Original Article

Intrapapillary vessel density using optical coherence tomography angiography in primary open-angle glaucoma and normal eyes

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ABSTRACT

Background: Optical coherence tomography angiography (OCTA) is used to quantify optic nerve blood flow in patients with primary open-angle glaucoma (POAG). Intrapapillary vessel density (iVD) has a high diagnostic accuracy for differentiating healthy from glaucomatous eyes. We compared the iVD of patients with POAG with that of healthy controls in an Egyptian tertiary referral center.

Methods: This cross-sectional study consecutively recruited patients with medically controlled POAG and age- and sex-matched healthy individuals. All study participants underwent a detailed medical history evaluation and comprehensive ophthalmic examination, with recording of the cup-to-disc ratio (C/D ratio) and intraocular pressure (IOP). Humphrey visual field evaluation using the standard 24-2 program was performed and global indices, including mean deviation (MD) and pattern standard deviation (PSD), were extracted. OCTA and spectral-domain (SD) OCT images were obtained. Average thickness of the retinal nerve fiber layer (RNFL) and thicknesses in the superior, inferior, nasal, and temporal quadrants were recorded. OCTA imaging was used to measure vessel density, and the automatically processed data for iVD were extracted.

Results: We included 86 eyes, 43 in the POAG and 43 in the healthy control group, with male predominance in both groups and mean (standard deviation [SD]) ages of 42.1 (9.4) and 39.3 (9.6) years, respectively. The two groups were comparable in terms of mean age, sex ratio, laterality of the included eyes, and mean IOP (all $P > 0.05$). The mean (SD) C/D ratio, MD, and PSD were significantly higher in the POAG group than in the control group (all $P < 0.01$). The mean (SD) average RNFL thickness and RNFL thicknesses in the four quadrants were significantly less in glaucomatous eyes than in healthy control eyes (all $P < 0.05$). Eyes with POAG had a significantly lower mean (SD) iVD than healthy control eyes ($P < 0.01$). Linear regression analysis revealed a significant positive correlation between iVD and average RNFL thickness ($r = + 0.52$; $P < 0.001$) and a significant negative correlation between iVD and PSD ($r = - 0.31$; $P = 0.042$) in eyes with POAG.

Conclusions: The structural, vascular, and functional parameters measured in this study deteriorated in eyes with POAG compared to controls. Significant circumpapillary RNFL thinning correlated well with reduced iVD in eyes with POAG. Similarly, a lower iVD detected using OCTA had a significant inverse correlation with PSD in the perimetry of eyes with POAG. Further studies with additional parameters and longer follow-up periods are required to verify our preliminary findings.

KEYWORDS

optical coherence tomography, optical coherence tomography angiography, automated perimetry exam, primary open angle glaucoma, matched group, intraocular pressures, optic nerve head, vascular density

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INTRODUCTION

Primary open-angle glaucoma (POAG) is a progressive, chronic optic neuropathy and one of the leading causes of visual impairment worldwide [1, 2]. High intraocular pressure (IOP) is associated with development and progression of POAG, yet other risk factors have been proposed [3, 4]. IOP reduction alone cannot prevent the progression of visual field loss in all patients [5]. Reduced optic nerve head blood flow has a role in continuous deterioration of glaucomatous optic neuropathy [6, 7].

Global indices of standard automated perimeter (SAP), such as mean deviation (MD) and pattern standard deviation (PSD), are diagnostic parameters for POAG [8, 9]. Retinal nerve fiber layer thickness is complementary to SAP in diagnosing and monitoring the progression of POAG [10]; however, it is limited by floor effect in monitoring advanced glaucomatous damage [11, 12].

Ocular blood flow can be assessed using fluorescein angiography, Heidelberg retinal flowmetry, and color Doppler imaging. However, the application of some of these methods is limited by their invasiveness, lack of quantitative measurements, and inability to visualize the microvasculature [13]. Optical coherence tomography angiography (OCTA) is a non-invasive, rapid, detailed, and quantitative imaging modality for assessing vascular density of the optic nerve and macula. It is widely used to quantify optic nerve blood flow in a spectrum of glaucomatous eyes, including those with POAG [14, 15]. OCTA can be used to monitor glaucoma progression and predict its rate of progression [15]. In a diagnostic accuracy study, the intrapapillary vessel density (iVD) in the radial peripapillary capillary layer had the highest accuracy (92.9%) in differentiating between healthy and glaucomatous eyes [16].

Genetic factors, racial background, and positive family history are known risk factors for the development of POAG [17, 18]. Race-based differences in vessel density have been observed using OCTA [19]. The diagnostic performance of vascular density in eyes with open-angle glaucoma is race dependent [20]. Therefore, we compared the iVD of healthy eyes and eyes with POAG among individuals attending a single tertiary referral center in Egypt. In addition, we investigated potential correlations between iVD and perimetric indices or structural parameters in eyes with POAG.

METHODS

This cross-sectional study consecutively recruited patients with medically controlled POAG and age- and sex-matched healthy individuals at the Ophthalmology Department, Suez Canal University Teaching Hospital, and the International Medical Center, Ismailia, Egypt, from February 2021 to February 2023. The study protocol was approved by the Research Ethics Committee of the University and complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants following an explanation of the study protocol.

We included eyes with a diagnosis of medically controlled POAG having confirmed glaucomatous damage in the SAP, documented glaucomatous optic nerve damage, and retinal nerve fiber layer (RNFL) thinning. Patients with retinal diseases, optic nerve comorbidities other than POAG, simultaneous ocular pathologies, previous ocular trauma or surgery, or history of neurological disease were excluded. Healthy individuals presenting for routine ocular examinations were enrolled from the outpatient clinic of our hospital and had normal detailed ocular examinations and no systemic comorbidities.

All participants underwent a detailed evaluation of medical history and demographic data (age and sex), along with a comprehensive ophthalmic examination, including assessment of best-corrected distance visual acuity, detailed anterior segment assessment using slit-lamp biomicroscopy (SL-D701; Topcon, Tokyo, Japan), IOP measurement using a Goldmann applanation tonometer (D-KAT; Keeler Ltd., Windsor, UK), gonioscopy using a Zeiss four-mirror goniolens (Volk Optical Inc., Mentor, OH, USA), and a dilated posterior segment examination under a slit-lamp biomicroscope with the aid of an auxiliary lens. The cup-to-disc ratio (C/D ratio) and IOP were recorded for analysis.

Perimetry was performed for all participants using the Swedish interactive thresholding algorithm (SITA) standard 24-2 program by a Humphrey field analyzer (HFA; Carl Zeiss Meditec AG, Germany), and reliable visual fields [21] were included. Global indices including MD and PSD were extracted for further analysis.

Spectral domain (SD)-OCT (RS-3000 Advance; Nidek, Gamagori, Japan) images were obtained during the same visit. Poor quality images [22, 23] were excluded. Average thickness of the RNFL and thicknesses in the superior, inferior, nasal, and temporal quadrants were recorded and assessed for compatibility with the ISNT rule (order of RNFL thickness in neuroretinal rim of optic disc is inferior > superior > nasal > temporal) [24, 25].

OCTA (RS-3000 Advance; Nidek) images were obtained during the same visit. OCTA scanning over a 4.5 × 4.5 mm^2 area centered on the optic disc was used to measure vessel density [26]. For purposes of this study, we extracted the automatically processed data for the percentages of vessel density at the optic nerve head (iVD) [16, 26]. Considering all the clinical, structural, functional, and vascular parameters, data from one eye were randomly selected from each participant and included in the final analysis.

Statistical analyses were performed using SPSS for Windows (version 26; IBM Corp., Armonk, NY, USA). Data were tested for normality of distribution using the Kolmogorov–Smirnov test. Quantitative data were compared between groups using an independent *t*-test and are expressed as means (standard deviations [SDs]). Categorical data were compared between groups using the nonparametric chi-square test and are expressed as frequencies (percentages). Pearson's product-moment correlation was used to detect correlation between iVD and average RNFL thickness and PSD. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

We included 86 eyes, 43 in the POAG group and 43 in the healthy control group, with male predominance in both groups (55.8% in POAG and 69.8% in controls) and mean (SD) ages of 42.1 (9.4) and 39.3 (9.6) years, respectively. Table 1 summarizes the demographic and clinical characteristics of study participants, as well as their measured structural, functional, and vascular parameters. The two groups were comparable in terms of mean age, sex ratio, and laterality of the included eyes (all $P > 0.05$). The mean IOP did not differ between the groups ($P > 0.05$).

Table 1. Demographic and clinical characteristics of the study groups

Variable	POAG group (n = 43)	Control group (n = 43)	*P*-value
Age (y), Mean ± SD	42.1 ± 9.4	39.3 ± 9.6	0.180 [a]
Sex (Male / Female), n (%)	24 (55.8) / 19 (44.2)	30 (69.8) / 13 (30.2)	0.181 [b]
Laterality (Right / Left), n (%)	21 (48.8) / 22 (51.2)	21 (48.8) /22 (51.2)	< 0.99 [b]
IOP (mmHg), Mean ± SD	15.8 ± 3.1	14.6 ± 1.6	0.183 [a]
C/D ratio, Mean ± SD	0.7 ± 0.1	0.4 ± 0.10	**< 0.001** [a]
MD (dB), Mean ± SD	- 6.9 ± 8.5	- 0.5 ± 1.5	**< 0.001** [a]
PSD (dB), Mean ± SD	4.8 ± 3.9	1.6 ± 0.7	**< 0.001** [a]
RNFL thickness (µm), Mean ± SD			
Average	77.4 ± 22.3	100.3 ± 13.1	**< 0.001** [a]
Superior	92.9 ± 37.8	126.1 ± 20.2	**< 0.001** [a]
Inferior	93.6 ± 30.6	129.4 ± 21.3	**< 0.001** [a]
Nasal	60.4 ± 17.9	72.7 ± 17.6	**0.002** [a]
Temporal	62.6 ± 20.5	73.0 ± 10.0	**0.004** [a]
iVD (%), Mean ± SD	10.2 ± 5.2	16.6 ± 9.7	**< 0.001** [a]

Abbreviations: POAG, primary open angle glaucoma; y, years; SD, standard deviation; n, number; %, percentage; IOP, intraocular pressure; mmHg, millimeter of mercury; C/D ratio, cup-to-disc ratio; MD, mean deviation; dB, decibels; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; µm, micrometers; iVD, percentage of vessel density at the optic nerve head. Note: *P*-values < 0.05 are shown in bolds; [a], *P*-value is derived from independent *t*-test comparing the glaucomatous eyes versus healthy control eyes; [b], *P*-value is derived from the nonparametric chi-square test comparing the glaucomatous eyes versus healthy control eyes.

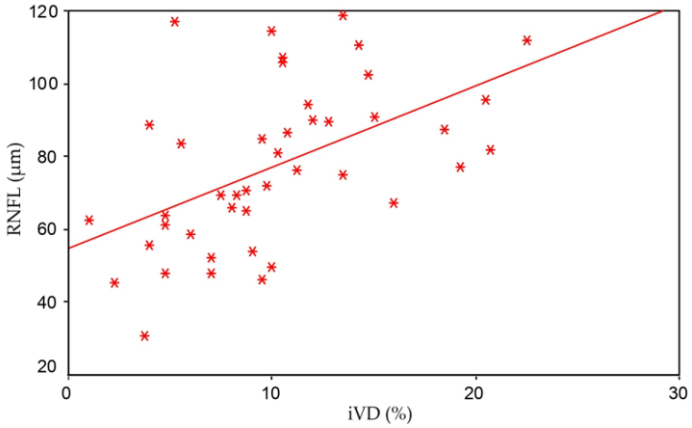

Figure 1. Scatterplots for Pearson's product-moment correlation between iVD and average RNFL thickness in eyes with primary open-angle glaucoma. Abbreviation: iVD, intrapapillary vessel density; RNFL, retinal nerve fiber layer; µm, micrometers; %, percentage.

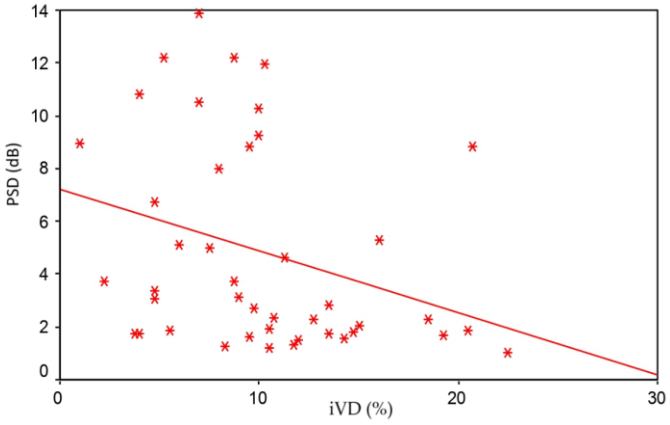

Figure 2. Scatterplots for Pearson's product-moment correlation between iVD and PSD in eyes with primary open-angle glaucoma. Abbreviation: iVD, intrapapillary vessel density; PSD, pattern standard deviation; dB, decibels; %, percentage.

The C/D ratio and perimetric parameters, including MD and PSD, were significantly higher in glaucomatous eyes than in healthy control eyes (all $P < 0.01$). The mean (SD) global indices were - 6.9 (8.5) dB for MD and + 4.8 (3.9) dB for PSD in the POAG group and - 0.5 (1.5) dB for MD and + 1.6 (0.7) dB for PSD in the control group (Table 1).

Likewise, the mean (SD) average RNFL thickness (77.4 [22.3] μm versus 100.3 [13.1] μm) and RNFL thicknesses in the superior (92.9 [37.8] μm versus 126.1 [20.2] μm), inferior (93.6 [30.6] μm versus 129.4 [21.3] μm), nasal (60.4 [17.9] μm versus 72.7 [17.6] μm), and temporal (62.6 [20.5] μm versus 73.0 [10.0] μm) quadrants were significantly thinner in glaucomatous eyes than in healthy controls (all $P < 0.05$). Considering the ISNT rule for RNFL thickness, both glaucomatous and normal eyes had the thickest RNFL inferiorly, followed by the superior quadrant. However, despite the thinner mean nasal and temporal RNFL thicknesses in both groups, the temporal RNFL was slightly thicker than the nasal RNFL (Table 1).

In parallel with the observed deteriorated global perimetry indices and RNFL thinning, eyes with POAG had significantly lower mean (SD) iVD than healthy control eyes (10.2 [5.2%] versus 16.6 [9.7%]; $P < 0.01$) (Table 1). Linear regression analysis revealed a significant positive correlation between iVD and average RNFL thickness ($r = + 0.52$; $P < 0.001$) (Figure 1) and a significant negative correlation between iVD and PSD ($r = - 0.31$; $P = 0.042$) (Figure 2) in eyes with POAG.

DISCUSSION

In this cross-sectional study, the two groups were comparable in terms of demographic characteristics. The mean IOP did not differ between the groups because the eyes in the POAG group were medically controlled. We found significantly lower optic nerve head vessel density and lower mean values for RNFL thickness on average and in all four quadrants in glaucomatous eyes than in normal controls. In parallel with these changes, global perimetry indices were significantly deteriorated in eyes with POAG compared to normal eyes, indicating the presence of functional changes in glaucomatous eyes. Vessel density was significantly inversely correlated with PSD and directly correlated with RNFL thickness in glaucomatous eyes, indicating concurrent structural, functional, and vascular deterioration with glaucoma.

The diagnostic performance of OCTA in individuals with open-angle glaucoma varies with race [20]. Parafoveal and perifoveal vessel density have performed poorly in detecting glaucoma in participants of African descent versus those of European descent [20]. Our results are significant in view of the inclusion of individuals from Egyptian backgrounds. We included eyes with medically controlled POAG and healthy age- and sex-matched controls, with male predominance in both groups. This sex-related discrepancy may have affected the final outcomes because of the observed significantly lower mean RNFL and vessel density in men than in women with POAG [27]. Further studies recruiting groups of individuals with similar sex distributions and known racial backgrounds could provide more accurate representations of our measured parameters, particularly iVD.

A comparison of eyes with open-angle glaucoma using age- and sex-matched controls revealed a significantly lower vessel density on OCTA [26]. Likewise, the average iVD was significantly lower in eyes with POAG than in controls in our study, although we limited the glaucomatous group to those with POAG. In a cross-sectional study using OCTA to compare eyes with various subtypes of glaucoma to those of healthy controls, Lommatzsch et al. [16] found significantly lower vessel density in the two segmentation layers. They observed the highest diagnostic accuracy for iVD, indicating the best diagnostic validity for this parameter [16]. Thus, we extracted data for iVD using OCTA for all participants. As in the study by Lommatzsch et al. [16], we found a significantly higher C/D ratio and thinner average RNFL in eyes with POAG than in controls, indicating concurrent deterioration of the structural and functional parameters and vessel densities in glaucomatous eyes.

Jia et al. [28] included only four patients with a diagnosis of preperimetric glaucoma and four healthy participants to quantify optic nerve head blood flow using OCTA. They observed an attenuated optic nerve head microvascular network in glaucomatous eyes with significant reduction in the flow index and vessel density, whereas the microvascular network was dense in normal eyes [28]. Another study reported similar findings [29]. In addition, sensitivity and specificity of 100% were reported for the disc flow index using an optimized cut-off [29]. The authors found a significant strong correlation between the PSD in perimetry and the flow index retrieved from OCTA. They proposed the use of OCTA to evaluate glaucoma progression [29]. This may indicate that the structural changes detected using OCTA precede the functional abnormalities observed by SAP in preperimetric glaucoma. Our study included eyes with confirmed glaucomatous damage in terms of SAP and RNFL thinning on SD-OCT. Similar to the findings of Jia et al. [28, 29], we found a significant reduction in iVD accompanied by functional and structural changes detected using SAP and SD-OCT, respectively.

In the current study, we observed structural and vascular changes using SD-OCT and OCTA, respectively, accompanying the functional changes detected using SAP in eyes with POAG. In a cross-sectional study, Durmus Ece et al. [30] investigated potential relationships between structural and vascular parameters using OCTA in eyes with POAG and pseudoexfoliation glaucoma. Glaucomatous eyes had a significantly lower vessel density than healthy controls [30]. As in the current study, they found a significant positive correlation between RNFL thickness and vessel density [30], indicating a parallel deterioration of structural and vascular parameters in glaucomatous eyes. Moreover, we observed a significant inverse correlation between vessel density and PSD; however, they did not perform functional tests using SAP to assess this possibility [30]. We found a significant correlation between iVD and RNFL thickness. Moghimi et al. [31] reported that lower baseline vessel density at the macula and optic nerve head was significantly associated with faster RNFL thinning in eyes with mild to moderate glaucoma [31]. Our results

may indicate the concurrent progression of visual field abnormalities with deterioration of vessel density; however, the latter may precede functional changes, as previously reported [28]. Using Doppler flowmetry, Piltz-seymour et al. [32] found a significant reduction in optic nerve blood flow in those with POAG compared with age-matched controls. The authors concluded that circulatory abnormalities could develop early in preperimetric eyes [32]. Further longitudinal studies are required to document the chronological sequence of these changes in glaucomatous eyes, particularly those with POAG.

Using OCTA in eyes within the spectrum of angle-closure disease, the investigators detected a significantly lower vessel density in eyes with primary angle closure, in which the attenuated microvasculature had a significant correlation with greater visual field loss [33]. Lin et al. [34] recruited eyes within the spectrum of angle-closure disease to investigate potential correlations between functional, structural, and vascular parameters. They found a significant positive correlation between vessel density and MD on perimetry and RNFL thickness measured using SD-OCT [34]. A significant correlation between optic disc perfusion and functional parameters was reported in eyes with primary angle-closure glaucoma using OCTA [35] and in eyes with POAG and normotensive glaucoma using optical microangiography [36]. The significant association between attenuated vessel density and severity of visual field damage may be independent of structural loss in POAG [37]. We detected a significant correlation between iVD and both functional and structural parameters among participants with medically controlled POAG of varying severity.

Wang et al. [5] found that the severity of glaucoma determined by visual field results correlated significantly with the disc flow index and vessel density using OCTA in eyes with open-angle glaucoma with different visual field changes [5], indicating that optic disc perfusion varies with glaucoma severity. Both flow index and vessel density were significantly lower in eyes with glaucoma than in healthy controls, and both parameters were significantly correlated with MD and RNFL thickness in glaucomatous eyes, but not in healthy controls [5]. Using optical microangiography, significant correlations were reported between optic nerve head perfusion and POAG severity as well as structural changes in glaucomatous eyes [38]. We did not subcategorize eyes with POAG based on severity level; thus, the comparison of our outcomes with those of previous studies [5, 38] in this context may not be practical. However, OCTA has acceptable reproducibility for peripapillary, optic nerve head, and macular vessel density assessments in both healthy and glaucomatous eyes, regardless of disease severity [39].

In a cross-sectional study, Hou et al. [40] assessed ganglion cell complex thickness and macular vessel density using OCT and OCTA, respectively, in healthy, preperimetric, and early glaucomatous eyes. Compared to healthy eyes, both preperimetric and early POAG eyes had significantly lower ganglion cell complex thickness and macular vessel density. Eyes with preperimetric POAG displayed similar losses in both structural and vascular parameters; however, in eyes with early POAG, structural loss was significantly greater than vessel density dropout. Ganglion cell complex thickness and macular vessel density have comparable diagnostic accuracies in differentiating eyes with preperimetric or early POAG from healthy eyes [40]. The strength of correlation between vascular density and structural parameters varies with retinal thickness [41]. We included iVD in the radial peripapillary capillary layer; however, other vascular density parameters from various retinal layers were not analyzed.

Our outcomes should be interpreted with caution because of the small sample size, nature of the study design, and lack of longitudinal evaluation, which may limit the generalizability of the results. The effect of topical antiglaucoma medication on ocular perfusion pressure is a matter of debate [42, 43]; thus, the main limitation of this study was that patients in the POAG group were using different classes of topical antiglaucoma medications that might affect vessel densities. Additionally, the lack of longitudinal analysis left the prognostic value of the angiogram undetermined. However, the age-matching of groups helped prevent age-related vascular effects on vessel density. Further studies with additional parameters and long-term follow-up are required to verify our preliminary findings. OCTA imaging has exhibited acceptable diagnostic accuracy for differentiating glaucoma and its severity levels [5, 16]. Artificial intelligence-based measurement of foveal avascular zone enlargement and irregularity using OCTA has been proposed as a good marker of ocular perfusion and the accompanying inferocentral visual field defect progression in eyes with open-angle glaucoma [44]. Combined artificial intelligence-assisted OCTA imaging for optic nerve head vessel density evaluation using machine learning-based methods—and particularly, deep learning-based techniques—may improve the diagnostic accuracy of this non-invasive imaging modality for detecting different severity levels of POAG in future studies.

CONCLUSIONS

As expected, the structural, vascular, and functional parameters measured in this study deteriorated in eyes with POAG compared to age- and sex-matched controls. We found significant circumpapillary RNFL thinning on average and in all four quadrants, which correlated well with reduced vessel density in eyes with POAG. Likewise, a lower iVD on OCTA imaging had a significant inverse correlation with PSD in the perimetric evaluation of glaucomatous eyes. Further studies with additional parameters and long-term follow-up are required to verify our preliminary findings.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the Research Ethics Committee of the Suez Canal University, Ismailia, Egypt and complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants following an explanation of the study protocol.

Conflict of interest: None.

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