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Rada Zečević[1,♣], Sunčica Srećković[2,3], Marko Kontić[1]

Optical coherence tomography angiography microvascular changes in the macular region in open-angle glaucoma

Микроваскуларне промене у жутој мрљи мерене оптичком кохерентном томографијом са ангиографијом код болесника са глаукомом отвореног угла

[1]Belgrade Ophthalmology Center Special Ophthalmology Hospital, Belgrade, Serbia;
[2]Kragujevac University Clinical Center, Clinic of Ophthalmology, Kragujevac, Serbia;
[3]University of Kragujevac, Faculty of Medical Sciences, Department of Ophthalmology, Kragujevac, Serbia

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♣Correspondence to:
Rada ZEČEVIĆ
Belgrade Ophthalmology Center Special Ophthalmology Hospital, 27. Marta 17–19 Street, 11000 Belgrade, Serbia
E-mail: **radiculjak_2901@yahoo.com**

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Микроваскуларне промене у жутој мрљи мерене оптичком кохерентном томографијом са ангиографијом код болесника са глаукомом отвореног угла

SUMMARY

Introduction/Objective Glaucoma is the leading cause of irreversible blindness worldwide. It is hypothesized that glaucomatous microvascular changes in superficial capillary plexus (SCP) may lead to early structural damage and correlate with visual field defects. The aim of this study was to quantitatively analyze microvascular characteristics of the SCP in the macular region of healthy eyes and in eyes with varying severity of open-angle glaucoma (OAG) with optical coherence tomography angiography (OCT-A).

Methods A total of 144 eyes was included in this cross-sectional study, 109 eyes with confirmed OAG and 35 healthy eyes. Based on Hodapp-Anderson-Parrish classification, patients were categorized into early, moderate and severe stage glaucoma. All subjects underwent visual field, optical coherence tomography and OCT-A examinations.

Results Significant reductions were observed in macular vessel density across glaucoma stages. Foveal vessel density decreased from 23 ± 1.9% in normal eyes to 13.9 ± 1.8% in severe glaucoma. Foveal and parafoveal vessel densities were significantly reduced even in early-stage glaucoma. OCT parameters progressively decreased with glaucoma severity. Total ganglion cell complex (GCC) thickness decreased from 108.5 ± 5.6 μm in healthy eyes to 61.2 ± 6.9 μm in severe glaucoma eyes. Total peripapillary retinal nerve fiber layer (pRNFL) thickness decreased from 106.2 ± 7.9 μm in healthy eyes to 48.7 ± 7.5 μm in severe glaucoma.

Conclusion Our findings support the hypothesis that macular vessel density decreases progressively with glaucoma severity. These results reinforce the potential clinical utility of OCT-A in detecting early glaucoma and monitoring disease progression.

Keywords: glaucoma; vascular density; intraocular pressure; optical coherence tomography

САЖЕТАК

Увод/Циљ Глауком представља водећи узрок иреверзибилног слепила у свету. Микроваскуларне глаукоматозне промене на нивоу површног капиларног плексуса у жутој мрљи, могу да доведу до структуралних промена које корелирају променама у видном пољу. Циљ ове студије је да се квантитативно анализира површни васкуларни плексус жуте мрље код здравих очију и очију са глаукома отвореног угла различитог стадијума, употребом оптичке кохерентне томографије са ангиографијом (OCT-A).

Методе У студију је укључено 144 очију, 109 са дијагнозом глаукома отвореног угла и 35 здравих очију. Према Ходап–Андерсон–Паришовој класификацији учињена је даља подела на рани, средњи и узнапредовали стадијум глаукома. Свим болесницима је урађено компјутеризовано видно поље, оптичка кохерентна томографија и *OCT-A*.

Резултати Уочена је статистички значајна редукција густине крвних судова жуте мрље у свим стадијумима глаукома. Фовеална густина крвних судова је редукована са 23 ± 1,9% код здравих очију на 13,9 ± 1,8% код узнапредовалог стадијума глаукома. Фовеална и парафовеална густина крвних судова је значајно редукована и у раном стадијуму болести. *OCT* параметри су се прогресивно смањивали са тежином обољења. Укупна вредност дебљине ганглијског ћелијског комплекса је редукована са 108,5 ± 5,6 *μm* код здравих очију на 61,2 ± 6,9 *μm* у узнапредовалом глаукому. Укупна дебљина перипапиларних нервних влакана ретине је смањена са 106,2 ± 7,9 *μm* код здравих на 48,7 ± 7,5 *μm* у узнапредовалом стадијуму глаукома.

Закључак Густина крвних судова жуте мрље се прогресивно смањује са напредовањем болести. Ови резултати подстичу потенцијалну употребу оптичке кохерентне томографије са ангиографијом у клиничкој пракси за детектовање раног стадијума глаукома, као и за праћење његове прогресије.

Кључне речи: глауком; жута мрља; интраокуларни притисак; густина крвних судова

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide. It is a multifactorial optic neuropathy characterized by progressive loss of retinal ganglion cells (RGCs) and their axons in both the macular and peripapillary regions with characteristic structural changes in the optic

nerve head (ONH) and corresponding functional visual field defects [1]. Among the many risk factors for glaucoma, intraocular pressure (IOP) is the only modifiable one. It is estimated that in 2020, approximately 76 million people were affected by glaucoma, with projections indicating a 74% increase by 2040 [2].

The primary goal of glaucoma treatment is to preserve patients' visual function and quality of life, at acceptable cost [1]. Lowering IOP is currently the only proven treatment to slow disease progression [3]. However, some patients continue to experience deterioration despite achieving target IOP, suggesting that optic nerve ischemia and reduced ocular blood flow contribute to glaucoma pathogenesis and progression [4, 5].

Optical coherence tomography angiography (OCT-A) is a novel, non-invasive imaging modality that provides detailed visualization of the retinochoroidal microvasculature, including blood flow around the ONH and macula, without the need for contrast dyes [6]. Because RGCs are predominantly supplied by the superficial macular vascular complex, it is hypothesized that glaucomatous microvascular changes in this layer may lead to early structural damage and correlate with visual field defects [7, 8]. Therefore, the macular region is considered a strategic location for detecting and monitoring glaucoma progression.

The aim of this study was to quantitatively analyze microvascular characteristics of the superficial capillary plexus (SCP) in the macular region of healthy eyes and in eyes with varying severity of open-angle glaucoma (OAG). Additionally, we sought to investigate correlations between macular vessel density and traditional structural and functional parameters of glaucoma.

METHODS

Study design

Subjects

A total of 109 eyes from patients aged ≥ 40 years with confirmed OAG in at least one eye was included. The control group comprised 35 healthy eyes from individuals over 40 years of age.

All participants underwent a comprehensive ophthalmic examination, including: best-corrected visual acuity (BCVA) using the Snellen chart, slit-lamp biomicroscopy, IOP measurement with Goldmann applanation tonometry, central corneal thickness (CCT) measurement (Topcon Aladdin Optical Biometer, Oakland, CA, USA), gonioscopy using a Goldmann contact lens, dilated fundus examination, standard automated perimetry (SAP) using Octopus 600 (Haag-Streit, Mason, OH, USA), OCT imaging of the ONH and macula, including retinal fiber layer

(RNFL) and ganglion cell complex (GCC) thickness measurements, macular vessel density assessment via OCT-A (Topcon Maestro 2, IMAGEnet6 software, Oakland, CA, USA).

Inclusion criteria

Age ≥ 40 years, confirmed diagnosis of OAG for at least one year, open anterior chamber angle on gonioscopy.

The control group included eyes with: IOP ≤21 mmHg, no history of elevated IOP, normal optic nerve appearance with intact neuroretinal rims and RNFL, normal visual field with no defects.

Exclusion criteria

Exclusion criteria for both healthy and glaucoma groups included: BCVA< 0.2, spherical refraction ≥5D or myopia >4D, pregnancy or breastfeeding, other types of glaucoma (angle-closure), age-related macular degeneration or other inherited/acquired macular diseases, uveitis, diabetic or hypertensive retinopathy/maculopathy, corneal diseases, history of ocular trauma or previous ocular surgeries (except cataract and glaucoma surgery), non-glaucomatous optic neuropathy, use of medications affecting retinal function (tamoxifen, antimalarial, phenothiazine, canthaxanthin, methoxyflurane), neurological disorders (Alzheimer's, Parkinson's, dementia, stroke).

Glaucoma classification

Based on the Hodapp-Anderson-Parrish classification, patients were categorized into:

• Early-stage glaucoma: Mean deviation (MD) > -6 dB

• Moderate-stage glaucoma: MD between -6 and -12 dB

• Severe-stage glaucoma: MD < -12 dB

• Control group: Healthy eyes

OCT Angiography and Structural Measurements

OCT-A Measurements

OCT-A scans were performed using the Topcon Maestro 2 (IMAGEnet6 software, Oakland, CA, USA). This device uses an 840 nm light source with an A-scan rate of 50.000 scans per second, providing high-resolution 3D visualization of retinal vasculature.

Superficial vessel density (SVD) was automatically calculated as the percentage of the scanned area occupied by blood vessels. Measurements focused on the SCP, spanning from the internal limiting membrane (ILM) to the inner plexiform layer (IPL).

A 3×3 mm² field centered on the fovea was analysed, with density assessed in:

• Foveal zone (1 mm diameter)

• Parafoveal zones (1–3 mm): Superior, inferior, nasal, and temporal sectors

OCT and OCT-A image quality review was completed according to the Imaging Data Evaluation and Analysis Reading Center protocol on all scans using standard Topcon Maestro 2 software (IMAGEnet6 software). Poor-quality scans were excluded from the study and analysis if one of the following criteria was met: signal strength index < 45, poor clarity, residual motion artifacts, image cropping or local weak signal due to vitreous floaters, segmentation errors, or images with off-center fovea.

OCT structural measurements

All participants underwent ONH and macular imaging, with measurements including:

• ONH: Disc area, rim area, cup-to-disc (C/D) ratios, and RNFL thickness

• GCC: Thickness from ILM to inner nuclear layer, including nerve fiber, ganglion cell, and IPL layers

Statistical analysis

Results are presented as mean ± standard deviation, median (25th-75th) and number (%). Graphical and mathematical methods are used to examine data distribution. Groups were compared using Chi Square test. Data were analysed with One Way ANOVA Kruscall Wallis test when three groups are compared. For One way ANOVA significant differences Tuckey post hoc analysis was used. Afterward Kruscall Wallis test MannWhiteney test was used as posthoc test. All $p< 0.05$ were considered statistically significant. Statistical analysis was performed by IBM SPSS Statistics 26 (IBM SPSS Inc., Chicago, IL).

Ethics: This cross-sectional study was approved by the Research Ethics Committee of the Belgrade Ophthalmology Center Special Eye Hospital on November 9, 2022 (approval number: 3/30/2022). The study was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

A total of 35 healthy eyes, 44 early-stage glaucoma eyes, 34 moderate-stage glaucoma eyes, and 31 severe-stage glaucoma eyes met the inclusion criteria.

Demographic and clinical characteristics of normal, early, moderate, and severe OAG eyes are presented in Table 1. The mean age increased progressively from normal eyes (55.8 years) to severe glaucoma (67.1 years). The proportion of males increased significantly with disease severity ($p = 0.005$), with severe glaucoma patients being predominantly male (77.4%). BCVA declined with increasing severity of glaucoma ($p = 0.003$). CCT decreased with increasing glaucoma severity ($p = 0.007$). The linear C/D ratio increased with disease severity ($p < 0.001$). Post hoc tests showed significant differences between all severity levels ($p < 0.001$). Similar to the linear C/D ratio, the vertical C/D ratio significantly increased with severity ($p < 0.001$), with all pairwise comparisons being statistically significant ($p < 0.001$). No statistically significant difference in IOP was observed between the groups ($p = 0.68$). MD worsened with increasing glaucoma severity ($p < 0.001$). Post hoc tests showed significant differences between all groups ($p < 0.001$), confirming progressive visual field loss across stages.

The data on structural characteristics of normal, early, moderate, and severe OAG eyes are presented in Table 2. Total GCC thickness progressively decreased with increasing glaucoma severity, from 108.5 ± 5.6 μm in healthy eyes to 61.2 ± 6.9 μm in severe glaucoma eyes ($p < 0.001$). Tukey HSD tests revealed significant differences between normal and moderate glaucoma (mean difference: –30.9 μm, $p < 0.001$) and between normal and severe glaucoma (mean difference: –47.3 μm, $p < 0.001$). Both superior and inferior GCC thickness decreased significantly across all stages of glaucoma ($p < 0.001$). Pairwise comparisons showed significant differences between normal and early glaucoma, as well as between early and moderate glaucoma (all $p < 0.001$).

Regarding peripapillary RNFL (pRNFL) thickness, a progressive reduction was observed with increasing disease severity ($p < 0.001$). Total pRNFL thickness decreased from 106.2 ± 7.9 μm in healthy eyes to 48.7 ± 7.5 μm in severe glaucoma. Pairwise comparisons showed significant differences between normal and early ($p < 0.001$), early and moderate ($p < 0.001$), and moderate and severe glaucoma groups ($p < 0.001$). Similar trends were observed for superior and inferior pRNFL thickness ($p < 0.001$). The average macular thickness decreased significantly with increasing glaucoma severity ($p < 0.001$), from 279.7 ± 11.1 μm in healthy eyes to 237.3 ± 14.7 μm in severe glaucoma.

The data on superficial macular vessel density in different retinal regions are presented in Table 3, Figure 1. Foveal vessel density progressively decreased from 23 ± 1.9% in healthy eyes to 13.9 ± 1.8% in severe glaucoma ($p < 0.001$). Post hoc analysis showed significant reductions between normal and early glaucoma (mean difference: 4.89%, $p < 0.001$), normal and moderate glaucoma (6.81%, $p < 0.001$), and normal and severe glaucoma (9.13%, $p < 0.001$). Differences between early and moderate glaucoma (1.92%, $p < 0.001$) and early and severe glaucoma (4.24%, $p < 0.001$) were also statistically significant.

Parafoveal vessel density in the superior sector declined significantly from 44.3 ± 2.5% in healthy eyes to 37.2 ± 3.5% in severe glaucoma ($p < 0.001$). Parafoveal vessel density in the inferior sector exhibited a similar pattern, decreasing from 45.4 ± 3.2% in healthy eyes to 36.7 ± 2.5% in severe glaucoma ($p < 0.001$). Parafoveal vessel density in the temporal sector was significantly lower in glaucoma eyes, decreasing from 44.8 ± 2.8% in normal eyes to 39 ± 2.9% in severe glaucoma ($p < 0.001$). Post hoc comparisons revealed a significant difference between normal and severe glaucoma (5.75%, $p < 0.001$), while differences between early and moderate glaucoma were not statistically significant. Parafoveal vessel density in the nasal sector also declined with disease progression, from 45.1 ± 2.8% in healthy eyes to 41.3 ± 3.1% in severe glaucoma ($p < 0.001$). Post hoc analysis between normal and early glaucoma showed significant differences for all parameters except for temporal and nasal parafoveal vessel density.

The correlation between OCT-A vessel density measurements and structural parameters in glaucoma group are presented in Table 4. A strong positive correlation was observed between total GCC thickness and macular vessel density measurements in all parafoveal sectors, with the highest correlation found in foveal region ($r = 0.602$, $p < 0.001$) followed by the the temporal sector ($r = 0.557$, $p < 0.001$). Significant correlations were also noted in the superior, inferior, and nasal parafoveal regions ($p < 0.001$; $p< 0.001$; 0.025). Conversely, linear and vertical C/D ratio exhibited strong negative correlations with vessel density parameters. The strongest negative correlation for the linear C/D ratio was in the foveal region ($r = -0.607$, $p < 0.001$), and for the vertical C/D ratio, the most pronounced correlation was, as well, in the foveal region ($r = -0.579$, $p < 0.001$). Total pRNFL thickness was positively correlated with vessel density, with the strongest correlation observed in the foveal region ($r = 0.536$, $p < 0.001$).

DISCUSSION

Both the mechanical and vascular theories are considered to play a crucial role in the pathogenesis and progression of glaucoma. While mechanical factors, such as increased IOP and ONH

deformation, have been extensively studied, the vascular hypothesis remains an area of growing interest. The vascular influence, particularly in macular region, warrants further investigation, as this area is frequently affected in glaucoma [9]. The irreversible loss of RGCs is believed to be caused, at least in part, by insufficient blood supply. Given their high metabolic demand, RGCs are heavily dependent on the SCP for perfusion. Their unequal distribution within the retina, with the highest concentration in the macular region, suggests that macular vessel density changes may play a role in glaucomatous disease progression [10].

To further explore these vascular changes, we measured and compared macular SVD across different stages of OAG using the Topcon Maestro 2 OCT and OCT-A device. We also assessed the correlations between capillary vessel density and structural parameters.

Our study confirmed that total GCC thickness progressively decreased with increasing glaucoma severity, consistent with findings from Srivastava et al. study [11]. Both superior and inferior GCC thickness decreased significantly across glaucoma stages, which aligns with findings from Soares et al. [12]. Moreover, pairwise comparisons confirmed significant differences between normal and early glaucoma, supporting results from Hasanen et al. [13].

These findings reinforce previous reports suggesting that glaucomatous damage primarily affects the inner retinal layers, leading to the thinning of these structures.

Regarding the pRNFL thickness, we found a significant reduction in all glaucoma stages. Similar trends were observed for superior and inferior RNFL thickness, aligning with findings from previous studies [14]. However, in contrast to our results, Bhat et al. reported that inferior pRNFL thinning was the most sensitive marker for glaucoma detection across all disease stages [15].

Our results, in line with previous research, found that macular SVD was significantly reduced in glaucoma eyes compared with healthy controls [16]. Specifically, foveal vessel density progressively decreased with glaucoma severity, consistent with study conducted by Hwang et al. [17].

Parafoveal vessel density declined significantly across all disease stages, with notable reductions in superior, inferior, temporal, and nasal sectors. The nasal parafoveal vessel density also declined with disease progression, although post-hoc analysis showed that differences between normal and early glaucoma were not significant for temporal and nasal parafoveal vessel density. This could be explained by the fact that these regions have higher vessel density in healthy eyes [18].

Kurysheva et al. found that SVD was more sensitive than GCC thickness in distinguishing early glaucoma from healthy eyes [19], supporting the idea that vascular changes may precede structural thinning in some cases.

To further explore the relationship between vascular and structural changes, we analysed correlations between macular vessel density and retinal structural parameters. Our results showed a strong positive correlation between total GCC thickness and macular vessel density across all parafoveal sectors, with the strongest correlation in the foveal region, followed by the temporal sector. However, it remains unclear whether RGC loss is primarily driven by vascular insufficiency or whether vessel density reductions are a secondary consequence of structural damage. Conversely, linear and vertical C/D ratios exhibited strong negative correlations with vessel density parameters, indicating that larger C/D ratios are associated with reduced vessel desnity. Total pRNFL thickness was positively correlated with vessel density, with the strongest correlation in the foveal region.

This study has several limitations that should be acknowledged. First, all patients were using different antiglaucoma medications, which could potentially influence ocular blood flow and retinochoroidal vessel measurements. Second, we used a 3×3 mm² scan instead of a 6×6 mm² scan, which might have led to different conclusions. Considering that RGCs are more concentrated in the perifoveal rather than the foveal and parafoveal regions, a larger scan size may yield different results. Last, this study does not provide longitudinal data on structural and functional changes over time. A longitudinal study would offer a more robust evaluation of the relationship between macular microvascular perfusion and glaucomatous optic neuropathy progression.

CONCLUSION

Our findings support the hypothesis that macular vessel density decreases progressively with glaucoma severity and that vascular and structural parameters are closely correlated. These results reinforce the potential clinical utility of OCT-A in detecting early glaucoma and monitoring disease progression. Future studies should aim to clarify the causal relationship between vascular insufficiency and RGC loss and further explore the longitudinal changes in macular microvascular perfusion in glaucoma.

Conflict of interest: None declared.

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Table 1. Demographic and clinical characteristics of normal, early, moderate, and severe open-angle glaucoma eyes

Parameter	Normal n = 35	Early n = 44	Moderate n = 34	Severe n = 31	p
Age (y)	55.8 ± 8.8	61 ± 10.4	64.4 ± 12.1	67.1 ± 10.7	< 0.001
Sex (female/male)	20 (57.1%) / 15 (42.9%)	27 (61.4%) / 17 (38.6%)	19 (55.9%) / 15 (44.1%)	7 (22.6%) / 24 (77.4%)	0.005
BCVA (Snellen)	0.9 ± 0.1	0.9 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.003
CCT (μm)	562.9 ± 17.7	552.7 ± 31.1	546.6 ± 24.4	541.9 ± 26	0.007
Linear C/D ratio	0.4 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0	< 0.001
Vertical C/D ratio	0.4 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	1 ± 0	< 0.001
IOP (mmHg)	16.4 ± 2.2	17.1 ± 2.8	16.5 ± 2.7	16.5 ± 3.2	0.68
MD visual field (dB)	0.5 ± 0.6	-2.5 ± 1.8	-8.8 ± 1.9	-18.4 ± 3.6	< 0.001

BCVA – best corrected visual acuity; CCT – central corneal thickness; IOP – intraocular pressure; MD – mean deviation

Table 2. Optical coherence tomography structural characteristics of normal, early, moderate, and severe open-angle glaucoma eyes

Parameter	Normal n = 35	Early n = 44	Moderate n = 34	Severe n = 31	p
Total GCC thickness(μm)	108.5 ± 5.6	89.6 ± 13.6	77.6 ± 6.6	61.2 ± 6.9	< 0.001
Superior GCC thickness(μm)	107.1 ± 4.9	90.9 ± 12.8	79.2 ± 11.4	62.5 ± 7.5	< 0.001
Inferior GCC thickness(μm)	110 ± 6.9	88 ± 16.3	76.1 ± 9.9	60.6 ± 6.5	< 0.001
Total pRNFL thickness (μm)	106.2 ± 7.9	84 ± 16.4	63.1 ± 10.9	48.7 ± 7.5	< 0.001
Superior pRNFL thickness (μm)	126.1 ± 13.2	98.1 ± 22.2	71.1 ± 19.8	55.4 ± 12.7	< 0.001
Inferior pRNFL thickness (μm)	139 ± 13.6	100.8 ± 26.1	65.9 ± 13.1	50.9 ± 6.6	< 0.001
Average Macular thickness (μm)	279.7 ± 11.1	266.1 ± 15.4	255.3 ± 14.1	237.3 ± 14.7	< 0.001

GCC – ganglion cell complex; pRNFL – peripapillary retinal nerve fiber layer

Table 3. Superficial macular vessel density measurements in normal, early, moderate, and severe open-angle glaucoma eyes

Parameter	Normal	Early	Moderate	Severe	p
Foveal VD (%)	23 ± 1.9	18.1 ± 1.6	16.2 ± 2.2	13.9 ± 1.8	< 0.001
Parafoveal VD Superior (%)	44.3 ± 2.5	40.7 ± 4.2	39.6 ± 3.7	37.2 ± 3.5	< 0.001
Parafoveal VD Inferior (%)	45.4 ± 3.2	40.3 ± 5.3	37.8 ± 4.3	36.7 ± 2.5	< 0.001
Parafoveal VD Temporal (%)	44.8 ± 2.8	44 ± 4.6	42.4 ± 4.5	39 ± 2.9	< 0.001
Parafoveal VD Nasal (%)	45.1 ± 2.8	43.2 ± 3.9	42 ± 4.5	41.3 ± 3.1	< 0.001

VD – vessel density

Table 4. Correlation between optical coherence tomography angiography (OCT-A) vessel density measurements and structural parameters in glaucoma group

N = 109		**OCT-A SCP fovea**	**OCT-A SCP parafovea superior**	**OCT-A SCP parafovea inferior**	**OCT-A SCP parafovea temporal**	**OCT-A SCP parafovea nasal**
GCC thickness total µm	R	0.602**	0.457**	0.435**	0.557**	0.214*
	P	< 0.001	< 0.001	< 0.001	< 0.001	0.025
linear c/d	R	-0.607**	-0.415**	-0.351**	-0.471**	-0.243*
	P	< 0.001	< 0.001	< 0.001	< 0.001	0.011
vertical c/d	R	-0.579**	-0.347**	-0.330**	-0.424**	-0.224*
	P	< 0.001	< 0.001	< 0.001	< 0.001	0.019
pRNFL thickness total µm	R	0.536**	0.326**	0.329**	0.448**	0.157
	P	< 0.001	0.001	< 0.001	< 0.001	0.102

SCP – superficial capillary plexus; GCC – ganglion cell complex; pRNFL – peripapillary retinal nerve fiber layer;

*p < 0.05;

**p < 0.001

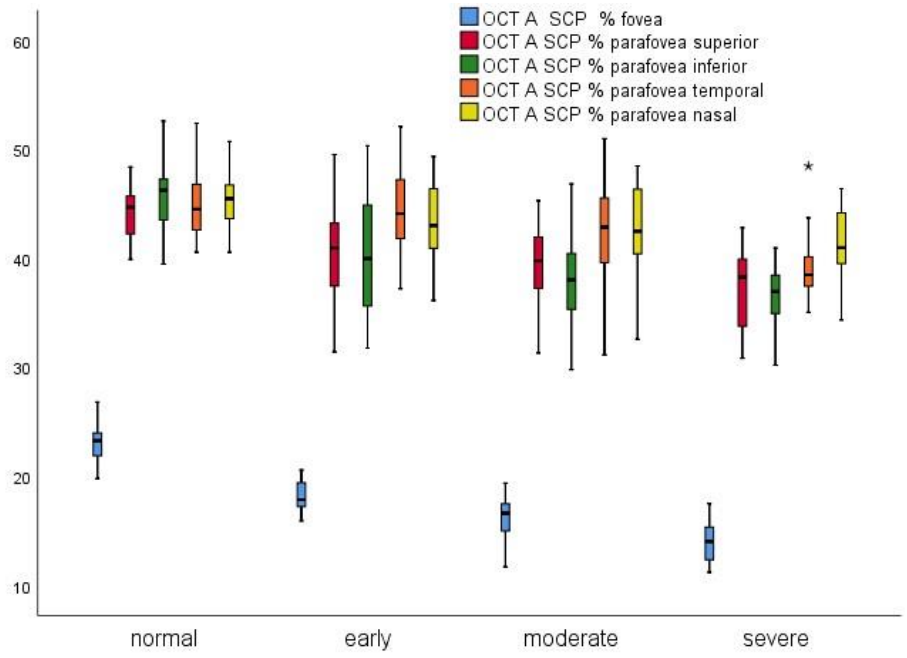

Figure 1. Superficial macular vessel density measurements in normal, early, moderate, and severe open-angle glaucoma eyes;
SCP – superficial capillary plexus

