glaucoma. GCIPL thickness has a more significant relationship with peripapillary perfusion than macular perfusion, suggesting

that the ONH circulation is responsible for apoptosis and subsequent axonal degeneration in ganglion cells rather than macular perfusion. Further research is needed on this subject.

Study Limitations

This study had some limitations, primarily the small sample size, and although the patients had glaucoma with asymmetric involvement, the glaucoma stages were different in each patient. Using average values instead of sectoral values in the vascular density measurements could be interpreted as another deficiency of the study. Another limitation was that the axial lengths of the patients were not taken as a study parameter. Although the axial length differences may affect the structural and vascular parameters (40), it was attempted to minimize this situation with the refraction range values found in the inclusion criteria. Despite these limitations, the strongest aspect of the study was that the systemic factors were eliminated due to the fact that both eyes of the same patients were included in the study.

Conclusion

Our study showed that both ONH and macular perfusion decrease as glaucoma progresses, independent of systemic factors. In the relationship between structural and vascular parameters, local perfusion reduction in the optic nerve head is significantly correlated with thinning of the RNFL thickness, while the high correlation between ganglion cell thickness and ONH perfusion suggests that axonal degeneration has an important place in ganglion cell deaths in addition to local perfusion. Both the ONH and the macular superficial VD decrease in glaucoma. However, ischemia in the peripapillary region shows a stronger correlation with structural parameters.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (number: 1648).

Informed Consent: Informed consent for participation in the study was obtained from the patients.

Authorship Contributions

Concept: T.O., Design: N.S., Data Collection and/or Processing: F.O., Analysis and/or Interpretation: B.K., Literature Research: T.O., Writing: T.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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