Research Article

OCT-A changes in the macula in early primary open angle glaucoma

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Abstract

Background: Glaucoma is one of the distinguished causes of irreversible blindness. It affects about 3.54% of people over 40. Glaucoma is an optic neuropathy characterized by the progressive loss of retinal ganglion cells and their axons in the peripapillary retinal nerve fiber layer as well as distinctive changes in the optic nerve head (ONH). Visual field loss is a symptom of the damage as it progresses. Vascular insufficiency is one of the factors that may contribute to glaucoma. Given that the superficial retinal capillary plexus supplies RGCs, glaucoma could be associated with decreased superficial retinal microcirculation in the macular area. **Purpose of the study:** the current study aimed to evaluate the macular vessel density and GCC thickness changes in early POAG eyes and compare them with healthy eyes .patients and methods: The participants were divided into two groups according to visual field findings. Group1: included 20 eyes of 12 patients of early POAG. Group 2: included 20 eyes of 10 normal individuals. All participants underwent thorough ocular examination, OCT imaging of the ONH and OCT-A of the macula. Early POAG and healthy eyes data were compared. Results: GCC thickness and whole image vessel density (wiVD) in the superficial capillary plexus were lower in the early POAG group than in healthy eyes, whereas deep capillary plexus vessel densities did not differ significantly between both groups. conclusion the inclusion of OCTA in glaucoma diagnostics helps in the early detection of glaucoma and improves our understanding of ocular blood flow changes in the disease.

Keywords: POAG , OCTA, Macular vessel density

Introduction

Glaucoma is believed to be one of the leading causes of irreversible blindness worldwide. It affects about 3.54% of people over the age of 40 years. Current studies estimate the global prevalence of glaucomatous individuals to rise from 52.68 million in 2013 to reach 79.76 million in 2040. Primary open-angle glaucoma (POAG) is known to be the commonest type of glaucoma. It accounts for about 74% of all cases worldwide. [1,2]

Glaucoma is an optic neuropathy characterized by progressive loss of the retinal ganglion cells (RGCs) and their axons in the peripapillary retinal nerve fiber layer (pRNFL) with

characteristic changes in the optic nerve head (ONH), that is associated with visual field loss as the damage progresses, and in which intraocular pressure (IOP) is a key modifiable factor. [3]

Many factors are involved in development of POAG including vascular insufficiency. RGCs are nourished by the superficial retinal capillary plexus, it is presumed that decreased superficial retinal microcirculation in the macular region may occur during glaucoma. It is reported that macular vessel density (MVD) is attenuated in early POAG, suggesting that significant microvasculature alterations in the macular

region may precede detectable visual field (VF) defects. [4]

Optical coherence tomography (OCT) is a noninvasive imaging technique that provides objective, quantitative and reproducible measurements of the macular ganglion cell complex (GCC), pRNFL thickness and ONH parameters which are useful for structural analysis in the assessment and diagnosis for glaucoma. [5] OCT angiography (OCTA) is used for observing the microcirculation in the peripapillary or macular areas. [6]

The aim of the work is to evaluate macular vessel density(MVD) and macular ganglion cell complex (GCC) thickness changes in early POAG eyes using OCT-A.

Patients and methods
This prospective non randomized comparative study included 40 eyes of 22 subjects. They were divided into two groups according to
1- Group 1 (glaucoma group): included 20 eyes of 12 patients of early primary open angle glaucoma.
2- Group 2(control group): included 20 eyes of 10 normal control individuals.
All patients and control subjects included in this study were verbally informed about the nature of the study. All individuals have signed informed consents. The study was approved by local ethical committee of Minia University and was in line with the tints of Declaration of Helsinki.
The study patients and control subjects were recruited, examined, evaluated and subjected to automated perimetry and optical coherence tomograph, in outpatient clinic of Ophthalmology Department, Mina University Hospital, in the period of march 2021 to April 2022.

Inclusion criteria: All participants were above 45 years old, cooperative, with good fixation with BCVA > 0.5 and refractive errors within ±5 DS. All individuals had clear ocular media and open anterior chambre angle in gonioscopy.

Early glaucoma is defined as patients who has at least 2 of the following in at least 1 eye: An optic nerve changes or nerve fiber layer defect suggestive for glaucoma in the form of (enlarged cup disc ratio, asymmetric cup disc

ratio, notching or narrowing of neuro retinal rim, disc hemorrhages or suspicious alterations in nerve fiber layer), elevated IOP above 21mmhg.Visual field defects consistent with early glaucoma according to Hodapp Parish - Anderson glaucoma grading scale. [7]

Healthy controls were defined as individuals who had intra ocular pressure IOP < 21 mmHg without history of elevated IOP, normal appearing optic nerve head, intact neuro retinal rim , and retinal nerve fiber layer(RNFL) , and reliable normal visual field.

Exclusion criteria: individuals with prior intra ocular surgery except for uncomplicated cataract, non-glaucomatous optic neuropathy or retinopathy, uveitis or ocular trauma or other causes of secondary glaucoma are all excluded from the study. Any other known disease that may cause optic neuropathy, retinopathy or visual field loss or closed angle of anterior chambre ar. Ocular or systemic disease such as DM or hypertension were not included in the study

All participants underwent comprehensive ocular examination including:
A) History Taking: careful history of systemic disease and ocular surgery or medications and family history of glaucoma.

B) Eye examination:
* Best corrected visual acuity using Snellen chart.
* Refraction using Nidek^{TM} auto refractometer(NIDEK CO., LTD., Japan)
* Snellen's chart for assessment of the best corrected visual acuity.
* Anterior segment examination using slit lamp to exclude media opacities that may contribute in low signal strength of the scans.
* IOP measurement using Goldmann applanation tonometer.
* Examination of angle of the anterior chambre by Goldmann 3 mirror lens to ensure its patency and exclude presence of vessel, pigments, adhesions or other causes of angle closure.
* fundus examination using the +90D Volk lens and slit lamp after pupil dilatation by 1% tropicamide eye drops

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C) Investigations:

- **Static automated perimetry (SAP):** Humphrey Field Analyzer (НГАП 745-40398-51.2/5.1.2, ZIESS, San Leandro, CA, USA) for recording visual fields. We used 24-2 Swedish Interactive Thresholding Algorithm(SITA) full-threshold for 54 retina locations. The following parameters were recorded for each test: Average mean (MD) deviation for staging of glaucoma, Pattern deviation (PD), Pattern standard deviation (PSD), visual field index(VFI) and glaucoma hemifield test (GHT).

- **Spectral domain optical coherence tomography (OCT)**: OCT ONH scans were done using AngioVue OCTTM system on RTVue XR 100 Avanti spectral domain-OCT device, version 2016 (Optovue Inc, Fremont, CA, USA) for RNFL and ONH analysis. Macular scans were obtained for GCC thickness analysis.

- **Optical coherence tomography angiography (OCTA):** OCTA scan was done for each patient using AngioVue OCTA^{TM} system on RTVue XR 100 Avanti spectral domain-OCT device (figure 12), version 2015 (Optovue, Inc., Fremont, California)^{TM}. 304 x 304 A-scans in approximately 2.6 seconds scan time to obtain 6mm X 6mm OCTA images. Each patient underwent a 6.0 x 6.0-mm-diameter perifoveal scan centered at the fovea. Superficial vessel density(SCP) in the macula was imaged from the ILM to the posterior boundary of the IPL. Deep capillary plexus (DCP)lies between the inner nuclear (INL) and outer plexiform (OPL) layers. Vessel density was calculated by the percentage area occupied by flowing blood vessels in the selected region using the intrinsic imaging system software (Optovue, Inc.) AngioVue™ first evaluates the whole VD (wiVD), then distinguishes a foveal region (fVD) from parafoveal region (pVD), and finally subdivides the parafoveal measurement into four quadrants (temporal, superior, nasal, and inferior).

Results

Demographic data &basic characteristics:

Forty eyes of 22 patients (12 females and 10 males) were enrolled in this study. The mean age of control group was 49.7 ± 4.4 and for the early POAG group was 54.6 ± 6.7.

The changes of the general ocular measurements

There were statistically significant differences between the two groups regarding best BCVA, IOP and vertical C/D ratio with no statistically significant difference between both groups regarding horizontal C/D ratio as shown in table 1.

The changes of the structural parameters between POAG group and normal group:

There were statistically significant reduction in all structural measurements of OCT in the early POAG than in control group, including average RNFL thickness and GCC thickness as shown in table 2.

The changes of the functional parameters between POAG group and normal group:

There were statistically significant differences in visual field measurements among the two groups, including MD, VFI and PSD as shown in table 3

The changes of the macular vessel density:

Superficial vessel density: In the superficial vascular complex (SCP) enface OCTA image, there were branching vessels in a centripetal manner which terminate in the central foveal avascular zone (FAZ). They were noticeably denser in normal eyes than in glaucomatous eyes (table 4).

Changes of deep capillary vessel density between normal and POAG: There were no statistically significant changes between normal group and POAG group as regarding vessel density of deep capillary plexus. It has been observed that the temporal quadrant shows significant lower VD in the POAG group than in normal controls as shown in table 5.

Table (1): Ocular measurements in POAG group *vs* control group (M±SE):

Groups (*n* = 20) / Parameters	Control	Early POAG	P value
BCVA(logMAR)	0.92	0.86	0.046*
Vertical C/D ratio	0.3 ± 0.2 (0.05-0.68)	0.62 ± 0.15 (0.3-0.92)	0.0001*
Horizontal C/D ratio	0.66 ± 0.19 (0.3-0.9)	0.52 ± 0.3 (0.15-0.89)	0.105
IOP (mmHg)	15.9±2.8 (11-20)	26.9 (20-31)	0.0001*

(Data represent mean ± S.E. *n*: number of eyes in each group.
*: significant difference from the control group. **Significant:** $P < 0.05$)

Table (2): OCT structural parameters in POAG group *vs* control group (M±SE)

Groups (*n* = 20) / Parameters	Control	Early POAG	P value
Average RNFL thickness (μm)	104.4 ± 7.7 (92-114)	87.7 ± 8.6 (72-104)	0.0001*
Superior RNFL thickness(μm)	107 ± 6.4 (95-116)	91.7 ± 10.8 (67-115)	0.0001*
Inferior RNFL thickness(μm)	100.6 ± 10.5 (86-115)	85.14 ± 13.8 (68-130)	0.004*
Total GCC thickness(μm)	106.7 ± 23.1 (93.58-171.43)	86.23 ± 8.3 (73.47-98.82)	0.001*
Superior GCC thickness(μm)	105.5 ± 22.1 (93-167.5)	87.63 ± 7.6 (71.4-100.6)	0.002*
Inferior GCC thickness(μm)	106.6 ± 21.6 (91.1-166.3)	84.5 ± 9.7 (68.6 ± 98.7)	0.0001*

(Data represent mean ± S.E. *n*: number of eyes in each group.
*: significant difference from the control group. **Significant:** $P < 0.05$)

Table (3): SAP functional parameters in POAG group *vs* control group (M±SE):

Group (n =20) / Parameters	Control	Early POAG	P value
Visual field mean deviation, dB	-0.94 ± 0.92 (-3 – -0.02)	-3.98 ± 2.2 (-6.9 – 0.45)	**0.0001***
Visual field index %	99.3 ± 0.82 (98-100)	93.57 ± 4.8 (83-99)	**0.0001***
Visual field pattern standard deviation, dB	1.4 ± 0.3 (1.02-1.94)	3.97 ± 2.76 (1.36-11.35)	**0.0001***

(Data represent mean ± S.E. *n*: number of eyes in each group.
*: significant difference from the control group. **Significant:** $P < 0.05$).

Table (4): Superficial capillary plexus vessel density VD (%) parameters in POAG group *vs* control group (M±SE): figure 1

Groups (*n* = 20) SCP Parameters %	Control	Early POAG	P value
VD wi	48.2 ± 1.97 (43.7-50.6)	42.95 ± 3.03 (37.6-47.65)	**0.0001***
Foveal VD	30.5 ± 4.5 (23.3-37.3)	24.9 ± 7.18 (14.22-41.78)	**0.041***
Para foveal VD	50.6 ± 2.7 (47.5-54.9)	45.72 ± 4.4 (37.69-52.12)	**0.001***
Superior hemi VD	50.2 ± 2.6 (47.2-54.25)	45.78 ± 4.43 (37.2-52.56)	**0.007***
Inferior hemi VD	51.3 ± 3.9 (46.6-55.6)	45.68 ± 3.9 (38.18-51.67)	**0.0001***
Temporal VD	51.4 ± 3.9 (42.4-55.1)	46.17 ± 4.4 (37.7-52.6)	**0.004***
Superior VD	51.2 ± 3.4 (45.7-56.7)	46.1 ± 5.16 (36.47-53.59)	**0.008***
Nasal	50.3 ± 5.6 (45.1-64)	44.28 ± 4.6 (37.19-50.94)	**0.004***
Inferior	50.9 ± 3.8 (42.8-56)	46 ± 3.9 (37.4-52.3)	**0.003***

SCP: superficial capillary plexus, VD wi: whole image vessel density. Data represent mean ± S.E. ***n:*** number of eyes in each group. ***:** significant difference from the control group. **Significant:** P < 0.05

Table (5): deep capillary plexus vessel density VD (%) parameters in POAG group *vs* control group (M±SE): figure 2

Groups (*n* = 20) DCP Parameters %	Control	Early POAG	P value
VD wi	52 ± 8.1 (36.7-62.5)	47.9 ± 5.8 (34.6-58.7)	0.129
Fovea VD	32.4 ± 9.3 (12.2-44.2)	27 ± 8.7 (15.3-51.2)	0.128
Para fovea	57.2 ± 7.2 (43.4-64.8)	53.3 ± 5 (42.9-62.8)	0.087
Superior hemi	57.4 ± 7.8 (42.9-65.2)	53.4 ± 5.3 (42.78-63.56)	0.105
Inferior hemi	57.1 ± 6.9 (43.9-64.7)	53.2 ± 4.97 (39.97-62.11)	0.08
Temporal	56.9 ± 5.9 (46.9-64.3)	51 ± 7.7 (28-82.9)	0.042*
Superior	57.7 ± 8.6 (39.9-65.7)	54.33 ± 5.4 (41.6-64.1)	0.197
Nasal	58 ± 7.8 (42.2-66.1)	55 ± 4.7 (43.5-62.53)	0.192
Inferior	56.4 ± 7.4 (44.7-65.4)	52.8 ± 5.9 (39.2-62.1)	0.16

DCP: deep capillary plexus, **VD wi**: whole image vessel density. Data represent mean ± S.E. ***n:*** number of eyes in each group. ***:** significant difference from the control group. **Significant:** P < 0.05
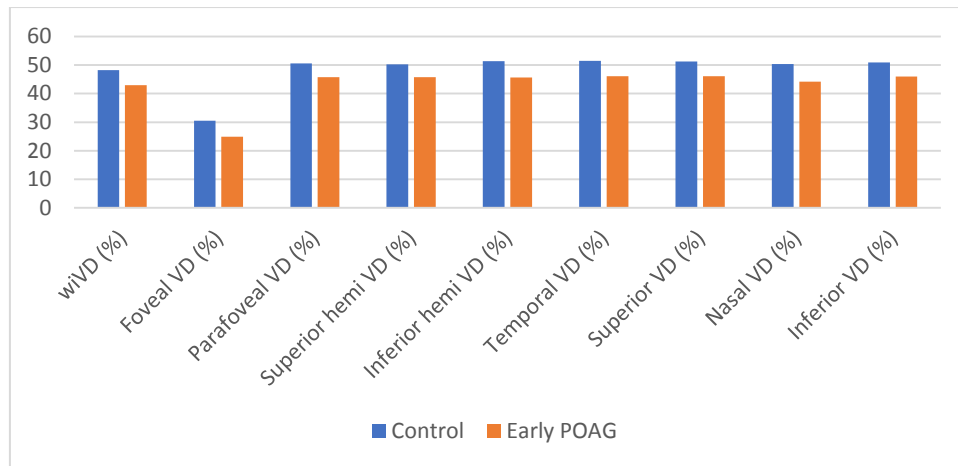
Figure (1): : Changes in superficial macular VD between the control and the early POAG groups
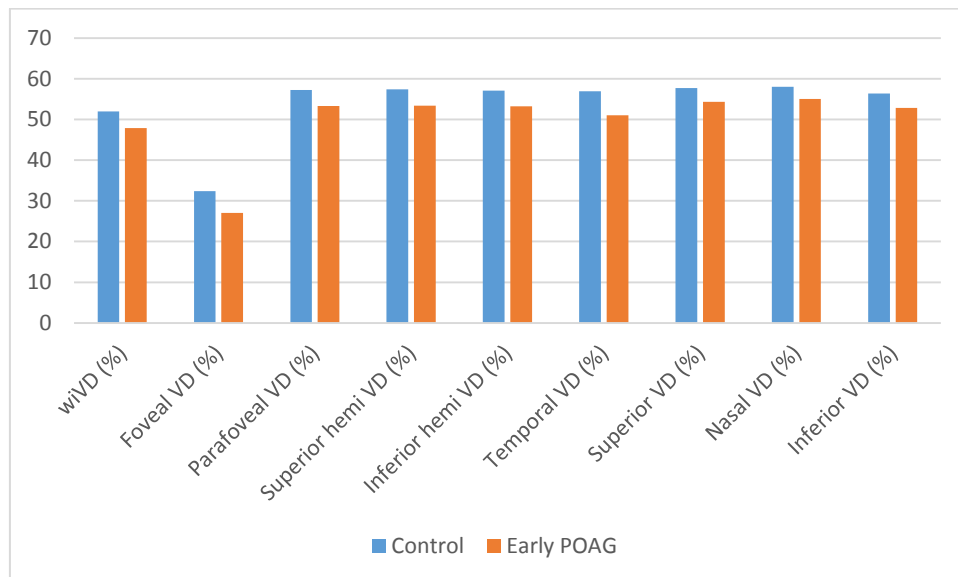

Figure (2) : Changes in deep capillary plexus VD between the control and the early POAG groups

Discussion

Primary open angle glaucoma (POAG) is the most common subtype of glaucoma It is characterized by progressive loss of retinal ganglion cells (RGCs) and their axons with subsequent visual field progressive defects in eyes with open anterior chamber angles, with or without elevated intraocular pressure (IOP)). [8] Only 60–75% of patients with glaucoma have IOP of greater than 21 mmHg while the remaining about 30% of patients, have a glaucomatous changes despite of their normal IOP. On the other hand many people have IOP above 21 mmHg without glaucoma which

means, not all phenomena of the disease can be explained by increased IOP. [9]

Vascular hypothesis is one of various mechanisms involved in the development of POAG. It states that due to insufficient blood supply, glaucoma is associated with loss of retinal ganglion cells (RGCs). [10] Due to uneven distribution of RGCs within the retina being more concentrated in the macula than the peripapillary region[11] and as they have a retinal capillary plexus to cover their high metabolic needs, the macular vessel density VD

may change as part of the glaucomatous disease.[12]

The recent application of optical coherence tomography angiography (OCT-A), a technique of non-invasive imaging of the blood vessels of the ONH and retina in-vivo, enhances our understanding of the role of microvasculature integrity in the pathophysiology of glaucoma.[13] OCTA uses the motion of red blood cells as an intrinsic contrast agent to form reproducible images of microvascular networks rapidly and non-invasively.[14] which can help as a complementary tool for early diagnosis of glaucoma.

For these reasons, we measured the macular VD (superficial and deep capillary plexuses) in 20 eyes of 12 early glaucomatous patients by AngioVue OCTA[TM] device. The results were compared with age matched 20 healthy eyes. This comparative prospective cross-sectional study conducted at ophthalmology department of Minia University Hospital.

As regard personal and clinical characteristics of the participants in the current study, most of participants were 45-65 years old of 12 females and 10 males, without a statistically significant difference between the two groups.

Our study found that the total GCC thickness was significantly thinner in early POAG group than in the healthy group (p = 0.001). which has been in line with Wang, Y., et al., study where seventy-nine eyes in 72 subjects (31 normal, 26 PPG, and 22 early PG eyes) were included and it was found that compared to healthy eyes, GCC thickness were significantly lower in PPG and early PG eyes (all P < 0.025).[15]

As regard the average RNFL thickness it was found to be significantly reduced in early POAG group than in healthy group (p =0.0001). Superior and inferior RNFL thickness also were found to be thinner in early glaucomatous eyes than in normal control group (p<0.001). this is similar to Lu, Peng, et al., study.[16]

In our study, the functional parameters of visual field have shown statistically significant changes among early glaucoma group in the form of decreased MD, PSD and VFI as compared to normal (p< 0.001) . Ravi Thomas

et al., study showed similar results as MD and PSD were significantly worse in patients with mild, moderate, and severe glaucoma compared to normal participants (all p< 0.001). [17]

Our study has found decreased superficial macular vessel density in early POAG eyes compared to eyes of normal subjects. Whole image, fovea and parafoveal vessel densities are all decreased in diseased group. This is consistent with Wang, Y., et al., the study that stated compared to healthy eyes, whole image VD (wiVD) was significantly lower in pre perimetric and early POAG eyes. [15]

Chen et al., described a reduced whole image (wiVD) in the superficial layer, but did not find a significant difference between diseased and healthy eyes for the sectoral division. In contrast to this, we show that VD is also significantly reduced within all sectoral divisions in glaucomatous eyes. [18] This may be explained by the larger measurement area of macula which has the advantage of detecting more peripheral changes.

On the other hand, our study didn't find any statistically significant difference of deep capillary plexus vessel density (DCP) between the two groups p=0.129. This was similar to Takusagawa et al., where 30 perimetric glaucoma and 30 age-matched normal partici-pants were included. Results of this study found that focal capillary dropout could be visualized in the SVC p< 0.001 but not the ICP and DVP p= 0.19.[19]

As the SCP supplies the NFL, GCL, and part of the IPL the anatomic layers most affected by glaucoma, it is not surprising that the SVC VD was greatly reduced in glaucomatous eyes, while the DCP was minimally affected by glaucoma, as it supplies the middle retinal layers that do not include the retinal ganglion cells.

Conclusion:
Retinal ganglion cells are so metabolically active and depend on regional capillary networks to meet their high metabolic require-ments, assessment of retinal vasculature in the macula region may improve our ability to detect glaucomatous changes Our results show reduced superficial macular vessel density in

early glaucoma eyes than in healthy eyes which can help as a complementary tool for early diagnosis of glaucoma.

Recommendations:
1. Further investigations, including the peripapillary capillary density, and the study of their changes in early glaucoma patients to determine their role as a complementary tool in the early diagnosis of the disease.
2. Investigating other groups as preperimetric glaucoma individuals may also help in detecting glaucoma before it causes visual field defects.

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