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Evaluation of Macular Vessels Density Changes in Patients with Primary Open Angle Glaucoma by Swept-source Optical Coherence Tomography Angiography

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Abstract:

Aim: *This study aimed to compare the macularvessels density changes in patients with primary open- angle glaucoma with control subjects by Swept source optical coherence tomography angiography.*

Methods: *This was a comparative cross-sectional study included 40 eyes with POAG and 40 control subjects. Detailed ophthalmic examination was done including measurement of intraocular pressure and visual field evaluation by using Humphrey (2003 Carl Zeiss Meditec, Germany). All subjects were scanned using Swept source OCTA (Triton, Topcon, Tokyo, Japan). Quantitative analysis of the retinal vasculature was achieved by evaluating vessel density as the ratio of the retinal area occupied by vessels at the superficial and deep retinal layer.*

Results: *The mean vessel density ratio in the superficial vascular plexuses (SVP) was 32.77 ± 3.79 and 42.45 ± 1.99 in POAG patients and control, respectively ($p<0.001$), the mean vessel density of SVP was statistically significantly lower in POAG patients. The mean vessel density in the deep vascular plexuses (DVP) ratio was 36.37 ± 4.13 and 44.48 ± 0.91 in POAG patients and control, respectively ($p<0.001$). The mean vessel density of DVP was statistically significantly lower POAG patients.*

Conclusion: *Macular superficial and deep vessel density by Swept-source optical coherence tomography angiography showed statistically significant decrease in POAG patients.*

Keywords: *POAG, OCT angiography, macula, vessel density.*

1. INTRODUCTION

Primary open angle glaucoma (POAG) is an optic neuropathy that that is described by the dynamic deterioration and functional thinning of the optic nerve, including the optic disc, causing a dynamic decrease in visual sensitivity and in some people irreversible visual impairment,. In early phases, it disturbs the proximal retinal activity, specifically, the ganglion cells. It is well recognized that substantial ganglion cell damage can occur earlier to the visual field anomalies appear in the static automated perimetry [1]**.**

POAG is a leading reason of irreversible blindness worldwide, and it is categorized by progressive deterioration of retinal ganglion cells (RGCs) and their axons. [2]While the path physiology of glaucoma is not well understood, there is growing suggestion that the vascular factor and ocular blood flow may have an important role in the path physiology of POAG. The vascular the oryre commends that diminished regulation of ocular blood flow results in periods of relative ischemia that injury neurons.[4]

The importance of macula in the detection of glaucomatous RGC damage has emerged; over one-third of RGCsin the eye reside in the macula within 4.5 mm of the foveal center.(Kim et al., 2019) Therefore, ocular blood flow measurement, might be helpful in the administration of glaucomatous eyes to decide the etiology and seriousness of disease procedure and to assess the result of careful treatment sooner rather than later[5]**.**

Glaucomatous eyes indicated a diminished optic disc and retinal blood supply when contrasted and normal eyes. **(Alnawaiseh et al., 2018).**

Optical coherence tomography angiography (OCTA) can visualize depth resolved images of the retinal and choroidal vessels by employing movement differentiation imaging to high-resolution volume blood flow records generating

angiographic pictures in merely seconds**(Spaide et al.,2018)**

Optical coherence tomography (OCT) angiography is able to measure regional blood flow near the site of injury, in the optic disc, per papillary nerve fiber layer (NFL) and in macular area. Injury to the nerve fibers due to high IOP or ischemia could reduce the functioning of the nerve fibers before the structures are lost. And this would be reflected in reduced blood flow in the optic disc and the surrounding NFL& in macular region.(Jonas, Nguyen, & Naumann, 2018)**.**

A Swept-Source OCT angiography is non-invasive imaging modality that detects blood flow through the motion contrast generated by red blood cells. It can be used to provide a quantitative assessment of the microcirculation of the retina and choroid in various layers, this provided an in depth imaging of the optic disc and macular capillary plexuses[5]

This study was conducted to assess macular superficial and deep vascular net work per fusion in POAG using Swept-source OCT angiography.

2. PATIENTS AND METHODS

2.1. Study Population

This was a comparative cross-sectional study conducted at Mansoura ophthalmic center, Mansoura university, Egypt. This study protocol was approved by Mansoura medical research ethics committee, faculty of medicine, Mansoura university (code number :MS/17.3.73) andinformed consent obtained from each participant in the study after assuring confidentiality.

Eighty eyes of 80 subjects were divided into two groups; group 1 included 40 eyes with POAG which sub divided into mild 12 eyes, moderate 13 eye,severe15 eyes, and group 2 included forty eyes of control subject.

Inclusion criteria included ;POAG patients with following criteria an age above 40 years, best corrected visual acuity ≥ 6/60 , refractive error within ± 6.0 diopters equivalent sphere and within ± 3.0 diopters astigmatism , open anterior chamber angle on gonioscopy, glaucomatous changes on the Humphrey 24-2 visual field test, evidence of glaucomatous optic nerve head damage. Control eyes; no history or evidence of ocular disease, surgery or laser, no family history of glaucoma, intraocular pressure of 21 mmHg or less, normal optic nerve head appearance based on clinical stereoscopic examination, and no visual field deterioration.

Exclusion criteria included; previous intraocular surgery or laser therapy, unreliable VF, neurological field loss, angle closure glaucoma and secondary glaucoma, indication of vitreoretinal disease or diabetic retinopathy. Also, media opacity such as cataract and low quality image achieved with OCT-A, contraindication of pupil dilatation were excluded.

2.2. Ocular Examination

All subjects underwent ophthalmic examination including measurement of the BCVA using Snellen cards and converted into log MAR, assessment of IOP using Goldmann applanation tonometer, assessment of anterior segment of the eye using slit lamp biomicroscopy. Pupillary dilatation done with my driacyl 1% eye drops, fundus examination using a Volk lens 90 diopter, assessment of anterior chamber angle using three mirror Goldmanngoniolens. The patients underwentcentral 24-2 full threshold automated static perimetry by Humphrey visual field (2003 Carl Zeiss Meditec, Germany).

2.3. Optical Coherence Tomography Angiography Examination

All subjects underwent a single imaging session with OCT angiography performed with a swept source OCT (Triton, Topcon, Tokyo, Japan). Measurements were conducted with 6 × 6 mm size centered at the fovea. The method has an achievement velocity of 100 000 An outputs for every second. Automatic retinal layer segmentation was performed by the software helped generate *en face* a pictures of the vascular plexus into SVP & DVP through *en face* slabs. Superficial vessel density in the macula was imaged from 2.6 μm beneath the internal limiting membrane to 15.6 μm beneath the interface of the inner plexiform layer and inner nuclear layer (IPL/INL). and deep vessel density was generated from 15.6 μm beneath the IPL/INL to 70.2 μm beneath IPL/INL.

Technique of OCT angiography scanning was done as follows; mydriatic eye drops were used to achieve as much pupil dilatation. Chair height, chin rest, and imaging machine were adjusted to approximate position, the patient's chin was positioned in the chin rest, the patient was asked to fixate on a target inside the instrument. Cases of poor vision with difficult

fixation, an external fixation target was used, OCTA examination was performed by selecting angiography mod from the main menu of the instrument for macular region centered 6×6 mm cube, by the same technique as before the patient was asked to fixate the new target then start scanning and we chose the good quality images with high resolution and without or with less artifacts which would not affect the results. The retinal perfusion in superficial and deep macular capillary plexuses was assessed by assessing the vessel density (VD) which is represented by the ratio of the areas by areas full by vasculature and the results were calculated by The GNU Image Manipulation Program V.2.10.8 (GIMP) software .

2.4. Quantitative Measurements

Quantitative analysis ofthe vessel density was performed using thepublically available GNU Image Manipulation Program GIMP 2.10.8(http://gimp.org). Average pixel density was determined from the vessels after background subtraction (Photoshop) as previously reported ,The software calculated the outlined area in pixels, and the measured area in pixels was converted to mm2 based on the scan dimensions (6 ×6 scan) for macular region and the 320-pixel width of the images. In order to perform quantitative analysis of the vessel density (VD), the enface images were "binarized" and vessels were defined as pixels having decor relation values above the threshold level. VD was assessed as the ratio of the retinal area occupied by vessels for the SRL, DRL.

2.5. Statistical Analysis

Data were studied using IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**).**Qualitative data were defined by number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were presented as mean ± SD for parametric data and median for non-parametric data. The two groups were compared with Student *t* test for parametric data and Mann Whitney test for non-parametric data. Pearson (parametric) and Spearman (non-parametric) correlation were used to correlate continuous data. Sensitivity and specificity at different cut off points were tested by ROC curve. P value was considered statistically significant (p > 0.05)

3. RESULTS

Eighty eyes of 80 subjects comprised of 40 eyes with POAG which were subdivided into mild12 eyes, moderate 13 eyes, severe 15 eyes, and 40 eyes of 40 controls were involved in the present study. The mean age of the glaucomatous patients was 58.20 ±8.12 years; 26 eyes (65.0%) were male and 14 eyes (35.0%) were female. The mean age of control subjects was 54.10 ±9.11 years; 14 eyes (35.0%) were male and 26 eyes (65.0%) were female.

Comparison between the clinical characteristics of the study groups showed that a statistically significant difference of BCVA, intraocular pressure, VF was detected between both groups with p value (p<0.001).

The our study showed that the vessel density in the superficial vascular plexuses (SVP)was 32.77 ± 3.79,and 42.45 ± 1.99 for glaucomatous patients and control, respectively (p<0.001) as shown in Table(1).The mean VD was statistically significantly lower in SVP in patients with POAG, and showed that the mean vessel density of superficial vascular plexuses were significantly lower in severe POAG (29.67 ± 2.87) ,moderate POAG (34.08 ± 3.28) , mildPOAG (35.25 ± 2.63) and control eyes (42.45 ± 1.99), (<0.001) ,for all pair wise comparison except between mild and moderate POAG eyes (P=0.584), as revealed in Table(2).

Table1: *Comparison between the studied groups according to vessel density of superficial vascular plexuses*

Vessel density of superficial vascular plexuses	**Patients(n = 40)**	**Control(n= 40)**	**t**	**P**value
Min. – Max.	28.0 – 39.0	38.0 – 46.0	14.292*	<0.001*
Mean ± SD.	32.77 ± 3.79	42.45 ± 1.99		
Median	32.0	42.0		

t: Student t-test

Table2: *Comparison between the studied subgroups according to vessel density of superficial vascular plexuses*

Vessel density of superficial vascular plexuses	**Patients(n = 40)**			**control (n = 40)**	**F**	**p** value
	Mild (n= 12)	**Moderate (n= 13)**	**Severe (n= 15)**			
Min. – Max.	32.0 – 38.0	30.0 – 39.0	28.0 – 39.0	38.0 – 46.0	13.880*	<0.001*
Mean ± SD.	35.25 ± 2.63	34.08 ± 3.28	29.67 ± 2.87	42.45 ± 1.99		

Median	35.50	32.0	29.0	42.0		
Significance	$P_1<0.001^*$, $P_2=0.584, p_3,<0.001^*, p_4=0.001^*$					

F: ANOVA test, P: p value for comparing between the studied groups, p1: p value for comparing between control and mild, p2: p value for comparing between mild and moderate, p3: p value for comparing between mild and severe, p4: p value for comparing between moderate and sever

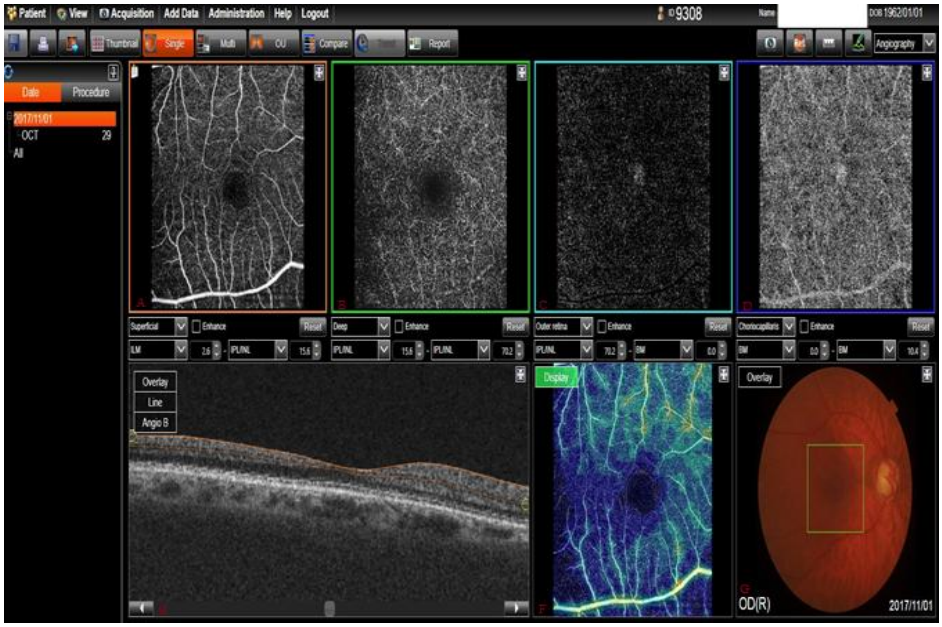

Fig1: *A.Superficial layer,B.Deep layer,C.Outer retina,D.Choriocapillaris,E.B-scan,F.Density Map,G.Fundus photo*

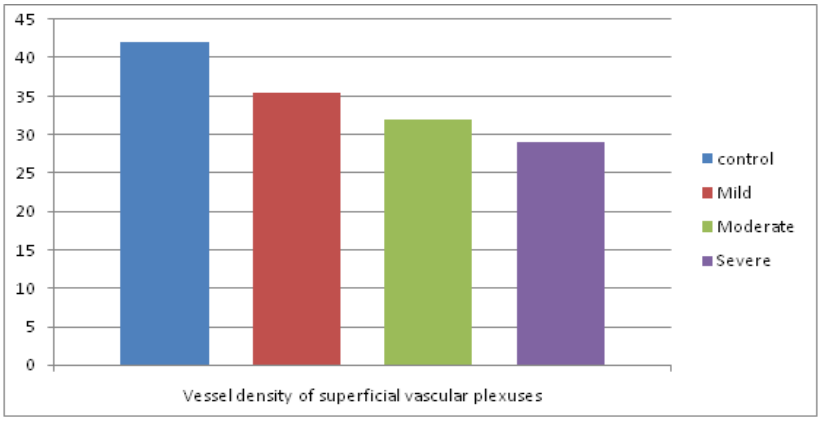

Fig2: *Vessel density of superficial vascular plexuses among the studied groups*

The present study showed that the vessel densityin the deep vascular plexuses (DVP), was 36.37 ± 4.13and 44.48 ± 0.91for patients with POAG and control, respectively (p<0.001), as shown in**Table (3).**The mean VD was statistically significantly lower in DVP in patients with POAG, and showed that the mean vessel density of DVP were significantly lower in severe POAG (32.07 ± 1.98),moderatePOAG (38.0 ± 3.32), mildPOAG (40.0 ± 0.85), and control (44.48 ± 0.91%), (<0.001),for all pairwise comparison except between mild and moderate glaucoma eyes (P=0.089) , as shown in **Table(4).**

Table3: *Comparison between the studied groups according to vessel density of deep vascular plexuses*

Vessel density of deep vascular plexuses	**Patients (n = 20)**	**Control (n = 20)**	**T**	**P**value
Min. – Max.	31.0 – 41.0	43.0 – 46.0	12.115^*	$<0.001^*$
Mean ± SD.	36.37 ± 4.13	44.48 ± 0.91		
Median	39.0	44.50		

t: Student t-test, P: p value

Table4: *Comparison between the studied sub groups according to vessel density of deep vascular plexuses*

Vessel density of deep vascular plexuses	**Patients(n = 40)**				**F**	**P** value
	Mild (n= 12)	**Moderate (n= 13)**	**Severe (n= 15)**	**control (n = 40)**		
Min. – Max.	39.0 – 41.0	32.0 – 41.0	31.0 – 39.0	43.0 – 46.0	44.647*	<0.001*
Mean ± SD.	40.0 ± 0.85	38.0 ± 3.32	32.07 ± 1.98	44.48 ± 0.91		
Median	40.0	39.0	32.0	44.50		
Significance	P_1<0.001*, P_2=0.089,p_3,<0.001*,p_4<0.001*					

*P: p value for comparing between the studied group, p_1: p value for comparing between **control** and mild , p_2: p value for comparing between mild and moderate p_3: p value for comparing between mild and severe, p_4: p value for comparing between moderate and severe*

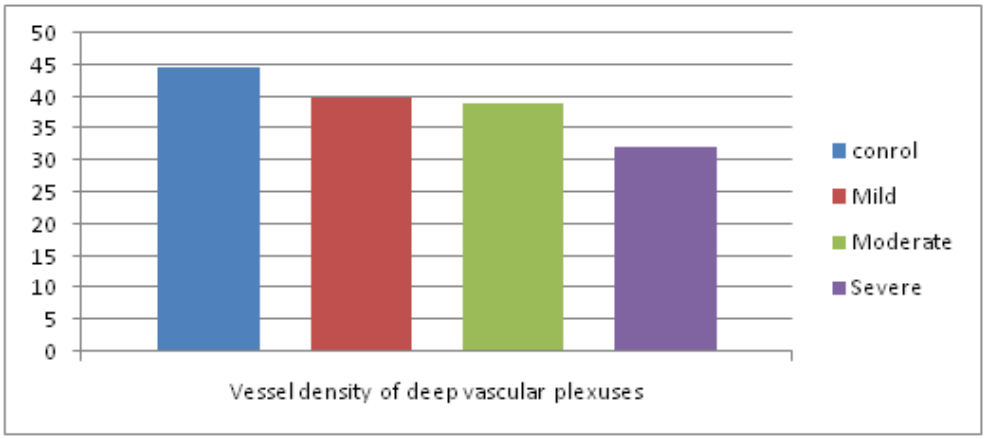

Fig3: *Vessel density of deep vascular plexuses among the studied groups*

The area under the (ROC) curve for discriminating control from glaucomatous patients by ROC curve and AUC was 0.976 for the VD at the superficial vascular plexuses (SVP)and 0.982 for the VD at the deep vascular plexuses as shown in **(Table 5)** .

The ROC curves showed that the cut-off point was 0.383 for vessels density at the superficial retinal layer (90%sensitivity to 95% specificity) and 0.411 for vessels density at the deep retinal layer (92.5 % sensitivity to 95% specificity) differentiating controls and glaucomatous eyes.

Table5: *Diagnostic accuracy of vessel density of superficial vascular plexuses and vessel density of deepvascular plexusesin prediction of patients based on ROC curve.*

	AUC	**95% CI**	**P value**	**Cut off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
VDSP	0.976	0.94-1	0.000	0.383	90%	95%	94.7	90.5	92.5%
VDDP	0.982	0.95-1	0.000	0.411	92.5%	95%	94.9	92.7	93.7%

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

4. DISCUSSION

A newly developed OCTA has confirmed the ability to quantify retinal and disc blood flow rapidly and correctly[6]**.**The our study used swept-source OCTA device to evaluate the vessels density SVP and DVP of the macula.

The present study revealed a statistically decrease vessels density of the capillary network in both SVP and DVP of glaucomatous eyes compared with control. This is in agreement with Akil et al., [7] who found a statistically significant decrease of vessels density was originate at the superficial and deep retinal layer between glaucomatous eyes and control .Albeit the two layers were seen as affected, an increasingly predictable and extreme decrease in vessels density was assessed in the superficial retinal layer.

This perception could be perfect with the hypothesis that the macular superficial capillary network in glaucoma has more vascular network changes than the DVP and choroid.

The present study is in conducted with the study of Takusagawa et al.,[2]who concluded that SVC vessel density and GCC thickness in the glaucomatous patient were significantly

decrease than in the control group (P < 0.001). The VD of the deeper plexuses in the glaucoma group was not significantly lower than in the normal group. Also, they found that VD of SVP was 35.25 ± 2.63 in POAG and 42.45 ± 1.99 in control group (p<0.001) .In contrast, the present study concluded that DVP was 40.0 ± 0.85 and 44.48 ± 0.91 for POAG and control , respectively (p<0.001). The mean vessel density was statistically significantly lower in the DVP in POAG.

Current study in agreement with the study of Choi et al., [8] , they concluded thatthe mean macular VD was a statistically significant lower in glaucoma than in the control group for superficial (P = 0.013), deep (P<0.001) vascular plexuses. The present study is in agreement with the study of Lommatzsch et al,[9], they revealed that macular vessels density was significantly decrease in superficial layer and deep layer in glaucomatous eyes than in healthy eyes (p = SL < 0.0001; DL = 0.009). Also, there was no significant alteration in vessels density between the SL and the DL.

The current study is in agreement with studies[10][11], they concluded decrease VD in the superficial layer and deep layer in patient with glaucoma compared with control.

The present study is in contrast with the study of Triolo et al., [12] that conducted their study on 40 controls, 40 glaucoma suspects, and 40 glaucoma patients. They noted that there was no difference detected in the macular vessel density between glaucoma patients, glaucoma suspects and control. The study appreciated significant differences for structural parameters but not for vascular parameters. In this regard, one may hypothesize that this structural and microvascular mismatch indicates that microvascular damage could be due to presence of a primary and therefore capillary dropouts may be secondary to loss of RNF. Akil et al., [7] showed that the mean VD at SRL In the POAG group was significantly correlated with macular GC-IPL thickness (r=0.42, p=0.04), but the significance was borderline with MD (r=0.4, p=0.06) and peripapillary RNFL thickness (r=0.5, p=0.06). The mean VD at DRL did not show statistically significant correlation with any other glaucoma parameter (p>0.05).

The present study is in agreement with the study of Akil et al., [7] concluded that VD at SRL in the POAG group was significantly correlated with macular GC-IPL thickness (r=0.42, p=0.04),but did not consistent with their results regarding mean VD at SRL. The present study revealed that POAG group was significantly correlated with MD (r=0.624, p=<0.001) and peripapillary RNFL thickness (r=0.678, p=<0.001), and The mean VD at DRL was significantly correlated with macular GC-IPL thickness (r=0.635, p=<0.001) and significantly correlated with MD (r=0.767, p=<0.001) and peripapillary RNFL thickness (r=0.795, p=<0.001), and the difference was non-significant with IOP (r=--0.264, p=0.100).

The present study is in agreement with the study of Wang et al., [13] they found that vessel density was significantly correlated with MD (r=0.404, p=0.001), RNFL thickness (r=0.465, p<0.001), and GCC thickness (r=0.45, p<0.001) .Also, they found a decrease vessel density in the glaucomatous eyes, which was correlated with the severity of glaucoma damage.

The present study is in agreement with the study of Yarmohammadi et al., [14]who found that vessel density measurements were lower in severe POAG. Specifically, the mean VD in moderate to severe POAG eyes was significantly lower (41.7%±5.5%) than in mild glaucomatous eyes (48.3% ±4.2%) (P < 0.001).

Since the nerve fiber and ganglion cell layer receives blood from the superficial retinal vascular plexus , a reduced VD exclusively in the superficial layer or at least a lesser reduction in the deep layer than in the superficial layer [15].

Akil et al.,[7]noticed the area under the receiver operating characteristic (ROC) curve for differentiating normal from POAG was 0.903 for the VD at the SRL and 0.91 for the VD at the DRL.

The ROC curves showed that the cut-off point was 36.5 for VD at the SRL (73% sensitivity to 95% specificity) and 41.1 for VD at the DRL (92% sensitivity to 99% specificity) between the controls and POAG eyes. ROC for differentiating normal from POAG was 0.87 (p<0.05) for the RNFL and 0.89 (p<0.05) for the GC-IPL.

The present study is in agreement with the study of Akil et al., [7]in the area under the ROC curve for differentiating normal from POAG by ROC curve and AUC was 0.976 for the VD at the SRL and 0.982 for the VD at the DRL as shown in .and the ROC curves showed that the cut-off point was 0.383 for VD at the

SRL (90%sensitivity to 95% specificity) and 0.411 for VD at the DRL (92.5 % sensitivity to 95% specificity) between the controls and POAG eyes.

Based on the results of the current study, we hypothesis that OCTA provides a new imaging strategy for assessment of VD of all retinal vasculature in the macular area has a potential good value in diagnosis , management and monitoring of glaucoma ,as well as, explaining the relationship between ocular microcirculation and glaucoma path physiology.

5. CONCLUSION

Significant decrease in vessel density of superficial and deep vascular plexuses was detected in POAG patients when compared to control group.

The assessment of macular blood flow by OCTA suggestions for diagnosis and management of glaucoma. The severity of specific micro vascular changes can be evaluated to monitor glaucoma progression.

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